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I-DSD

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I-DSD Symposium 2026

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ABSTRACTS

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CONTENTS

I-DSD Symposium 2026

Invited Speaker Abstracts

001

Gonad development

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While we have made great strides in understanding the developmental molecular and cellular events that underlie gonad development it is far from complete picture. Crucial insights into the regulation of gonad development have come from analysing patients with Differences of Sex Development (DSD). Our gene discovery and functional variant analysis has more than tripled the number of 46,XY DSD patients receiving a diagnosis. This has enhanced prognostic accuracy (cancer risk, adrenal insufficiency) and assisted with their clinical management. However, at least 60% of 46,XY DSD patients remain without a genetic diagnosis. Furthermore, women with ovarian failure have diagnostic rates as low as 20%, leaving a 80% undiagnosed. A subset includes 46,XX Premature Ovarian Insufficiency (POI) affecting up to 1% of young women and is associated with cessation of menstruation and ovarian hormones before the age of 40. These women are infertile and at an elevated risk for cardiovascular disease, diabetes, osteoporosis and earlier mortality. There is often a genetic basis to POI but the known genes only account for about a quarter of cases. Using genomic analysis we have identified 20 novel POI genes which will assist with clinical management. Clearly, additional genes critical for human gonad development and dysfunction remain to be identified before diagnostic rates and clinical care for patients can be improved. One such new gene we discovered was SART3. We showed SART3 gene variants underlie a new spliceosomopathy characterised by failure of testis development and neuronal defects. This implicates the splicesome components in testis development. In addition, we showed that disrupted testis-specific regulatory enhancer sequences impact testis development and cause DSD. We identified SOX9 enhancers that, when duplicated or deleted, result in 46,XX or 46,XY sex reversal, respectively. These enhancers provide the missing link by which SRY activates SOX9 initiation, upregulation and maintenance in human testis development. Finally, we developed a protocol to differentiate human iPSCs into early bipotential gonadal cells, showing these can be aggregated to form testis-like organoids. This testis organoid model will be another powerful tool for understanding human testis development and dysfunction.

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002

Disease gene prioritization using single-cell data for gene discovery in differences of sex development

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Clinical exome and genome sequencing have substantially advanced the diagnosis of differences of sex development (DSD). However, many cases remain unsolved, in part due to the limited functional annotation of genes and–critically–non-coding regulatory elements that control sex-specific developmental programs. Current gene prioritization approaches do not adequately capture the cellular and temporal complexity of gonadal development, hindering the interpretation of both coding and non-coding variants. Here, we present single-cell tissue-specific gene prioritization using machine learning (STIGMA), a framework that leverages single-cell RNA sequencing (scRNA-seq) data to prioritize candidate genes and regulatory elements in a developmental context. STIGMA models the spatiotemporal dynamics of gene expression across cell types during gonadal differentiation, enabling the identification of genes and regulatory regions that are active in sex-specific lineages. Applying STIGMA to single-cell datasets of developing gonadal tissues, we demonstrate its ability to resolve cell-type-specific expression programs underlying testis and ovary development. Integrating these profiles with genomic data from individuals with DSD allows prioritization of both coding variants and non-coding variants affecting key regulatory networks. This approach highlights candidate genes and regulatory elements acting in supporting cells, germ cells, and steroidogenic lineages, thereby refining variant interpretation beyond conventional gene-centric methods. Overall, STIGMA provides a framework to link genetic variation to disrupted developmental trajectories in DSD. By capturing the cellular and temporal specificity of gene regulation, this approach improves the identification of causal genes and non-coding regulatory variants, offering new insights into the molecular basis of human sex development and its disorders.

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003

Making sense of sex in neuroscience

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Sex and gender are fundamental dimensions of human biology and experience – yet they remain among the most systematically neglected variables in neuroscientific research. This talk addresses the *gender data gap* in neuroscience: the persistent omission of sex and gender from basic and clinical research designs, the blind spots this creates in our understanding of brain function and mental health, and the steps needed to close them. Sex and gender shape the prevalence, symptomatology, and clinical course of mental disorders, as well as individual responses to prevention and treatment. Women are particularly vulnerable during hormonal transition phases – the menstrual cycle, hormonal contraception, pregnancy, and menopause transition – periods accompanied by profound neurobiological changes that are insufficiently captured by research designs built around male-default assumptions. Drawing on work from the DFG-funded International Research Training Group *"Women's Mental Health across the Reproductive Years"* (IRTG 2804), conducted in collaboration with Uppsala University (Sweden), this talk illustrates how hormonal fluctuations modulate emotion, stress processing, and social behavior – and why these dynamics matter for clinical practice. Moving beyond the biological, the talk argues for a neuroscience that integrates both sex and gender – including non-binary variation, longitudinal hormonal transitions, and the interaction between biological and sociocultural determinants of brain health. While reporting frameworks such as the SAGER guidelines have catalyzed progress, sex- and gender-sensitive recommendations remain largely absent from clinical practice guidelines for mental disorders. This is a critical gap: failing to account for sex and gender in diagnostic and treatment pathways means that a substantial proportion of patients may receive care that was never designed with them in mind. Bridging this gap requires optimal study designs, adequately powered and diverse samples, standardized assessment of sex and gender, and strong stakeholder involvement. Ultimately, making sense of sex in neuroscience means embracing the full diversity of human development – including differences in sexual development – as a source of scientific insight rather than a methodological inconvenience. This is not only a scientific imperative, but a prerequisite for individualized medicine and equitable care for all.

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004

Advances in male fertility preservation

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The impact of DSD on fertility will depend on multiple factors. The key determinant of fertility potential will be gonadal development and function, and ultimately whether the individual has ovarian tissue with viable oocytes, or a testis capable of producing functional sperm. Whilst fertility preservation options are well established for many patient groups, such as those receiving treatment for cancer, fertility preservation options for those with DSD are less well established. Fertility preservation is primarily conducted for those who are due to receive gonadotoxic treatment that will damage an otherwise healthy ovary or testis. Egg/embryo collection and cryopreservation of sperm are well established options for fertility preservation for adults facing such treatment. For prepubertal individuals, gonadal tissue cryopreservation is the only viable option. Ovarian tissue cryopreservation and re-transplantation is an established method for fertility preservation and restoration in those facing sterilising treatments. However, for prepubertal males there are currently no proven clinical options to preserve and restore fertility. Current experimental approaches include removing testicular tissue from the patient prior to treatment for cryostorage and subsequent re-transplantation or in-vitro maturation of germ cells to generate sperm. In 2015, the first UK clinical research programme to develop approaches to preserve fertility in prepubertal and adolescent males facing gonadotoxic therapies was established in Edinburgh. This session will describe the current status of fertility preservation for young people with DSD, focusing on those with testicular tissue present. We will also discuss the clinical challenges associated with fertility preservation and restoration in those with DSD.

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005

Importance of androgens in the development and function of the human foetal testis

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Androgens are essential regulators of human foetal testis development and play a critical role in male sexual differentiation. Following sex-determination, the bipotential gonads develops into testes under the control of the SRY gene, and subsequently the paracrine and endocrine activity of the foetal testis becomes central to further male development. In the human foetal testis, Leydig cells begin producing testosterone from approximately 7–8 weeks of gestation, initiating androgen-dependent processes that are essential both within the testis itself and in peripheral target tissues. Testosterone supports the maintenance of the Wolffian ducts and the differentiation into internal male reproductive structures, but the foetal Leydig cells also secrets INSL3 which plays a critical role directing testicular descent. The secreted testosterone is converted to the more potent dihydrotestosterone (DHT) in target tissues, which is essential for the masculinisation of the external genitalia. Accordingly, disruption of androgen synthesis or action due to either genetic or non-genetic factors can result in incomplete virilisation of the male foetus. Within the foetal testis itself, androgens exert important paracrine effects that support the development of testicular organisation, cell lineage differentiation, and function. These aspects were recently examined in an ex vivo culture model of human fetal testis in which pharmaceutically induced reduction in androgen exposure was found to affect both Leydig and Sertoli cell function as well as germ cell numbers. Although neither Sertoli cells nor germ cells express the androgen receptor at this developmental time-point, both cell populations exhibited alterations in response to reduced androgen exposure. This suggests that androgen signalling was mediated indirectly through other testicular cell types, most likely fetal Leydig cells–to exert effects on the overall foetal testis development and function. In conclusion, sufficient androgen exposure and action, particularly during a critical developmental window in early fetal life is essential to ensure correct differentiation and function of all cell types within the developing testis. Thus, the androgens produced by the human foetal testis are indispensable, both locally for testicular development and systemically to ensure male sexual differentiation.

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006

Ethics of fertility preservation in young people

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While fertility preservation is recommended practice for paediatric oncology, fertility preservation in children with different types of DSD can mean different things: to preserve functional gonads, to support development with hormonal treatments, or to reshape genitals by surgery to align them to a typical female or male shape, in order to make them suitable for sexual intercourse. Many factors contribute to the ethical complexity of this area of parental decision-making and paediatric practice. My talk intends to map this complexity in order to better understand what is at stake morally. The ethical and legal consensus position in more and more countries is to postpone as many decisions about invasive and irreversible treatments, such as genital surgeries, until the time when the young person can make their own choices. Treatments that are necessary to avert danger to health and cannot be delayed are, however, exempt under what I call the ‘health exemption’. Reproductive health should arguably be part of it. However, it is not entirely clear how broad that concept of reproductive health should be and how central reproductive functions are to the health of the person. For instance, the capacity to conduct peno-vaginal intercourse might not necessarily, under all circumstances, be part of it, given that there are also other ways to be sexually active and fertile. I will argue that a complete inclusion of all assumed fertility problems into the concept of reproductive health will unduly reduce the autonomy of the person later in their life and conflict with the intended meaning of the 2025 recommendation of the Council of Europe. On the other hand, if fertility preservation were not regarded as part of health, all fertility-preserving interventions in smaller children would be avoided and certain groups of DSD patients would, in effect, be sterile. Decisions need to avoid these two extremes: to obliterate autonomy and to block out fertility. A defensible understanding of the child’s well-being under these circumstances needs to consider both aspects and to be developed in a way that respects the young person’s moral subjectivity, which will lead to autonomy later in life, already at the time of decision-making. Will parents be able to explain their decision to the young person later in their life, or is their decision based on principles that they have reason to expect the person reasonably to reject?

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007

Assessment of the quality of care in DSD

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DSD is not a diagnosis but an umbrella term for a wide variety of rare congenital conditions concerning sex determination or differentiation. These conditions lead leading to complex requirements in diagnosis and healthcare. Like other rare conditions, the treatment of DSD poses unique challenges for the healthcare system. A lack of expertise and standards can lead to delayed diagnoses or misdiagnoses, while a lack of structured and evidence-based treatment services may result in over-treatment, under-treatment, or inadequate treatment causing poor outcomes. For this reason, national and international guidelines recommend specialised medical and psychosocial care for people with DSD from multi-disciplinary teams in designated centres. However, the implementation of these recommendations has often been difficult, unstructured, and rarely evaluated. The DSDCare project, funded by the German Federal Ministry of Health from May 2020 to August 2023, aimed to implement a standardised care model for people with DSD, and to evaluate the quality of care in 10 centres in Germany. This talk describes the development of quality indicators for the evaluation of healthcare quality, as well as the assessment of healthcare quality in the participating specialized DSD centres which is conducted via a newly developed patient registry (DSDReg), starting in May 2021. Following the completion of the DSDCare-project, the DSDReg was successfully integrated into the German Reference Network DSD (DRN-DSD), thereby ensuring the long-term evaluation of healthcare quality. As of the end of 2025, 821 individuals with DSD have been included in the registry.

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008

Assessment of the quality of care in CAH

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Benchmarking is an approach for implementing best practices and involves comparing indicators of practice amongst centres. A key feature includes its integration within a continuous and participatory policy of continuous care quality improvement (CQI). Benchmarking in healthcare improves efficiency, quality of care, patient safety and patient satisfaction. The process involves identification of a point of comparison to compare indicators of practice, development of standards, sharing of best practice and identifying potential areas for improvement. In the context of congenital adrenal hyperplasia (CAH), benchmarking may focus on gathering indicators for long-term monitoring or outcome (e.g. anthropometric measures, psychosocial outcomes) or facilitate a comparison of morbidity outcomes (e.g. the incidence of acute adrenal insufficiency related adverse events including sick day episodes, adrenal crises and hospitalisations). The objective is to identify quality indicators that are relevant, valid and may be used to distinguish good from suboptimal quality of care. Studies using real world data from the I-CAH registry have provided an opportunity to collect this information, providing collaborating centres with a perspective on their clinical care outcomes compared to other centres via centre-specific benchmarking reports which the majority of centres have found beneficial. Understanding the reasons for variation in CAH care and identification of care deficits may enable targeting of resources resulting in overall improvement in patient care over time. This lecture will provide an overview of the developments in this area and describe the challenges for developing quality indicators and benchmarking in CAH.

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009

Lessons learnt from DSD care in India

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Actual prevalence of DSD in India has not been determined. Child with DSD is a social emergency in our country. Parents and the extended family after a birth of a child are eager to know if it is a boy or a girl, the answer usually is not so straightforward. Establishing the diagnosis takes time and limited availability of clinical and laboratory expertise can be challenging in. Recognising that this baby needs specialist evaluation and is referred in time still does not always happen. Parents are many a times not willing to come forth with a child with atypical genitalia as it is felt that the child is probably a hijra, the child maybe taken away by members of that community. The next challenge is as to what should be the sex of rearing, In earlier times the sex of rearing was decided by the chromosomal sex or the extent of development of external genitalia, especially the phallus, so as the patient raised as a boy can void standing or can have successful sexual function and medical and surgical treatment was done accordingly. With the changing paradigm in the west, in our country state of Tamil Nadu has also brought out similar guidelines. This is extremely difficult in our country because of societal norms, the pressure and social stigmatization family is likely to face, literacy and understanding of the parents and religious beliefs and practices. Untreated children with atypical genitalia face social stigmatization likely to be bullied in school and society and an infertile girl is a big burden for the parents. All these cultural issues need to be addressed while managing children with DSD. Studies are limited but clearly show that parents of children with DSD want that the sex of rearing be decided as early as possible and surgery according to that should be done early. Grown up (>12 years) and adult patients with DSD also prefer that the sex was decided early on, feel that parents have a right to decide about their treatment and surgical interventions should be done in early childhood. Adult DSD have not shown major gender dysphoria.

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010

The influence of biology on athletic performance

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Athletic performance is influenced by the interaction of biological, environmental and psychological factors. Among biological factors, endocrine function is particularly important, with sex steroid hormones influential in the regulation of muscle protein synthesis, erythropoiesis and skeletal development, all of which influence phenotypes directly relevant to athletic performance. Variation in hormone exposure, androgen sensitivity and developmental timing contribute to observed differences in muscle mass, haemoglobin concentration and cardio-pulmonary capacity. Indeed, it is sustained differences in androgen exposure during puberty that are associated with the typical sex-related divergence observed in key athletic phenotypes such as strength, power and endurance. Differences of sex development (DSD), however, encompass a range of distinct biological variations in which chromosomal, gonadal and hormonal characteristics may not align with typical developmental patterns. Consequently, the impact of these sex variations on biological phenotypes relevant to athletic performance is less clearly defined. In sport, athlete classification has typically relied on biological markers intended to reflect relevant physiological characteristics, including circulating testosterone concentrations and, more recently, the presence of Y chromosome material. Such markers, however, do not account for variation in receptor function or developmental history, limiting their ability to fully capture the biological diversity observed in athletes with DSD and their relationship to performance. While evidence directly linking DSD-related biology to athletic performance remains limited, emerging performance analyses from elite sport suggest that outcomes among athletes subject to DSD-related regulations are variable and generally fall within the range observed in the women's sport category, without clear separation from elite female performance. Together, these findings emphasise the need to interpret biological markers within the broader context of athletic performance when considering DSD in sport.

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011

Managing biological differences in the sporting world

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The challenges of sport's and their governing bodies to provide a balance between duty of care, inclusivity, fairness and safety when implementing eligibility criteria and policies in sport. Sport is an integral part of society contributing to health, social interaction, competitiveness, national identity, entertainment and the economy. Indeed, it both reflects and influences the culture of society. With that, the relationship between societal norms have seen the rules of sport constantly evolving. This is never more evident and complex than in inclusion of diverse populations within the sporting environment. In particular, this has become evident in women's sports, where there has been longstanding balance between inclusivity, fairness and safety. An increasing number of countries and sports have now determined that protecting the integrity of female sport, fairness and sometimes safety, is best served by using biological sex as the determinant for participation, as per the UK Supreme Court ruling in 2025. This has seen the opportunity for transgender participation in many women's sports now removed. However, the rules and policies to determine the participation of individuals with differential sex development are not captured in these rulings and indeed remain outdated or non-existent. This has seen high profile cases in Olympics, UK athletics and other sports reflect the lack of clarity in how to proceed when faced with a participant with a DSD condition. The impact of the decisions, testing methodology, social media and on the individuals are profound and supported by powerful testimony from those affected. There is no doubt that some DSD conditions produce advantageous masculinisation and performance benefits but characterising this is problematic and implications on new policy individuals of any widespread testing/screening program such as for SRY gene will be profound. The roles of the sports, through national and international governing bodies, working with expert groups are essential to create evidence based and measured policies. Prof Nick Peirce will attempt to illustrated some of the challenges of implementation from the perspective of a sport's national governing body that oversees professional and recreational men's and women's sport and has a duty of care to its participants and the need to create, if necessary, case by case policies that try to marry the competing elements of complex medical condition and understandable eligibility policies.

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012

Gaps in current hormone replacement therapies

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When faced with patients presenting with gonadal or adrenal insufficiency, whether primary or secondary to pituitary dysfunction, pediatric and adult endocrinologists have a wide range of hormone replacement therapies at their disposal. However, while these treatments often achieve the desired clinical balance, they do not systematically replicate human physiology. Numerous molecules exist, with clinical practices varying considerably between countries and medical teams. These treatments must always be discussed on a case-by-case basis with the patients concerned. For decades, however, few new developments have emerged in the therapeutic field of gonadal or adrenal insufficiency. Undoubtedly, one of the most striking examples of therapeutic innovation concerns congenital adrenal hyperplasia, where the approach has been highly innovative in recent years, with the simple objective of sufficiently suppressing the production of adrenal steroids without causing secondary clinical hypercortisolism in these patients with adrenal insufficiency. We will discuss these therapeutic approaches as well as the interest in considering new markers that could involve a more tissue-specific view of hormone replacement treatments, always with the underlying aim of achieving the desired effects on the different target tissues without inducing significant side effects.

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013

Mimicking the adrenal gland: novel developments

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Adrenal insufficiency (AI) is a life-threatening endocrine disorder arising from insufficient adrenal hormone production. Congenital adrenal hyperplasia (CAH), most commonly caused by 21-hydroxylase (CYP21A2) deficiency, which accounts for over 90–95% of CAH cases, represents the predominant etiology of primary adrenal insufficiency in pediatric populations. Standard of care relies on lifelong glucocorticoid and mineralocorticoid replacement, yet this approach fails to recapitulate the circadian rhythmicity and stress-responsive dynamics of endogenous adrenal hormone secretion. The consequent inadequacy of hormonal control predisposes patients to adrenal crises, impairs linear growth and metabolic homeostasis, and substantially diminishes quality of life, collectively underscoring the urgent need for innovative, physiologically faithful treatment modalities. Recent advances in regenerative medicine have enabled the directed differentiation of human induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) into fetal zone adrenocortical-like cells, a process guided by Sonic Hedgehog (SHH) signaling and the master steroidogenic transcription factor NR5A1/SF-1. In parallel, mouse ESCs have been successfully differentiated *in vitro* in three-dimensional (3D) cultures into adrenocortical-like cells that exhibit both angiotensin II- and ACTH-responsive steroidogenesis, recapitulating fundamental features of adrenal cortex physiology. Complementary advances in 3D human adrenocortical organoid systems have yielded expandable platforms that maintain zona fasciculata identity and sustain cortisol production. Encapsulation technologies, most notably alginate-based constructs housing bovine or porcine adrenocortical cells, afford immunoisolation and sustained hormone secretion, with successful reversal of adrenal insufficiency demonstrated in rodent models. For CAH, iPSC-derived human induced steroidogenic cells (hiSCs) from patients accurately model disease phenotypes, including hypocortisolism, which can be corrected ex vivo by lentiviral delivery of wild-type CYP21A2, restoring physiological steroid profiles. CRISPR/Cas9-mediated gene correction of CYP21A2 in patient-derived cells is advancing in preclinical studies, with lipid nanoparticle delivery strategies targeting adrenocortical progenitors. These novel cell and gene therapy strategies hold transformative promise for the treatment of adrenal insufficiency and CAH, aiming to restore autonomous, regulated adrenal hormone production and potentially obviate the need for lifelong hormone replacement. Key challenges remain, including durable engraftment, immune compatibility, physiological regulation, and scalability, but ongoing research is rapidly advancing the field toward functional cures that could fundamentally alter disease management and patient outcomes.

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014

Mimicking the testis: generating stem-cell derived organoids

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The testes develop from a bipotential gonad upon the presence of the Y chromosome and activation of the male genetic cascade. Much of what we currently know of sex determination and testis development stem from *in vivo* studies and cases of Differences of Sex Development (DSD). Yet, the gonads develop at embryonic stages, where the amount of biological material that can be retrieved, and accessibility, pose a major limitation to understanding sex determination and gonad development. Developing an *in vitro* stem cell-derived testis organoids could promote our mechanistic understanding of sex determination in health and disease. We have previously developed stem cell-derived differentiation protocol enabling to get Sertoli cells upon combination of defined media and forced expression of transcription factors. We also developed primary *in vitro* embryonic and pre-pubertal testis organoids able to recapitulate the *in vivo* testis. Here, we refined and improved our previous protocol and now able to generate all the somatic lineages of the testis: Sertoli, Leydig and Peritubular Myoid cells in a single protocol relying solely on defined media and 3D scaffolding. Our stem cell-derived testis organoids are highly similar to *in vivo* testis, and the protocol mimics the *in vivo* developmental trajectories. Transcriptomic analysis confirms their high resemblance to *in vivo* counterparts. Culturing these cells in 3D, they are able to organise in a manner resembling the *in vivo* testis. Future applications of this system to better explore sex determination under normal and pathological conditions will be discussed.

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015

Environment of hypospadias and its link to surgical outcome

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The occurrence of hypospadias remains unexplained in most cases. A complex, multimodal environment is likely involved in the development of genital malformations. Beyond contributing to the occurrence of the malformation, this environment also influences its prognosis. The genetic environment classically involves genes responsible for gonadal development, hormone biosynthesis, and hormonal sensitivity. Additionally, genes involved in cell adhesion and placental development may constitute a favorable or unfavorable background, potentially affecting respectively postoperative complications or growth restriction in these children. The hormonal environment, a key etiological factor, may also serve as a prognostic determinant in the management of these children. A deficiency in androgen synthesis or action affects the overall development of the genital tubercle, glans diameter, and possibly urethral plate width, all of which are prognostic factors for postoperative complications. The external environment, suspected to contribute to the occurrence of hypospadias through the action of endocrine disruptors chemicals, may also alter tissue healing and increase the rate of post-operative complications. Finally, the surgical environment determines prognosis. Center surgical volume, national organization into referral centers, and multidisciplinary management all influence the overall outcome of care in children with hypospadias. Overall, hypospadias should be understood within a multifactorial framework in which genetic, hormonal, environmental, and surgical factors interact. These interconnected environments not only contribute to the occurrence of the malformation but also shape its phenotypic severity and influence key anatomical determinants relevant to repair, thereby impacting prognosis and surgical outcomes.

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016

Long term management after female genitoplasty

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Feminizing genitoplasty has been historically performed to reduce the size of the clitoris, to separate the urethra from the vagina, and/or to increase the diameter and length of the vagina in those with variations in sex characteristics. These procedures are often performed in infancy and childhood by pediatric surgical subspecialists and may involve clitoroplasty, labioplasty, urogenital sinus mobilization, and/or vaginoplasty. Surgical outcomes research is most commonly focused on short term complications; patients are rarely followed long enough postoperatively to robustly assess sexual function and complications in adolescence and adulthood. Long term outcomes studies are commonly limited due to absence of non-operative control groups, low numbers of participants, heterogeneity in surgical techniques, and lack of phenotype, genotype, and gender identity subtype analyses. Adults who have undergone feminizing genital surgery experience significant rates of impaired sexual function and satisfaction. Long term complications of clitoral surgery include altered clitoral sensation and anorgasmia. Vaginoplasty complications include introital and proximal stensosis, bothersome hair growth, and abnormal discharge and lubrication. Difficulties with penetrative sexual activity and dyspareunia are common. Early vaginoplasty is associated with high rates of additional surgery later in life to address functional or aesthetic concerns. Individuals may experience medicalization of their genitals, which may result in avoidance of sexual intimacy and fear of sex.

Mangement of these complications is challenging. In conclusion, patients and parents should be counseled about the risk of sexual dysfunction and the limitiations of long term outcomes data following feminizing genital surgery. Additionally, providers who care for patients with variations in sex characteristics need to know how to assess and manage complications of surgical interventions in adolescence and adulthood.

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017

Standardized assessment of surgical outcomes

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In recent years, there has been a significant evolution in the surgical approach to individuals with Differences of Sex Development (DSD). There is an increasing debate worldwide about the role of surgery and the ideal timing for surgical interventions in this population. Many teams have developed multidisciplinary clinics and apply the principles of shared decision-making and peer involvement when informing families about possible surgical outcomes. However, a review of the available data and literature on this topic reveals a lack of transparency regarding the actual prevalence and timing of surgical interventions worldwide. Additionally, structured and well-defined outcome data regarding long-term functional and psychological outcomes in this population is lacking. Therefore, our aim is to identify a comprehensive technical, surgical, and outcome dataset for DSD surgery. The standardised data collection will ultimately help to improve the quality of care, strengthen the evidence base and provide guidance on the long-term care of individuals with DSD. Our first step was to establish a baseline surgical dataset, informed by a thorough literature review and discussions within our national expert group. This dataset includes information on surgical techniques, postoperative complications, and functional as well as psychosexual outcomes. To reach a broad consensus on the essential data elements, we initiated a three-step Delphi process involving three online surveys in which participants were asked to assess predefined data categories. This will be followed by a final sounding board meeting. Participants in this process include paediatric urologists, paediatric endocrinologists, gynaecologists, psychologists, and peers. In conclusion, we are developing a core surgical dataset for DSD through a thorough process based on current evidence and an international expert consensus. By defining this dataset, we aim to improve the quality of future care and to better define the demographic landscape by obtaining standardised outcome data.

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Oral Communication Abstracts

Session 1

OC1.1

Dysregulated free fatty acid metabolism in men with Klinefelter Syndrome

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Background

Klinefelter syndrome (KS) is associated with hypergonadotropic hypogonadism as well as obesity, insulin resistance, and dyslipidemia. While impaired glucose metabolism has been described, adipose tissue lipolysis and free fatty acid (FFA) kinetics have not previously been directly examined in this population.

Aim

The purpose of this study was to evaluate FFA metabolism and adipose tissue insulin sensitivity in men with KS and to investigate if 6 months of TRT in males with KS would affect the regulation of FFA.

Methods

In this randomized, double-blinded, placebo-controlled, crossover study we recruited 13 patients and 13 healthy age-matched controls. Men with KS received 160 mg/day Andriol or placebo treatment for 6 months and were then crossed over. At the end of each treatment period, we applied a hyperinsulinemic euglycemic clamp with a palmitate tracer to quantify the regulation of lipolysis.

Results

The concentration of palmitate during clamp was 32.2 micromole/l for KS and 21.8 micromole/l for controls ($P = 0.0002$). KS men had a significantly higher basal palmitate flux compared to controls (mean = 194.2 and 121.2 micromole/min, respectively; $P = 0.0264$). The palmitate flux was significantly higher in KS compared with controls under clamp conditions (mean = 79.5 and 33.3 micromole/min, respectively, $P = 0.0044$). No linear association was observed be-tween palmitate flux and energy expenditure in KS, in contrast to controls. Six months of TRT did not affect palmitate con-centration or flux in men with KS.

Conclusion

Reduced insulin suppression of lipolysis shows that KS men have an abnormal regulation of FFA and are insulin-resistant with respect to the regulation of lipolysis. The absence of a metabolic effect of TRT suggests that dysregulated lipid metabolism in KS is not solely attributable to hypogonadism. These findings support the presence of intrinsic alterations in adipose tissue metabolic regulation in this population.

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OC1.2

Phenotyping and hierarchical clustering in genetically unresolved DSD: identifying clinical signatures to prioritize genomic discovery

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Background

Individuals with genetically unsolved differences of sex development (DSD) are typically treated based on clinical and biochemical parameters related to their symptoms and signs of DSD, and other (related) health issues. However, having a clear genetic diagnosis may be essential for understanding the hereditability of the condition and predicting outcomes. A considerable subset of individuals with DSD lack an identifiable genetic aetiology. Our aim was to characterize phenotypic patterns of these unresolved cases and assess whether their multisystem anomalies resemble established genetic DSD and form distinct clusters indicative of previously unrecognized mechanotypes.

Methods

We analysed existing data on the the SDMregistrires platform for individuals with 46,XY or 46,XX DSD who lacked a molecular diagnosis. Our approach combined two complementary strategies: 1) unsupervised hierarchical clustering (Gower distance) to identify phenotypic subgroups, and 2) supervised phenotype-guided classification using reference fingerprints for *NR5A1*/SF-1 and POR (PORD) deficiency.

Results

Among 1,391 individuals screened, 345 (24.8%) met inclusion criteria based on the presence of additional organ anomalies. The cohort was predominantly 46,XY (83.8%). The most prevalent anomalies were small for gestational age (28.1%), cardiac (21.4%), CNS (15.7%), and renal (14.5%). Unsupervised clustering resolved five phenotypic groups, including a novel CNS-dominant cluster (10% of unclassified cases) and a craniofacial-dominant group. Phenotype-guided classification showed that 11% of cases displayed an SF-1-like pattern (blood/CNS/adrenal involvement), while 22% exhibited a PORD-like profile (adrenal/skeletal/craniofacial involvement).

Conclusions

Genetically unresolved DSD frequently presents in recognizable phenotypic clusters mimicking established syndromes or suggesting novel or known underlying regulators and genes. Systematic phenotyping is essential for identifying known signatures such as SF-1-like or PORD-like and provides a roadmap for targeted genomic re-evaluation, including searching for regulatory variants or related genes. It allows to bridge the diagnostic gap, refine clinical classification, and support individualized management.

Acknowledgements

We would like to acknowledge the help of all the centres that have contributed cases to the I-DSD Registry.

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OC1.3

Exploring the underlying gene expression profiles of differences of sex development phenotypes through transcriptome analysis

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Background

Differences of sex development (DSD) comprise a heterogeneous group of conditions characterized by atypical chromosomal, gonadal, or anatomical sex. Although many genetic causes have been identified, the transcriptional programs that control human gonadal differentiation and their disruption in DSD remain poorly understood.

Methods

Bulk RNA sequencing was performed of gonadal tissue from 11 individuals with DSD and compared their transcriptomes to developmental stage–matched control gonads obtained from public datasets. Dimensionality reduction using curated sex-differentiation gene sets was applied to position samples along male–female transcriptional axes. Differential expression and pathway analyses were used to identify disrupted molecular programs, which were interpreted in the context of available histological and clinical data.

Results

DSD gonads did not cluster with typical male or female controls but instead occupied an intermediate transcriptional space, reflecting variable degrees of testicular and ovarian differentiation independent of chromosomal sex. Key sex-determining genes were not within the normal range, with reduced ovarian markers and altered expression of testis-associated genes. In 46,XY DSD samples, pathways related to spermatogenesis, cell cycle progression, and metabolism were broadly downregulated, consistent with impaired testicular development. Adult PGD cases showed transcriptional signatures of reduced mitotic activity and defective germ cell maturation, whereas prepubertal PGD samples retained expression of testis-maintaining factors such as *DMRT1* and activation of developmental and proliferative pathways. In 46,XX OT-DSD samples, both testicular and ovarian gene networks were simultaneously active, in line with mixed histological phenotypes. Across all DSD groups, the epigenetic regulator *CBX2* was consistently downregulated, suggesting a shared defect in stabilization of sex-specific regulatory programs.

Conclusion

Human gonadal fate in DSD is best described as a transcriptional spectrum rather than a binary outcome. Transcriptome profiling reveals molecular states that are not predicted by karyotype or external phenotype alone, highlighting the importance of RNA-based analyses for understanding the biology and clinical heterogeneity of DSD.

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OC1.4

Reliance on diagnostic genetics in reaching a diagnosis of androgen insensitivity syndrome (AIS) – results from the I-DSD registry

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Introduction

The practice of reaching a diagnosis and the reliance on diagnostic genetics in suspected cases of Partial and Complete AIS (PAIS, CAIS) remains unclear.

Methods

To understand the use of Androgen Receptor (*AR*) analysis for reaching a diagnosis of Complete and Partial AIS (CAIS/PAIS), the I-DSD registry on the *SDMregistries* platform was used to identify all cases reported as AIS. Centres with eligible cases were approached to obtain more information on clinical features and diagnostic findings.

Results

At study launch in 2025, of the 10,375 cases on the platform, 831 (8%) cases were reported as AIS (CAIS:PAIS:NK, 479:348:4). At first data tranche, of these 831 cases, data were available in 664 (80%) (CAIS:PAIS:NK, 381:280:3) from 43 centres in 20 countries. Of the 381 cases of CAIS, *AR* analysis was reported in 125 (33%) cases, and a gene abnormality was reported in 116 (93%). Of the 280 cases of PAIS, details of *AR* analysis were available in 100 (36%) cases, and a gene abnormality was reported in 54 (54%). Comparing the 12 high income centres and 8 low/middle income centres, the number of centres that had performed *AR* analysis was 11 (92%) and 6 (75%), respectively. The median age (10th, 90th) at diagnosis was available in 230 cases and was 9.7yrs (0.06, 18.5) and 0.6yrs (0.04, 12.6) in CAIS and PAIS, respectively ($P < 0.01$). In those cases of PAIS where the diagnosis was associated with an *AR* abnormality, the median age at diagnosis was 1.3yrs (0.01, 28.1) whereas in those cases where there was no report of *AR* analysis, the age at diagnosis was 0.3yrs (0.04, 2.0) ($P < 0.01$). In CAIS, the median age at diagnosis for the two groups was similar at 10.9yrs (0.02, 18.8) and 8.5yrs (0.2, 38.0) (NS).

Conclusion

The preliminary analysis of the I-DSD Registry shows that there is a high level of genetic certainty of diagnosis in cases of AIS who have had genetic analysis. However, almost 50% of the cases were reported as AIS despite the absence of genetic confirmation. In cases of PAIS, an earlier diagnosis was less likely to be associated with genetic confirmation.

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OC1.5

Retinoic acid signaling is an important regulator of genotoxic stress in somatic and germ cells in individuals with various infertility phenotypes including DSD

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Background

Genotoxic stress causes DNA damage that impairs gonadal cell function and fertility. Individuals with DSD, similar to men with non-obstructive azoospermia (NOA), exhibit increased DNA damage and altered DNA repair in blood and gonads, associated with dysgenic gonads, germ cell tumors, and compromised genomic integrity. Retinoic acid (RA), produced by Sertoli cells, is essential for meiosis, spermatogenesis, and germ cell differentiation. Our preliminary data revealed altered RA signaling genes in infertile individuals, including reduced expression of RA synthesis enzymes and increased expression of receptor genes, particularly RARA, under genotoxic stress. This study investigated whether balanced RA signaling in blood and gonadal cells modulates genotoxic stress and may represent a potential target for infertility treatment.

Methods

Blood samples from individuals with DSD ($n = 11$) and controls ($n = 6$) were treated with the RA activator TTNPB (0.5 μM), RA inhibitor WIN (1 μM), or RARA inhibitor AR7 (10 μM) for 2 hours. Primary testicular cells were exposed to RA (2 μM for 15 days) and Olaparib (100 μM for 24 hours) in ≥4 experiments. Gonadal tissues from individuals with NOA ($n = 5$) and DSD ($n = 3$) were analyzed for RARA/RARB colocalization and used for primary cell isolation. The DSD group included Swyer syndrome, CAIS, and Turner syndrome. ANOVA was used to statistics.

Results

In leukocytes from individuals with DSD, AR7 increased inflammatory and genotoxic stress markers, including *IFNA, IFNB, IL1, IL6, IL12A*, γH2AX, P62, and AR, mimicking the effects of RA hyperactivation by TTNPB. In contrast, WIN had minimal effects on these markers. *ALDH1A1, ALDH1A2, RDH10, RDH11,* and *RARA* were controls for treatments. Nuclear RARA and RARB were significantly increased in γH2AX-positive DNA-damaged Sertoli cells in gonads of DSD and NOA. *In vitro*, RA supplementation improved testicular cell integrity by increasing AR+ Sertoli cells and SALL4+ spermatogonia while reducing γH2AX+ cells. RA treatment rescued Olaparib-induced genotoxic stress, promoting RARA, Ki67, and SALL4 while reducing DNA damage.

Conclusions

Treatment of blood and gonadal cells from individuals with DSD and NOA individuals revealed a RA signaling-based molecular mechanism centered on RARA that mitigates genotoxic stress.

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OC1.6

Long term mental, psychosocial and gender identity outcomes in adolescents and adults with differences of sex development from a tertiary care centre in India

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Background

Individuals with Differences in sex disorders (DSD) may experience mental and psychosocial challenges related to stigma, gender identity, sexual health and multiple therapeutic interventions which are influenced by cultural and societal contexts. Long-term psychosocial and psychosexual outcome data in individuals with DSD remains limited, particularly from developing countries.

Methods

This cross-sectional study included 30 individuals with DSD aged ≥14 years, along with 15 age-matched healthy controls and 15 disease controls (Type 1 Diabetes). Participants completed validated instruments including the Rosenberg Self-Esteem Scale (RSES), Hospital Anxiety and Depression Scale (HADS), Coping with DSD and Core Gender Identity, Gender Role Behaviour and Gender Orientation Scale. Self-constructed questionnaires for pshychosexual health and sociodemographic factors were administered.

Results

The mean age of DSD participants was 21.3 ± 4.6 years (9 reared male, 21 reared female), compared with 23 ± 3.8 years and 23.7 ± 4.2 years in healthy and disease controls respectively. Clinically significant anxiety and depression (HADS scale >10) were observed in 4(13%) and 1(3.3%) DSD participants respectively. Reports of suicidal ideation were more frequent in individuals with DSD compared with disease controls (30% vs 0%), while lack of psychological support was also commonly reported. Self-esteem remained comparable among DSD and both control groups.Gender identity was largely concordant with sex of rearing across all DSD subgroups ($P > 0.05$). Statistically significant differences in self-esteem and clinical depression scores across DSD categories ($P = 0.012$ and $P = 0.026$ respectively) were noted. Individuals with DSD reared as males exhibited lower self-esteem and higher psychological distress. 46,XY DSD – female rearing – partial androgen effect subgroup showed comparatively higher anxiety scores though not statistically significant. High levels of perceived shame and stigmatization were observed (mean ± SD: 14.2 ± 4.5/20) along with decreased openness related to disease.

Conclusions

These findings underscore the need for long-term multidisciplinary care incorporating psychological support, gender counselling, and sexual health services.

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OC1.7

DMRT3: a gatekeeper of DMRT1 activity in human male sex development

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Background

Differences/disorders of sex development (DSD) affect ~1% of live births and involve chromosomal, gonadal, or genital abnormalities. Diagnosis is often lengthy and inconclusive, with gonadal dysgenesis yielding a genetic diagnosis in only ~50% of cases. We aimed to increase DSD diagnostic yield by identifying causative DSD genes.

Methods

We report a 46,XY DSD patient presenting with perineal hypospadias, clitoromegaly, and cryptorchidism. Whole exome sequencing (WES) was performed, and variants were prioritized based on allele frequency, predicted pathogenicity, and relevance to sex development pathways, leading to the identification of a compound heterozygous DMRT3 variant. Functional effects were assessed using two luciferase reporter assays in HEK293T cells. An ESR1 promoter–luciferase construct was used to measure the impact of wild type and variant DMRT3 proteins on ESR1 transcription. A p4xDMRT luciferase reporter containing synthetic DMRT1 binding sites was used to evaluate how the DMRT3 variants influence DMRT1 mediated transcriptional activation.

Results

WES identified a compound heterozygous DMRT3 variant, which was prioritized as the most plausible genetic contributor. In the ESR1 promoter assay, both DMRT3 variants produced increased promoter activity compared with wild type DMRT3, indicating a potential gain of function effect on ESR1 regulation. Consistent with prior findings that DMRT1 preferentially forms heterodimers with DMRT3 rather than homodimers (Murphy, 2007), our p4xDMRT luciferase assay showed that DMRT3 suppressed DMRT1 driven transcriptional activation. Notably, the DMRT3 variants exhibited even stronger suppression than the wild type. Together, these results demonstrate that DMRT3 can inhibit DMRT1's ability to bind and activate its target sites, and that the patient specific variants enhance this inhibitory effect.

Conclusions

These findings implicate DMRT3 variants as contributors to 46,XY DSD through dual disruption of sex determining pathways. By increasing ESR1 promoter activity while suppressing DMRT1 dependent transcription, the variants appear to shift the balance between pro testicular and pro ovarian signaling. This work highlights a previously unrecognized role for DMRT3 in human gonadal development and supports its relevance as a candidate gene in DSD, with potential implications for improved genetic diagnosis and future therapeutic strategies.

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Session 2

OC2.1

Total, autoimmune, and cardiometabolic comorbidity burden across turner syndrome karyotypes: a nationwide danish cohort study

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Background

Turner syndrome (TS) is associated with increased morbidity across the lifespan, yet the cumulative diagnostic burden and variation by karyotype remain insufficiently characterized. This study aimed to quantify diagnostic accumulation in TS and compare comorbidity burden across karyotype groups, with separate analyses of total, autoimmune, and cardiometabolic diagnostic burden.

Methods

We conducted a nationwide cohort study based on Danish national registries, including all females with a karyotype consistent with TS. Karyotypes were classified into three mutually exclusive groups: Monosomy TS (non-mosaic 45,X), Variant TS (structural X-chromosomal abnormalities and/or Y-chromosomal material), and Mosaic TS (mosaic karyotypes including a 45,X cell line). Outcomes included the cumulative number of ICD-10 subchapter diagnoses, as well as specific autoimmune and cardiometabolic diagnoses. Diagnostic accumulation was assessed using multiple-failure Cox regression models estimating hazard ratios (HRs). Age-specific cumulative incidence functions (CIFs) were estimated for participants born in or after 1977.

Results

The cohort comprised 1,381 women with TS: 468 with Monosomy TS (33.9%), 386 with Variant TS (27.9%), and 527 with Mosaic TS (38.2%); median follow-up was 40.6 years. Overall diagnostic accumulation was similar in Variant TS and Monosomy TS (HR 1.00, 95% confidence interval (CI) 0.91-1.10), but lower in Mosaic TS (HR 0.71, 95% CI 0.65-0.78). Autoimmune burden was higher in Variant TS (HR 1.46, 95% CI 1.08-1.97) and lower in Mosaic TS (HR 0.47, 95% CI 0.33-0.66) than in Monosomy TS. Cardiometabolic accumulation was lower in Mosaic TS (HR 0.62, 95% CI 0.47-0.83), whereas Variant TS showed a higher point estimate (HR 1.31, 95% CI 1.00-1.72). In the subcohort born in or after 1977 ($n = 703$), cumulative incidence curves showed that many women with TS reached ≥ 10 ICD-10 subchapter diagnoses before age 40, although this generally occurred later in Mosaic TS.

Conclusions

Women with TS accumulate substantial comorbidity across the lifespan. Although diagnostic burden differ by karyotype and is lowest in Mosaic TS, all groups were markedly affected. Variant TS resembled Monosomy TS overall, but showed higher autoimmune burden and a possible increase in cardiometabolic morbidity. These findings support lifelong, systematic follow-up with screening and management of comorbidities in girls and women with TS.

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OC2.2

A new variant in the 3'-UTR of the SRD5A2 gene leads to highly efficient exonisation of an Alu element and contributes to 5α-steroid reductase type 2 deficiency

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Background

Steroid 5α-reductase deficiency is a rare autosomal recessive condition caused by mutations in the *SRD5A2* gene and results in a diminished synthesis of dihydrotestosterone during foetal development. This leads to a severe androgenisation deficit of the external genitalia in people with a 46,XY karyotype. Here we report an adult 46,XY person with clinically confirmed steroid 5α-reductase deficiency.

Methods

Sanger sequencing, whole genome sequencing (WGS), PacBio RNA Isosequencing.

Results

Sanger sequencing revealed a compound heterozygous, pathogenic c.692A>G; p.(His231Arg) variant within the *SRD5A2* reading frame and a very rare c.*66T>G variant 66 nt after the canonical stop codon in the 3’-UTR. Sanger sequencing of RT-PCR products from the individual’s derived genital skin fibroblasts revealed that only the maternal pathogenic c.692A>G variant is expressed, while the paternal c.*66T>G variant could not be detected. Short-read whole genome sequencing excluded additional mutations that might affect *SRD5A2* expression, both within the *SRD5A2* gene promoter or intronic regions. PacBio RNA Isosequencing of patient-derived transcripts revealed that the rare variant c.*66T>G introduces a new strong splice donor site that is spliced to an inverted *Alu* sequence located 15 kb downstream of the stop codon in the majority of cases. In minor cases this splice donor is spliced to a cryptic splice acceptor 860 nt downstream in the 3’-UTR. In all paternal, but none of the maternal transcripts, we found a new exon junction 66 nt after the stop codon within the 3’-UTR. Mammalian transcripts with an intron excision site >55 nt downstream from a termination codon are subject to degradation by the nonsense-mediated decay (NMD) pathway.

Conclusion

We conclude that the pathogenic maternal c.692A>G variant, together with the NMD-triggered downregulation of the paternal allele, are causative for the observed SRD5A2 deficiency. To our knowledge this is the first description of a mutation-induced *Alu* exonisation in the 3’-UTR of a DSD related gene.

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OC2.3

New genes/loci underlying human sex-determination and DSD revealed by integrating single-cell multi-omics and clinical genomics datasets

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Background

Understanding the genetic causes of DSD remains challenging. Our data show that >50% of all DSD cases do not have a genetic diagnosis. Many unexplained cases may be caused by variants in non-coding regulatory regions that disrupt gene regulatory networks (GRNs) essential for gonad development. Recent single-cell omics studies of human fetal gonads show substantial differences in gene expression profiles compared with mice. These differences may explain why several genes that cause human DSD fail to produce gonadal phenotypes in mouse models. This highlights the limitations of these models to reflect the precise GRNs that active during human SD. When disrupted, these GRNs may result in DSD.

Methods

Here, we integrated GRN inference from single-cell epigenomic and transcriptomic datasets with human clinical genomics. Using published human fetal gonadal scRNA-seq and scATAC-seq datasets, and advanced GRN inference tools, we reconstructed and prioritized lineage and sex-specific GRNs. In parallel, we mapped rare/novel genomic variants from 165 individuals with unexplained DSD to candidate gene regulatory elements (GREs) predicted by our GRN models, and independently to all regions of open chromatin active during gonadal differentiation. Potentially pathogenic non-coding variants were prioritized using stringent filtering criteria and an in-house pipeline designed to identify high-confidence pathogenic variants across the entire human genome

Results

Integration of scATAC-seq with scRNA-seq analysis defined core regulons in human fetal Sertoli and pre-granulosa cells. These regulons included regulatory hubs of known DSD genes and novel genes potentially involved in DSD. We then integrated these findings with clinical genomics. Rare/novel variants from 46,XY gonadal dysgenesis cases were mapped to - (i) 37,132 candidate GREs predicted by our GRN models, and (ii) 627,158 regions of active open chromatin during gonadal differentiation. Following a strict variant prioritization protocol, we identified 14 non-coding loci in predicted GREs associated with DSD. These included 4 genes known to cause 46,XY gonadal dysgenesis (enrichment P value 10^{-8}) and two other genes linked to either DSD or SD.

Conclusions

This integrative approach establishes a framework of putative GRN/GREs in human Sertoli/Granulosa cell specification and development as well as defining new genetic causes of DSD due to non-coding variants.

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OC2.4

The perception of women diagnosed with congenital adrenal hyperplasia on feminising surgery in childhood

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Background

Many patients with 46, XX congenital adrenal hyperplasia (CAH) were born with a masculinized genital appearance. Early feminizing surgery has been offered to promote acceptance of gender, optimize social participation and to enable penovaginal intercourse. These procedures have been criticized for being unethical and harmful. The Belgian and Dutch Ministries of Health explore possibilities to legally prohibit genital feminizing and masculinizing surgery in underaged children.

Aim

TO explore the perspectives of Belgian and Dutch women diagnosed with CAH, who underwent genital surgery in childhood, on the discussion described above.

Methods

Two focus groups - one in Belgium, one in The Netherlands - to discuss participants’ experiences and perspectives on the present debate. Participants were 18 years or above, had been diagnosed with 46,XX CAH and had undergone feminizing surgery in childhood. Discussions were audio-recorded, transcribed and uploaded in NVivo, software for computer-assisted non-numerical data analysis to conduct thematic analysis.

Results

Ten women aged 24 – 65years, volunteered; five participated in the focus groups and five shared their experiences in an individual interview as they felt uncomfortable to do this in a group. Four women had given birth to nine children. All women emphasized that feminizing surgery facilitates social participation, psychological wellbeing and body acceptance. Older women stressed the psychological burden of growing up with an atypical genital appearance and the desire for congruence between body and gender identity. Women agreed that invasive and irreversible surgery had disregarded their bodily integrity and autonomy. They noticed a challenge to determine an appropriate cut-off age at which such surgeries can be done and decisional distress in adolescence.

Conclusions

Although participants reported psychological distress, physical discomfort and traumatic memories related to surgery and follow-up examinations, they valued alignment of body and gender and protection against societal harm. We observed a gap between the complex lived experience of patients with CAH and activists’ perspectives, underscoring the necessity for patient-centered management and further investigations in both surgical and non-surgical options for CAH. Important limitations in our study were the absence of participants who identified as male or non-binary and the small number of participants.

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OC2.5

Genetic architecture of penile volume in the general population highlights potential genetic contributors to DSD

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Background

Male genital development is driven by fetal androgen exposure, yet the genetic determinants underlying interindividual variation in adult penile volume remain largely unexplored, particularly due to sample size constraints and potential cohort and measurement biases. Defining the genetic architecture of penile volume through large-scale, population-based genomic analysis is therefore vital for understanding male genital ontogeny and disorders of sex development (DSD).

Methods
We leveraged magnetic resonance imaging (MRI) data from a population-based cohort of $\sim$30,000 adult men of European ancestry. Total erectile tissue volume (comprising bulb, crura, corpora and glans) was quantified under resting (flaccid) conditions using automated deep learning-based segmentation. Genome-wide association analysis (GWAS) was performed using Regenie (adjusting for age, age^2, genotyping batch and first 10 PCs). SNP-based heritability and genetic correlations were estimated via linkage disequilibrium score regression (LDSC). Bivariate MiXeR analysis quantified polygenic overlap with hypospadias as a proxy for androgen-dependent congenital malformations.
Results
Mean (SD) total penile volume was 117.8 ± 27.0 mL. We identified 20 independent genetic loci associated with penile volume at genome-wide significance ($P < 5\times10^{-8}$). SNP-based heritability (h^2) was estimated at $\sim$30% (SE 2%), indicating a substantial polygenic component. Several loci were located near genes involved in androgen signaling and local steroid metabolism, including *SRD5A2*, *CYP21A2* and members of the *AKR1* family, consistent with the established role of androgen conversion and tissue-level androgen activity in male genital development. Additional loci highlighted pathways involved in somatic growth and developmental size regulation. Genetic correlation analyses revealed strong overlap with lean mass and height ($r_g \approx 0.30$-0.40), while correlations with adult circulating testosterone were modest ($r_g \approx 0.09$) and no correlation was observed with SHBG. Bivariate MiXeR estimated that $\sim$80% (SE 16%) of hypospadias' inferred causal component was shared with penile volume but represented only $\sim$6% (SE 1.4%) of the latter's polygenic signal.
Conclusion
Penile volume is a substantially heritable, polygenic trait whose genetic architecture is shaped by androgen metabolism and somatic growth pathways – reflecting both local endocrine exposure and tissue responsiveness. Our findings provide a population-level genomic framework for understanding variation in male genital development, highlighting potential genetic contributors to DSD.

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OC2.6

Analysis of the management of children with congenital adrenal hyperplasia in the United Kingdom and Ireland, using real-world data from the SDMregistries

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Background
To better understand current clinical practice in the treatment of children with congenital adrenal hyperplasia (CAH), a five-year observational initiative collecting longitudinal real-world data was launched in March 2022. The project focuses on patients younger than 18 years with 21-hydroxylase deficiency (21OHD) receiving care at specialist centres across the United Kingdom and Ireland, with annual data collection designed to capture evolving management patterns over time.
Methods
Data were extracted in April 2025 from the SDMregistries platform, comprising 1,291 clinic visits from 182 patients managed across 15 centres since January 2016. The number of enrolled patients per centre ranged between 1-34 (median 8). Regression analyses performed in R evaluated age- and sex-related variation in treatment regimens, biochemical markers, and World Health Organization height standard deviation scores (SDS). Glucocorticoid (GC) dosing was standardised by converting regimens into hydrocortisone (HC) equivalents adjusted for body surface area.
Results
Hydrocortisone administered three or four times daily was used in 95% of patients, while eight individuals aged 7–18 years received prednisolone. The mean GC exposure was 12.2 ± 4.0 mg HC-equivalent/m^2/day, with individual averages ranging from 4.6 ± 1.2 to 22.3 ± 0.4 mg/m^2/day. Marked inter-centre variability was observed, with mean dosing between 9.8-16.7 mg/m^2/day. GC dose increased modestly with age (0.2 mg/m^2/day annually), varied between centres, and was influenced by sex, with males receiving on average 0.8 mg/m^2/day less than females. Timing of administration also differed, with six centres prescribing late-evening doses between 22:00-24:00. Fludrocortisone exposure varied widely (18–869 μg/m^2/day) and differed significantly across centres ($R^2=0.02$, $P<0.01$). Biochemical control was inconsistent: 17-hydroxyprogesterone levels were elevated in 42% and suppressed in 14% of visits, while androstenedione levels were elevated in 25% and suppressed in 20%. Growth patterns changed across childhood, with mean height SDS rising from -0.5 in infancy to $+1.2$ at about 10 years, before declining to -1.0 by 17.5 years.
Conclusions
These findings demonstrate substantial variability in therapeutic strategies for paediatric CAH across centres. Further analyses linking treatment approaches with outcomes are needed to inform best practice, support benchmarking, and improve care for children with CAH in the United Kingdom and Ireland.

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OC2.7

Investigation of psychological impact of change of surgical CAH treatment on affected families – a preview with focus on anxieties

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Background
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency results in cortisol and aldosterone deficiency and increased prenatal androgen, causing virilization of external genitalia in females. Early genital surgery has therefore been common practice, but reports on unsatisfactory long-term outcomes have resulted in postponing surgery to an age when the girl can participate in the decision. However, the psychological impact of this change in practise on families has rarely been studied.
Methods
Participants with CAH from different DSD centres in Sweden aged 0-18 years and their parents have been interviewed with a semi-structured interview to access their history, well-being, anxiety; in general and specifically concerning genital surgery. The group was divided into girls operated in early age (2), girls who had not been operated (17) and boys (14). Boys with CAH were used as baseline to understand the impact of CAH on the families. The girls were asked if and to what extend their clitoris was visible when standing up. The study is still ongoing.
Preliminary results
A total of 36 family interviews have been conducted, including two families who have been interviewed both before and during puberty. The children were interviewed from the age of 5.Parental anxiety concerning CAH reduces over time with a peak in the newborn period. No significant differences between the groups could be detected. Parents to girls without early surgery expressed worries concerning the possibly upcoming operation and about problems related to the appearance of their daughters' genitals, regarding social interaction with peers, partners and future sexual function. The patients with CAH expressed no worries about CAH. The girls described their clitoris to be slightly visible and were less

concerned regarding a future genital operation than their parents. The girls liked to go to school, have friends, and participate largely in different sports.

Conclusions

Postponing the genital operation did not seem to significantly affect the overall anxiety concerning CAH. Parents expressed concerns related to the appearance of their daughters' genitals while the girls were less concerned and seemed not to be limited in their social interactions.

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OC2.8

Gonadal management in 45,X/46,XY and 46,XY differences of sex development: a care quality evaluation

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Background/aims

Individuals with 45.X/46,XY and several forms of 46,XY differences of sex development (DSD) have an increased risk of gonadal germ cell cancer (GGCC). Previously prophylactic gonadectomy was commonly performed but this is now more often delayed or declined. Thus, more individuals require lifelong gonadal management. Although monitoring protocols have been published, mostly based on self-examination or (bi)annual imaging with or without serum tumor marker screening, their implementation in clinical practice remains unclear. This care evaluation aims to assess adherence to recommendations for gonadal monitoring and its yield.

Methods

All individuals with 45,X/46,XY or 46,XY DSD with retained gonads were included. Data from 2020-2025 on imaging (ultrasound and/or MRI), tumour markers beta hCG and alpha-fetoprotein, and gonadal surgery were collected.

Results

Fifty-eight individuals had gonads *in situ*. Their median age in 2025 was 15.5 years (IQR 10–18); forty were registered as male (69%), the others as female; gonads were abdominal/inguinal in 21 (36%) and labioscrotal in 37 (64%). Twenty-two (38%) had 45,X/46,XY or XY gonadal dysgenesis, considered high-risk diagnoses for GGCC, the others had forms of XY DSD considered at lower risk. During the five-year period, 33 (57%) underwent ≥ 1 ultrasound and three (5%) an MRI. No findings suspicious for malignancy were reported. Imaging was more frequent for inguinal/abdominal vs labioscrotal gonads but similar between high-risk vs low-risk diagnoses and age groups <15 vs ≥ 15 years. Nine individuals (16%) underwent serum tumour marker screening with normal or marginally elevated results. Five patients (8.6%) eventually underwent prophylactic gonadectomy; none had a pre-malignancy or malignancy.

Conclusions

A substantial proportion of patients did not receive gonadal imaging, with no differences between high-risk vs low-risk diagnoses or age groups. For labioscrotal gonads imaging was less common, possibly because self-examination was advised as an alternative but this was not assessed. No evidence of malignancy was detected on imaging or based on serum tumour markers, which were only determined in a minority. The variability in follow-up of individuals with DSD with retained gonads may be due to the absence of evidence-based guidelines. Uniform implementation of follow-up recommendations and periodic evaluation of screening outcomes will help improve care.

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Poster Abstracts

PO1

Hypogonadism, adipose tissue inflammation, and adipose tissue circadian clock disruption independently promote metabolic dysfunction in Klinefelter syndrome – genomic underpinnings and testosterone treatment effects

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Background

Klinefelter syndrome (KS; 47,XXY) features early hypogonadism, adiposity and insulin resistance. The metabolic impact of testosterone replacement therapy (TRT) or X-chromosome dosage is not clear.

Methods

We assessed numerous markers of metabolic function longitudinally among 149 men with KS and 178 controls, stratifying KS by TRT at each visit. We applied mixed models to estimate TRT-associated changes in body composition, insulin sensitivity, and adipokines. Adipose tissue biopsies underwent transcriptomic and DNA methylation profiling; factor analysis identified latent programs, and circadian integrity was assessed with TimeTeller and clock-gene co-expression.

Results

TRT reduced body fat by 4.4 percentage points (15%), and increased lean mass by 2.6 kg, but body fat remained higher and normalized fat-free mass lower in both KS groups vs controls. TRT lowered HDL, reduced leptin (43%) and adiponectin (21%), but did not improve HOMA2-derived insulin resistance. From multi-omics factor analysis, we identified an adiposity-linked inflammatory factor associated with insulin resistance in all participants, whereas a KS-specific factor associated with insulin resistance independent of body fat was enriched for downregulated insulin/circadian regulators and corresponded to circadian disruption with adipose epigenetic age acceleration among KS males. Here, we observed significant disruption of circadian rhythmicity in KS compared with controls, and epigenetic age acceleration was also significantly increased in adipose tissue from KS compared with controls. Commonly applied metrics for prediction of body fat perform poorly in KS. We provide XGBoost models using anthropometrics (± testosterone) predicting KS body fat accurately (training $R^2=0.83$; external RMSE 3–4%).

Conclusions

KS metabolic dysfunction is only partially responsive to TRT and likely involves disrupted adipose genomic and circadian mechanisms, supporting monitoring of body fat and therapies beyond hormone replacement.

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PO2

Phenotypes and genotypes of mayer-rokitansky-küster-hauser (MRKH) syndrome in Denmark

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Background

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a congenital disorder characterized by uterovaginal aplasia in women with a normal female karyotype and secondary sex characteristics. The condition is typically diagnosed during late adolescence and has profound psychosocial and reproductive consequences. MRKHS is classified into two groups, *i.e.* type I (isolated) and type II (with extragenital malformations typically involving the kidneys, skeleton, heart, and auditory system). Although the aetiology remains largely unknown, increasing evidence suggests a heterogeneous genetic background. This nationwide study aims to comprehensively characterize the phenotypic and genetic spectrum of MRKHS patients in Denmark.

Methods

Supported by nationwide population-based registry data, we aim to recruit approximately 150 women nationwide with MRKHS for detailed clinical, biochemical, and genetic evaluation. Parents and affected relatives are also recruited for genetic analysis when possible. Phenotypic evaluations include gynaecological and anthropometric assessments, as well as imaging (pelvic and kidney MRI, spine X-ray, and echocardiography) to detect associated extragenital anomalies. Biological samples (blood, urine, cheek, and vaginal swabs) are collected to establish a biobank for molecular analyses. High-fidelity long-read genome sequencing (PacBio) of family trios is performed to identify and characterize single nucleotide variants, copy number variants, and structural genomic rearrangements associated with MRKHS.

Results

To date, 35 patients have been included in the project. In addition, 12 patients are awaiting clinical evaluation, and 14 additional individuals have registered for participation.

Discussion/conclusions

We anticipate that this study will provide unprecedented insight into the clinical heterogeneity and molecular basis of MRKHS. Establishing the genetic architecture of MRKHS will advance understanding of Müllerian duct development and its malformations. Furthermore, emerging reproductive options such as uterus transplantation and gestational surrogacy are likely to increase the number of affected individuals seeking reproductive counselling, highlighting the growing need for accurate genetic diagnostics and informed genetic counselling on recurrence risk.

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PO3

Patient characteristics and increased mortality in mayer-rokitansky-küster-hauser (MRKH) syndrome: a nationwide population-based study from 1977 to 2023

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Background

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a congenital anomaly characterized by uterovaginal agenesis in 46,XX females. The current literature on MRKHS is dominated by single-center cohorts/case-series and population-based evidence is warranted. We aimed to identify a large nationwide cohort and investigate the patient characteristics and mortality of MRKHS patients in Denmark.

Methods

To identify individuals with putative MRKH, we searched the Danish National Patient Registry (DNPR) from 1977 to 2023 for patients with uterovaginal agenesis/aplasia/hypoplasia diagnosis codes among women with no record of pregnancy or abortion. We retrieved karyotype data from the Danish Cytogenetic Central Registry. For initial case prioritization, we reviewed their complete DNPR diagnosis/procedure history, followed by case validation and characterization through medical records. The validated cohort was finally uploaded to Statistics Denmark, allowing us to investigate long-term outcomes in MRKHS vs matched comparators.

Results

We identified a total of 1449 individuals in the DNPR search. We excluded 829 individuals based on DNPR history and another 47 patients based on cytogenetic data (XY females, $n = 44$; monosomy X, $n = 3$). Medical records were retrieved from 438/586 eligible patients, confirming the diagnosis in 278. Median (IQR) age at diagnosis was 17.6 (16.4-19.3) years. Patients typically presented with primary amenorrhea ($n = 252$, 90.6%) but also abdominal pain ($n = 76$, 27.3%) and dyspareunia ($n = 60$, 21.6%). Type I (isolated) and type II (with extragenital anomalies) were found in 113 (56.8%) and 86 (43.2%), respectively, while 77 had insufficient data for classification. The most common extragenital feature was renal anomalies, identified in 64 (33.3%) of 192 patients, who had a renal exam. Karyotype information was available for 232 patients of which 220 (94.8%) had a normal 46,XX karyotype. Median (IQR) follow-up time after the date of MRKHS diagnosis was 18.6 (9.3-32.0) years. MRKHS was associated with increased mortality (HR 3.03, 95% CI:1.57-5.87), particularly for type 2 (HR 3.80, 95% CI:1.32-10.97), while no association was found restricted to type 1 (HR 1.53, 95%CI: 0.34-6.95).

Conclusions
Through nationwide registry data and diagnosis validation, we have established a population-based MRKHS cohort, constituting a valuable resource for epidemiological MRKHS research. Type 2 MRKHS was found to be associated with increased mortality.

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PO4

Treatment of sex diversity in the GDR: a medico-historical analysis of clinical practice in the 1950s

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Background
Scholarship on the history of intersex medicine has focused predominantly on Western European and North American contexts, while everyday clinical care in the GDR remains largely understudied. This project examines how internationally circulating concepts of sex assignment were translated into clinical routines in the GDR during the 1950s, and how these early stabilisations shaped later routinisation and local adaption in the 1970s and 1980s.
Methods
Drawing on a praxeological history of medicine, the study focuses on everyday clinical routines, decision-making processes and the implicit logics of treatment. Sources include a systematic analysis of the medical periodicals *Kinderärztliche Praxis* and *Experimental and Clinical Endocrinology*, unpublished archival materials from the University Children's Hospital Leipzig and Oral History Interviews with three former paediatricians and surgeons, coded using MAXQDA.
Results
In the early 1950s, intersex variations framed in GDR medical literature as requiring prompt clarification, closely aligned with internationally circulating sex-assignment paradigms, especially John Money's optimum gender of rearing model, and linked to administrative imperatives of early legal sex registration. As cortisone was introduced in the clinic in the early 1950s, congenital adrenal hyperplasia (CAH) entered the discourse as a hormonally treatable condition. The introduction of cortisone transformed CAH into a chronic, manageable condition and reshaped sex-assignment decisions. CAH functioned as a gateway diagnosis: by normalising early intervention, it extended established clinical pathways to other forms of intersex variation. A 1957 publication by Waltraute Thieme (University Children's Hospital Leipzig) illustrates the convergence, synthesising international research with local clinical cases. Findings from the 1950s closely resemble sex-assignment practices documented in Western Europe and the United States, pointing to the early adoption of internationally shared models within GDR clinical practice.
Conclusions
Medical treatment of people with variations in sex characteristics in the GDR was stabilised during the 1950s through internationally shared clinical paradigms, therapeutic innovation and administrative imperatives. Rather than representing a distinctly socialist medicine, early GDR clinical practice closely followed international models. These stabilisations provided the conditions for later local adaptions within socialist healthcare institutions. This finding contributes to a more differentiated picture of both history of intersex medicine and the place of GDR medicine within global health history.

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PO5

Antiandrogens and human sex differentiation: experimental practice and pharmaceutical research in 1970s West Germany

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Background
Antiandrogens emerged in 1970s West Germany at the intersection of pharmaceutical research, animal experimentation, and clinical endocrinology. This study traces how antiandrogens became central tools for conceptualizing human sex differentiation. Focusing on the Antiandrogens Working Group and the work of Schering researcher Friedmund Neumann, the article situates West German antiandrogen research within a longer experimental tradition of androgen-centered models of prenatal sex development. It argues that antiandrogens functioned not only as therapeutic substances but as epistemic instruments that reshaped scientific understandings of sex differentiation in the late twentieth century.
Methods
Archival materials and medical periodicals were analyzed using historical hermeneutical source interpretation.
Results
It argues that antiandrogens functioned as what Lara Keuck termed 'exploratory tool': an experimentally productive category that enabled new forms of knowledge about prenatal hormonal effects and sex differentiation. Antiandrogen research allowed Schering researcher and veterinarian Friedmund Neumann to inscribe his research on antiandrogens into already established experimental systems for researching the role of androgens in human sex development. While since the 1950s the search for the hormonal causes of sexual development focused on the psyche, the brain, and behavior, Neumanns approach diverged from contemporary research. Although drawing on the work of Alfred Jost, Neumann did not focus on behavior but continued to investigate sex development. By examining antiandrogens as both therapeutic substances and epistemic objects, the aim is to show how a substance which today is used in gender-affirming care, linked industrial research and experimental practices.
Conclusions
Findings complicate dominant historiographies that locate late-twentieth-century research on sex differentiation primarily in psychology and brain organization theory. In contrast to U.S.-centered narratives emphasizing brain organization theory, West German antiandrogen research sustained a material, experimental, and genital-focused model of sex development. Possible applications and communication of the potential of androgens in sex development research were not only shared within the practitioners working group but also communicated to a broader medical audience. Antiandrogens as potent substances had thus arrived in the broader medical community in the 1970s and were established as antagonistic to androgens, having a lasting impact on knowledge about sexual development.

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PO6

Phenotype and genotype correlation of 46,XY female reared patients with primary amenorrhea; identification of novel variants in CYP17A1

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Background
The *CYP17A1* gene encodes the enzyme cytochrome P450c17, which plays a crucial role in steroidogenesis. Biallelic pathogenic variants in the *CYP17A1* gene are responsible for autosomal recessive combined or partial 17α-hydroxylase/17,20-lyase deficiency (17-OHD), characterized by cortisol and sex steroid deficiencies, as well as excessive mineralocorticoid production.
Aim
This study investigated three patients with 46,XY DSD, who presented with hypergonadotropic hypogonadism and hypertension that developed later in life.
Methods
This study included three female reared patients with the complaint of primary amenorrhea. All patients were subjected to full history taking, pedigree analysis, thorough clinical examination, pelvic imaging and assessment of hormonal profiles. Patients underwent karyotyping, laparoscopy with gonadal biopsy, and histopathological examination. Exome sequencing (ES) was performed.
Results
Exome sequencing identified two homozygous variants in the *CYP17A1* gene. Computational and in silico analyses indicated that both variants, p.Ser379Phe and p.Trp406Ter, are predicted to result in the loss of enzymatic function.
Conclusions
Patients with 17-hydroxylase deficiency (17-OHD) typically exhibit a full range of symptoms associated with the disorder. Molecular analysis is crucial for confirming the diagnosis in patients with 17-OHD, as the hormonal and clinical features can be quite challenging to interpret. The limited availability of advanced steroid profiling techniques, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), poses additional diagnostic challenges, highlighting

the need for improved access to these technologies. The detection of novel homozygous variants expands the genotypic spectrum and underscores the importance of studying additional patients while considering the clinical and hormonal criteria for diagnosing 17-OHD.

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PO7

genetic study of female with premature ovarian failure and 46 XX gonadal dysgenesis

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Background

The genetics of premature ovarian failure (POF) are diverse, involving genetic and chromosomal abnormalities that disrupt ovarian function. Key genetic causes include X-chromosome abnormalities (like Turner syndrome), expansions in the FMR1 gene (associated with fragile X syndrome), and mutations in other genes like AIRE, FSH, and FOXL2 which are involved in folliculogenesis, DNA repair, and hormonal signaling. Genetic testing, including karyotyping and gene sequencing, is essential for diagnosing POF and providing personalized reproductive and genetic counseling, especially in cases with a family history of the condition.

Methods

Karyotype and exome sequencing were performed for all idiopathic 46 xx female (18 patients) presenting with primary amenorrhea with lack of secondary sexual characters and premature ovarian failure

Aim of the study

Is to detect variants associated with idiopathic premature ovarian failure and 46 xx gonadal dysgenesis

Results and conclusion

This is the first genetic study of patients with POI and gonadal dysgenesis in an Egyptian population. It showed a high yield of novel and previously reported mutations which highlights unique genetic architecture. this helped in providing an accurate genetic counselling.

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PO8

Unraveling the spectrum of disorders of sex development: experience from two egyptian tertiary centers

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Introduction

The global incidence of disorders of sex development (DSD) is estimated at 1:4500–1:5000 live births, higher rates have been reported in some regions, including Egypt. Diagnosis often requires a multidisciplinary approach; however, limited access to advanced genomic technologies in resource-limited settings frequently necessitates reliance on hormonal evaluation and imaging. This study aims to describe the clinical profile, etiological spectrum, diagnostic approach, and management of Egyptian patients with DSD presenting to tertiary centers in Cairo and Alexandria.

Patients and methods

This cross-sectional study included 161 Egyptian patients aged 0–18 years with suspected DSD presenting to Pediatric Endocrinology Clinics at Cairo and Alexandria University hospitals. All patients underwent detailed clinical evaluation, genital assessment using the Prader scale or External Masculinization Score, karyotyping, and hormonal testing. Selected cases underwent hCG stimulation testing and AMH measurement. Radiological and surgical findings were reviewed when available.

Results

Among 161 patients, 78 (48.5%) had 46, XY DSD and 78 (48.5%) had 46, XX DSD, while chromosomal DSD were identified in four patients (2.4%) and 46, XXY in one patient (0.6%). The median age at presentation was 12 months (range 0.1–204 months). Consanguinity was reported in 29.2% of patients and 14.9% had a positive family history. In 46, XY DSD, defects in androgen synthesis or action were the most common etiologies (41%), predominantly androgen insensitivity syndrome (32%). The most frequent presenting features were hypospadias (70.5%), micropenis (51.3%), and impalpable gonads whether unilateral (21.8%) or bilateral (41.0%). In 46, XX DSD, the majority of patients (76/78) had classic congenital adrenal hyperplasia, 80% due to 21-hydroxylase deficiency.

Conclusion

DSD in our cohort showed a heterogeneous clinical spectrum with nearly equal proportions of 46, XY and 46, XX DSD. Congenital adrenal hyperplasia was the predominant cause of 46, XX DSD, while androgen synthesis or action defects, particularly androgen insensitivity syndrome, were the leading causes of 46, XY DSD. The wide age at presentation highlights delays in recognition. In resource-limited settings, accurate clinical assessment and targeted hormonal evaluation remain essential for diagnosis, emphasizing the need to expand access to specialized multidisciplinary care and molecular diagnostics.

Key words

Disorders of sex development; Etiology; Clinical profile; Pediatric; Egypt

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PO9

The evolution and clinical predictors of molecular findings in 46XY DSD patients: experience from a single multidisciplinary centre

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Introduction

46XY disorders of sex development (DSD) are rare genetic conditions presenting with a nonspecific phenotype. Molecular diagnosis is a cornerstone of clinical care.

Objectives

To assess the clinical/biochemical profile in patients with 46XY DSD, the diagnostic yield of applied genetic panel and correlations between phenotype and genetic results.

Methods

Retrospective clinical data was collected for patients with suspected 46XY DSD from West of Scotland who underwent next generation sequencing (NGS) of 56 DSD-associated genes or a single gene of interest in Glasgow between 2018-2025. Genetic variants were classified according to ACGM guidelines. Chi-square test was performed for correlation analysis.

Results

In the 165 eligible patients, median age at presentation, genetic request and genetic report was 1.0, 3.3, and 3.9 years, respectively. The most common presenting phenotypes were complex genital abnormalities (34.5%), isolated undescended testes (27.3%) and isolated hypospadias (26.7%). EMS was available for 159 patients with severe, moderate or mild/no undervirilization in 56 (35.2%), 56 (35.2%), and 47 (29.6%), respectively. Endocrine assessment of testosterone, gonadotrophin and AMH levels was available for 163 patients and revealed no abnormalities in 117 (71.8%), and one, two or three abnormal results in 23 (14.1%), 17 (10.4%) and 6 (3.7%) patients, respectively. Genetic result was normal in 124 patients. A total of 53 variants were identified in 41 (24.8%) patients - 40 variants of unknown significance (VUS) in 20% and 13 pathogenic/likely pathogenic (P/LP) variants in 7% of the patients. The presence of a P/LP variant correlated with a higher number of biochemical abnormalities ($P = 0.001$) and lower EMS ($P = 0.02$). There was no correlation between EMS and presence of biochemical abnormalities ($P = 0.354$). Over the 8-year period, the patients with a higher EMS undergoing genetic analysis increased and the proportion of cases of reported variants decreased.

Conclusions

Patients with a higher number of biochemical abnormalities and lower EMS were more likely to have a P/LP variant but some patients with normal biochemistry also had a P/LP variant. The lower number of positive genetics results in recent years may be attributed to stricter reporting criteria from 2020 onwards, and to testing patients with milder phenotype.

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PO10

Clinical predictors of molecular results in hypogonadotrphic hypogonadism: experience from the routine use of a targeted gene panel in a multidisciplinary centre

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Introduction

Hypogonadotropic hypogonadism (HH) is a rare condition with a variable presentation where molecular diagnosis is often not reached.

Objectives

To assess the clinical/biochemical profile in patients with HH, the diagnostic yield of genetic panels and correlations between phenotype and genetic result.

Methods

Retrospective clinical data was collected for patients with suspected HH form West of Scotland who underwent NGS analysis of 21 HH or 56 DSD-associated genes between 2018-2025. Phenotype was analysed separately for children (<18 y) and adults. Male patients were grouped according to external masculinisation score (EMS) into severely (4-7), moderately (7.5-10) and mildly/not undervirilised (10.5-12). Genetic variants were classified according to ACMG guidelines. Chi-square test was performed for correlation analysis.

Results

Of the 78 patients who underwent genetic testing, 9 did not fit the inclusion criteria leaving 69 (46XY – 57, 46XX – 12) eligible for analysis. Median age at first clinical assessment, genetic request and genetic report was 17.1, 18.4, and 18.6 years, respectively. Six (8.8%) patients had other pituitary hormone deficiencies. The most common presentation in children (35 patients) was delayed puberty (41.2%) and in adults - symptoms of low testosterone (29.4%). EMS was available for 50 patients with severe, moderate, and mild/no undervirilization in 2, 23 and 25, respectively. All patients had baseline gonadotrophins and 34.8% had a LHRH-stimulation test. Pituitary MRI was performed in 52 patients, of whom 5 had absent/hypoplastic olfactory bulbs and 8 had other abnormalities. 10 pathogenic/likely pathogenic (P/LP) variants were found in 9 (13%) patients, 12 variants of unknown significance (VUS) in 9 (13%), and no variants found in 51 patients. The presence of a P/LP variant correlated with lower EMS ($P = 0.008$) but not with anosmia ($P = 0.27$) or olfactory bulb abnormalities on MRI ($P = 0.14$). Of the 17 patients who reported anosmia, 5 had olfactory bulb abnormalities, none with an identified genetic cause.

Conclusions

When used as part of routine clinical practice, a targeted gene panel leads to a molecular diagnosis in approximately 13% of the patients. The likelihood of a pathological variant was correlated with the genital phenotype but not with anosmia or olfactory bulb abnormalities on MRI.

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PO11

A case of 46,XX, SRY-negative sex reversal – when the adolescent patient doesn't know

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Introduction

46,XX, SRY-negative sex reversal is among the rarest forms of DSD. Management is complicated by the psychological issues that patients and families face.

Case report

A boy born to healthy, non-consanguineous parents had bilateral inguinal testes since birth. By 2 years of age both testes were impalpable. The boy was referred for orchidopexy during which a left hypoplastic gonad and a tubular structure were found. Histology showed fragments of an ovary, Fallopian tube and uterine body. The right side was not explored. Further investigations revealed 46,XX, SRY-negative karyotype and no testosterone response to hCG stimulation test. MRI demonstrated a hypoplastic uterus, blind-ending vagina, and right ovary. Genetic analysis was recommended but not performed. The boy first presented to our clinic at 11.1 years with recent weight gain and breast enlargement. On examination he had impalpable gonads, hypoplastic scrotum, micropenis, EMS 6.5, II stage pubic hair and gynecomastia. Hormonal investigations showed undetectable testosterone, oestradiol and AMH, LH - 3.39 mIU/ml (0.8-7.6) and FSH - **14.4** mIU/ml (0.7-11.1). A DSD-gene panel and WES analyses were negative. At 13.9 years, there were no signs of puberty. Hormonal results showed undetectable testosterone and oestradiol, LH - **23.8** mIU/ml, FSH **- 53.2** mIU/ml. Pubertal induction with testosterone was initiated. On psychological assessment, he shared feeling different, but had male gender identity. Despite the numerous advice by the medical team, the parents refused to explain the condition to the boy and he was unaware of the presence of ovaries and uterus. At 15 years, he was progressing through puberty (P4, SPL 4.5 cm), had no gynecomastia and was growing appropriately. Since the right gonad was not explored, the histology and tumour risk remain unknown. For this reason, laparoscopy with gonadal biopsy/gonadectomy and Mullerian structure removal is necessary but the boy needs to be fully informed of his condition first.

Conclusion

Patients with DSD are at risk for life-long health issues but these cannot be properly addressed if the child/adolescent is not aware of their condition. Emphasis should be given on the importance of informing the child early on in an age-appropriate way with psychological support.

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PO12

Patient information materials in DSD care: an international clinician survey with focus on androgen insensitivity syndrome

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Background

Limited evidence exists on how androgen insensitivity syndrome (AIS)-specific and differences/disorders of sex development (DSD)-related information materials are used, perceived, and distributed in routine clinical practice. This study explores current practices and perceived gaps in patient information provision from the perspective of healthcare professionals involved in AIS care.

Methods

Centre leads on the I-DSD Registry with registered AIS cases were invited to complete an online survey ($n = 70$). The questionnaire assessed current use of patient information materials, perceived usefulness and adequacy, and priorities for future development. Responses were obtained from 45 centre leads from 25 countries, mainly paediatric endocrinologists working in university hospitals (67%) and specialised DSD centres (25%).

Results

Only 33% of respondents reported routinely providing AIS specific patient information materials. Among clinicians who provided materials, websites were the most commonly used format (73%), followed by printed brochures (33%) and other formats, including personalised letters and structured educational materials (27%). Videos and mobile applications were rarely used. Two thirds of respondents reported providing written or digital materials consistently or often. Available materials were most frequently rated as moderately useful (73%), while 27% considered them very useful. Overall, 67% of respondents agreed or strongly agreed that there is a lack of adequate AIS specific information materials in clinical practice. Priority areas for improved or updated materials included fertility and reproductive counselling, long term endocrine management, psychosexual development, gender identity, and surgical considerations. Structured information materials were considered particularly beneficial at diagnosis (87%), during adolescence (78%), and during transition to adult care (69%). Age specific materials were rated as very or extremely important by 93% of respondents, with adolescents and young adults identified as the groups with the greatest unmet needs. The majority (96%) of respondents indicated that they would be likely/very likely to use a centralised, structured AIS information platform in clinical practice.

Conclusion

This survey identifies substantial gaps in the availability, adequacy, and use of AIS specific patient information materials and supports the need for a centralised, age specific, culturally sensitive, and clinically integrated information platform to support patients, families, and healthcare professionals, particularly at diagnosis, during adolescence, and throughout transition to adult care.

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PO13

Investigation of self-rated concerns among parents to children with atypical genitalia and CAH

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Background

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency results in cortisol and aldosterone deficiency and increased prenatal androgens resulting in varying degrees of virilization of external genitalia in females. Early genital surgery was until recent decades common practice. Unsatisfactory long-term outcomes and human rights perspectives have resulted in a shift in praxis towards postponed surgery to an age when the girl can participate in the decision making process herself. We study the psychological impact for the affected families of postponing surgery.

Methods

Parents to children with CAH, age 4-17 years, answered validated questionnaires on parental protectiveness (PPS), perceived stigma, future concerns (Parent self-report PSR), decisional regret and quality of life for both parents and children. Participants were 42 parents to 27 children. They were divided into parent of 'girl no surgery' ($n = 19$), and 'girl early surgery' ($n = 4$). Parents of boys with CAH ($n = 19$) were included to control for the situation of having a child with CAH *per se*.

Results

No differences were seen between the groups regarding parental protectiveness, and the large majority $>80\%$ did not meet the clinical cut-off. More than 50% of parents to girls with no surgery reported moderately high concerns regarding future genital appearance, limitation in sexual and social relationships. Decisional regret varied among the parents to girls with no surgery. The parents of boys with CAH were significantly more worried that their child would die due to their condition compared to those with a daughter.

Conclusions

Parents to girls who did not have early genital surgery reported moderately high concerns related to the genital virilisation but did not report increased parental protectiveness. Future studies on psychological effects for the girls themselves throughout childhood and their perception and views on their own decision-making process on genital surgery at a later age is warranted.

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PO14

Gender-related behaviour in children with different DSD diagnoses using the validated questionnaire KI-GRB

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Background

Gender- related behaviour is described to be influenced by many different factors. Prenatal exposure to sex hormones has been previously shown to play a role in the development. Girls with congenital adrenal hyperplasia (CAH) show more masculine behavior patterns but the relationship between prenatal exposure and postnatal behavior in children with other disorders of sex development (DSD) is less studied.

Aim

To investigate the relationship between prenatal exposure to sex hormones and gender-related behaviour in children with different DSD diagnoses. To test the validated KI-GRB (KI-gender related behaviour) questionnaire as a tool for studying DSD patients.

Material and Methods

The study included 107 participants aged 3-17 years from both Stockholm and Gothenburg with various forms of DSD and healthy controls. Gender-related behaviour was evaluated using the validated KI-GRB questionnaire, with responses categorized as masculine, feminine, or neutral.

Results

CAH girls showed a more masculine behaviour pattern compared to matching controls ($P < 0,001$) with an increasing effect according to disease severity. Boys with hypospadias showed higher feminine scores ($P = 0.001$) and XY girls higher masculine scores ($P = 0.049$) compared to controls. Neutral behavior increased with age in both sexes, significant in girls ($P = 0.007$).

Conclusions

Our study confirms that prenatal androgen exposure influences gender-related behavior while revealing unexpected patterns in hypospadias. These findings highlight the complex interplay between hormonal, developmental, and social factors in behavioural development. The KI-GRB questionnaire proved to be a useful tool in the study of gender-related behavior of children with DSD, confirming previous results in the CAH group.

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PO15

Transdermal vs oral estrogen in girls with Turner syndrome: trends in use and stakeholder perspectives

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Background

Pubertal induction with transdermal or oral estradiol (E2) is essential in the care of girls with Turner syndrome (TS), but long-term data comparing both regimens are limited. Additionally, current practice patterns and factors influencing the choice of regimen remain underexplored. A better understanding of these factors can optimize counseling and support shared decision-making.

Methods

Trends in estrogen use for pubertal induction were analyzed using data from the Dutch National Registry of Growth Hormone Treatment, a nationwide quality registry established in 1998. All girls with TS initiating E2 therapy were included. Additionally, two surveys were conducted among girls with TS aged 11–18 years and pediatric endocrinologists in the Netherlands, assessing decision-making on route of administration, reasons for regimen choice, and treatment experiences.

Results

A total of 526 girls with TS met the inclusion criteria in the Registry (transdermal: $n = 52$, oral: $n = 474$). After the introduction of transdermal E2 in Dutch guidelines in 2011, 84% of patients initiated oral estrogen. Median age at puberty induction decreased from 13.0 (IQR 12.4–14.7) years before 2011, to 12.3 (IQR 11.9–13.6) years from 2011 onwards.Fifty patients completed the survey (transdermal: $n = 15$, oral: $n = 35$). Among girls receiving transdermal E2, 40% reported that the route of administration was determined by their clinician. In contrast, 40% of girls treated with oral E2 made this choice themselves/with parents, primarily because of ease of use. In 22% of respondents, regimen choice was not explicitly discussed. Of 34 responding clinicians, those with >5 years of experience ($n = 14$) more often preferred transdermal E2 because of perceived effectiveness and safety, whereas those with >5 years of experience ($n = 20$) more often favored oral E2 because of ease of use and personal experience. Overall, clinicians reported a need for more evidence on effectiveness and safety, as well as practical guidelines and educational materials.

Conclusions

Our data show that transdermal E2 remains much less frequently used than oral regimens for pubertal induction in girls with TS, with an apparent generational difference in preference among clinicians. These findings can inform development of information and decision-support tools that incorporate stakeholder perspectives to improve shared decision-making.

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PO16

Standardized multidisciplinary care program for children and adolescents with differences of sex development: experiences in the first year following implementation

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Background

In March 2025, we launched a structured, multidisciplinary follow-up program for children and adolescents with differences of sex development (DSD). The program aims to facilitate data-driven outcome evaluation and scientific research to further improve quality of care. This study describes our experiences during the first year following implementation.

Methods

The program comprises three structured care pathways for patients with (1) XX and XY DSD, (2) Turner syndrome, and (3) sex chromosome trisomies. Following implementation, several evaluation meetings were conducted with the core team, as well as two evaluation sessions with the broader multidisciplinary team (MDT). During these meetings, we identified challenges and key factors for successful implementation.

Results

Two main challenges emerged. First, complete data registration in the electronic health record was difficult within the simultaneous consultation model, where all clinicians see the patient together. Second, patient-reported questionnaires to support consultation preparation initially had low completion rates due to technical problems and limited awareness among families. Education and training of clinicians in use of structured consultation forms, and ensuring adequate technical equipment, improved data registration. Information on the importance and rationale of the questionnaires, as well as practical information on use of the digital portal was provided to patients and parents. A dedicated planner was assigned, reminding families to complete the questionnaires sent prior to the consultation. In these questionnaires, patients and parents indicated concerns and/or questions they wished to discuss, e.g. regarding gonadal surgery, timing of hormonal therapy, fertility and sexual function. Clinicians reported that with this information they felt well prepared and better able to focus on the most relevant issues during the consultation, contributing to improved quality and efficiency of care. The interactive dashboards provided real-time feedback on adherence to the structured care paths, data quality and patient outcomes. Evaluating these outcomes was highly motivating for the MDT to optimize data registration.

Conclusion

This evaluation demonstrated that our structured, multidisciplinary follow-up program for children and adolescents with DSD is feasible. Continuous evaluation and optimization are essential to maintain high quality, effective care. These insights may guide the development of similar programs in other healthcare settings.

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PO17

Functional characterization of NR5A1 variants in patients with 46,XY partial gonadal dysgenesis

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Background

Variants in *NR5A1*/SF-1 are associated with a wide spectrum of conditions, ranging from primary ovarian insufficiency to 46,XY Partial Gonadal Dysgenesis (PGD) with variable degrees of virilization of the external genitalia. This study aimed to determine the *in vitro* consequences of two missense *NR5A1* variants identified in three 46,XY partial gonadal dysgenesis individuals.

Methods

The c.76G>C, p.Gly26Arg variant was found in two siblings. The proband presented female external genitalia with discrete clitoromegaly and palpable testis in the inguinal region, whereas her brother presented micropenis, penoscrotal hypospadias and testis located in the scrotal region. The c.232A>T, p.Met78Leu variant was identified in a 46,XY PGD patient with micropenis, penoscrotal hypospadias and testis located in the scrotal region. Whole-exome sequencing (WES) was performed in the proband's sibling to identify other genetic variants that could explain the phenotype disparity. Site-directed mutagenesis was performed to insert the variants of interest within NR5A1 cDNA contained on the expression vector pMyc-SF1. Transactivation capacity of WT and mutant NR5A1 were compared using human *AMH* or *STAR* promoter containing reporter genes in transiently transfected HEK-293T cells.

Results

WES performed in the proband's sibling did not identify additional variants in known DSD-associated genes. Luciferase Assay results indicated a reduction of approximately 50% of SF-1 transcriptional activity on *AMH* promoter region for the p.Met78Leu variant ($P < 0.05$) and no statistical significance on the *STAR* promoter, while the p.Gly26Arg variant indicated a near null transcriptional activity ($P < 0.05$) in both promoters.

Conclusions

Both variants were found to significantly reduce *NR5A1* transcriptional activity. As p.Gly26Arg is located in the DNA-binding domain (DBD), which is essential for protein DNA-binding capability, a more severe outcome was expected. Additionally, our negative WES result demonstrates a classical example of phenotypic heterogeneity due to a same *NR5A1* variant, extensively documented in the literature. Further *in vitro* studies, such as Western blot analysis, are currently being performed to determine the consequences of both variants on protein expression. Therefore, these findings support the pathogenic role of these variants in gonadal development, while reinforcing the importance of functional assays for the interpretation of *NR5A1* variants in patients with 46,XY PGD.

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PO18

Gender identity in XY DSD individuals raised as girls: analysis of the SDMregistries

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Background

Assigning sex in individuals with DSD remains challenging, with increasing consideration of genetic and prenatal hormonal influences rather than external genital appearance alone. Although more infants with a Y chromosome are now raised as boys, evidence on gender outcomes in those raised as girls remains limited. This study evaluated gender identity and sex reassignment in individuals with XY DSD raised as girls using multicentre registry data, exploring associations with diagnosis, clinical characteristics and psychosocial context.

Methods

Individuals registered in I-DSD on the SDMregistries platform with 46,XY DSD who had been raised as girls and were aged 12–21 years were included. Data regarding diagnosis, phenotype, pubertal development, surgical history, gender identity related outcomes, and psychological support at key stages of care were analysed.

Results

Data were obtained from 73 subjects from 23 centres. The most common diagnoses were complete androgen insensitivity syndrome (34.2%) and complete gonadal dysgenesis (20.5%). Disorders of androgen synthesis accounted for 24.6% of the sample. Median age was 8.4 (0–19.8) years at follow-up start and 17.7 (12.4–21) years at last evaluation. The median age at the onset of puberty was 12.4 years (10.3–19.8), with hormonal induction in 69.9%. Gonadectomy occurred in 71.2%, mainly due to tumour risk, with a median age of 11.9 years (0–18.3). The majority (80.8%) did not undergo genital surgery. Sex reassignment from female to male occurred in 4 (5.5%) subjects (11.8–17 years), and gender distress in 6 (8.2%) (including one under 10 years old); gender questioning occurred in 12 (16.4%), predominantly during adolescence. Sex reassignment, gender questioning, and distress were more frequent in disorders of androgen synthesis ($P < 0.05$). Sex reassignment was also more frequent in individuals who had not undergone gonadectomy ($P < 0.01$).

Conclusion

Most individuals with 46,XY DSD who were raised as girls had female gender identity, without gender distress or questioning. Gender-related concerns were more frequently observed in individuals with disorders of androgen synthesis and in those with preserved gonads. These findings are limited by the number of individuals assessed but highlight important factors for future studies to investigate.

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PO19

Sexual and urologic functioning and psychosocial outcomes in young adults with differences of sex development (DSD)

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Background

Differences of sex development (DSD) can impact individuals’ sexual and urinary functioning, but few studies examine their associations with psychosocial outcomes such as body image, adjustment, and resilience. This study evaluated sexual and urologic functioning and psychosocial outcomes in a sample of young adults with DSD using a multi-site, multi-methods approach.

Methods

Forty participants completed surveys with questions about sexual and urologic functioning, perceptions of genital appearance, body image, psychosocial adjustment, and resilience. Twenty-three participants also completed interviews that discussed romantic relationships and intimacy.

Results

Participants were mostly White ($n = 30$, 75%), non-Hispanic ($n = 37$, 92.5%), cisgender ($n = 38$, 95%), heterosexual ($n = 30$, 75%) women ($n = 26$, 65%), reared as females ($n = 27$, 67.5%) and averaged 20.6 ± 2.3 years of age. Sixty percent of participants ($n = 24$) reported a history of sexual activity, with an average age at first sexual activity of 16.8 ± 2.1 years. For these participants, all reported experiencing pleasure with sexual activity, but most also reported discomfort or pain during sexual intercourse ($n = 14$, 60.9%). Urologic problems were reported by 30% of participants and were significantly related to body image dissatisfaction ($b = 0.40$, $P < .05$). Perceptions of atypical genital appearance were significantly related to body image dissatisfaction ($b = 0.29$, $P < .01$) and internalizing problems ($b = 4.92$, $P < .05$). Satisfaction with sexual functioning was significantly associated with lower internalizing symptoms ($b = -4.56$, $P < .01$), total adjustment problems ($b = -3.20$, $P < .05$), and greater resilience ($b = 4.89$, $P < .053$). Qualitative analyses yielded five main themes: 1) body image concerns; 2) anticipatory anxiety about sexual intimacy; 3) surgery and intimacy; 4) unperceived genital differences; and 5) partner support.

Conclusions
Satisfaction with sexual functioning appears to be protective and associated with better psychological functioning and resilience. These findings support recommendations for interdisciplinary care that incorporates education and psychosocial support for individuals with DSD as they navigate intimate relationships during the transition from adolescence to adulthood.

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PO20

Evaluating adherence to recommended health screening practice guidelines in patients with 45,X/46,XY mosaicism

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Background
Recent guidelines suggest that patients with 45,X/46,XY mosaicism follow the same screening surveillance as patients with classic Turner Syndrome (TS), regardless of gender or phenotypic presentation, due to similar multisystem morbidities. This study aims to evaluate the adherence to TS screening guidelines for this patient population and identify patient characteristics affecting screening completion rates.

Methods
This is a retrospective cohort study of patients with 45,X/46,XY mosaicism who had at least one visit at a urology or endocrinology outpatient clinic in a tertiary care pediatric hospital between 2001-2026. Health screenings were considered 'complete' if done following the guideline's specified frequency; 'sporadic' if not done following the practice guideline's frequency, but done at least once; or 'incomplete' if the screenings were never done.

Results
Forty seven patients (26 female and 21 male) met inclusion criteria and were included in the study. The average patient age was 15.96 ± 8.87 years. Overall, patients should have completed an average of 33.62 (±4.41) health screenings based on age category. However, only 37.67% of these screenings were complete. The remaining screenings were either sporadic (27.59%) or went incomplete (34.74%). Older participants were more likely to have sporadic screenings (r = 0.45, $P<0.01$) or incomplete screenings (r = 0.34, $P<.05$), while younger participants were more likely to have complete screenings (r = -0.56, $P<0.001$). Further, patients assigned female at birth had significantly higher rates of complete screenings (P = .05), and significantly lower rates of incomplete screenings (P = .05), than patients assigned male at birth. Rates of sporadic screenings did not significantly differ between male and female patients. Of screenings completed, 22.67% indicated abnormal results, including hypertension, cardiac concerns, and BMI concerns. Patients did not significantly differ in the percent of normal vs abnormal screening results on the basis of sex assigned at birth or age.

Conclusions
Despite recent recommendations suggesting that patients with 45,X/46,XY mosaicism follow Turner Syndrome health screening guidelines, the majority of these patients are undergoing sporadic screenings or not being screened at all. Given that almost a quarter of screenings completed yielded abnormal results, these findings expose a critical gap in clinical care.

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PO21

Evaluating blood serum y material mosaicism, sex assigned at birth, and virilization in patients with 45,X/46,XY

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Background
Patients with sex chromosome mosaicism (SCM) such as patients with Turner syndrome with Y chromosome material (45,X/46,XY), can vary widely on external genital appearance, ranging from typical female to typical male genitalia. Virilization may also progress with puberty. Advances in noninvasive prenatal testing have allowed for earlier identification of patients with SCM, however the potential for gonadal hormone production and additional virilization with puberty is unknown, which complicates the discussion regarding gender assignment and timing of gonadectomy. It is unknown whether percentage of mosaicism affects phenotype, potential for additional virilization with puberty, or gender identity. This study aims to evaluate the association between level of mosaicism of Y chromosome material, genital appearance, and gender identity.

Methods
This is a retrospective cohort study of patients with 45,X/46,XY mosaicism who had at least one visit at a urology or endocrinology outpatient clinic in a tertiary care pediatric hospital between 2001-2026. Information gathered from the charts included karyotype, including percent of Y chromosome material, phenotype, and gender identity. Patients were considered virilized if they presented with a phenotype other than typical female.

Results
Forty-seven patients (26 female and 21 male) were included in the study. With regards to genital appearance, 19 patients presented as typical female (42.2%); 5 patients presented as typical male (11.1%); 5 patients presented with clitoromegally (11.1%); and 16 presented with hypospadias (34%). Two patients (4.3%) did not have a phenotype recorded in their charts. Mean percent of Y chromsome material was 35.68±24.73%. Patients assigned male at birth were more likely to have a a larger percent of Y chromosome material (50.39±18.92%) than their female counterparts (20.98±5.45%; $P<.001$). The average percentage of Y chromosome mosaicism was significanly higher in oatients with virilization (47.33±21.99%) than patients with typical female appearance (22.38±21.19%; $P<0.01$).

Conclusions
Patients with 45X, 46XY mosaicism vary greatly in phenotypic appearance. There is a positive association between percentage of Y chromsome material and phenotype, with patients with a higher proportion of Y chromosome material more likely to have a virilized appearance and male gender identity. Future studies are needed to identify any relationship between level of sex chromosome mosaicism, gonadal hormone production with puberty, and risk of gonadoblastoma.

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PO22

Incidence and clinical characteristics of gonadoblastoma in patients with 46, XY complete gonadal dysgenesis (swyer syndrome): a 22-year experience

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Background
Complete gonadal dysgenesis (CGD) or Swyer syndrome is a rare genetic condition which belongs to the group of 46,XY differences of sex development (DSD), due to impaired gonad (testis) development. Diagnosis is typically in adolescence due to delayed puberty or primary amenorrhea. There is a 15%-50% reported risk for gonadal tumour development with onset greatest at or after the time of puberty. Current recommendations for CGD advise early bilateral gonadectomy upon diagnosis. The study aimed to evaluate the clinical features and risk of gonadal germ cell tumours (GGCT) in 46,XY complete gonadal dysgenesis in the Ireland over the last 22 years.

Methods
Retrospective review of patients with 46,XY complete gonadal dysgenesis who underwent gonadectomy in Children's Health Ireland from 2003-2022 and prospectively from 2022-2025.

Results

11 patients were diagnosed with 46,XY CGD between 2003-2025, two of whom were siblings. The most frequently reported presentation was primary amenorrhea ($n = 5$); followed by incidental finding on karyotype ($n = 2$), discordance between antenatal karyotype and external genitalia at birth ($n = 1$), family history ($n = 1$) and precocious puberty with abdominal mass ($n = 1$). Karyotype reported 46,XY chromosomes with presence of the *SRY* gene in 10 cases; one case was *SRY* negative. A genetic aetiology was identified in 27% of the cohort, with common gene defects in *SRY* and *DMRT1* reported. All 11 patients underwent gonadectomy. Histopathological examination of gonadal tissue reported GGCT in 9/11 (81%) cases with malignant transformation to dysgerminoma reported in 3/9 (30%) cases. All gonadal tumours were located intra-abdominally. Median age of GGCT diagnosis was 14 years (IQR 10-16); 4/11 (36%) patients were diagnosed prepubertally, with youngest aged 2.41 years. Elevated tumour markers (HCG, LDH) were reported in 2 individuals diagnosed with dysgerminoma. 8/11 (72%) cases commenced HRT post-gonadectomy; three cases with dysgerminoma required 3-monthly surveillance with pelvic ultrasound and HCG levels.

Conclusion

There is a high estimated incidence of gonadal tumours in 46XY CGD in our cohort (81%) which is higher than reports in international literature, and a significant number reported in childhood. Early prophylactic gonadectomy should be considered as soon as the diagnosis is made in CGD to prevent development of malignancy.

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PO23

Childhood gonadectomy in Ireland in differences of sex development (DSD): clinical characteristics, historical and current practices, and incidence of gonadoblastoma

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Background

Clinical recommendations in DSD gonadectomy have evolved over time due to improved knowledge of diagnosis-specific risks of gonadal germ-cell tumours (GGCT), in addition to changing societal, legal and ethical norms. There is currently a lack of established international consensus on the practice of gonadectomy in the management of gonads in DSD conditions generally, due to paucity of population incidence studies looking at risk for gonadal tumours. This study aimed to investigate DSD gonadectomy practice in Ireland over the last 26 years and to determine the risk of developing gonadal tumours in DSD conditions.

Methods

Retrospective review of patients with DSD who underwent gonadectomy in Children's Health Ireland from 1999-2022 and also prospectively since late 2022-2025.

Results

62 patients underwent gonadectomy [females ($n = 50$);males ($n = 12$)]. Gonadectomy was most frequently performed in mixed gonadal dysgenesis($n = 21$), followed by complete gonadal dysgenesis(CGD) ($n = 10$), partial gonadal dysgenesis(PGD) ($n = 10$), mixed ovotesticular (OT) DSD($n = 8$), complete androgen insensitivity syndrome($n = 7$), 46,XX OT DSD ($n = 3$), disorder of androgen synthesis($n = 2$) and LH receptor defect ($n = 1$). The most frequently reported indication for gonadectomy was mitigation of future tumour risk (58%), followed by biopsy/imaging indicating malignancy (18%), incongruent hormone production (16%), concordance to sex assignment (3%), rudimentary testis (3%), and patient request (2%). The median age at gonadectomy was 5.91 years (IQR 1.33 – 15.58). GGCT was confirmed in 31% (19/62) of cases on gonadal histopathology [46XY CGD (8/19; 42%), PGD (2/19; 11%), mixed GD(8/19; 42%), mixed OT DSD (1/19; 5%)]. Gonadoblastoma was reported in 84% ($n = 16$) of cases, with malignant transformation to dysgerminoma in 11%($n = 2$) of cases, both arising in CGD. Combined GB/GCNIS was reported in mixed OT DSD ($n = 1$). The estimated risk of GGCT in our cohort is 80% in CGD, 20% in PGD, 38% in Mixed GD and 12.5% in mixed OT DSD.

Conclusion

The majority of gonadectomies were performed in dysgenetic gonads, to mitigate tumour risk. Given the high incidence of gonadal tumours in dysgenetic gonads in our cohort, particularly in 46XY CGD, which is higher than reports in the international literature, early prophylactic gonadectomy should be considered, only after multidisciplinary team discussion, with an emphasis on shared decision making with patients and families.

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PO24

The need for a global registry for charting the natural history of klinefelter syndrome

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Introduction

Although Klinefelter Syndrome (KS) represents the most common sex chromosome aneuploidy, several gaps in knowledge persist regarding optimal management of boys and men with this condition. In particular, large international datasets describing the natural history of KS across the lifespan remain limited. Individuals with KS can have a diverse phenotype including endocrine, neurodevelopmental and cardiovascular manifestations.

Methods

Review of current cases of KS within the *SDMRegistries*.

Results

In January 2026, the *SDMregistries* platform that consists of dedicated registries for a wide range of rare conditions affecting sex development and maturation included a total of 10,658 individuals and of these, 777 (7%) individuals from 17 countries had karyotypes consistent with 47,XXY or mosaic forms containing an XXY cell line. Considering those with an 47,XXY alone, the median year of birth was 1994 (range 1939, 2025) resulting in a median current age of 32 (1, 87) years.

Conclusion

The *SDMRegistries* platform represents the largest contemporary cohort of individuals with KS of varying ages across the lifespan currently available worldwide, offering a unique opportunity to undertake collaborative natural history studies in KS through the development of a KS specific registry. Continued evaluation of existing data and identification of research priorities remain essential to improving long-term outcomes and quality of life for individuals with KS, with the likelihood of increased ease with the launch of the new I-KS module.

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PO25

Development of a training toolkit for differences of sex development (DSD) – an initiative of the SDMregistries learning & training committee

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Background

Differences of Sex Development (DSD) are rare, complex conditions requiring highly specialised, multidisciplinary care. Despite advances in clinical practice and international collaboration there is a need for structured generic training of all the clinical disciplines that may deliver specialist DSD care within the multidisciplinary team (MDT).

Objective

To develop a structured curriculum and training toolkit to support specialist healthcare professionals of various disciplines in delivering high-quality evidence-based care in the field of DSD.

Methods

A comprehensive curriculum toolkit was developed in 2024 through expert consensus within the *SDMregistries* Learning and Training Committee in response to requests from clinicians at *SDMregistries* events. The toolkit defines core learning outcomes across seven domains, including clinical management, psychological care, surgical considerations, gonadal management, transition to adult services, MDT working, and engagement in research and quality improvement. It incorporates workplace-based assessments, reflective practice, and evidence of clinical exposure and promotes integration with regional, national, and international DSD networks with a view to supporting standardisation of training while allowing flexibility for local implementation. The toolkit was launched in 2025 and is available via the *SDMregistries* (https://sdmregistries.org/dsd-training-toolkit/). Feedback questionnaires have been disseminated to initial users.

Results

To date feedback is available from 5 users of the toolkit from 4 centres in 4 countries who have trialled the toolkit. Of these 3 (60%) had a paediatric endocrinology background, one (20%) was from clinical genetics and one (20%) was from urology. Four (80%) of the users 'strongly agreed' and one (20%) 'agreed' that there is a need for a training toolkit in DSD. Three (60%) 'strongly agreed' and 2 (40%) 'agreed' that the toolkit is easy to understand and that it supports meaningful learning in DSD care. All users rated the resources provided as 'useful' and all participants reported that they would recommend the toolkit for DSD training.

Conclusions

The *SDMregistries* DSD Training Toolkit offers a practical approach to improving workforce capability in DSD. By embedding multidisciplinary practice with attention to quality evaluation and research, it aims to enhance patient care and facilitate collaboration within *SDMregistries* and beyond. Opportunities to provide feedback on the toolkit are ongoing.

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PO26

International variation in testosterone replacement therapy in boys and men with klinefelter syndrome: an I-DSD study

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Background

Klinefelter syndrome (KS) is associated with hypergonadotrophic hypogonadism that requires testosterone replacement therapy (TRT). Currently there is a gap in evidence regarding optimal initiation of TRT. As such the aim of this study is to understand contemporary TRT in KS using real world data from *SDMregistries*.

Methods

The study was approved by the *SDMRegistries* Data Access Committee and all participating centres that had reported 47,XXY cases that were between the ages of 12-37 years at the time of the study were identified on the *SDMregistries* platform and asked to complete the I-DSD module.

Results

Of the 798 registered boys and men with KS, 406 (51%) met eligibility criteria, and of those, 373 (92%) were registered at centres that agreed to participate. Overall, longitudinal data were available for 267 (72%) from 16 centres and 11 countries worldwide with a median number of 5 cases per centre (1-133). The median (range) age of these cases at the time of the study was 22.2 yrs (12.4-37.6). Spontaneous onset of puberty was reported in 209 (78%). Overall,103 (39%) were on TRT: 50 (49%) on intramuscular, 31 (30%) on transdermal and 18 (17%) on oral preparations. The median (range) age of starting TRT was 16.7 yrs (11.2-34.4). At initiation of therapy, raised serum luteinizing hormone (LH), raised serum follicle stimulating hormone (FSH) and low serum testosterone (T) were reported in 63 (61%), 64 (62%) and 32 (31%) respectively. Of the 164 men not reported to be on testosterone therapy, the current median age was 16.6 yrs (12.9-35.9). Eight (5%) of these men were reported to have completely normal LH, FSH and T. Of the remaining 156, raised LH, raised FSH and low T was reported in 68 (41%), 90 (55%), and 13 (8%). There was significant inter-centre variability in median age of starting testosterone when adjusting for biochemistry ($P < 0.001$).

Discussion

As expected there is great variability in the age, timing, and hormone profiles at which TRT is introduced across the world. The cases in I-DSD registry on the *SDMregistries* platform present a valuable opportunity to perform pragmatic trials of TRT in KS.

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PO27

Exploratory machine learning approach in routine steroid profiles of rare adrenal disorders

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Background

Routine steroid profiling is an established part of the diagnostic workup of rare adrenal disorders. While individual steroid markers are well characterized, the combined interpretation of multi analyte profiles remains challenging in clinical practice. Building on previous work by Zalas *et al.*, this study explores the potential of machine learning methods to extract diagnostic patterns from measured steroid panels.

Methods

Steroid profiles from individuals with 21 hydroxylase deficiency (21OHD, $n = 40$), 11 hydroxylase deficiency (11OHD, $n = 10$), adrenocortical carcinoma (ACC, $n = 10$), and obese persons ($n = 60$) were analyzed. All steroid concentrations were Z log transformed. A Random Forest model was used as an exploratory tool to assess group separation and identify informative steroid markers. Feature importance, proximity analysis, and surrogate decision trees were applied to support interpretation.

Results

The Random Forest analysis revealed distinct steroid patterns across the diagnostic groups. 21OHD was characterized by elevated 17 hydroxyprogesterone and androstenedione. 11OHD showed increased 11 deoxycortisol and 11 deoxycorticosterone. ACC displayed broader and more variable alterations, involving multiple precursors and downstream metabolites. Obese persons showed comparatively uniform profiles with lower variability. Across all groups, the model consistently highlighted combinations of precursors and downstream metabolites that contributed to separation and aligned with known biosynthetic pathways. Proximity and surrogate tree analyses indicated subgroup structures and occasional atypical profiles within the dataset.

Conclusions

This exploratory work suggests that data driven analytical approaches may complement the interpretation of routine steroid profiles in endocrine disorders. While not intended to replace established diagnostic reasoning, such methods can help uncover multidimensional biochemical signatures, support hypothesis generation, and inform future analytical frameworks for complex steroid datasets.

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PO28

Intracrine androgen production in human genital skin fibroblasts: impact of AR and SRD5A2 mutations

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Background

Differences of sex development (DSD) in 46,XY individuals include conditions that impair androgen action, such as complete androgen insensitivity syndrome (CAIS) and 5α-reductase type 2 deficiency (SRD5A2 deficiency). While CAIS affects androgen receptor signaling, SRD5A2 deficiency impairs the conversion of testosterone to dihydrotestosterone (DHT). We hypothesized that these conditions exhibit distinct intracrine androgen steroid patterns in genital skin fibroblasts compared with 46,XY controls. We aim to map intracrine androgen biosynthesis pathways in these conditins and link functional steroid profiles to underlying genetic mutations.

Methods

We analysed GSFs from molecular proven CAIS and SRD5A2 individuals and GSFs from 46, XY controls. GSFs were cultured in DMEM-based medium at 37°C, 5% CO_2. Cells were seeded in 6-well plates (6×10^4 cells/2 ml/well) and incubated with testosterone, DHEA, and 17-hydoxyprogesterone (17OHP) at three concentrations (1, 10 and 100 nM). Supernatants were analyzed by LC-MS/MS.

Results

CAIS cell lines showed reduced DHT production compared to controls (9.4 ± 14.05 nmol/l vs. 26.47 ± 25.09 nmol/l at 100 nM testosterone). In contrast, androstenedione (A4) levels were elevated in CAIS cells (55.26 ± 50.35 nmol/l vs. 0.63 ± 0.49 nmol/l), suggesting altered downstream androgen metabolism and possible back-conversion. Mutation-specific differences were observed, with exon 7 AR mutations showing the highest A4 accumulation. Similarly, SRD5A2-deficient cells demonstrated markedly reduced DHT production (5.39 ± 1.78 nmol/l vs. 26.94 ± 25.09 nmol/l in controls at 100 nM testosterone) and increased A4 levels, indicating enhanced back-conversion of testosterone to A4.

Conclusions

Our findings demonstrate that both CAIS and SRD5A2 deficiency are associated with markedly reduced DHT production but differ in their underlying metabolic patterns. In CAIS, defective AR function is accompanied by altered downstream androgen metabolism and increased accumulation of precursor metabolites such as androstenedione. In SRD5A2-deficient cells, reduced enzymatic conversion of testosterone to DHT leads to pronounced back-conversion and pathway shifts consistent with the molecular defect. These results support our hypothesis that molecularly defined XY-DSD subtypes display distinct intracrine androgen signatures in genital target tissue.

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PO29

Comparison of plasma- and salivary steroid profiles in the medical management of congenital adrenal hyperplasia based on LC-MS/MS routine data

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Introduction

Congenital adrenal hyperplasia (CAH) requires lifelong glucocorticoid therapy and careful biochemical monitoring. Salivary steroid measurement offers a less invasive alternative to blood sampling, but data on its correlation with plasma levels are limited. This study evaluated the correlation between salivary and plasma steroid profiles in patients with and without plasma hyperandrogenemia.

Methods

Real-world data from 2020–2023 were extracted from the routine laboratory database Opus L (Dedalus) and provided as an analyzable Excel dataset. Data were systematically filtered according to relevant CAH diagnoses, and only corresponding cases were selected for analysis. Plasma concentrations of 17-hydroxyprogesterone (17-OHP) and androstenedione were extracted and mean salivary 17-OHP values were calculated and included in the analysis. A relevant hyperandrogenemia was defined as plasma androstenedione concentrations exceeding the age- and sex-specific upper reference limit (Kulle, A E *et al.* 2010). Matched plasma–saliva sample pairs from the same patients with a CAH diagnosis were identified who had both a plasma and a salivary sample collected within a 30-day interval. These matches (n = 373, 165 female [f], 208 male [m]) were stratified based on hyperandrogenemia status and analyzed in two groups: hyperandrogenemia (f: n = 49; m: n = 71) vs. non-hyperandrogenemia (f: n = 108; m: n = 117). In 28 cases, plasma androstenedione data were not documented (n = 28).

Results

Plasma androstenedione showed a significant positive correlation with age across all groups (with and without hyperandrogenemia; males and females) (r = 0.68–0.76; all $P < 0.05$). In contrast, salivary 17-OHP was not significantly correlated with age, regardless of hyperandrogenemia status or sex (all $P > 0.05$). Plasma 17-OHP also showed no significant age-related correlation in most groups; only females without hyperandrogenemia demonstrated a moderate positive correlation (r = 0.48; $P < 0.05$). A significant positive correlation between plasma 17-OHP and mean salivary 17-OHP was observed in all groups (r = 0.43–0.60; all $P < 0.05$).

Conclusion

Significant sex differences were observed across all analyzed parameters. Boys showed higher plasma androstenedione, plasma 17-OHP and salivary 17-OHP levels than girls, both in the presence of hyperandrogenemia and within normal androstendione in plasma (all $P < 0.05$). Sex differences were most pronounced for plasma 17-OHP, both in patients with plasma hyperandrogenemia (f: 43.7 [11.9-126] vs. m: 119 [38.3-265]) and in those without (f: 3.7 [0.7-11.6] vs. m: 15.4 [6.5-41]).

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PO30

Converting testosterone to estrogen: CYP19A1 transfection redirects steroidogenesis in murine leydig cells

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Background

Patients with complete androgen insensitivity syndrome (CAIS) have a genetic defect in the androgen receptor, resulting in female external genitalia and intra-abdominal testes. Although these intra-abdominal testes serve as a critical source of endogenously regulated steroid hormones during puberty, studies indicate that prioritizing estrogenic over androgenic activity is of greater clinical relevance in the management of CAIS. Therefore estrogenic pathways are of primary importance, with estrogen therapy generally being preferred over testosterone due to superior patient tolerance. This study aims to redirect steroidogenesis from testosterone toward estrogen by transfecting Leydig cells with an aromatase (*Cyp19a1*) construct.

Methods

The murine Leydig cell line (MLTC-1) served as a proof-of-concept model. Cells were transfected with a construct with CMV promoter driving Cyp19a1 expression for periods of 24 and 48 hours. To evaluate the shift in the steroidogenic profile, cell supernatants were collected at both time points. The concentrations of androgens and estrogens were subsequently quantified using Liquid Chromatography-Mass Spectrometry (LC-MS).

Results

Transfection was successful, with confirmed expression of the construct in the MLTC-1 cells. Data indicated that the expression of aromatase significantly increased estrogen concentration in the supernatant after 24 hours. Dihydrotestosterone (DHT) levels were simultaneously reduced. Testosterone production levels remained unaffected by the transfection. These results validate the ability to enhance the conversion of testosterone into estrogens within the primary androgen-producing cells of the testis.

Conclusions

The preliminary *in vitro* findings demonstrate that tissue-specific modulation of the estrogen synthesis is feasible. Future research will transition to *in vivo* mouse models using an AAV-based delivery approach to target the testes and gonadal adipose tissue. This approach offers a promising outlook for achieving systemic physiological hormone regulation. A further objective of this study is to optimize the conversion efficiency and conduct a more detailed analysis of the underlying mechanisms, as no significant reduction in testosterone concentrations has yet been observed.

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PO31

Identification of novel genetic causes in differences of sex development by genome sequencing and high-throughput functional assays

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Background

Genetic causes of Differences of Sex Development (DSD) are identified in only approximately one third of individuals using standard-of-care exome sequencing, leaving a majority without a molecular diagnosis. Variants in non-coding regulatory regions and complex structural variants (SVs) are likely contributors to this diagnostic gap, yet are systematically excluded and still very challenging due to our limited molecular understanding outside of protein-coding sequence effects.

Methods

We analyzed genome sequencing data from over 120 individuals using short-read and long-read sequencing technologies. While more cost intensive, long-read sequencing provides improved discovery of SVs and haplotype-resolved methylation states, enabling investigation of epigenetic contributions to DSD. We implemented computational pipelines for singleton and trio analysis. Identified genetic variants were scored for potential disease relevance, filtered against population databases and cross-referenced with clinical databases to prioritize likely disease-causing alterations. To functionally investigate regulatory variants in genes implicated in sex development, we additionally developed experimental saturation mutagenesis using massively parallel reporter assays (MPRA), targeting promoters and enhancers of multiple DSD-relevant loci.

Results

We developed tier-based reports for short (SNV/InDels) and long sequence variants (SVs). TALOS-based prioritization of short variants identified high-confidence causative variants in established DSD genes including *WT1, SF1 (NR5A1), ATRX, HSD17B3*, and *SRD5A2*, as well as syndromic candidates *PROKR2* and *PPP1R12A*. This highlights several coding variants missed in prior analyses. We are currently analyzing potential SV candidates and new non-coding mechanisms of disease shared across individuals. Complementary MPRA experiments are being applied to systematically map the transcriptional effects of regulatory variants across promoters and enhancers of key sex-development genes, enabling nucleotide-resolution functional maps for interpretation of candidate variants. In an initial set of experiments, we have mapped promoter motifs of the Androgen Receptor across three cell-types.

Conclusions

To increase diagnostic yield, shorten the diagnostic journey and to enable a genetically informed counseling of DSD patients, genetic analyses need to extend to the whole genome, and specifically include non-coding variant and SV interpretation. High-throughput functional assays substantially expand our ability to interpret pathogenic variation in regulatory sequences.

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PO32

Structural variation due to isolated DMRT1 microdeletions cause 46,XY gonadal dysgenesis without syndromic features

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Background

Deletions within the 9p24.3 region are frequently associated with 46,XY gonadal dysgenesis (46,XY GD), but the definitive causative gene remains to be clearly identified. *DMRT1*, located within this region, plays a highly conserved role in the sex development across metazoans and is a strong candidate for GD. However, previous characterisations of 9p24.3 deletions often lacked precise breakpoint resolution and often involved neighbouring *DMRT* genes. Here we present two unrelated patients (one previously described(1), one novel) with partial GD and *DMRT1* microdeletions.

Case Presentations & Methods

Case 1: Previously described by Ledig *et al*. (1). Initial presentation at 2 years and 2 months; 46,XY karyotype; phallus 3.5 cm; prominent glans (1.2 cm in diameter); asymmetric labioscrotal folds; right-sided palpable gonad. Introitus with an almost female appearance; no uterus.Case 2: Initial presentation at 12 weeks; 46,XY karyotype; phallus 3.5 cm; penoscrotal hypospadias. Laparoscopy showed small bilateral gonads as well as remnants of fallopian tubes, and a uterus with left-sided predominance. Array comparative genomic hybridization and whole-exome sequencing identified a suspected microdeletion in the *DMRT1* gene. Long-read whole-genome sequencing (WGS) enabled the precise characterisation of the extent of the deletion and the breakpoints, as well as the exclusion of potential other known genetic causes of DSD.

Results

Long-read WGS confirmed distinct *DMRT1* microdeletions in both patients. Detailed breakpoint analysis revealed a deletion of exons 3 and 4 in case 1 and of exon 4 in case 2. Involvement of other exons or surrounding *DMRT* genes was ruled out. WGS also excluded other known genetic causes of DSD. In both patients, deletion breakpoints were located within repetitive *Alu* elements, suggesting non-allelic homologous recombination as the cause of the deletions.

Conclusion

Our findings strengthen the evidence that *DMRT1* haploinsufficiency is a primary cause of 46,XY GD. Through comparison with nearly identical deletions associated solely with azoospermia (2), our study underscores that loss of *DMRT1* can lead to GD but exhibits highly variable penetrance. Other (epi)genetic or environmental factors are likely to contribute significantly to the expression of the phenotype.

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PO33

Depot-specific steroidogenic gene expression signatures in human adipose tissue-derived preadipocytes

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Background

Adipose tissue is an active endocrine organ that is capable of local steroid metabolism, including the peripheral conversion of sex steroids. This may contribute to metabolic dysfunction in obesity. Sex-specific variations in adipose tissue distribution and endocrine function are closely linked to metabolic health and reproductive outcomes. In women, obesity is associated with alterations in the sex steroid composition and conditions such as polycystic ovary syndrome (PCOS). While mature adipocytes contribute to adipose endocrine function, the role of adipose precursor cells in regulating steroid metabolism remains incompletely understood. This study aims to identify depot-specific gene expression patterns related to steroid metabolism in primary human preadipocytes, focusing on obese female donors to capture potential sex-specific regulatory features.

Methods

Transcriptomic data from human abdominal adipose tissue was analysed using the publicly available GSE25401 data set. Differential expression analysis was performed to identify depot-specific genes associated with steroid metabolism and adipocyte function. Candidate genes of interest were selected based on statistical significance and biological relevance, with attention to pathways involved in glucocorticoid metabolism, adipogenesis and lipid synthesis. These exploratory findings will inform subsequent analyses of primary human subcutaneous and omental preadipocytes isolated from obese female donors.

Results

Exploratory transcriptomic analysis revealed several genes related to adipocyte function and steroid metabolism, including *HSD11B1, LEP*, and *FASN*. The observed expression patterns suggest involvement of glucocorticoid metabolism and adipocyte metabolic pathways, whereas classical enzymes of de novo sex steroid biosynthesis were not prominent in this dataset.

Conclusions

This work highlights preadipocytes as a potential regulatory stage in adipose endocrine function and supports the role of adipose tissue in peripheral steroid metabolism. These findings may improve the understanding of how adipose tissue influences sex steroid regulation, metabolic risk, and reproductive health in obesity.

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PO34

Real-world multicenter outcomes following transition to modified-release hydrocortisone in congenital adrenal hyperplasia and adrenal insufficiency

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Background

Congenital adrenal hyperplasia (CAH) and adrenal insufficiency (AI) from other causes are associated with increased cardiometabolic morbidity, reduced quality of life, and higher mortality. These outcomes are partly attributed to limitations of conventional glucocorticoid (GC) replacement therapy, which fails to replicate the natural circadian rhythm of cortisol secretion. In CAH, supraphysiological GC doses are often required to suppress androgen excess, further contributing to adverse effects. Modified-release hydrocortisone (MR-HC), designed to mimic physiological cortisol secretion, has recently been shown to allow GC dose reduction in CAH and to improve fatigue and quality of life in AI. However, real-world data outside controlled research settings remain limited.

Aim

To assess changes in glucocorticoid dosing, androgen levels, and anthropometric parameters in patients with CAH and other forms of AI after transition to MR-HC therapy.

Methods

A retrospective multicenter chart review was conducted between October 2023 and January 2026. Data were extracted from electronic medical records and are presented as medians with interquartile ranges.

Results

The cohort included 97 patients (54 females): 26 with salt-wasting CAH, 14 with simple virilizing CAH, 44 with non-classic CAH, 6 with 11β-hydroxylase deficiency, and 7 with AI from other causes. Median age at diagnosis was 3.0 years [0.1–8.3], and median age at transition to MR-HC was 17.0 years [13.0–30.0]. Hydrocortisone-equivalent dose adjusted for body surface area decreased significantly after transition, from 13.4 [9.1–15.7] to 11.3 [8.8–14.1] mg/m^2 ($P = 0.005$). Friedman test analysis across multiple time points showed a progressive dose reduction following transition ($P<0.001$), with no difference between classic and non-classic CAH. Median androstenedione and testosterone levels (nmol/l) decreased from 10.4 [4.9–14.9] to 6.5 [1.6–10.9] and from 1.2 [0.80–1.58] to 0.8 [0.40–1.3], respectively ($P<0.001$ and $P = 0.015$). Patients with non-CAH AI reported improved energy and well-being. Fourteen patients discontinued MR-HC, mainly due to cost. No adrenal crises requiring hospitalization were reported before or after transition.

Conclusions

In this real-world multicenter cohort, transition to MR-HC was associated with reduced glucocorticoid dosing alongside improved androgen control. These findings support MR-HC as an effective, physiologically aligned therapeutic option for patients with CAH and AI.

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PO35

Altered telomeres dynamics linked to genotoxic stress and cGAS-STING pathway is a common feature of human infertility

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Background

Individuals with Differences of Sex Development (DSD) exhibit DNA damage, chromosomal variations, gonadal dysgenesis, Germ Cell Tumors (GCT) and infertility. DSD patients and men with Nonobstructive Azoospermia (NOA) show compromised genome stability linked to deregulated autophagy, Androgen Receptor (AR) signaling, and cGAS-STING pathway (CGSP) upregulation. This study investigates CGSP's role in regulating Telomere Length (TL) via autophagy and AR signaling in the context of infertility.

Material and Methods

Blood leukocytes were collected from individuals with DSD ($n = 40$); including Swyer, Turner syndrome, DSD diagnosed with GCT (DSD-GCT)), and from men with nonobstructive azoospermia ($n = 18$) having abnormal embryogenesis after ICSI or diagnosed with spermatogonia arrest (SGA). Average relative TL was assessed by qPCR, long ($>$4,5kb) and short ($<$4,5kb) telomeres by Southern blot. Telomerase complex protein GAR1 was knocked-down (GAR1-KD) with siRNA in lymphoblastoid cell lines derived from individuals with DSD that were treated with AR-inhibitor Enzalutamide, autophagy inhibitor Bafilomycin A1 or activator Rapamycin. Fresh leukocytes samples from individuals with DSD were treated with genotoxic stress agent Olaparib, STING inhibitor H151 and activator G10. Statistical comparisons were conducted using ANOVA.

Results

NOA males showed increased long ($P = <0,0001$) and short ($P = 0,0002$) telomers without changes in relative TL. Upregulated TL in Swyer ($P = 0,0069$) and Turner ($P = 0,0064$) but DSD-GCT was paralleled with increased long ($P = <0,0001$) and short ($P = 0,012$) telomer fragments. In GAR1-KD DSD cells Enzalutamide treatment increased long ($P = 0,0201$), short ($P = 0,025$) and average ($P = 0,0472$) TL, which was suppressed by Bafilomycin A1. The treatment with G10, but not H151 showed an increase in long ($P = <0,0001$) and short ($P = 0,0031$) telomere fragments without changing average TL compared to control.

Conclusions

Our findings reveal altered telomere dynamics in infertile individuals with various diagnoses, characterized by accumulation of short and long telomeric fragments, reflecting telomere instability in parallel with telomere elongation. Functional studies proved autophagy to be critical for GAR1-dependent telomere synthesis. Modulation of cGAS-STING pathway further supports a mechanistic link between impaired DNA damage response, dysregulated autophagy and telomere fragmentation likely contributingto infertility and tumor susceptibility.

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PO36

Clinical and genetic spectrum of XY gonadal dysgenesis from a tertiary care center in India

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Background

Gonadal dysgenesis (GD) is a heterogeneous group of disorders of sex development caused by impaired gonadal formation. It includes complete gonadal dysgenesis with streak gonads and female phenotype, and partial gonadal dysgenesis with varying degrees of genital ambiguity. We aimed to characterize the clinical presentation, hormonal profile, and genetic determinants of patients with GD.

Methods

This observational study included patients diagnosed with gonadal dysgenesis at a tertiary referral endocrine center over a period of one year. Clinical characteristics were recorded. Hormonal evaluation included serum gonadotropins and sex steroids. Cytogenetic analysis was performed using conventional karyotyping, and targeted molecular testing was undertaken where indicated. Imaging assessed internal reproductive structures, and histopathological findings were reviewed in patients undergoing gonadectomy.

Results

Among 60 patients with 46,XY DSD, 18 patients (30%) were diagnosed with gonadal dysgenesis. The median age at presentation was 105.5 months (IQR 21–186). Ten patients were reared as female and eight as male. The predominant clinical presentations were atypical genitalia ($n = 12$), primary amenorrhea ($n = 4$), and delayed puberty ($n = 2$). Cytogenetic analysis demonstrated a 46,XY karyotype in 17 patients, while one patient had mosaicism. Complete gonadal dysgenesis typically presented with female phenotype and streak gonads, whereas partial gonadal dysgenesis showed variable genital ambiguity and gonadal differentiation. Biochemical evaluation revealed hypergonadotropic hypogonadism, with median LH 23.9 IU/L (IQR 17.4–30.8). Median testosterone was 0.59 nmol/l (IQR 0.087–5) and AMH 4.8 pmol/l (IQR 5–87.6). Targeted molecular testing identified pathogenic variants in genes involved in sex determination and gonadal differentiation in 50% of cases, including SRY, NR5A1, DHH, MAP3K1, MYRF, and SOX9. Gonadectomy was performed in nine patients, primarily in those with complete gonadal dysgenesis or as part of definitive gender assignment. Histopathological evaluation did not reveal premalignant or malignant germ cell tumors.

Conclusion

Gonadal dysgenesis demonstrates substantial clinical and genetic heterogeneity, highlighting the importance of integrated evaluation using clinical, hormonal, cytogenetic, and molecular approaches to guide diagnosis and multidisciplinary management.

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PO37

The DSD infographic toolbox. A set of communication tools for parents and children with DSD

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Background

DSDs are congenital conditions that require adaptation and coping in every stage of life. Coping is facilitated through communication, disclosure and acceptance. To communicate a DSD diagnosis within the family and one’s wider social network can be challenging given the lack of knowledge among lay people, and the (perceived) social taboo that may surround these conditions. Now that feminizing and masculinizing surgery in infancy are less commonly performed, there is an increased need for patients and parents to be open about their/their child’s condition. As this can be challenging, many patients and parents need additional support. In order to communicate a DSD diagnosis well, patients and parents must be well informed and be comfortable to discuss DSD and related delicate topics. We developed the DSD Infographics Toolbox to facilitate communication on the DSD diagnosis and personal needs.

Method

Development of infographics in a format that is suitable for cell-phone, tablet or laptop. The infographics consist of illustrations and easy-to-read compact text messages in plain language that aim to reach a large and diverse group of users – parents and children of 8 years onwards from different social, cultural and ethnic backgrounds.

Results

The DSD Infographic Toolbox contains 14 digital infographics and provides information on the most prevalent diagnoses. Children and adolescents can use the infographics to enhance their own understanding of the condition, and to inform their (intimate) friends and social network (e.g. sports coaches). Parents can use the toolbox to inform their children, close relatives and friends, and their social network. The provided information is essential but compact to enable parents and children to adapt information and make it suitable to apply in their own community.

Conclusions

The DSD Infographic Toolbox will be presented at the 12th I-DSD symposium. The toolbox is available in Dutch, French and English. The DSD Infographic Toolbox is granted by Ghent University Special Research Fund BOF/MVF/202309/014 and the Stichting Sophia Kinderziekenhuis Fonds (SKZF) WEL26-02

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PO38

“It’s all about genetics”: genetic testing experiences and genetic counseling needs among adolescents and young adults living with differences of sex development

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Background

Adolescents and young adults (AYAs) with differences of sex development (DSD) face unique challenges related to understanding their diagnosis, including their genetic etiology. Little is known about how AYAs experience genetic testing or perceive the role of genetic counseling within their care. This qualitative study sought to understand the experiences of AYAs making important decisions about their DSD, including those related to genetic testing.

Methods

Twenty-five AYAs with DSD (mean age = 17.0 years; range = 11-24 years) from one US-based children’s hospital completed an hour-long interview focused on decision making related to their DSD. Participants who had genetic testing completed during adolescence and young adulthood were asked about this decision. Interviews were recorded, transcribed, and emerging themes identified.

Results

Twelve (48%) AYAs in our sample discussed genetic testing. Related themes included that: 1) knowing the genetic etiology was helpful; 2) having genetic information, particularly the karyotype, impacts AYA’s understanding of their sex and gender; 3) if the condition was heritable, it would be important to share this with a partner; and 4) AYAs do not like blood draws, which they associate with genetic testing. Additionally, significant gaps in understanding were identified, with several participants unaware of whether they had undergone genetic testing, uncertain of its purpose, or unaware of results documented in their medical records. Among those introduced to the concept of genetic counseling, interest in and openness to these services was expressed, suggesting an unmet need.

Conclusions

These findings highlight important gaps in AYA understanding of genetic testing and an unmet need for genetic counseling integration in DSD care. Age-appropriate education and resources are essential to improving the genetic care experience for this population.

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PO39

Genomic yields for differences in sex development (DSDs) across clinical settings

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Background

Differences in Sex Development (DSDs) encompass a broad group of conditions that include atypical chromosomal, gonadal or anatomic sex, and affected individuals can present across clinical settings. The underlying etiologies of DSDs are diverse, and a variety of genetic testing is routinely performed, including karyotypes, microarrays, targeted panels, exome/genome analysis and functional studies. Due to these various testing strategies, the cumulative diagnostic yield for this population has not been well characterized, especially in the era of clinical genome analysis.

Methods

We retrospectively reviewed 3 years (Jan 2023- Dec 2025) of clinical data for 133 children, adolescents and young adults with features of a DSD undergoing a genetics evaluation. We excluded those with Congenital Adrenal Hyperplasia and the common sex chromosome aneuploidies, including Klinefelter syndrome (47,XXY) and Turner syndrome (45,X and 45,X/46,XX).

Results

An underlying genetic etiology was identified for 47/133 (35.3%) of individuals overall. For those seen in the outpatient setting with isolated/nonsyndromic DSDs the diagnostic yield was 27/84 (32.14%), for those seen in the outpatient setting with a DSD and additional syndromic features the yield was 11/27 (40.7%), and for those seen in the inpatient setting, all of whom had syndromic features, the yield was 9/22 (40.9%). The most commonly recurring diagnoses included sex-chromosome abnormalities (mosaicism, aneuploidy, unbalanced translocation, $n = 12$), Androgen insensitivity syndrome (AIS, $n = 6$) and *CHD7*-related disorders ($n = 4$). For those with typical 46,XY chromosomes the molecular yield was 33/96 (34.4%), and for those with 46,XX chromosomes it was 2/25 (8%).

Conclusions

These results are consistent with other recent studies and highlight a higher genetic yield with increasing clinical complexity, as well as a notably higher single-gene yield in the context of a 46,XY chromosome complement compared to 46,XX. Clinical genetics evaluations continue to evolve, and over the last 3 years our team has shifted to a genome-first approach for most individuals with features of a DSD, especially for those with syndromic features. The diagnostic yield of genetic testing is expected to continue to increase with advancements in both technology and our understanding of human genetics.

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PO40

Anthropometric benchmarks of care in congenital adrenal hyperplasia (ABC-CAH): initial results from an international, multi-centre registry benchmarking exercise

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Background

Impaired anthopometric indices in patients with 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) are commonly described. This study aims to establish international benchmarks for children with CAH that can be used for comparing and improving care.

Methods

CAH cases in the I-CAH registry with height and weight data collected from birth to 18.5yrs were included. One clinic visit per year of life was selected for each case by proximity to birthday and country specific reference data were used when available to calculate standard deviation scores (SDS) for height. BMI SDS were calculated using WHO reference data. Multifactorial analysis was undertaken describing medians and ranges by year of life, sex and age bands.

Results

16,021 longitudinal visits between 1969 – 2025 from 1,282 cases with CAH across 26 countries in 5 continents were available and from these, 8,025 single visits per year of life were analysed with a median of 9 visits per case (1, 18) at a median age of 7yrs (1, 18) at time of visit. Median height SDS was -1.0 (-4.0, 3.7) in the 1-3yrs age band (n, 882), 0.4 (-3.4, 4.0) in the 7-9yrs age band (n, 682) and -1.1 (-3.9, 2.1) in the 16-18yrs age band (n, 312). Median BMI SDS for 4-6yrs (n, 768), 7-9yrs (n, 682) and 16-18yrs (n, 312) was 0.7 (-3.8, 4.0), 1.1 (-3.7, 4.0) and 0.7 (-2.4, 4.0), respectively. For these groups, 296 (38.5%), 354 (51.9%) and 112 (39.1%) were >1 BMI SDS, respectively. There was marked international variation between centres compared to these global benchmarks, with mean height SDS for around 10% of centres being more than 3SD above or below the mean for all centres. Of the 1282 cases, 635 (50%) were born before 2011 and more recent year of birth was associated with greater height SDS in the age groups spanning 10-18yrs ($P < 0.05$).

Conclusions

The rich international resource of real-world anthropometry data in I-CAH has allowed the creation of anthropometric benchmarks that show temporal and regional variations. It is anticipated that the production of centre-specific anthropometric reports will facilitate an improvement in the quality of care in CAH.

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PO41

The experience of using the PRO-CSD tools in the real world as part of routine clinical practice

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Background/Aims

A paucity of condition-specific tools for assessment of health-related quality of life (HRQoL) in individuals with conditions affecting sex development (CSD) has led to the recent development of short, HRQoL instruments (PRO-CSD) for parents of children with CSD who are less than 7yrs old. These instruments can be used routinely and the aim of the current project was to explore their use in the clinic setting.

Methods

PRO-CSD instruments, a parent self-report (PSR) and parent-proxy report (PPR), were completed as part of routine clinical service by parents of 26 children (median age 4.2 years; range 0.1 to 6.9) with conditions affecting sex development, attending endocrine clinics over a 5-month period at a tertiary children's hospital in Glasgow, UK. Parents were asked to complete questionnaires in the clinic waiting area prior to their appointment.

Results

Of the 38 eligible patients, 26 parents (69%), including 23 mothers, completed a PSR for 26 children aged <7yrs; a subset of these (n,17) also completed a PPR for children aged 2 to 7 years. Reasons for non-participation included: non-attendance (n,4), non-distribution (n,3), unknown reasons (n,3), not fluent in English language (n,1) and telephone appointment (n,1). Of the 43 completed questionnaires, 39 (91%) were completed pre-clinic. Of the 26 children, 18 (69%) were boys, with a median EMS of 9.5 (range 2-12); 9 boys (50%) had an EMS of >9. Eleven (61%) had bilateral undescended testes, 7 (39%) had proximal hypospadias. Nine boys (50%) had previous surgical intervention including hypospadias repair and orchidopexies and all parents had experienced stress at the time of surgery. Amongst the 8 girls, 4 (50%) had 21 hydroxylase deficiency congenital adrenal hyperplasia. Comparison of all PSR scale scores showed that greatest parental stress was experienced upon receiving their child's diagnosis ($P<0.05$) and regarding future concerns (social problems, future relationships) ($P < 0.05$).

Conclusions

PRO-CSD instruments may be used routinely for screening of health-related quality of life in conditions affecting sex development. Further studies in large, multicentre cohorts are required to determine potential associations between demographic and clinical features and rates of psychosocial distress.

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PO42

Temporal trends in acute adrenal insufficiency related adverse events in children with 21-hydroxylase CAH (AE-CAH): an I-CAH registry study

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Background
It is uncertain whether targeted monitoring of acute adrenal insufficiency (AI)–related adverse events, including sick day episodes (SDEs), adrenal crises (AC) and hospitalisations affects the occurrence of these events in children with 21-hydroxylase deficiency congenital adrenal hyperplasia (21-OHD CAH). This study aimed to evaluate temporal trends in AI-related adverse events in children with 21-OHD CAH using real-world data in the I-CAH registry.
Methods
Data on SDE, AC and hospitalisations were collected from 2022 to 2025 for children with 21-OHD CAH aged <18 years. These data were compared to results from 2016–2019 and 2019–2022.
Results
In 2025, 980 children (55 centres, 25 countries) with 5,053 visits and 1,723 patient-years were evaluated. Registry participation increased over time [222 patients (27 centres, 17 countries, 256 patient years data) in 2016–2019 and 513 patients (38 centres, 21 countries) with 880 patient years in 2019–2022]. There were no differences in the proportion of centres from low/middle-income vs high-income countries [33% (9/27) vs 67% (18/27), 29% (11/38) vs 71% (27/38) and 33% (18/55) vs 67% (37/55), $P > 0.1$] in 2016, 2022 and 2025, respectively. The proportion of patients with salt-wasting (SW) CAH were lower over time [92% (204/222) in 2016, 79% (405/513 and 771/976) in 2022 and 2025, respectively], $P < 0.05$. Daily glucocorticoid dosing regimens (hydrocortisone equivalent, mg/m^2/day) differed, with a decrease in doses within the recommended range [59% (1288/2172) vs 56% (1734/3112] and an increase in values in the higher range [20% (439/2172) vs 23% (723/3112)] in 2019 and 2025, respectively, $P = 0.02$. The median SDEs per patient-year per centre was 0.6 (10th,90th: 0,8.3) in 2016–2019, 0 (0,1.7) in 2019–2022 and 0 (0,1.2) in 2022–2025 ($P = 0.04$). Amongst 32 centres that participated in both 2022 and 2025 exercises, SDE rates decreased in 28% (9/32), increased in 31% (10/32) and remained unchanged in 40% (13/32).
Conclusion
I-CAH enables global benchmarking of acute AI-related adverse events in CAH and the number of centres that are participating in this exercise continues to increase. The fall in SDE rates that was previously observed in 2022 has been sustained over the following three years.

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PO43

Characterisation of leydig cells in individuals with genetic defects of androgen signalling

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Background
Androgens play an important role in the proper differentiation of mammalian Leydig cells, including humans. Recently, we have shown that defective androgen signalling in adolescents and young adults with complete androgen insensitivity syndrome (CAIS) and *CYP17A1*-deficiency is associated with altered steroidogenesis, defective differentiation of Leydig cells and maintenance of foetal testicular features. Interestingly, in CAIS, HSD17B3 protein is expressed in Sertoli cells and not in Leydig cells, which is a feature known for the foetal mouse testis. Here, we further investigate the effects of defective androgen signalling on Leydig cells in complete and partial androgen insensitivity syndrome, (PAIS) and *CYP17A1*-deficiency.
Methods
Archived formalin-fixed, paraffin-embedded gonadal tissues from one adolescent and three young adults with CAIS, one child and one young adult with PAIS, and one young adult with *CYP17A1*-deficiency, one adolescent and two adult testicular tissues from Caucasians with no comorbidities were characterised by immunohistochemistry and single-molecule fluorescent *in situ* hybridisation (RNAscope).
Results
HSD17B3 mRNA was exclusively expressed in Sertoli cells in adolescent and young adult CAIS gonads and in the prepubertal PAIS gonad, a feature that have been known for the foetal mouse testis, and also shown by us recently in foetal, neonatal and prepubertal human testis. In the young adult PAIS gonad, however, the expression of *HSD17B3* mRNA switched individually to some Leydig cells. HSD17B3-expressing Leydig cells showed higher expression of the mature/adult Leydig cell marker *INSL3*, while HSD17B3 non-expressing Leydig cells showed higher expression of the immature/foetal Leydig cell marker *DLK1*. Upregulation of *HSD17B3* in Leydig cells in the young adult PAIS gonad was associated with its downregulation in the neighbouring Sertoli cells suggesting a coordinated, androgen-dependent progression of differentiation of both cell types.
Conclusions
Defective androgen signalling in CAIS and *CYP17A1*-deficiency is associated with an altered steroidogenesis and differentiation of Leydig cells, which is partially rescued in PAIS, suggesting that androgen signalling plays an essential role in Leydig cell development in humans. Further investigation of the coordinated development of Leydig and Sertoli cells in these conditions will be performed using spatial transcriptome analysis.

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PO44

Exploring gonadal development in differences of sex development using spatial transcriptomics

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Background
Despite the growing identification of genetic variants that cause Differences of Sex Development (DSD), it is still unclear how these mutations impair testicular cellular organization and cell-cell communication at the tissue level. This knowledge gap is critical: clinical management decisions have historically relied on limited understanding of gonadal tissue biology. One prevailing hypothesis suggests that DSD gonads retain features of fetal development, resulting in developmental arrest or delay in tissue differentiation.
Methods
To elucidate the molecular and spatial etiology of DSD, we applied Visium HD spatial transcriptomics at near-single-cell resolution to compare an adult testis from an individual with a *MYRF* mutation to a healthy adult control.
Results
Spatial clustering revealed a striking paradox: despite the complete absence of germ cells, which comprise multiple developmental stages in healthy testis, the *MYRF*-mutant sample exhibited greater cellular fragmentation (16 spatial clusters) compared to the healthy control (10 clusters). In healthy adult testis, clusters represented expected cellular diversity, including germ cells, Sertoli cells, Leydig cells, and peritubular myoid cells. In contrast, the *MYRF*-mutant testis displayed fragmented spatial organization that could suggest pronounced Sertoli cell heterogeneity, indicating retention of transitional or immature cell states rather than terminal differentiation. The proportional distribution of cells per cluster shifted from balanced diversity in healthy tissue to highly skewed distribution in *MYRF* tissue, with several clusters showing restricted spatial domains suggestive of incomplete differentiation. These spatial patterns support the hypothesis of retained fetal characteristics: rather than progressing to stable, mature cell types, the DSD tissue maintains molecular signatures of developmental intermediates.
Conclusions
Our study establishes a framework for spatially mapping gonadal dysgenesis and reveals unexpected cellular heterogeneity that may reflect differentiation arrest, altered proliferative states, or retention of fetal characteristics. To distinguish between these hypotheses, we are integrating publicly available single-cell atlases spanning human fetal testis maturation, which will enable molecular comparison of MYRF-mutant clusters to normal developmental trajectories. This foundational spatial atlas contributes to closing the knowledge gap in DSD gonad biology and provides molecular evidence that may inform re-evaluation of clinical decision-making based on tissue developmental status rather than assumed risk alone.

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PO45

Characterization of testicular developmental defects in MYRF-associated DSD

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Background

Variations in sex development represent a natural condition that provides insights into fertility and gonadal development. Research on pathogenic variants associated with DSD not only improves the diagnosis and prognosis, but can also identify previously unrecognized concomitant diseases. *Myelin Regulatory Factor* (*MYRF*) is a critical transcriptional regulator essential for CNS myelination and is also expressed in other tissues. Disruptive variants in *MYRF* lead to a recently described syndrome involving cardiac and urogenital syndrome (CUGS) and DSD.

Methods

We analyzed archived FFPE gonadal tissue from a patient with DSD carrying a *MYRF* mutation (p.Q838*) and compared it with control gonadal tissue. We performed IHC, IF, RNAscope *in situ* Hybridization and VisiumHD spatial transcriptomics using the WTA probes. These approaches were used to explore defects in somatic and germ cell differentiation through gene and protein expression analysis at near single-cell resolution.

Results

The patient's testicular tissue is characteristic of Sertoli cell-only Syndrome. The peritubular structure showed a thick lamina around the seminiferous tubules. *ACTA2* IF staining revealed two distinct layers of peritubular myoid cells, suggesting an abnormal organization of the tubular basal lamina. Sertoli cells (SCs) have lost their polarity and immunostaining for the tight junction protein CLDN11 contributing to the blood-testis-barrier (BTB) revealed an irregular and disrupted pattern along the seminiferous tubules. While some SCs expressed CLDN11 protein others did not. This finding was also confirmed by RNA expression, indicating a disruption of the BTB. VisiumHD data showed a high number of Leydig cells (LCs) positive for *INSL3* and *DLK1*. In the patient VisiumHD sample we analyzed 116,148 spatial barcodes representing segmented cells. Most of these LCs (23.9%, 27612 barcodes) express only the immature LCs marker *DLK1, while* 6.5% (7370 barcodes) express only the mature LC marker *INSL3*, and 8.8% (10114 barcodes) express both genes.

Conclusions

Our findings revealed immature features of testicular architecture in a patient with a *MYRF* variant, characterized by Sertoli cell-only syndrome with immature Sertoli cell characteristics and disruption of the BTB. We also observed an abnormal peritubular organization. Transcriptomic analysis suggests altered LCs maturation, with a prevalence of cells expressing the immature marker *DLK1*.

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PO46

Hypospadias and beyond: 20 years of surgical management in differences of sex development (DSD) at a tertiary centre

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Background/Aims

Hypospadias is one of the most common genital variations, and when proximal or complex, may fall within the spectrum of Differences of Sex Development (DSD). Surgical management in this setting is challenging, with high complication rates and limited long-term outcome data. This study aimed to evaluate management pathways, surgical approaches and outcomes for individuals with DSD and hypospadias managed at a single tertiary centre over two decades.

Methods

A retrospective chart review was conducted of individuals with DSD and hypospadias presenting between 2001–2021. Data collected included phenotype, diagnosis, hormonal and surgical management, complications, and outpatient follow-up.

Results

A total of 206 individuals were identified; 192 underwent hypospadias surgery. Most were diagnosed in the neonatal period (97%). The median External Genitalia Score (EGS) was 7.5, indicating the presence of significant genital variation. Of the 192 who underwent surgery, the median number of hypospadias-related procedures was three (range 1–18). Overall, complications occurred in 63% ($n = 121/192$), with 55% requiring further procedures for complications such as fistula or meatal stenosis. Rates of complications did not differ between planned single-stage and two-stage repairs overall, though meatal stenosis and epididymo-orchitis were more frequent in the two-stage group. Pre-operative testosterone was used in 27% but was not associated with complication rates. Almost half (49%) of those eligible were lost to follow-up in adolescence.

Discussion

This study highlights the considerable surgical complexity of hypospadias in the context of DSD, with complication rates at the higher end of those reported internationally. The frequency of multiple procedures emphasises the importance of transparent pre-operative counselling and shared decision-making with families. The suboptimal adolescent follow-up also draws attention to the need for structured systems of longitudinal care, given the risk of late complications and the importance of fertility and psychosocial counselling during this life stage. These findings are particularly relevant in the context of international debate about the most appropriate timing of surgery and a global shift towards deferring non-urgent interventions until individuals can participate in decisions about their care.

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PO47

Advancing the genetic understanding of differences of sex development through whole genome sequencing

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Background/Aims

Currently a genetic diagnosis is found for up to 40-50% for individuals with a difference of sex development (DSD), indicating that there are likely other genomic aetiologies that need to be considered. This study aimed to improve the rates of genetic diagnoses for a cohort of individuals with DSD using whole genome sequencing (WGS), and develop insights into the utility of WGS for rare disease cohorts.

Methods

Individuals with severe forms of DSD such as 46,XY gonadal dysgenesis, who were undiagnosed after previous genomic testing (whole exome sequencing or targeted gene panel) were identified from the Reproductive Development laboratory group's biobank. Previous data were reanalysed with an updated gene list, including undertaking an analysis of copy number variants (CNVs) using a locally developed CNV-caller. Whole genome sequencing (Illumina DNA, PCR-free with ~30x post alignment 2x150bp NovaSeq 6000 sequencing) was performed for 76 individuals, including 27 affected probands and their family members. Analysis and variant curation was undertaken, focusing on 138 diagnostic and candidate genes (and their surrounding genomic regions, as well as introns) known to be associated with DSD. Identified variants (likely pathogenic and pathogenic) were confirmed with Sanger Sequencing, and functional work undertaken to assist with classification.

Results

CNV analysis revealed an individual with a *WT1* deletion, not previously identified through standard analysis of whole exome sequencing. Whole genome sequencing yielded a cohort of 3 individuals with loss-of-function variants in *PPP1R12A*, as well as a variant of uncertain significance in *DAAM2*. Additionally, we have identified a variant in a potential enhancer of a key DSD gene, *NR5A1*, in a family with two affected individuals (sisters with 46,XY gonadal dysgenesis). Luciferase assays showed a reduction in activity in the variant compared to wild type.

Conclusion

This work has identified the activity of an enhancer upstream of *NR5A1*, with reduced *NR5A1* expression being a proposed reason for gonadal dysgenesis in these individuals. Additionally, the benefit of reanalysis of genomic data with new technologies and new gene lists is shown. Analysis of this first cohort of WGS has led to insights on looking at regions upstream of key DSD genes, which will guide future analysis approaches for WGS in rare disease.

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PO48

MAP3K7, a candidate gene for syndromic 46,XY DSD

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Background
MAP3K7 mutations cause Cardiospondylocarpofacial (CSCF) and Frontometaphyseal dysplasia 2 (FMD2), characterized by skeletal malformation, facial dysmorphism, cardiac abnormalities, hearing loss, and intellectual disability. However, involvement of *MAP3K7* in gonadal development and DSD was not known.

Methods
Clinical informatiom of cases were gathered. Extracted DNA for whole exome sequencing analysis. MAP3K7 knock out was done by using CRIPSR technique. MAP3K7 mutagenesis to generate constructs carrying WT or MAP3K7 variants. TOP/FLOPFLASH assay on HEK293T cells overexpressing MAP3K7 WT or variants to examine the beta catenin signalling pathway. Western blot was used to determine p-p38 expression.

Results
We report three new syndromic cases of 46,XY DSD with cardiospondylocarpofacial (CSCF) or frontometaphyseal dysplasia type 2 (FMD2) carrying novel missense variants in *MAP3K7*. The DSD phenotypes include cryptorchidism and micropenis (Case #1 and #2), small testis (Case# 2) and hypospadias (in all three Cases). *MAP3K7* is highly expressed in human fetal Sertoli cells (https://www.reproductivecellatlas.org/gonads/human-main-male/). *MAP3K7* knock-out in NT2/D1 cells was lethal. *MAP3K7* knock-out in HEK293T cells led to downregulation of *GATA4* and *FOG2* expression by RNA-Seq. All 3 *MAP3K7* variants occur in the kinase domain at highly conservative positions among mammals. Like *MAP3K1*, *MAP3K7* phosphorylated p38 - unexpectedly all 3 *MAP3K7* variants over-phosphorylated p38 compared to wildtype. In TOP-FLASH assays two *MAP3K7* missense mutants (Case #1 & #2) ectopically activate beta catenin/Wnt signalling. Our data suggest that *MAP3K7* contributes to male sex differentiation through its kinase activity and by regulating *GATA4* and *FOG2* expression, and antagonizing beta-catenin signalling, and that one or more of these activities were likely affected in 3 cases of 46,XY DSD with CSCF/FMD2 during sex development.

Conclusions
Our data suggests that MAP3K7 contributes to male sex differentiation through its kinase activity, regulating *GATA4* and *FOG2* expression, and antagonizing beta-catenin signalling

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PO49

Expanding the genetic landscape of DSD: deep intronic CYB5A variant in 46,XY gonadal dysgenesis

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Background
Diagnostic yield for 46,XY DSD remains low at about 50%. Whole-genome sequencing (WGS) can detect coding and non-coding variants, offering a more comprehensive approach than exome sequencing or panels to increase the likelihood of identifying potential pathogenic DNA changes missed by routine diagnosis. Here we report a family from Vietnam with compound heterozygous mutations in the *CYB5A* gene, which encodes a CYP17A1 co-factor essential for 17,20-lyase activity.

Methods
Clinical manifestations and hormone test were examined. WGS was performed on peripheral blood DNA extract from two affected siblings with 46,XY DSD. DNA sequencing data were processed using an in house bioinformatics pipeline. Variant calling, annotation, and prioritization were conducted to identify rare or novel variants potentially associated with DSD. Minigene RNA splicing assays in HEK293 cells assessed the functional impact of a deep intronic *CYB5A* variant. Variants were curated according to ACMG guideline.

Results
Two siblings presenting with 46,XY DSD, with female external genitalia, no uterus and bilateral inguinal cryptorchidism. Blood test showed increased 17OHP and low testosterone. WGS identified compound-heterozygous variants in *CYB5A*: a paternally inherited missense variant (p.Val34Glu) and a maternally inherited deep intronic deletion (c.129+862_129+863del), located 861 bp downstream of exon 1 which is predicted impact on splicing by SpliceAI. Both siblings carried both variants. Val34Glu is classified as likely pathogenic (ACMG). The intronic deletion is pathogenic by (ACMG) and SpliceAI predicts. Minigene assays confirmed new cryptic acceptor and donor sites created by the intronic variant produce a pseudoexon between exon 1 and exon 2, introducing a premature stop codon which results to nonsense-mediated decay. The variant is classified as pathogenic.

Conclusion
Only three validated *CYB5A* variants have been reported previously in DSD – all homozygous. The elevated 17-OHP and reduced testosterone in our patients are consistent with impaired CYB5A-dependent 17,20-lyase activity. A single heterozygous *CYB5A* mutation would not be diagnostic. We show that compound-heterozygous *CYB5A* variants, including the deep intronic deletion, likely underlie the DSD phenotype in this family. Under appreciated and underdiagnosed are the combined effect of compound-heterozygous variants, especially 'hidden' deep intronic defects. Our findings underscore the value of WGS and functional assays in validating clinically relevant non-coding variants.

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PO50

Implementation of multilevel data quality metrics in an international registry for rare endocrine conditions

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Background
To implement and evaluate a multilevel framework of quality metrics assessing investigator activity, centre engagement and case-level data completeness within the International Registries for Rare Conditions Affecting Sex Development and Maturation (https://sdmregistries.org) platform.

Methods
A multidimensional quality monitoring framework was applied to routine registry activity data, defining metrics across investigator, centre and case levels. Ages at assessment were analysed using recommended developmental follow-up milestones.

Results
A total of 175 centres from 47 countries contributed data on 10,413 cases, with a median of 26 cases per centre (1, 1,021). Of these, 4,885 (47%) were registered with access to the DSD module (I-DSD) only, 3,750 (36%) as I-CAH, 1,641(16%) as Turner syndrome, and 137(1.3%) as hypogonadotropic hypogonadism. Among patients within I-DSD, 4,881 (100%) had reached 1 year of age, of whom 928 (19%) had at least one follow-up assessment recorded during the first year of life with the median of 0 visits (0, 5). Completeness differed at later milestones: 3.2% at age 4 years, 2.1% at age 8 years, 3.8% at age 10 years, and 7.1% at age 16 years. Across centres, the median percentage of patients with a recorded DSD assessment was < 1% at all age groups. Of the 4,885 cases within I-DSD, 769(16%) had a karyotype consistent with Klinefelter syndrome. In I-CAH, 1,785 patients were aged < 18 years, of whom 1,227(69%) had at least one assessment recorded with the median 6 visits per patient (0, 59). Among 1,965 adults with CAH, 593 (30%) had at least one assessment with the median of < 1 visits (0, 35). Across centres, the median percentage of patients with at least one CAH assessment was 82% and 19% in those aged < 18 years and adults, respectively. The median number of assessments per patient per centre was 3.5 (0, 30) and 0 (0, 15), respectively. Of the total 10,490 cases, 6,683 (64%) were involved in 33 studies launched within the last five years.

Conclusions
Multilevel quality metrics enable systematic monitoring of international registry performance, identify reporting gaps, support centre engagement, and strengthen real-world evidence generation. Follow-up data completeness was higher in younger patients than adults.

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PO51

The persisting presence of absence in female sex development: a critical interdisciplinary reflection

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Background
For much of the twentieth century, developmental endocrinology was structured around a binary framework in which male differentiation was understood as an active, hormone-driven process, while female development was conceptualized as the passive result of androgen absence. This model has profoundly shaped experimental designs, interpretive frameworks, and broader conceptualizations within reproductive and developmental biology. Yet, empirical evidence in molecular endocrinology, alongside insights from the history of science and feminist science studies, prompt renewed scrutiny of this paradigm and its enduring influence on scientific thought.
Methods
We conducted a multidisciplinary critical analysis combining historical, empirical, and material-semiotic approaches. First, we examined key experimental systems in twentieth-century embryological endocrinology to trace how the androgen-centered model of sex differentiation emerged and stabilized within the discipline. Second, we synthesized findings from developmental and molecular endocrinology concerning the roles of oestrogens and their receptors in mammalian female genital development. Finally, we situated the scientific "absence model" of femaleness within its broader cultural and symbolic contexts, analyzing how scientific concepts of sex are co-constituted with social meanings.
Results
Our historical analysis shows that experimental emphasis on androgens contributed to defining female development as a default or negative state. This methodological privileging rendered oestrogenic processes comparatively invisible. However, evidence from molecular and developmental endocrinology demonstrates that oestrogens and their receptors play active, regulatory roles in female genital differentiation. These findings support a shift away from reductionist, absence-based interpretations toward a model that recognizes female sex development as hormonally mediated and developmentally dynamic. The material-semiotic analysis further reveals that scientific representations of sex differentiation are shaped by, and help reproduce, broader cultural assumptions about gender and activity.
Conclusion
Integrating biomedical research with historical and feminist science studies perspectives, we argue for a more accurate and equitable understanding of female development - one that recognizes oestrogenic activity as central to sex differentiation and challenges the reduction of femaleness to hormonal absence. This cross-disciplinary approach demonstrates the transformative potential of critically re-examining foundational paradigms in developmental endocrinology.

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PO52

Modeling hormone-associated differences in human neurodevelopment using hiPSC-derived GnRH neurons

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Background
Biological sex differences arise from the interaction between genetic and hormonal factors. These differences extend from external genitalia to the developing brain. Neurons exhibit sex-dependent transcriptional profiles that are associated with variations in neurodevelopmental processes and disease susceptibility. Steroid hormone receptors, including the androgen receptor (AR) and the estrogen receptors (ESR1 and ESR2), are present at low levels in certain cell types in the developing human brain. This suggests that neuronal differentiation may be sensitive to variations in hormone levels. Gonadotropin-releasing hormone (GnRH) neurons are of particular interest because they are part of the hypothalamic-pituitary-gonadal axis, which links brain development with steroid hormone production and feedback. Complete androgen insensitivity syndrome (CAIS) is a condition in which hormone signaling is altered. CAIS-derived human induced pluripotent stem cell (hiPSC) lines provide a human model to investigate neurodevelopment influenced by hormones.
Methods
Fully characterized CAIS-derived hiPSC lines were used to establish a 30-day differentiation protocol for GnRH neurons. To enable controlled, mechanistic studies of steroid hormone signaling, hiPSC lines derived from donors with intact steroid hormone receptors serve as the basis for CRISPR/Cas9-mediated genome editing. Loss-of-function mutations are introduced into the AR, ESR1, and ESR2 genes in both 46,XX and 46,XY genetic backgrounds to generate isogenic cell models.
Results
The differentiation protocol reliably produces GnRH neurons and provides a platform to compare neuronal populations derived from control and CAIS hiPSC lines. Preliminary analysis reveals transcriptional differences between 46,XY control and CAIS neuronal populations, indicating altered transcriptional programs associated with impaired androgen signaling. The CRISPR/Cas9-generated receptor knockout lines will enable receptor-specific perturbation while minimizing the impact of genetic variability between cell lines.
Conclusion
The combination of wild-type and genome-edited isogenic hiPSC lines establishes a human *in vitro* platform to investigate how steroid hormone signaling influences neuronal development. Together with long-read genomics approaches, the investigation of receptor-specific effects on transcriptional programs and transcript architecture during GnRH neuron differentiation will be allowed.

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PO53

Parent involvement in child-centred sequences: a conversation analysis of paediatric transgender and DSD/intersex consultations

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Background
This article attends to parents' involvement in child-centred sequences in paediatric transgender and differences of sex development (DSD)/intersex care. In these healthcare settings where the child's wish is pre-eminently crucial, parents may find themselves in a complex position as they must balance their involvement and the child's participation.
Methods
We used conversation analysis to examine parents' contributions after healthcare providers' (HPs) child-directed questions in 20 video-recorded clinical consultations.
Results
In our collection, parents were found to corroborate their child's response, pursue a (further) response from their child or extend their child's response. With response corroborations, parents facilitate both progression of the interactional activity at hand and child participation. Parents' response pursuits, however, halt progression of the interaction in favour of the child's participation. With response extensions, parents treat both interactional progression and child participation as subordinate to their own contribution. In general, HPs remained largely oriented to children as the primary interlocutor. We analyse one deviant case in which the HP addresses the parents as respondent to their next action.
Conclusions
Our findings advance our understanding of parental involvement in paediatric transgender and DSD/intersex care. HPs are offered valuable insights to reflect on their own role regarding parents' involvement in clinical consultations.

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PO54

Uncertainty in transgender and DSD/intersex care for children and adolescents – experiences of healthcare professionals

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Background

Uncertainty is pervasive within transgender and differences in sex development (DSD)/intersex care for children and adolescents. In both contexts, healthcare professionals (HCP) are confronted with complex treatment decisions which raise questions about the meaning of sex and gender, informed consent in minors, and unpredictable treatment outcomes. Thus, HCP may be confronted with both factual and moral uncertainties. We sought to address the current lack of understanding regarding HCP's experiences of uncertainty in transgender and DSD/intersex healthcare for children and adolescents.

Methods

We conducted individual, semi-structured, in-depth interviews with 20 purposively selected healthcare professionals in the Netherlands. Participants represented somatic and mental health disciplines involved in transgender and DSD/intersex care for children and adolescents at two specialized healthcare centers. We conducted an inductive thematic analysis.

Results

Factual and ethical uncertainty were interwoven within three central themes. First, HCP tried to anticipate and appropriately support a young person's uncertain future. Second, they tried to determine when they were sufficient certain enough to make decisions, given their limited perspective. Third, HCP attempted to collaboratively reach 'good' decisions while navigating irreducible remaining uncertainty. Underlying the uncertainty, we identified various implicit norms guiding HCP's practice.

Conclusions

Results imply that HCP may contain fundamental ethical uncertainties through so-called 'moral settlements' – a collection of implicit norms which prescribe how to act. Elucidating such implicit norms may facilitate clinical and societal discussion about what constitutes optimal care. Eventually, this may enable HCP, parents and young persons in managing and discussing uncertainty, and facilitate collaborative decision making.

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PO55

Long-term health issues related to differences in sex development

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Background

Differences in sex development (DSD) comprise a heterogeneous group of conditions that require complex, lifelong management. Owing to their multi-faceted nature, continuous follow-up and a holistic, multidisciplinary approach are essential. However, data regarding long-term health outcomes beyond childhood remain limited.

Objective

To assess general health status, metabolic outcomes, and therapeutic management in individuals with DSD followed at a tertiary pediatric center.

Methods

Clinical data were retrospectively collected from medical records and included demographic characteristics, medical history, medication records, anthropometric measurements, and laboratory findings.

Results

A total of 109 individuals with DSD (82.6% male) were evaluated over a median follow-up period of 16 years (range 6–35 years). The cohort included 73 patients with 46,XY DSD (66.9%), 15 with 46,XX DSD (13.7%), and 11 with sex chromosome DSD (9.2%). Karyotype data were unavailable for 10 patients (9.2%), including 3 who were referred but did not complete the recommended evaluation and 7 who were not referred for testing. Neuropsychiatric morbidity was identified in 20.2% of patients, acne before age 20 in 18.3%, dyslipidemia in 11%, and osteoporosis in 4.6%. Attention-deficit/hyperactivity disorder was the most prevalent psychiatric diagnosis, followed by anxiety disorders, autism spectrum disorder, developmental delay, depression, and obsessive–compulsive disorder. Chromosomal karyotype was significantly associated with the presence of dyslipidemia. Sixteen patients (14.6%) were lost to follow-up, and five (4.5%) continued hormone replacement therapy under primary care without structured specialist supervision.

Conclusions

DSD constitutes a chronic condition with significant long-term physical and mental health consequences, underscoring the need for lifelong, multidisciplinary care. The early emergence of morbidity reinforces this requirement. The loss of follow-up in approximately one-fifth of patients highlights the critical importance of structured and accessible transition to adult care services. Increased awareness is also needed to ensure completion of karyotyping and etiological evaluation in patients diagnosed in childhood with incomplete diagnostic assessment.

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PO56

Different faces of the same coin : two distinct presentations of 11β-hydroxylase deficiency in 46,XX DSD

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Background/Aims

11β-hydroxylase deficiency (11β-OHD) is the second most common form of congenital adrenal hyperplasia and an important cause of virilized 46,XX differences of sex development (DSD). It is typically characterized by prenatal virilization, androgen excess, and hypertension due to accumulation of 11-deoxycorticosterone. However, early biochemical findings may be inconsistent with the classic phenotype. We report two 46,XX patients with genetically confirmed 11β-OHD who demonstrated atypical biochemical profiles.

Methods

A retrospective review of two patients evaluated at a tertiary DSD center. Clinical data, serum and urinary steroid profiles, ACTH stimulation testing, imaging studies, and molecular analyses were assessed.

Results

Case 1: A neonate presented with Prader stage 3–4 virilization, including clitoromegaly, fused labioscrotal folds, and a single urogenital opening. No gonads were palpable; pelvic ultrasound revealed a uterus and ovaries. Electrolytes were normal. ACTH stimulation demonstrated impaired cortisol response (251 nmol/l) with markedly elevated 11-deoxycortisol and adrenal androgens. Hydrocortisone was initiated. Notably, plasma renin and aldosterone were repeatedly elevated rather than suppressed. Genetic testing identified two pathogenic CYP11B1 variants (likely in trans), confirming the diagnosis. *Case 2:* A newborn with Prader stage 4 virilization had normal electrolytes and no hyperpigmentation. Initial ACTH stimulation showed apparently sufficient cortisol secretion (621 nmol/l). Early serum steroid measurements showed only mild or borderline elevation of 11-deoxycortisol (including one normal value) with elevated 17-hydroxyprogesterone. Pelvic imaging did not clearly identify Müllerian structures or gonads. Diagnostic clarification was achieved through urinary steroid profiling, which demonstrated accumulation of upstream precursors consistent with 11β-OHD. Repeat imaging and later laparoscopy confirmed normal internal female anatomy. Serial ACTH testing demonstrated preserved cortisol reserve until 3 years of age, when impaired response (408 nmol/l), androgen excess, and advanced bone age emerged. Hydrocortisone therapy resulted in biochemical control and normal growth. Molecular testing confirmed 11β-OHD.

Conclusion

11β-OHD may present with normal electrolytes, borderline or fluctuating steroid abnormalities, preserved early cortisol reserve, and non-suppressed renin–aldosterone profiles. Comprehensive steroid profiling, including urinary analysis, and timely genetic testing are essential for accurate diagnosis. These cases underscore the biochemical heterogeneity of 11β-OHD and the need for continued endocrine surveillance, even when early findings appear reassuring.

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PO57

Reference intervals for circulating steroid hormones in healthy infants: a longitudinal LC–MS/MS study

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Background

Infancy is characterized by profound endocrine adaptation, including postnatal remodeling of the adrenal cortex and transient activation of the hypothalamic–pituitary–gonadal axis during minipuberty. Although these processes are reflected in the circulating steroid metabolome, longitudinal serum data generated by liquid chromatography–tandem mass spectrometry (LC–MS/MS) remain limited.

Objective

To characterize the temporal dynamics of the serum steroid metabolome during the first year of life in healthy term infants and to establish sex- and age-specific reference curves for clinical use.

Methods

This study was embedded in the prospective COPENHAGEN Minipuberty Study and included healthy, term, singleton infants followed longitudinally during the first year of life. Serum concentrations of 16 steroid hormones were quantified by isotope dilution on-line TurboFlow LC–MS/MS in 446 samples from 189 infants (88 girls, 101 boys), collected between 5 and 485 days of age. Free testosterone was calculated using the Vermeulen equation. Age-specific reference curves were modelled using generalized additive models for location, scale and shape (GAMLSS). Repeated measures were analyzed using linear mixed-effects models, and estimated steroidogenic enzyme activities were derived from steroid ratios.

Results

The serum steroid metabolome showed marked age-dependent remodeling across infancy. Most progestins, adrenal androgen precursors, and several glucocorticoid- and mineralocorticoid-related steroids declined after birth, including progesterone, 17-hydroxyprogesterone, 17-hydroxypregnenolone, dehydroepiandrosterone sulfate, dehydroepiandrosterone, androstenedione, and aldosterone. In contrast, cortisol, corticosterone, 11-deoxycorticosterone, and 11-deoxycortisol displayed an initial rise before declining later in infancy, consistent with maturation of adrenal steroidogenesis. Sex differences were limited for most analytes, indicating broadly similar adrenal developmental patterns in girls and boys. As expected, testosterone, dihydrotestosterone, and free testosterone were significantly higher in boys, reflecting minipuberty. Estimated enzyme activities were largely comparable between sexes, although 17β-hydroxysteroid dehydrogenase and 17α-hydroxylase activities were higher in boys, whereas 5α-reductase activity was higher in girls.

Conclusions

This study provides comprehensive longitudinal LC–MS/MS-based reference data for serum steroid metabolome in healthy infants during the first year of life. These sex- and age-specific reference curves may support earlier recognition, diagnosis, and monitoring of rare disorders of steroidogenesis and improve interpretation of steroid profiles in pediatric endocrine practice.

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PO58

Fertility preservation in differences of sex development: early institutional experience

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Background

Ovarian tissue cryopreservation (OTC) is an established fertility-preservation method in paediatric oncology but is rarely reported in children with differences of sex development (DSD). Patients with DSD, especially those with gonadal dysgenesis, require careful tumour surveillance due to an increased risk of germ cell malignancy, particularly with Y-chromosome material, intra-abdominal gonads, or atypical genitalia. When gonadectomy is recommended, OTC may provide an opportunity for fertility preservation.

Materials and Methods

In 2021, a multidisciplinary OTC protocol for children at risk of ovarian function loss was established at our institution. The pathway includes endocrine and radiological evaluation, surgical consultation, psychological counselling, ethical review, standardized ovarian tissue processing, and cryobiology logistics.

Results

OTC was performed in four patients: three with Turner syndrome (TS) and one with mixed gonadal dysgenesis (MGD), at a mean age of 6.9 years (range 4.7–12.4 years). In two TS patients and in the patient with MGD, gonadectomy was indicated due to an increased risk of germ cell malignancy. Both TS patients had Y-chromosome material in their karyotype and biochemical and radiological evidence of gonadal insufficiency (AMH 0,01 ng/mL, FSH > 10 IU/L, no follicles on ultrasound). Despite the low likelihood of viable follicles, parents opted for cryopreservation at the time of bilateral gonadectomy. In the patient with MGD, the intra-abdominal dysgenetic gonad was removed because of its high oncologic risk, while the contralateral gonad with testicular characteristics was preserved, acknowledging that gender identity development may evolve over time. Although antral follicles had been visualized during minipuberty, histopathology at age 5 revealed fibrotic ovarian stroma without follicles or neoplasia. Similar findings were observed in the two TS patients. The third TS patient underwent OTC after spontaneous menarche with diminished ovarian reserve (AMH 0,55 ng/mL, FSH 10 IU/L, antral follicles detectable on ultrasound). Histopathology confirmed the presence of follicles ($20/mm^2$).

Conclusions

OTC in patients with DSD is feasible but challenging. In TS with Y-chromosome material and ovarian insufficiency, cryopreservation may provide reassurance to families that all possible steps toward fertility preservation had been explored. Early consideration of fertility preservation and transparent counselling regarding realistic outcomes are essential.

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PO59

Uncommon 46,XY/47,XYY/45,X mosaicism causing ambiguous genitalia and challenging management

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Background

Sex chromosome mosaicism is a recognized cause of disorders of sex development (DSD); Mixed gonadal dysgenesis (MGD) most often associated with 45, X/46 XY with broad phenotypes from m ambiguous genitalia to typical male or female appearance. Management is complex and multidisciplinary (sex assignment, surgical planning, fertility and tumor surveillance) Three lines mosaicism are uncommonly reported their phenotypic expression is unknown.

Method, Observation

Non consanguineous parents presented their child of pediatric endocrinology at 15 months of age for evaluation of ambiguous genitalia, raised as a girl with legal sex still undeclared. Examination revealed a phallic structure of 1.5 cm with a single mid-ventral urethral opening, asymmetrical rugose labioscrotal folds resembling a hypoplastic scrotum, a palpable right gonad, and no palpable left gonad including along the inguinal canal. Growth parameters were normal, and no dysmorphic features were observed. Born at term, with no particular familiar history. Hormonal evaluation at 2 days of life showed testosterone 7.56 nmol/l, low AMH 13.18 ng/mL, DHT 0.41 nmol/l, FSH 1.05 IU/L, LH 0.09 IU/L, and 17-hydroxyprogesterone 10 ng/mL, suggestive of detectable Leydig cell function with Sertoli dysfunction. At 1month urogenito-cystograhy and ultrasounds(US)revealed left lateralized uterus, vagina communicating with a male type curved urethra and a right testis within the scrotal bursa. Constitutional Karyotyping at 10 months demonstrated a rare three-line mosaicism: 46, XY (60%), 47, XYY (20%), 45, X (20%).

Results/Outcome

All finding consistent of gonadal dysgenesis. Parents were counseled regarding fertility, surgical reconstruction, and hormonal therapy. Initially,they intended to raise the child as a girl. However, following evaluation by a national multidisciplinary DSD board, male sex assignment was recommended and was subsequently accepted. Two Testosterone injections resulted in phallic growth and right testicular development. Ultrasound at 21 months suggested a hypoechogenic structure in the left inguinal hernia, likely a hypotrophic left gonad. AMH levels normalized, indicating improved Sertoli cell function.

To conclude : The child is now 3 years old, awaiting surgical staff/intervention, highlighting the prolonged diagnostic, legal, and therapeutic pathway in complex DSD

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PO60

Exome reanalysis revels the molecular etiology of a previously inconclusive DSD case

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Background

Syndromic Disorders/Differences of Sex Development (DSD) represent a subgroup of DSD characterized by genital atypia associated with additional clinical features such as intellectual disability or neurodevelopmental delay, short stature or weight-for-height deficit, major congenital anomalies, or dysmorphic features. While establishing a molecular diagnosis in DSD is often challenging, it becomes more difficult in syndromic cases due to phenotypic overlap and multisystem involvement. Despite the use of Whole Exome Sequencing (WES), many cases initially remain unsolved because variants may occur in genes whose disease associations were recognized only after the initial analysis. This highlights the importance of periodic reanalysis of exome data as knowledge of gene–disease associations continue to grow.

Methods

In 1993, a full-term newborn presented at 44 days of life with ambiguous genitalia and multiple syndromic features, including craniofacial dysmorphisms, clinodactyly, congenital heart defects, and pulmonary and ocular anomalies. Genital examination revealed a 1.5-cm phallus with chordee, perineal hypospadias, partial fusion of labioscrotal folds, and non-palpable gonads (Prader grade III; External Genitalia Score 2.5). Karyotype was 46,XY. Initial genetic evaluation, including Sanger sequencing of known DSD-associated genes, was inconclusive. WES performed in 2016 also failed to identify pathogenic variants. Following recent reports of novel gene–disease associations in DSD, the original WES data were reprocessed and reanalyzed.

Results

Reanalysis of the patient's WES data identified a heterozygous c.1745C > A variant in exon 12 of the *MYRF* gene, resulting in the nonsense variant p.Ser582*. The variant is predicted to generate a truncated protein lacking the transcription factor domain. To date, this variant has not been reported in the literature.

Conclusion

This report describes a patient whose initial WES analysis was inconclusive; however, recently described associations between *MYRF* and DSD enabled the identification of a pathogenic variant upon exome reanalysis years later. Notably, the molecular diagnosis was established more than 30 years after the patient's initial clinical evaluation, reflecting advances in genomic knowledge and its application in clinical practice. This case highlights the crucial role of periodic genetic data reinterpretation and clinical persistence in resolving the molecular etiology in Syndromic DSD.

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PO61

In vitro functional characterization of the novel CYP11B1 intronic variation c.1200 + 5G > C associated with adrenal congenital hyperplasia

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Background

Congenital adrenal hyperplasia (CAH) is a group of monogenic disorders, with autosomal recessive inheritance which is classified as a sexual development disorder due to androgen excess. It results from a defect in one of the steroidogenic enzymes which leads to the accumulation of intermediate metabolites affecting the production of Glucocorticoids, Mineralocorticoids, and/or sex steroids, resulting in a wide spectrum of clinical presentations. CAH resulting from 11β-hydroxylase (11β-OHD) deficiency is caused by pathogenic variants occuring in the *CYP11B1* gene, located on the long arm of chromosome 8 (8q24.3). This gene encodes for 11β-OHD, a mitochondrial hemoprotein formed by a 503 amino acid chain and expressed mainly at the adrenal gland. In the present study, we identified a novel homozygous intronic variant c.1200 + 5G > C located in intron 7 of *CYP11B1* gene in a Tunisian family. The aim of this study was to characterize the functional consequences of this variant on the *CYP11B1* function.

Methods

In the way to characterize the functional implications of this variation on mRNA splicing, we conducted, as a first intention, an *in-silico* prediction and modeling study to determine if it can activate or inhibit acceptor or donor canonical splicing sites or if it is involved only in the activation of other cryptic splice sites. In the second step, to confirm and assess the outcome of the *in-silico* analyses, we performed an *in vitro* functional study using the "Exon Trapping" approach.

Results

The *in-silico* analysis suggested that the c.1200 + 5G > C variant would result in retention of intron 7 leading to a frameshift and the appearance of a premature stop codon which would alter the conformation as well as the function of the mutated protein. However, *in vitro* functional studies revealed that the variation would rather result in the excision of exon 7 located just upstream site. In essence, our *in vitro* assays confirmed the pathogenicity role of the c.1200 + 5G > C variant as well as its association with a severe clinical phenotype.

Conclusions

The divergence between the results of the *in-silico* prediction and the *in vitro* functional analysis highlights the complementarity and limitations of bioinformatic tools, which although predictive, must systematically be validated by experimental approaches.

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PO62

From clinical misdiagnosis to molecular diagnosis: the power of next-generation sequencing in 46,XY DSD

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Background

Disorders of Sex Development or DSD are congenital abnormalities characterized by a discordance between genetic, gonadal and phenotypic sex. Phenotypes range from moderate malformations of the external genitalia or sexual ambiguities to complete sex reversal. Accurate molecular diagnosis through Next Generation Sequencing (NGS) and Whole Exome Sequencing (WES) contributes to better personalized patient management. The aim of this study was to establish a molecular diagnosis in 3 Tunisian patients with 46,XY DSD using the WES technique.

Methods
WES, using Novaseq 6000 technology, was conducted in 3 Tunisian patients with 46,XY DSD : gonadal dysgenesis in 2 patients and androgen insensitivity in the 3rd patient.
Results
The performed NGS demonstrated that the patients of our study were clinically misdiagnosed. In fact, the WES results allowed us to identify 2 hemizygous *AR* novel variations in 2 gonadal dysgenesis patients and a novel homozygous *DHH* variant in androgen insensitivity syndrome patient. In essence, next generation sequencing allowed the revision of the clinical diagnosis in these 46,XY DSD patients.
Conclusions
In conclusion, 46,XY DSD is a complicated polygenic disease hence the interest of the NGS that allows to establish an accurate molecular diagnosis regardless of the severity of the disease and reassessment of the clinical diagnosis

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PO63

The prevalence of nephrocalcinosis among patients with congenital adrenal hyperplasia due to 21 hydroxylase deficiency – one-centre experience. Do we need a regular screening?

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Introduction
In the literature, there are reports about nephrocalcinosis (NC), hypercalcemia, and hypercalciuria risk in patients with congenital adrenal hyperplasia (CAH). The prevalence and background of nephrocalcinosis is not established. Nephrocalcinosis refers to diffuse calcification in the renal parenchyma, generally in renal pyramids.
Aim of the study
The study aimed to evaluate the prevalence of nephrocalcinosis and nephrocalcinosis risk factors such as hypercalciuria, hyperphosphaturia, hyperuricosuria, hyperoxaluria, hypomagnesuria, and hypocitraturia among patients with CAH due to 21 hydroxylase deficiency.
Results
In 54 patients with confirmed 21 hydroxylase deficiency, an abdominal ultrasound was performed, and the excretion of electrolytes, uric acid, oxalates, and citrates was analyzed twice. A retrospective chart review was conducted for all patients. In 11 out of 54 (20%) patients with confirmed 21 hydroxylase deficiency nephrocalcinosis was described in the abdominal ultrasound. All 11 patients have salt-wasting CAH. The nephrocalcinosis was found in most cases accidentally during ultrasound examination due to different issues. The medium age of the diagnosis was 2 years 6 months (2 months - 7 years). In three patients, after a couple of years, the vanishing of the nephrocalcinosis features in the ultrasound was observed. All patients were treated with hydrocortisone, fludrocortisone, and salt supplementation during the 1st year of life. In 4 out of 11 patients with described NC, transient episodes of hypercalcemia during the 1st year of life were observed. In 5 out of 11 patients, hypercalciuria and 6 out of 11 increased calcium/creatinine ratio were identified. In 8 out of 11 patients, hiperphosphaturia was observed, and in 9 out of 11 hyperuricosuria was noted. In 4 out of 11 patients, hyperoxaluria was found. In 1 out of 11 patients, hypocitraturia was described, and in 5 out of 11 patients, a decreased magnesium/creatinine ratio was observed. Statistical analysis didn't find a correlation between the prevalence of nephrocalcinosis and a dose of hydrocortisone in the 1st year of life. Statistical analysis showed that patients treated with a dose of hydrocortisone higher than 50 g/m^2 during the first six months of life have two times higher risk of developing nephrocalcinosis than patients treated with hydrocortisone dose lower than 50 mg/m^2 and showed that patients treated with a dose of fludrocortisone higher than 75 mg during the 1st year of life have 2,6 time higher risk of developing nephrocalcinosis than patients treated with fludrocortisone dose lower than 75 mg.
Conclusions
According to our research, children with salt-wasting congenital adrenal hyperplasia are at high risk of nephrocalcinosis development. In our study group also, the prevalence of nephrocalcinosis or nephrolithiasis risk factors such as hypercalciuria, hyperphosphaturia, hyperuricosuria, hyperoxaluria, hypomagnesuria, and hypocitraturia was high. In the group of patients with SW-CAH statistical analysis didn't find a correlation between the prevalence of nephrocalcinosis and a dose of hydrocortisone in the 1st year of life. In the group of patients with SW-CAH statistical analysis showed that patients treated with a dose of hydrocortisone higher than 50 g/m^2 during the first six months of life have two times higher risk of developing nephrocalcinosis than patients treated with hydrocortisone dose lower than 50 mg/m^2, and showed that patients treated with a dose of fludrocortisone higher than 75 mg during the 1st year of life have 2,6 time higher risk of developing nephrocalcinosis than patients treated with fludrocortisone dose lower than 75 mg. The background, etiology, and natural history remain unclear. The impact of nephrocalcinosis on renal function in this group of patients lasts inexplicit. Further studies are needed to determine the prevalence, etiology, impact, and natural history of nephrocalcinosis in CAH.

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PO64

Visceral-to-subcutaneous fat ratio and metabolic correlates in adults with classical congenital adrenal hyperplasia

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Background
Adults with classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency may present alterations in body composition and increased cardiometabolic risk. The visceral-to-subcutaneous adipose tissue ratio (VAT/SAT) has emerged as a marker of adverse fat distribution and metabolic risk. However, data regarding visceral fat distribution and its metabolic and hormonal correlates in adults with CAH remain limited.
Methods
A cross-sectional study included 23 adults with classical CAH (mean age 38 ± 11.5 years; 18 females; 12 with the salt-wasting form) and 23 healthy volunteers matched for sex, age, and body mass index (BMI). Visceral (VAT) and subcutaneous (SAT) adipose tissue areas were measured by abdominal computed tomography. Anthropometric data included BMI and waist circumference. Metabolic parameters comprised fasting glucose, HbA1c, and lipid profile. Hormonal markers of disease control (17-hydroxyprogesterone and androstenedione) and hydrocortisone-equivalent glucocorticoid dose (mg/m^2) were assessed in CAH patients. Twenty patients were considered well-controlled. Group comparisons were performed using the Mann–Whitney test and correlations using Spearman coefficients.
Results
Most patients (62%) received low doses of dexamethasone (mean hydrocortisone-equivalent dose was 5.8 ± 4.9 mg/m^2/day). Twelve patients (52%) received fludrocortisone (mean dose 50 ± 28 mg/day). The VAT/SAT ratio tended to be higher in CAH patients compared with controls (0.55 ± 0.28 vs 0.41 ± 0.26), although without statistical significance ($P = 0.18$). In patients with CAH, VAT/SAT showed a significant positive correlation with BMI ($r = 0.52$, $P = 0.03$), suggesting an association between visceral fat distribution and overall adiposity. A trend toward an inverse correlation between VAT/SAT and HDL cholesterol was observed ($r = -0.41$, $P = 0.09$), indicating a potential relationship between visceral adiposity and an unfavorable lipid profile. No significant correlations were found between VAT/SAT and hormonal control markers, including 17OHP or androstenedione. Likewise, VAT/SAT was not associated with hydrocortisone-equivalent glucocorticoid dose.
Conclusion
Adults with classical CAH may present a tendency toward higher visceral fat distribution compared with healthy controls. However, visceral adiposity appears to be more closely related to overall adiposity rather than hormonal disease control or glucocorticoid exposure. Larger studies are needed to confirm these findings. Study Grant from FAPESP #2019/26780-9 and #2023/11168-1.

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PO65

Preserved cardiac structure in well-controlled adults with classical congenital adrenal hyperplasia: a pilot study

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Background
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is often associated with increased cardiovascular risk. However, evidence regarding cardiac function in CAH remains limited, particularly in adult. This study aimed to evaluate cardiac structure and function by echocardiography in well-controlled adults with classical CAH.
Methods
A cross-sectional study including 23 classical adults (mean age 38 ± 11.5 years; 18 females; 12 with salt-wasting form) and 23 healthy volunteers matched for sex, age, and body mass index (BMI). Cardiac structure and function were assessed by echocardiography. Anthropometric data, blood pressure and metabolic parameters were evaluated. Hormonal markers of disease control (17-hydroxyprogesterone and androstenedione) and hydrocortisone-equivalent glucocorticoid dose (mg/m^2) were assessed in CAH patients. Twenty patients were well-controlled. Group comparisons were performed using the Mann–Whitney test and correlations using Spearman coefficients.
Results
Most patients (62%) received low doses of dexamethasone (mean hydrocortisone-equivalent dose was 5.8 ± 4.9 mg/m^2/day). Twelve patients (52%) received fludrocortisone (mean dose 50 ± 28 mg/day). BMI was similar between patients and controls (27.3 ± 6.3 vs 28.4 ± 8.7 kg/m^2, $P = 0.64$), as were systolic and diastolic blood pressure. No participants were using antihypertensive medications. Echocardiographic parameters—left atrial size, left atrial volume, left ventricular mass index, and pulmonary systolic pressure—did not differ between groups. There was a trend toward lower left ventricular ejection fraction in CAH patients compared with controls (60.8 ± 10.4% vs 65.4 ± 3.4%, $P = 0.055$), although values remained within the normal range. In CAH patients, systolic blood pressure showed a slightly positive correlation with left atrial volume ($r = 0.52$, $P = 0.07$), with all values within the normal range. No correlations were observed between echocardiographic parameters and hydrocortisone/fludrocortisone doses or hormonal control markers.
Conclusion
Cardiac structure and function appear preserved in well-controlled adults with classical CAH receiving relatively low glucocorticoid doses. Although left ventricular ejection fraction was slightly lower in CAH patients, values remained within the normal range. These findings suggest that long-term treatment with physiological glucocorticoid and mineralocorticoid doses may not be associated with clinically relevant structural cardiac alterations; however, larger studies are needed toÂ confirm these observations. Grants from FAPESP #2019/26780-9 and #2023/11168-1.

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PO66

Cross-sectional assessment of health status in adults with CAH in the UK and Ireland – CaHASE2

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Background
Congenital adrenal hyperplasia (CAH) is a common form of primary adrenal insufficiency, affecting approximately 1 in 15,000 individuals. Previous international studies have indicated that adults living with CAH often experience suboptimal health status and care provision. The CaHASE2 initiative was established to evaluate the current clinical status and healthcare outcomes of adults with CAH across the UK and Ireland.
Methods
To date, 488 adults have been recruited from 23 specialist centres. This cross-sectional analysis utilizes real-world clinical data from 254 patients (156 females) across 14 centres, collected during clinic visits between November 2022 and September 2025.
Results
The cohort consisted primarily of younger to middle-aged adults (median age 39.2 years; range 18–86.1), with 26% aged 50 or older. Significant metabolic comorbidities were observed: 26% were overweight, 35% were obese, and 10% were severely obese. Only 34% maintained normal random blood pressure, while 14% required antihypertensive therapy. Additionally, 7% had type 2 diabetes. Mental health concerns were prevalent, with depression in 10% and anxiety in 7% of patients, though data were missing for 16% and 20% respectively. Regarding lifestyle, 9% were current smokers. Treatment predominantly involved prednisolone (42%) and standard hydrocortisone (40%). The median relative hydrocortisone equivalent dose was 12.06 mg/m^2/day. The median fludrocortisone dose was 150 µg. Biochemical control varied: one-third of patients had 17-hydroxyprogesterone (17OHP) levels below 10 nmol/l, one-third between 10–36 nmol/l, and one-third above 36 nmol/l. Most patients (70%) had androstenedione levels below 8 nmol/l. Notably, no correlation was found between glucocorticoid dosage and patient weight or body surface area.
Conclusion
These findings provide clear signals of ongoing impaired health status and suboptimal disease control in adults with CAH. Future efforts will focus on enhancing longitudinal data completeness to facilitate benchmarking and improve healthcare provision variations.

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PO67

Lifelong complications and care gaps in congenital adrenal hyperplasia: a scoping review

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Background
Congenital adrenal hyperplasia (CAH) is a rare inherited disorder, usually due to 21-hydroxylase deficiency, causing reduced cortisol and aldosterone production with excess adrenal androgens. Although corticosteroid replacement and new treatments have improved outcomes, people with CAH still experience serious long-term complications. Managing CAH remains complex, with challenges in optimising treatment, preventing adrenal crisis, and enhancing quality of life.
Methods
Following Arksey and O'Malley's scoping review framework, we systematically searched multiple databases, including MEDLINE, EMBASE, and CINAHL, for studies published from 2001 onwards that address CAH-related complications, treatment approaches, and patient outcomes. The search strategy included the MeSH term "Congenital Adrenal Hyperplasia" and its variations, covering both children and adults. We excluded case reports, review articles, and molecular studies. The Rayyan platform was used to record, screen, and organise the articles. Two independent reviewers screened the articles, with any disagreements resolved by a third reviewer.
Results
Of 3,016 records identified after removal of duplicates, 250 studies met inclusion criteria. Most were retrospective ($n = 69$) and single centre ($n = 131$) in design. Research predominantly focused on care provision ($n = 92$), growth and bone health ($n = 63$), metabolic ($n = 61$), cardiovascular ($n = 53$), cognitive and

mental health ($n = 50$), quality of life ($n = 25$), and adrenal crisis and hospital attendance ($n = 18$). Of all, many adverse outcomes were associated with long-term or supraphysiological glucocorticoid exposure. Evidence gaps included limited prospective data ($n = 27$), underrepresentation of non-classic CAH ($n = 67$), uneven geographical distribution with more than half of the studies from US, UK and other European countries, limited use of national ($n = 34$) and international ($n = 9$) registries, inconsistent outcome definitions, and fragmented models of care.

Conclusion

This review provides a comprehensive map of current evidence, clarifies where knowledge gaps remain, and offers practical directions for future research and clinical practice. Improving CAH care requires ongoing multidisciplinary efforts to develop more personalised, safe, and effective management strategies that address the full spectrum of patient needs across the lifespan.

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PO68

Prenatal androgen exposure and its relation to affective behavior and psychological traits in females with congenital adrenal hyperplasia

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Background

Steroid hormones play an important role in shaping behavioral and emotional development. Individuals with Congenital Adrenal Hyperplasia (CAH) experience elevated prenatal and/or postnatal androgen exposure, providing a valuable clinical model to examine how prenatal hormonal variations relate to affective behavior and vulnerability to emotional symptoms. This ongoing study investigates the impact of prenatal androgen exposure on affective behavior, as it has been implicated in psychiatric conditions, for which individuals with CAH show an increased predisposition, and it further examines related psychological characteristics in females with classic and non-classic CAH compared with typically developed controls.

Methods

Participants complete the Approach–Avoidance Task (AAT) and the Monetary Incentive Delay (MID) task during functional MRI. Standardized questionnaires assess reward and punishment sensitivity, personality traits, anxiety, chronic stress, and depressive symptoms, while saliva and blood samples measure hormone concentrations. Behavioral data are analyzed using mixed-effects models, and questionnaire results are compared between groups and associated with behavioral and neural outcomes.

Results

Data acquisition is ongoing. Preliminary results will report group differences in self-reported affective traits and behavioral tendencies, as well as associations between questionnaire measures and behavioral outcomes. We hypothesize that females with classic CAH will exhibit reduced threat avoidance and increased reward sensitivity relative to controls, along with psychological profiles characterized by higher reward responsiveness, altered punishment sensitivity, and elevated levels of anxiety, depressive symptoms, and perceived stress. Females with non-classic CAH are expected to show intermediate patterns.

Conclusion

This study aims to provide a comprehensive clinical and behavioral characterization of affective behavior in females with CAH. Findings may clarify how prenatal androgen exposure and current hormonal status contribute to affective tendencies and psychological vulnerability, offering insights relevant to clinical care in this population.

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PO69

Title: Identification of two novel likely pathogenic NR5A1 variants associated with DSD and infertility in two Kuwaiti families

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Background

Nuclear receptor subfamily 5 group A member 1 gene (*NR5A1*) plays a crucial role in adrenal and gonadal development. *NR5A1* mutations are associated with a wide phenotypic spectrum of differences of sex development (DSD). While, heterozygous inheritance is the prevalent pattern, *NR5A1* dosage significantly influences its biological function.

Case description

We report the first two Kuwaiti families with identifiable *NR5A1* mutations. **Case1:** A 13-years-10-month-old individual, raised as a female, and presented with delayed puberty. Clinical examination revealed Tanner stage 1 breast development, Tanner stage 4 pubic hair, posterior labioscrotal fusion, a 4.5 cm phallus and bilateral palpable inguinal testes (External genital Score was 6.5). Laboratory tests indicated hypergonadotropic hypogonadism, low anti-Mullerian hormone (AMH) and high testosterone levels. MRI pelvis confirmed bilateral small testes at external inguinal rings with no mullerian structures. Karyotype was 46, XY (SRY+). Whole exome sequencing (WES) and Sanger sequencing revealed a novel heterozygote in-frame deletion (c.1070_1075del; p. Gln357_Leu358del). The father, carrying the same mutation, had severe oligospermia and required assisted reproductive techniques (ART) for conception. **Case 2:** A 1-month-old 46, XY infant presented with penoscrotal hypospadias and bilateral undescended testes. Post-human chorionic gonadotropin (hCG) testing indicated an adequate testosterone response. WES and Sanger sequencing revealed a novel heterozygous missense (c.1105G>T; p.Val369Phe) variant in the NR5A1 gene. Although, parents were not genetically tested, the father also had severe oligospermia and required ART. Both cases have normal adrenal functions by ACTH stimulation test and a normal spleen on ultrasound.

Conclusion

Trio sequencing (patient and parents) is crucial to establish inheritance patterns. The broad phenotypic spectrum of *NR5A1* gene mutations within and across families may be related to the epigenetic modifiers or coinheritance of pathogenic variants in different testis/ovarian-determining genes. These findings expand the mutational spectrum of *NR5A1* and highlight the importance of genetic screening in DSD and infertility cases.

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PO70

Luteinizing hormone supression and snoring as predictors of testosterone therapy-induced erythrocytosis in individuals with differences of sex development

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Background

Testosterone therapy (TT) is essential for individuals with Differences of Sex Development (DSD) requiring androgen replacement, but carries the risk of erythrocytosis, which increases cardiovascular and thrombotic risk. Risk factors for TT-induced erythrocytosis in this population remain incompletely characterized.

Objective

To evaluate the prevalence of erythrocytosis and identify clinical and laboratory predictors in a cohort of individuals with DSD undergoing TT.

Methods

This retrospective cohort study included 57 adult individuals with DSD receiving testosterone. Erythrocytosis was defined as hematocrit >50%. Clinical, anthropometric, and laboratory variables were compared between erythrocytosis and non-erythrocytosis groups. Univariate logistic regression was performed to identify predictors of erythrocytosis.

Results

Erythrocytosis was identified in 17 of 57 individuals (29.8%). Groups did not statistically differ in karyotype distribution (despite higher erythrocytosis rate on 46,XX individuals), BMI, age at TT onset, or EPO levels. The erythrocytosis group showed significantly higher absolute reticulocyte counts (P =0.015), reticulocyte percentage (P =0.047), and lower LH levels (0.2 vs. 5.6 mIU/mL,

$P=0.004$), with no difference in testosterone levels. Snoring was markedly more prevalent in the erythrocytosis group (66.7% vs. 16.7%, $P=0.003$). On univariate logistic regression, snoring was the only significant predictor of erythrocytosis ($OR=9.46$; $P=0.007$). Testosterone formulation showed a trend toward significance, with cypionate use more frequent than undecanoate in the erythrocytosis group (88.2% vs. 62.5%, $P=0.064$). Of the 8 patients who underwent polysomnography, 50% were diagnosed with OSAS.

Conclusion

In this cohort of DSD individuals on TT, erythrocytosis prevalence was 29.8%, a rate comparable to that reported in cisgender male cohorts without DSD. Snoring emerged as a strong and independent predictor of erythrocytosis ($OR \approx 9.5$), reinforcing OSAS as a key modifiable risk factor in this population. Deeper LH suppression in the erythrocytosis group suggests gonadotropin axis suppression, highlighting the need for individualized dosing, as testosterone levels alone may not be sufficient. Clinicians should actively screen for snoring and OSAS when managing TT in DSD individuals to optimize treatment safety; LH may further serve as a marker of excessive testosterone dosing in this population.

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PO71

Longitudinal assessment of cardiometabolic risk factors in adults with classic congenital adrenal hyperplasia: influence of hormonal control

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Background

Adults with classic congenital adrenal hyperplasia (CAH) may be predisposed to cardiometabolic complications due to lifelong glucocorticoid (GC) exposure and/or periods of androgen excess. However, longitudinal data extending into adulthood, particularly those regarding of the influence of hormonal control on metabolic outcomes, remain limited. This study aimed to evaluate long-term changes in metabolic risk factors in adults with classic CAH from the transition period to adulthood according to hormonal control status.

Methods

This longitudinal observational study was conducted at a single tertiary referral center. Fifty-nine adults with classic CAH were followed from late adolescence (mean age 18.6 ± 1.5 years) for an average of 14.8 ± 9.2 years; the evaluation of these patients generated a total of 2783 data points for analysis. Hormonal control was classified using serum androstenedione and 17-hydroxyprogesterone levels. Long-term changes and mixed-effects predictors of BMI, fasting blood glucose, HOMA-IR, and serum lipid profile (LDL-c, HDL-c, and triglycerides) were evaluated.

Results

Participants received relatively low GC doses, which declined from 11.2 ± 8.1 to approximately 6–7 mg/m^2/day (in hydrocortisone equivalents) during follow-up. BMI was already increased at baseline (25.4 ± 5.0 kg/m^2) and remained stable throughout follow-up. Mean fasting blood glucose and lipid parameters remained within normal ranges. BMI and age were strong predictors of higher LDL-c and triglycerides, while higher BMI and androstenedione levels were associated with lower HDL-c. BMI was the main determinant of insulin resistance, and HOMA-IR decreased from 3.52 ± 2.95 at the transition period to lower values in later assessments. Higher BMI was also associated with lower mean GC doses, consistent with clinical dose-adjustment practices.

Conclusions

In adults with classic CAH treated with relatively low GC doses, cardiometabolic parameters remained stable across follow-up. Notably, many individuals already entered adulthood with overweight or obesity. Adiposity and age, rather than GC exposure or hormonal control, were the main determinants of metabolic variability, highlighting the importance of early weight-management strategies in this population.

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PO72

When choosing comes later: patient organisation-led insights into delayed decision-making in DSD care

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Background/Aims

In DSD care, clinical guidelines increasingly recommend postponing non-medically necessary interventions until children can participate in decision-making. While this shift reflects important ethical and clinical developments, its practical and psychosocial implications remain insufficiently understood. Patient organisations are well positioned to capture lived experiences across generations and care trajectories. This study explores how decision-making in DSD care is experienced by people with a DSD and parents of children with a DSD, with the aim of identifying what families need when choices are deferred rather than resolved early.

Methods

This qualitative study was initiated and conducted by DSD Nederland, the Dutch patient organisation for people with a DSD and their families. Data were collected through two focus groups (adults with a DSD; parents of children with a DSD) and three additional in-depth interviews (two parents and one child). Focus groups were co-moderated by trained experiential experts from the organisation. Conversations were analysed thematically, with strict anonymity ensured and verbatim quotations used to illustrate participants' experiences.

Results

Participants described delayed decision-making not as the absence of choice, but as an ongoing process requiring continuous guidance. Decisions were experienced as recurring moments rather than single events. Key themes included whether to intervene, timing and age, shame and guilt, the influence of the social environment, openness and disclosure, and the role of parents in navigating uncertainty. Participants also discussed medical examinations and hormonal treatments, access to psychological support, availability of information, peer contact, and the impact of language and diagnostic labels. While postponing interventions was often seen as supporting children's future autonomy, participants emphasised that delayed decision-making can create prolonged uncertainty and emotional burden for families when adequate support is lacking.

Conclusion

From a patient organisation perspective, delaying non-medically necessary interventions shifts, rather than removes, the need for care. Experiential knowledge highlights that delayed decision-making must be accompanied by ongoing communication, psychosocial support, access to peer contact, and careful use of language. Integrating patient-led qualitative insights alongside medical expertise is essential for translating policy changes into meaningful, supportive DSD care.

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PO73

Assessment of quality of life (QOL) in paediatric patients with congenital adrenal hyperplasia (CAH) and parental perceptions in a tertiary care pediatric hospital in a low middle income Asian country

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Background

Congenital adrenal hyperplasia (CAH) is a lifelong endocrine disorder requiring pharmacotherapy, surgical interventions with potential life-threatening complications. This study aimed to assess child- and parent-reported QOL using the Pediatric Quality of Life Inventory (PedsQL) and explore clinical factors associated with QOL.

Methods

A descriptive cross-sectional study was conducted at a pediatric endocrine clinic. Children with CAH and their parents were participated. PedsQL questionnaires were administered to both children and their parents. Statistical analysis included Wilcoxon signed-rank tests for parent-child comparisons and Mann–Whitney U tests to explore associations with clinical variables with Effect sizes.

Results

The cohort included 44 children (22 males), with a median age of 7.2 years (IQR 5–9). Most patients presented in the neonatal period (84.1%), and classic salt-losing CAH was most common (79.5%). Advanced bone age was present in 40.9%, peripheral precocious puberty in 31.8%, and central precocious puberty in 13.6%. Feminizing genitoplasty and hypospadias repair were performed in 38.6% and

18.2% of children, respectively. Children reported significantly higher total PedsQL scores than their parents' proxy reports ($Z = -2.461$, $P = 0.014$, $r = 0.57$), particularly in emotional ($Z = -2.480$, $P = 0.013$) and social functioning ($Z = -2.021$, $P = 0.043$, $r = 0.37$). No significant differences were observed in physical ($Z = -1.875$, $P = 0.061$, $r = 0.28$) or school functioning ($Z = -1.643$, $P = 0.10$, $r = 0.25$). Children with advanced bone age had lower total PedsQL scores compared with those without advanced bone age ($U = 145.0$, $P = 0.033$, $r = 0.32$). Total scores were not significantly associated with CAH type, sex, surgical history, age at presentation, or current grade.

Conclusion

Children with CAH perceived better overall quality of life than their parents' proxy reports, especially in emotional and social domains. Possibly due to low predicted adult height advanced bone age was associated with poorer child-reported QOL. Total scores were slightly higher than those reported in other pediatric populations. These findings suggest that clinical outcomes, rather than demographic or sub-type factors alone, may influence perceived quality of life, highlighting the potential importance of ongoing monitoring and disease management.

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PO74

Aromatase deficiency masquerading as CAH in two 46, XX DSD cases

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Background

Aromatase deficiency is a rare cause of 46, XX disorder of sex development (DSD) resulting from mutations in the CYP19A1 gene. Virilized genitalia at birth often leads to an initial misdiagnosis of congenital adrenal hyperplasia (CAH), delaying the correct diagnosis.

Methods

We report two adolescents with 46, XX DSD initially managed as CAH, both were subjected to through clinical examination, laboratoty investigations (s.cortisol, ACTH, FSH, LH, Estradiol, serum Sodium and potassium), imaging (Both did MRI and one of them underwent laproscopy), and whole exome sequencing for genetic testing.

Results

Case 1: A 14-year-old patient was born with atypical genitalia and initially assigned as male. Initial basal hormonal evaluation revealed slightly elevated 17-hydroxy progesterone, adrenal androgens. Hydrocortisone therapy was started at 4 months for presumed congenital adrenal hyperplasia (CAH). Karyotype later revealed 46, XX with negative SRY. Feminizing genitoplasty was performed at 1.5 years and reassigned as female. At 14 years old, she presented with severe short stature (height SDS: −3 SD), absent pubertal development, markedly delayed bone age (8 years) while she was maintained on very low dose of hydrocortisone (3mg/m^2/day). Hormonal assessment revealed hypergonadotropic hypogonadism, markedly elevated after stimulation (FSH 59.5 mIU/ml, LH 25.6 mIU/ml; low estradiol). Pelvic ultrasound showed an infantile uterus and visible ovaries with normal adrenals. Genetic testing confirmed a mutation in CYP19A1, establishing aromatase deficiency. Hydrocortisone was safely withdrawn and stopped and pubertal induction using estrogen was attempted. **Case 2:** A 15-year-old patient presented at 2 months with atypical genitalia and was initially diagnosed as CAH with subsequent hydrocortisone therapy. She underwent genitoplasty at 5 years old and female sex reassignment at that age. At 13 years old, she had short stature (height SDS: -2.6 SD), absent pubertal development with elevated gonadotropins (FSH 94.15 mIU/ml, LH 32.26 mIU/ml) and very low estradiol (<5 pg/ml). Abdominal ultrasound and laparoscopy failed to visualize the uterus while ovaries were properly detected. Genetic testing established the diagnosis of aromatase deficiency. The patient declined estrogen therapy for pubertal induction and experienced significant psychosocial distress requiring psychiatric support.

Conclusions

These cases highlight the diagnostic challenges of virilized 46, XX DSD, where aromatase deficiency may be initially misdiagnosed as congenital adrenal hyperplasia. Virilized 46, XX individuals without biochemical evidence of adrenal steroid excess, particularly when associated with hypergonadotropic hypogonadism and markedly low estradiol, should prompt reconsideration of the diagnosis and evaluation for aromatase deficiency. Early genetic testing for CYP19A1 is essential for accurate diagnosis, appropriate pubertal induction, and avoidance of prolonged unnecessary glucocorticoid therapy.

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PO75

The clinical presentation spectrum and diagnostic yield in children with gender development disorder: a single-center experience

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Background

Disorders of sex development (DSD) are a heterogeneous group characterized by variations in chromosomal, gonadal, and anatomical sex development. Clinical presentation varies widely, and phenotypic findings during the initial evaluation

Table 1. Distribution of patients' general characteristics according to their karyotype

	Group 46, XY ($n = 186$)	Group 46, XX ($n = 24$)	Group Chromosomal abnormality ($n = 10$)
Age at presentation (Years) (Median (Min.-Max.)	1.7 (0.15–19)	2.8 (0.6–17)	1.82 (0.25–12)
Consanguineous marriage (n, %)	43 (23.1%)	13 (54.2%)	1 (10%)
Maternal virilization during pregnancy (n, %)	2 (1.1%)	-	-
Reason for referral to our clinic			
Suspected genital abnormalities (n, %)	51 (27.4%)	19 (79.2%)	7 (70%)
Isolated hypospadias (n, %)	61 (32.8%)	-	1 (10%)
Undescended testis (n, %)	56 (30.1%)	-	2 (20%)
Primary amenorrhea (n, %)	8 (4.3%)	3 (12.5%)	-
Inguinal hernia (n, %)	7 (3.8%)	-	-
Underdeveloped breasts (n, %)	1 (0.5%)	1 (4.2%)	-
Precocious puberty (n, %)	1 (0.5%)	-	-
Microlithiasis (n, %)	1 (0.5%)	-	-
Absence of the uterus (n, %)	-	1 (4.2%)	-
Dominant phenotype			
Male (n, %)	161 (86.6%)	10 (41.7%)	10 (100%)
Female (n, %)	25 (13.4%)	14 (58.3%)	-
External genital score (Median (Min.-Max.))	10 (0–12)	3.5 (0–8.5)	8.25 (5–10.5)
Penis			
$<$10 mm (n, %)	13 (7%)	6 (25%)	-
10–20 mm (n, %)	17 (9.1%)	6 (25%)	1 (10%)
21–25 mm (n, %)	20 (10.8%)	5 (20.8%)	2 (20%)
26–30 mm (n, %)	20 (10.8%)	6 (25%)	2 (20%)
$>$30 mm (n, %)	116 (62.4%)	1 (4.2%)	5 (50%)
Scrotal fusion			
None (n, %)	23 (12.4%)	10 (41.7%)	-
Posterior fusion (n, %)	4 (2.2%)	5 (20.8%)	4 (40%)
Total fusion (n, %)	159 (85.5%)	9 (37.5%)	6 (60%)
Bifid scrotum (n, %)	51 (27.4%)	8 (33.3%)	5 (50%)
Cardiac (n, %)	70 (37.6%)	2 (8.3%)	5 (50%)
Presence of Müllerian structures (n, %)	18 (9.7%)	20 (83.3%)	6 (60%)
Presence of gonads on ultrasound			
Absent (n, %)	7 (3.8%)	-	-
Ovaries (n, %)	2 (1.1%)	23 (95.8%)	-
Testis (n, %)	175 (94.1%)	-	9 (90%)
Ovotestis (n, %)	-	1 (4.2%)	1 (10%)
Dysgenetic (n, %)	2 (1.1%)	-	-
Diagnosis	Gonadal Development Disorders • Gonadal dysgenesis ($n = 10$) Testosterone Synthesis-Action Defect • 17-beta-hydroxysteroid dehydrogenase ($n = 5$) • Antley-Bixley Syndrome ($n = 1$) • 5-alpha reductase deficiency ($n = 13$) • Complete/Partial Androgen Resistance ($n = 6$) Persistent Müllerian Duct Syndrome ($n = 7$) Noonan syndrome ($n = 2$) Prader-Willi Syndrome ($n = 2$) Down syndrome ($n = 4$) Idiopathic ($n = 136$)	Gonadal Development Disorders • 46 XX Ovotestis ($n = 1$) Androgen Excess • 21-Hydroxylase Deficiency ($n = 15$) • 11 Beta-hydroxysteroid dehydrogenase deficiency ($n = 1$) Rokitansky-Küster-Hauser-Mayer Syndrome ($n = 3$) Idiopathic ($n = 7$)	• 45 X, 46 XY: mosaic ($n = 2$) • mos45,X/46, X+mar SRY+ ($n = 1$) • 47 XXY ($n = 2$) • mos45/46,XY ($n = 1$) • mos45,X-Y/46,X, del(Y)(q11.23)/46,Xi(Y)(q11.23) ($n = 1$) • 46,X, Yqh ($n = 1$) • 46,XX (74%) /47,XXY (26%) ($n = 1$) • 8q21.3q22.1x1, Yq11.223q11.23x2 ($n = 1$)

LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; USG: Ultrasonography.

Table 2. Comparison of cases with and without an identified genetic etiological cause of sexual development disorder among those who underwent genetic testing.

	Genetic CGB (n=71)	Idiopathic CGB (*n*=25)	*P*
Age at presentation (Years) (Median (Min.-Max.))	1.7 (0.5–19)	1.6 (0.25–15.25)	0.207
Consanguineous marriage (n, %)	35 (49.3%)	5 (20%)	0.020
Reason for referral to our clinic			<0.001*
Suspected genital (n, %)	38 (53.5%)	8 (32%)	
Isolated hypospadias (n, %)	3 (4.2%)	13 (52%)	
Undescended testis (n, %)	19 (26.8%)	4 (16%)	
Primary amenorrhea (n, %)	5 (7%)	0 (0%)	
Inguinal hernia (n, %)	6 (8.5%)	0 (0%)	
Underdeveloped breasts (n, %)	-	-	
Precocious puberty (n, %)	-	-	
Microlithiasis (n, %)	-	-	
Absence of the uterus (n, %)	-	-	
Dominant phenotype			0.002
Male (n, %)	47 (66.2%)	25 (100%)	
Female (n, %)	24 (33.8%)	0 (0%)	
External genital score (Median (Min.-Max.))	7 (0–11)	10 (5–11.5)	<0.001
Phallus			0.267
<10 mm (n, %)	8 (11.3%)	1 (4%)	
10–20 mm (n, %)	13 (18.3%)	1 (4%)	
21–25 mm (n, %)	11 (15.5%)	6 (24%)	
26–30 mm (n, %)	10 (14.1%)	3 (12%)	
>30 mm (n, %)	29 (40.8%)	14 (56%)	
Scrotal fusion			0.012**
None (n, %)	20 (28.2%)	0 (0%)	
Posterior fusion (n, %)	6 (8.5%)	3 (12%)	
Total fusion (n, %)	45 (63.4%)	22 (88%)	
Bifid scrotum (n, %)	23 (32.4%)	10 (40%)	0.657
Cord (n, %)	14 (19.7%)	17 (68%)	<0.001
Presence of Müllerian structures (n, %)	29 (40.8%)	4 (16%)	0.045
Presence of gonads on ultrasound			0.008***
Absent (n, %)	3 (4.2%)	0 (0%)	
Ovaries (n, %)	17 (23.9%)	0 (0%)	
Testis (n, %)	50 (70.4%)	25 (100%)	
Ovotestis (n, %)	1 (1.4%)	0 (0%)	
Disgenetic (n, %)	-	-	
Testosterone response a			0.379
Insufficient response (n, %)	14 (31.87%)	4 (18.2%)	
Adequate response (n, %)	30 (68.2%)	18 (81.8%)	

CGB: Sexual development disorder; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; USG: Ultrasonography.

[a] *Cases in which the testosterone response was not evaluated were excluded from this analysis.*

**Isolated hypospadias was significantly more common in the "Idiopathic CGB" group.*

***Complete scrotal fusion was significantly more common in the "Genetic CGB" group, while the absence of fusion was significantly more common in the "Idiopathic CGB" group*

****On ultrasound, the gonads were assessed as ovaries significantly more frequently in the "Genetic CGB" group and as testes in the "Idiopathic CGB" group.*

play an important role in guiding the diagnostic approach. This study aimed to describe the clinical and phenotypic characteristics of DSD cases evaluated at our center and to analyze their distribution according to karyotype. A secondary objective was to evaluate differences between cases with and without an identifiable genetic etiology.

Methods

The clinical data of patients diagnosed with CGB were retrospectively reviewed. Demographic characteristics, clinical findings, and external genital scores (EGS) were recorded. Cases were classified according to karyotype as 46,XY, 46,XX, or chromosomal abnormalities. The distribution of demographic, clinical, and laboratory findings among these groups was evaluated. Final diagnoses were determined based on clinical, biochemical, and genetic assessments. Among cases who underwent genetic testing, differences between patients with identifiable genetic etiologies and those without (idiopathic) were analyzed.

Results

A total of 220 cases were included, with a median age at presentation of 1.8 (0.15–19) years and a median EGS of 9.5. Most patients had a 46,XY karyotype ($n = 186$, 84.5%), followed by 46,XX ($n = 24$, 11%) and chromosomal abnormalities ($n = 10$, 4.5%). The clinical and phenotypic characteristics according to karyotype groups are summarized in Table 1. Genetic testing results were available for 96 cases. Among them, 71 had an identifiable genetic diagnosis and 25 were classified as idiopathic. The median EGS was significantly lower in the genetic diagnosis group (7 vs. 10; $P < 0.001$), and consanguinity was more frequent (49.3% vs. 20%; $P = 0.020$). The presence of Müllerian structures (40.8%) and ovarian detection on ultrasound (23.9%) were also more common in this group ($P < 0.05$). In contrast, isolated hypospadias (52%), complete scrotal fusion (88%), and chordee (68%) were more frequently observed in cases without a genetic diagnosis ($P < 0.05$). Detailed comparisons between groups are presented in Table 2. The overall diagnostic yield of genetic testing was 64%, reaching 69.2% among 46,XY cases.

Conclusions

CGB cases exhibit a broad clinical spectrum. Phenotypic evaluation, particularly the external genital score, may provide important clues regarding the likelihood of identifying a genetic etiology and help guide the diagnostic approach.

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PO76

Parental decision-making regarding sex/gender registration in variants of sex development (DSD)

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Background/Aim

With the introduction of a third sex/gender category ('divers') in German law in 2018, new legal possibilities emerged for individuals whose sex/gender does not align with binary categories. This exploratory study examines how parents of children and adolescents with variants of sex development (DSD) navigate decisions regarding their child's legal sex/gender registration in light of this legislative change, and which factors shape their engagement with this new option.

Methods

Drawing on narrative interviews with parents ($n = 19$), we analyzed parental decision-making regarding sex/gender registration, how parents understand and negotiate these options, and what meanings they attribute to the 'divers' category.

Results

Our preliminary findings reveal substantial variation in how parents approach the registration decision. Some parents view 'divers' as a self-evident choice reflecting their child's bodily reality; others deem it irrelevant to their specific situation, raise concerns about its political implications, or express pragmatic worries about navigating within predominantly binary-structured environments. Several parents view the category as a temporary placeholder for their child's future self-determination, rather than as a fixed identity category. Beyond examining how parents conceptualize the 'divers' category, we also investigated what practical significance, if any, they attribute to it. For some, it appears to shape their conception of expectations about how their child will be perceived and accepted in social contexts. Others, however, approach it as a purely administrative matter, without attributing broader social significance to it. Parental understandings of the 'divers' category vary considerably, reflecting divergent conceptualizations of what the category signifies and what relevance it holds for their situation.

Conclusions

These variations in meaning-making suggest that sex/gender registration decisions involve not merely formal choices, but fundamentally different interpretations of the category's social, legal, and personal significance.

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PO77

Refining the upstream SOX9 regulatory landscape through whole-genome sequencing in 46,XY complete gonadal dysgenesis

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Background

A genetic diagnosis in differences of sex development (DSD) can currently be made in about 30% of patients. New causal genes are reported only sporadically and account for very few cases, suggesting an important contribution of non-coding variants. Precise regulation of *SOX9* is essential for human testis determination, and pathogenic variants in the coding region have been reported in 46,XY gonadal dysgenesis. In addition, copy-number variants affecting distal enhancers upstream of *SOX9* have been described in cases of 46,XY complete gonadal dysgenesis (CGD), suggesting an important role of non-coding regulatory elements.

Methods

We performed whole-genome sequencing (WGS) in a cohort of 16 unrelated individuals with DSD, including 7 with CGD, 1 with partial gonadal dysgenesis, 5 with ovotesticular DSD, and 3 with primary ovarian insufficiency, following negative exome sequencing. Structural variants in the upstream *SOX9* regulatory region were analyzed. The minimal critical interval was refined by integrating previously reported pathogenic variants with public epigenomic datasets, including DNase I hypersensitivity, ATAC-seq, and ChIP-seq data, as well as publicly available single-cell transcriptomic and epigenomic datasets from human gonadal tissues.

Results

Two out of seven individuals with 46,XY CGD were found to carry heterozygous deletions located 644-345kb and 639-500kb upstream of *SOX9*, encompassing the distal enhancer region. Integration with previously reported pathogenic copy-number variants allowed delineation of a shortest region of overlap within the upstream *SOX9* regulatory landscape. Epigenomic annotation of this interval revealed open chromatin and enhancer-associated histone marks, together with strong vertebrate sequence conservation. Integration of single-cell datasets showed that this region corresponds to active enhancer signatures, supporting a role in testis-specific gene regulation.

Conclusions

Whole-genome sequencing identified deletions affecting a distal regulatory region upstream of *SOX9* in individuals with 46,XY CGD. Integration of epigenomic resources refines the candidate cis-regulatory elements within this interval and supports the pathogenic role of non-coding variants disrupting *SOX9* regulation. These findings highlight the importance of analyzing distal regulatory regions in the genetic diagnosis of DSD, particularly in patients with unexplained 46,XY CGD.

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PO78

From X to Y and everything in between: navigating care for patients with 45,X/46,XY mosaicism

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Background/Aims

Individuals with 45,X/46,XY mosaicism vary widely in phenotype, gender identity, and clinical needs, often resulting in disparities in care across different clinic settings. This can lead to variable counseling around gonad management, malignancy risk, fertility, hormone replacement therapy (HRT), gender assessment, and neuropsychological needs. Recent guidelines for individuals with Turner syndrome (TS) do not provide clear direction for this patient population. We aimed to define clinical care practices for patients with 45,X/46,XY mosaicism at our institution, with the goal to inform optimal care.

Methods

We identified patients with 45,X/46,XY mosaicism seen by Endocrinology/TS and/or the Differences of Sex Development (DSD) clinics at Cincinnati Children's from 2019–2025, using diagnostic billing codes. Chart review included clinical services, genital phenotype, gonadectomy status, gonad pathology, HRT, gender counseling, and neuropsychological referrals.

Results

Of 46 patients with 45,X/46,XY mosaicism, clinical services were provided by TS ($n = 22$), DSD ($n = 13$), both DSD and TS ($n = 7$), and Endocrinology ($n = 4$) clinics. Sex assignment and genital phenotype were strong determinants: most with female sex and phenotype were seen in TS clinic, while most with a genital difference were seen in DSD clinic. Gonadectomy was undertaken in 32, at ages ranging from 6 months to 18 years; 10 had surgery after age 10, due to late diagnosis. Three had premalignant/malignant pathology (ages 5, 11, and 12). Half of individuals who underwent gonadectomy were not counseled preoperatively by the DSD team or a team member. Gender counseling was documented for 16 of 46 patients, nearly all within the DSD clinic. Of 23 patients on HRT, 16 received treatment in TS clinic without documentation of gender focused counseling. Neuropsychological evaluation was inconsistent, with only 3 of 21 referrals from the DSD clinic.

Conclusions

Individuals with 45,X/46,XY mosaicism experience a range of clinical care practices straddling services provided by TS/Endocrinology and/or DSD clinics, resulting in variable counseling around gonad management, gender identity, and neuropsychological needs. Standardized triage pathways and integrated care between TS and DSD clinics may improve consistency. Future study of care models across centers is needed to inform updated guidance for optimizing clinical care.

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PO79

Minipuberty hormonal profile in PPP1R12A-related persistent müllerian duct syndrome

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Background

Persistent Müllerian Duct Syndrome (PMDS) is a rare disorder of sex development and maturation characterized by the retention of Müllerian structures during fetal development in individuals with a 46,XY karyotype. It is typically due to mutations in *AMH* or its receptor *AMHR2*.

Case presentation

We report a novel *de novo* heterozygous loss-of-function frameshift variant in *PPP1R12A* (p.Lys197IlefsTer13) identified in a 46,XY neonate presenting with bilateral cryptorchidism and a Müllerian remnant detected on pelvic ultrasound. Hormonal evaluation during the first days of life and mini-puberty revealed expected activation of the hypothalamic-pituitary-gonadal axis and preserved gonadal function: serum Inhibin B : 108pg/mL, AMH: 174.4pmol/l, Testosterone : 1.4nmol/l, and Inhibin B: 259pg/mL, AMH: 342pmol/l, testosterone: 9.2nmol/l, LH: 10.4IU/L, FSH: 19.1IU/L, respectively. However, subsequent assessment suggested the development of secondary gonadal impairment (Inhibin B: 76pg/mL and AMH: 149.8pmol/l at age 10 months). Although in silico analyses predict impaired protein synthesis, the endocrine profile supports a model were *PPP1R12A* gene variant contributes to PMDS primarily through abnormal duct Müllerian development rather than primary gonadal failure.

Conclusions

These findings broaden the endocrine phenotype associated with this syndrome and suggest a role for *PPP1R12A* gene in Mullerian duct rather than gonads development.

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PO80

Progressive gonadal failure in prenatally diagnosed SRY-positive 46,XX testicular DSD: serial hormonal monitoring and multidisciplinary management from infancy to adolescence

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Background

46,XX testicular disorder of sex development (T-DSD) is rare. Most cases present in adulthood with infertility, fewer present at birth with genital ambiguity. SRY-positive cases typically have normal external genitalia and remain undiagnosed until adolescence. Prenatal diagnosis through karyotype analysis enables prospective characterisation and early multidisciplinary planning from birth. Recent I-DSD Registry data suggest gonadal dysfunction begins earlier than previously recognised, but serial quantitative hormonal data during adolescence remain scarce. We aimed to describe the longitudinal endocrine course and progression of gonadal dysfunction in two boys with prenatally diagnosed SRY-positive 46,XX T-DSD followed from birth.

Methods

A retrospective longitudinal analysis of two boys with prenatal diagnosis of a 46,XX karyotype and SRY/ZFY positivity by FISH, confirmed postnatally, with a male foetal phenotype on prenatal ultrasound. Both had normal male external genitalia, no cryptorchidism, and were raised male. Serial assessments from birth included auxological evaluation, Tanner staging, hormonal measurements (LH, FSH, testosterone, inhibin B, and AMH), and tumour markers. Multidisciplinary care involved paediatric endocrinology, neuropsychology, andrology, and structured family counselling.

Results

Both boys entered puberty spontaneously but developed progressive gonadal failure. Patient 1 (current age 15y): Puberty onset 14y. Serial hormones demonstrated rapid Sertoli cell failure (FSH 2.6→14.9→31 IU/L; inhibin B declined from 339 to 18 pg/mL over 14 months), followed by emerging Leydig dysfunction (testosterone 4.0→2.72 mg/L; LH 5.1→9.7 IU/L). Andrological consultation at 14y offered fertility counselling; family declined cryopreservation. Neurocognitive assessment revealed dyslexia and dysgraphia. Patient 2 (current age 12y): Puberty onset 11y, currently Tanner stage PH IV with penile activation. At age 12y showed severe Sertoli failure (FSH 26.9 IU/L, inhibin B declined from 129 to 9.9 pg/mL, AMH declined from 59.5 to 3.90 mg/L) with maintained testosterone (3.23 mg/L). Multidisciplinary counselling provided developmental guidance to family. Negative tumour markers in both patients.

Conclusions

Prenatal recognition of SRY-positive 46,XX T-DSD enables structured multidisciplinary follow-up and informs future management of progressive gonadal failure. Severe Sertoli dysfunction emerges at 12-14y with rapid progression, followed by Leydig dysfunction. These longitudinal data support structured: (1) serial hormonal monitoring from age 11-12y, (2) early fertility counselling by 12-14y, and (3) proactive multidisciplinary care including neuropsychological support.

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PO81

Characterizing the phenotype of 48,XXYY sex chromosome tetrasomy through insights from six clinical cases

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Background

48,XXYY is a sex chromosome tetrasomy with an array of associated findings including cardiac malformations, ventriculomegaly, asthma, tooth and nail differences, radioulnar synostosis, pes planus, endocrinopathies (i.e., hypergonadotropic hypogonadism), cryptorchidism, facial dysmorphisms (i.e., hypertelorism), developmental delays, behavioral concerns, and difficulties with reading and language processing. While sharing commonalities with 47,XXY, Klinefelter Syndrome (KS), 48,XXYY remains a unique condition deserving of dedicated study. As with KS, tall stature and hypergonadotropic hypogonadism are common features in adults with 48,XXYY, though are not generally present in childhood. Instead, childhood presentations of 48,XXYY consist of a heterogenous constellation of symptoms warranting a higher index of suspicion for an underlying genetic condition. Earlier identification through improved access to genetic testing has provided an opportunity to better characterize childhood presentations of 48,XXYY and to open a discussion about indications for genetic testing and development of evidence-based guidelines for patients.

Methods

In our case series of six pediatric patients with 48,XXYY presenting to a pediatric interdisciplinary Differences of Sex Development (DSD) clinic, we describe the unifying and differentiating aspects of their presentations. Information was gathered through retrospective chart review.

Results

There were 6 male patients between the ages of 9 months and 15 years seen in DSD clinic at the University of Utah from 2024-2026. This case series echoes trends observed in other studies, notably the heterogeneity in musculoskeletal and other organ system involvement and the near ubiquity of developmental and behavioral differences. While hypergonadotropic hypogonadism and tall stature are considered hallmark features in 47,XXY, our case series featured 2 patients with spontaneous pubertal development and progression and 1 patient with short stature.

Conclusion

Given the neurodevelopmental manifestations of 48,XXYY, genetic testing in children with relevant developmental concerns could lead to earlier identification, more supportive services, and subspecialty care/surveillance during childhood and adolescence. Furthermore, increased and earlier identification of patients with 48,XXYY will necessitate dedicated guidelines on preventative care and surveillance for this population, comparable to those developed for other sex chromosome aneuploidies such as 47,XXY.

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PO82

Broad spectrum of DSD with NR5A1 variants: challenges to address/confirm mechanisms of variable expressivity and incomplete penetrance

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Background

NR5A1 (SF 1) is a key transcription factor essential for gonadal and adrenal development, and pathogenic variants are a major cause of 46,XY/46,XX differences of sex development (DSD). Despite extensive case series, the broad phenotypic spectrum remains difficult to explain. This has raised interest in mechanisms contributing to variable expressivity and incomplete penetrance, including genetic, epigenetic and regulatory influences, transcript or protein level effects and environmental factors. Many of these are likely tissue specific or dependent on developmental timing, requiring biological material that is often unavailable. We therefore investigated NR5A1 expression in blood from individuals with heterozygous *NR5A1* variants (DSD subjects and asymptomatic carriers) and from wild type controls, to assess whether NR5A1 expression differs in blood, and whether blood is suitable for mechanistic studies.

Methods

We investigated six unrelated families with *NR5A1* variants, who provided blood samples. Total RNA was extracted from EDTA blood (Zymo-Kit Whole Blood), converted to cDNA, and NR5A1 transcript levels were quantified by qPCR using gene specific primers. Clinical information, including DSD severity, was provided in pseudo anonymised form by the clinicians. For each family, we documented variant inheritance, and the phenotypic range among affected individuals and carriers.

Results

Across the six families, individuals carrying *NR5A1* variants displayed variable clinical presentations, from asymptomatic carriers to those with mild or mild or pronounced phenotypic variations. The variants included missense, nonsense, and frameshift changes, frequently inherited from minimally affected relatives. Despite this variability, NR5A1 expression in blood was uniformly low across all groups. qPCR analyses showed no meaningful differences between affected individuals, asymptomatic carriers, and wild type relatives. High Ct values confirmed that NR5A1 is a low abundance transcript in blood, and expression levels did not vary within or between families.

Conclusions

NR5A1 expression in blood is uniformly low and does not correlate with genotype or the clinical severity of DSD in individuals carrying heterozygous *NR5A1* variants. These findings indicate that blood is not a suitable surrogate tissue for investigating NR5A1–related mechanisms underlying phenotypic variability. Mechanistic studies will require access to tissues or model systems in which NR5A1is more robustly expressed and biologically relevant, particularly those reflecting gonadal or adrenal developmental contexts.

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PO83

Why does my infant with CAH need to see a psychologist? The importance of mental health support as part of a multidisciplinary team- case examples

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Background

There is strong support both in research and subjectively for the importance of having a mental health professional as part of a multidisciplinary DSD team.

Methods

Four de-identified case examples will be provided, outlining the types of contributions a psychologist can make to a treatment team.

Results

The role of the psychologist varies greatly depending on many factors. Case 1: newborn with CAH Case 2: young adult with sacral agenesis Case 3: older teen with MRKH Case 4: adult with late-diagnosed CAH

Conclusions

Parents, patients and members of the multidisciplinary DSD team sometimes initially need assistance in understanding what roles a psychologist might contribute to the treatment of individuals with DSD variations across the lifespan. Important functions include processing the diagnosis, encouraging coping with associated stress, education and anticipatory guidance across development, linkage with broader supports, contributing to shared decision making, and providing a mental health perspective to the team's communication.

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PO84

Best interests, worst assumptions? German courts and surgeries on intersex children

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Background

In Germany, §1631e Civil Code allows parents to consent to surgeries that adjust their child's bodily appearance to normative ideals of male or female, provided the surgeries are deemed medically necessary. However, parents' consent requires authorization by a family court. Our research investigates the court decisions taken so far according to §1631e GCC. Previous research on medical treatment of VSC has demonstrated how guidelines refer to social and cultural norms when assigning a gender to an intersex child (e.g., Karkazis, 2020; Kessler, 1990). Our research wants to extend the research on medical interventions on children with VSC to the legal arena.

Methods

Based on a qualitative analysis of 40 unpublished decisions by German courts between 2021 and 2024, we analyze courts' definitions of the best interest of the child by coding the documents openly and independently (Emerson *et al*., 2011) with MAXQDA. After determining key categories, a second round of closed coding using categories deducted from the legal regulations followed.

Results

We have identified seven tropes in the analyzed court decisions: 1) ambigious genitalia challenge a healthy psychosexual development, 2) parental insecurities with a child's genitalia challenge the child's psychosocial development, 3) 'ambigious' genitalia aren't functional for sexual intercourse, 4) Being sexed binarily supports the child in feeling normal, 5) Surgery results are better at a younger age, 6) Early surgeries cause less pain/trauma, 7) Surgeries at a younger age avoid medical complications in the future.

Conclusions

Courts grant permission for surgeries on children with VSC by relying on arguments involving normative standards about a good life. Embodied intersex lives are not considered. We argue that by not considering possible alternatives for people with VSC, courts strengthen the medical role in the management of VSC.

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PO85

Dilemmas of adolescent patient with XY gonadal dysgenesis, trisomy 21 and combined congenital heart disease

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Background

This case report reflects complex management of patient with two chromosomal pathologies and congenital heart disease.

Case presentation

A phenotypic girl was born with signs of trisomy 21 and hypoxemia from non-consanguineous parents. Cardiac evaluation confirmed Ebstein anomaly, ventricular and atrial septal defects, pulmonary artery stenosis and cardiovascular insufficiency. Karyotype revealed 47 XY +21. In pelvic MRI small uterus was seen, but without differentiated ovaries. At the age of 7 streak gonad extirpation was performed, and tissue samples were without signs of malignancy. Patient has also undergone surgery for pulmonary valve dilation at the age of 5, however maintains significant right ventricular outflow tract obstruction. Because of double aortic arch partial compression of trachea and esophagus is also observed. At the moment patient has cardiovascular insufficiency, chronic hypoxemia with associated polycythemia (Hb >18 g/dl, hematocrit >50%) and receives daily aspirin and carvedilol. At the age of 12, osteodensitometry (DXA) showed decreased bone mineral density, with Z-score -2.3 SD. Patient was recommended to use vitamin D3 5000 IU and calcium 250 mg daily. Currently (15 years of age) patient has no signs of puberty, obesity (BMI 30.9 kg/m^2), height corresponds 62. percentile (trisomy 21 charts) and bone age is delayed by 2.6 years. DXA scan reveals osteopenia with Z-scores -2.3 SD (lumbar spine), -2.9 SD (left femur), -2.4 SD (right femur), spinal x-ray shows compression fractures in 12th thoracal and 1st lumbar vertebrae. Despite repeated consultations about initiation of low-dose estrogen replacement treatment that has been recommended by paediatric endocrinologist and gynecologist, it has been postponed by cardiologist because of high thrombosis risk.

Conclusion

Management of patient with multiple serious comorbidities demands multi-disciplinary team and risk-benefit analysis for therapeutical decisions. Treatment with bisphosphonates should be considered in patients with hypergonadotropic hypogonadism and osteopenia with relative contraindications for hormone replacement treatment.

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PO86

Describing the metabolome of sex variability in cultured fibroblasts

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Background/Aims
Sex development at a cellular level involves complex interactions between chromosomal, hormonal, and cellular factors. Differences in sex development (DSD) provide a unique opportunity to explore how different factors influences metabolism. This study aims to investigate metabolic profiles of 46, XX fibroblasts, 46,XY fibroblasts and fibroblasts from DSD individuals. Extensive replication of the fibroblasts will lead to a senescent state of the cells that is characterized by permanent cell cycle arrest, altered morphology, and changes in metabolic activity. This will allow to investigate the effect of population doubling levels on metabolism.
Methods
Skin fibroblasts from 2 individuals with androgen insensitivity, and six 46, XX and six 46, XY fibroblasts are cultured under defined conditions. So far, cells have been harvested at a proliferating state. and intracellular metabolites were extracted using a chloroform/methanol protocols. Metabolomic profiles have been obtained using nuclear magnetic resonance spectroscopy and analysed using principal component analysis (PCA) to identify patterns associated with chromosomal state.
Results
Buffer preparation and metabolite extraction protocols were optimized to yield reproducible intracellular metabolite profiles, minimizing technical variability. Intracellular metabolomic profiling was performed so far on four fibroblast pellets. Principal component analysis (PCA) of these preliminary samples revealed metabolic variability among fibroblast lines at comparable proliferation stages. All cells were in a proliferative state, and none had reached senescence. Two fibroblast lines exhibited tighter clustering, whereas one showed greater intra-line variability, likely reflecting interindividual or donor-specific differences.
Conclusion
This project aims to investigate metabolic commonalities and differences in a human cellular model to better understand variations in sex development. Ongoing work will focus on expanding the NMR metabolomics analysis to additional fibroblast lines and biological replicates, including cells at later proliferation stages and replicative senescence. Furthermore, planned bulk RNA sequencing will allow integration of metabolomic and transcriptomic data to identify pathways associated with sex differences and DSD conditions. These next steps will help to better understand how chromosomal background and cellular aging influence metabolic regulation.

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PO87

Chromosomal differences of sex development involving monosomy X: clinical, hormonal, and cytogenetic characteristics

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Background
There is significant variation in the phenotypic profiles of cases with chromosomal differences in sex development (DSD), including those with a mosaic form of monosomy X in their cell lines. The study aims to describe variations in clinical, hormonal, and cytogenetic findings in cases with chromosomal DSD, particularly those involving monosomy X.
Methods
The study recruited DSD cases from 4 hospitals in our region; cases with mosaic monosomy X were analyzed for clinical data on age, ethnicity, hormonal and cytogenetic results, and the presence of the SRY gene.
Results
Excluding 46,XX DSD cases, the study included 59 DSD cases. Six of these exhibited mosaicism involving a monosomy X cell line. Among them, two were raised as boys (aged 2 and 5.5 years), who carried XX/XO cell lines detected by FISH, and only one had the SRY gene. Their external genitalia scores were 2.5 and 9, respectively. CytoSNP array analysis showed aberrations on chromosomes 3 and X. The remaining four cases (aged 1.7–16.7 years) had a Y chromosome in their cell lines, either XYY, XY, or XXY, and all carried the SRY gene. Two cases of girls presented with clitoromegaly and absence of Müllerian structures with high levels of gonadotrophins. The other two boys were examined due to undervirilized external genitalia.
Conclusion
The study emphasizes the wide variation in clinical findings in cases with mosaic monosomy X, underscoring the complexity of these cases. The findings also highlight the importance of comprehensive clinical, hormonal, and genetic assessment in individuals with DSD to characterize their condition and guide appropriate management accurately.

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PO88

Genetic and clinical analysis of differences of sex development in multidisciplinary clinic: 5-year single-center experience

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Background
Differences of sex development (DSD) encompass a heterogeneous group of congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. DSD have diverse genetic etiologies and overlapping phenotypes. Genetic testing is increasingly integrated into multidisciplinary DSD care, yet real-world diagnostic yield, testing strategies, and clinical impact remain variably characterized.
Methods
We performed a retrospective cohort study of 112 patients evaluated in a multidisciplinary DSD clinic over a 5-year period. Clinical data, referral characteristics, time to diagnosis, and genetic testing modalities were extracted through medical record review. Genetic diagnostic yield and clinical impact were analyzed.
Results
Genetic testing was pursued in 105 patients (93.8%), with an overall diagnostic yield of 45.7%. Yield varied significantly by karyotype, with higher yield among 46,XY patients compared to 46,XX patients (51.9% vs. 13.5%, $P = 0.0002$). Diagnostic yield also differed by testing modality, with highest yields observed for targeted single-gene testing when a specific monogenic condition was suspected, followed by gene panel testing and exome sequencing. Among patients without a known diagnosis at referral who ultimately received a genetic diagnosis, the median time from referral to diagnostic confirmation was 4.4 months. Genetic testing directly informed or altered clinical management in 18.1% of patients ($n = 19$), including diagnostic clarification, modification of gonadectomy or hormone replacement recommendations, changes in surveillance for malignancy or multisystem disease, and changes in sex assignment within a multidisciplinary context.
Conclusions
Genetic testing plays a critical role in the evaluation and management of patients with DSD, with meaningful impact on diagnosis, counseling, and individualized care. Diagnostic yield varies by karyotype and testing modality, underscoring the need for karyotype-informed and phenotype-driven testing strategies and early integration of genetics expertise. Multidisciplinary DSD clinics facilitate timely diagnostic resolution and coordinated care. However, ongoing efforts to standardize testing algorithms, to address barriers to access, and to incorporate evolving genomic technologies and variant interpretation are needed to optimize outcomes. Based on our findings and clinical experience, we propose a genetic diagnostic algorithm for DSD that emphasizes karyotype- and phenotype-guided decision-making to inform the use of targeted vs broader genomic testing.

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PO89

Once daily atumelnant (CRN04894) enables lowering of glucocorticoid doses with sustained androgen reduction in adults with congenital adrenal hyperplasia

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Background

Atumelnant (CRN04894) is a first-in-class, once-daily, oral, selective melanocortin type 2 receptor antagonist in development for the treatment of congenital adrenal hyperplasia (CAH). A 12-week, Phase 2, open-label study (NCT05907291) was conducted to evaluate the efficacy and safety of atumelnant in adults with classic CAH (21-hydroxylase deficiency).

Methods

Participants with morning A4 level ≥ 1.5 times the upper limit of normal were enrolled in 4 dose cohorts of once-daily, oral atumelnant. Cohorts 1-3 (40, 80, or 120 mg at bedtime) maintained stable glucocorticoid (GC) dosing (≥ 15 mg hydrocortisone equivalent) throughout the study. Cohort 4 (80 mg in the morning [AM]) had stable GC dosing (≥ 11 mg/m^2/d hydrocortisone equivalent) prior to screening, and reduced GC dose stepwise to target < 11 mg/m^2/d. The primary efficacy endpoint was change from baseline (CFB) to Week 12 in early morning pre-GC serum A4. Percent CFB in GC daily dose was an exploratory endpoint for Cohort 4.

Results

Thirty-eight participants (55.3% women; mean [range] age 33.2 [20-64] years; mean [range] GC dose 27.1 [20-40] mg/d [hydrocortisone equivalent], median [range] A4 34.2 (4.03-96.19) nmol/l [reference range: women, 1.05-6.98 nmol/l; men, 1.40-5.24 nmol/l]) were enrolled (40-mg, $n = 11$; 80-mg, $n = 11$; 120-mg, $n = 6$; 80-mg AM with GC reduction, $n = 10$). Two participants discontinued, both from Cohort 4 (withdrew consent). At Week 12, median (range) percent CFB in morning serum A4 was: 40-mg, −65.2% (−94.3%, −5.5%); 80-mg, −80.1% (−98.7%, −21.6%); 120-mg, −81.6% (−91.4%, −53.5%); 80-mg AM, −74.9% (−89.7%, −26.6%). In Cohort 4, the mean (SE) percent change from baseline at Week 12 in GC daily dose was −17.6% (9.1%), with 7/8 participants (87.5%) achieving a physiologic daily GC dose at Week 12. In all, 31 participants had ≥ 1 treatment-emergent adverse event (TEAE); none were severe or serious. Sixteen participants experienced TEAEs related to treatment, but none led to treatment discontinuation.

Conclusions

In adults with classic CAH, GC dose reduction did not diminish the atumelnant-induced androgen reduction. Additionally, morning atumelnant dosing resulted in similar A4 reductions as those observed with evening administration. These results highlight the potential for ACTH antagonism to achieve control of androgen levels with physiologic doses of GC replacement.

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PO90

Whole-exome sequencing in girls with anomalies of uterus and/or vagina reveals a spectrum of autosomal dominant disorders

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Background

Congenital malformations of the reproductive organs are characterized by a variety of anatomical variants that lead to functional disorders due to complete or partial organ obstruction, infertility and adverse reproductive outcomes. The etiology of congenital uterine and/or vaginal malformations remains a subject of debate; several studies present data on candidate genes. This study aimed to investigate the genetic basis of uterine malformations in Russian patients.

Methods

A retrospective study was conducted on 108 girls with congenital malformations of the reproductive organs. The cohort included 45 patients with aplasia of the uterus and vagina (Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome: type 1 - 19 patients, type 2 - 26 patients), 38 patients with uterine duplication, and 25 patients with vaginal atresia. Whole-exome sequencing was performed on DNA isolated from peripheral blood (NovaSeq 6000 Illumina). The clinical significance of the identified variants was assessed according to the recommendations for the interpretation of data obtained by high-throughput sequencing methods.

Results

Genetic variants potentially explaining the development of uterine and/or vaginal malformations were found in 17/108 patients (15.7%). In the MRKH group, variants were identified in 12/45 patients (27%), including MRKH type 1 - in 1/19 (5%), and MRKH type 2 - in 11/26 (42%). In patients with uterine duplication, variants were found in 3/38 (8%); these patients had Herlyn-Werner-Wunderlich syndrome. In cases of vaginal atresia, variants were detected in 2/25 patients (8%). Of the 17 genetic variants found, 12 were copy number variations: microdeletions of chromosomes 2q14.3q21.2, 16p11.2, 17q12, 22q11.21, and a microduplication of chromosome 5p13.2. Chromosomal micro-rearrangements were mainly detected in MRKH type 2 (8 cases), as well as in vaginal aplasia (2 cases) and Herlyn-Werner-Wunderlich syndrome (2 cases). In 5 cases, single nucleotide variants were found in the *GREB1L* (2 cases), *WNT4*, *FLT4*, and *POGZ* genes. All identified genetic variants follow an autosomal dominant inheritance pattern, which could potentially lead to the transmission of the uterine malformation to the patients' daughters.

Conclusions

Comprehensive genetic testing of patients with uterine and vaginal malformations is advisable to clarify the etiology and provide a prognosis for planning pregnancy with autologous oocytes.

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PO91

I-HH: longitudinal insights into diagnosis, treatment and fertility outcomes in hypogonadotropic hypogonadism

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Background
Hypogonadotropic hypogonadism (HH) is a heterogeneous disorder of pubertal development with long-term fertility implications. The I-HH registry (SDM Registry Module 4) collects longitudinal international clinical, imaging and genetic data to define phenotype-genotype relationships and evaluate treatment strategies, including sex steroid and gonadotropin therapies. Mini-puberty (neonatal hypothalamic-pituitary-gonadal axis activation) is increasingly recognised as an important early marker for later testicular function. Early hormonal replacement during infancy remains highly experimental and is undertaken in very few specialist centres, necessitating global data collection.

Methods
Registry data to October 2025 were analysed; updated analyses to April 2026 will be presented at the conference. The core registry includes 107 unique patients (66 male; 41 female); 63 patients have detailed longitudinal assessments. We summarised olfactory subtype, genital anomalies, genetics, imaging, hormone therapy and fertility outcomes. The registry has been amended to collect mini-puberty data to assess its role as a severity marker and the impact of early hormonal replacement on later pubertal and fertility outcomes.

Results
Of 107 patients, 51 had anosmic HH and 55 normosmic HH. In the longitudinal cohort ($n = 63$), micropenis was recorded in 10 males; undescended testes in 16 (12 bilateral); orchidopexy in 18. Pathogenic/likely pathogenic variants were identified in 23 patients (predominantly *ANOS1*, *FGFR1*, *PROP1*, *NR0B1*, *CHD7*). MRI abnormalities were common. Testosterone was used in 29 males and gonadotropins in 20 (13 received both). Limited semen data showed marked heterogeneity, both in gonadotropin regimens and spermatogenic response.

Conclusions
The I-HH registry is a powerful platform for longitudinal study of HH. Current data highlight the burden of early genital anomalies and provide substantial genetic diagnostic yield. Diverse therapeutic pathways and variable clinical responses highlight the need for robust evidence to guide hormonal management. Importantly, the registry's forthcoming mini-puberty dataset will inform whether absence of neonatal HPG activation predicts poorer spermatogenic outcomes and whether early, targeted gonadotropin therapy can mitigate that risk. This international registry offers the first realistic opportunity to determine whether early mini-puberty replacement therapy can alter the natural history of HH and enable severity-stratified, personalised fertility management.

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PO92

Estrogen receptor (ESR1) mutation and abnormal gonadal development in a 46,XY male: a case report

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Background
Androgen insensitivity is classically recognised as a sex development disorder (DSD) 46,XY. However, estrogen insensitivity due to a mutation in the estrogen receptor (ESR1) is not included in current DSD classifications, probably due to its rarity and historically centred conception on the role of androgens in male differentiation.

Methods
We present the case of a 15-year-old boy referred for delayed puberty with anorchidism, initially considered to be a simple testicular cryptorchidism.

Results
The patient is the only child of consanguineous parents from Algeria. On examination, he had a marked pubertal delay, short stature, with a height below −4 DS and significant delay in bone age. Genital examination revealed a micropenis, hypoplastic scrotum with no palpable testes. Abdominal and pelvic ultrasound did not identify any testicular tissue, a result that was also confirmed by pelvic MRI. Laboratory testing revealed hypogonadism with hypergonadotrophinemia, with low inhibin B levels The LH-RH stimulation test showed a high oestradiol level reaching 200 pg/mL. Exploration by laparoscopy revealed rudimentary testicular structures. A biopsy of presumed testicular tissue revealed an absence of identifiable testicular tissue and the presence of only an embryonic relic, suggesting a major gonadal developmental anomaly. Genetic testing identified a mutation in the oestrogen receptor gene (ESR1), consistent with oestrogen insensitivity. The patient received androgen replacement therapy, leading to the progressive development of secondary sexual characteristics. Vitamin D supplementation was also initiated in view of the potential impact of impaired estrogen signaling on bone maturation.

Conclusions
Estrogen insensitivity in boys can affect initial sexual differentiation, and can alter gonadal maturation, testicular descent and pubertal progression. This picture suggests the potential involvement of this hormonal pathway in testicular development. These results support the idea that oestrogens play a major role in gonadal development, even in boys, which requires further research.

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PO93

Clinical characteristics and management of children with hypogonadotrophic hypogonadism in a single tertiary centre in Hong Kong

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Background
Hypogonadotropic hypogonadism (HH) results in deficient sex steroid production. Diagnosis, particularly in congenital HH (CHH), remains challenging, and management varies. Gonadotropin therapy is increasingly used to induce testicular maturation and spermatogenesis, though optimal regimens and accessibility remain uncertain. This study described demographics and management of HH in our centre.

Methods
Patients with HH managed at the Hong Kong Children's Hospital from January 2019 to December 2025 were included. Patients with functional/primary hypogonadism or constitutional delay in puberty were excluded.

Results
44 patients were included (59% males, age 16.9 ± 5.1 years); 11 (63.6% males) had CHH and 33 (57.6% males) had acquired HH. Acquired HH was most often due to brain tumour (72.2%), followed by hypoxic brain injury or brain malformation. Among those with CHH, 7 (63.6%) had anosmia/hyposmia with absent/hypoplastic olfactory bulbs on MRI. Three (1.2-3.0 years) presented with micropenis ± undescended testes, while others (15.1-27.3 years) had absent puberty. Genetic analysis revealed known HH-associated variants in 5 (*CHD7, ANOS1, FGFR3*). A pathogenic *ZNF462* variant (Weiss-Kruszka syndrome), recently reported in a Japanese cohort, was identified in a male patient through whole-genome sequencing. Compound heterozygous variants in the *POLR3A* gene, causing 4H syndrome (hypomyelinating leukodystrophy, hypodontia, hypomyelination, CHH) were detected in a female. Pubertal induction began at 15.4 ± 1.9 years for males and 14.5 ± 2.3 years for females. One male completed gonadotropin therapy (rFSH for 4 months, then rFSH and hCG for 17 months). While testicular size increased from 2ml to 8ml, FSH remained <4 IU/L and semen analysis showed oligospermia. Another patient has been receiving combined rFSH and HCG therapy for 15 months with fair compliance, and testes remained at 4-6ml. Intramuscular testosterone and oral estradiol were used in the remaining cohort. DXA among ambulant patients ($n = 26$) showed low BMD in TBLH in 63.6% and in LS in 28.0%.

Conclusion
Genetic analysis enhanced etiologic diagnosis and identified novel CHH variants. Early experience suggests variable response to gonadotropin therapy, but long-term fertility outcomes are yet to be defined. The high prevalence of low bone mineral density underscores the need for ongoing skeletal monitoring in this population.

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Author Index