Phenotype-genotype analysis in patients with GnRH deficiency in a single center

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CONCLUSION: This CHH cohort displays marked clinical heterogeneity including patients with 4H syndrome, CHARGE syndrome and congenital adrenal hypoplasia. We identified mutations in the majority (80%) of cases and those patients without mutations did not exhibit any CHH-associated phenotypes. Exome sequencing is an efficient and effective tool for exploring the complex genetic architecture of CHH.

BACKGROUND: Congenital hypogonadotropic hypogonadism (CHH) results from isolated GnRH deficiency and may present with normal sense of smell (nCHH), anosmia (Kallmann syndrome, KS) or in syndromic forms. Genetic defects are identified in approximately half of CHH cases and oligogenicity is noted in almost 10%. Further, spontaneous reversal of is seen in 15% of patients.

DESIGN: We analyzed the clinical characteristics of 37 Serbian CHH probands (34 sporadic, 3 familial). Genetic testings are available in 15 patients (Pitteloud, Switzerland; Tuttelmann, Germany; Bernard, Canada). Prof Pitteloud group: Genetic analyses of probands were conducted using Sanger (n=4) and exome sequencing (n=11). Rare variants (minor allele frequency <1%) were considered mutations if they were nonsense, frameshift, splice-site-altering variants or missense variants predicted to be deleterious *in silico*.

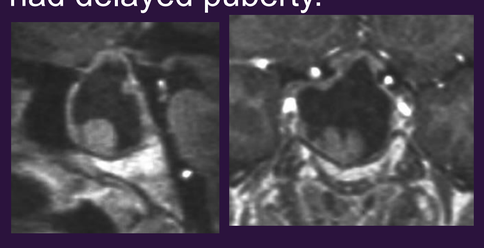
RESULTS: We analyzed clinical characteristics of 37 Serbian CHH probands (34 sporadic, 3 familial; Table 1)

	Kallmann Sy n=11 (30%)	Normosmic HH n=22 (59%)	CHH+Congenital Adrenal Hypoplasia n=1	Sy CHARGE n=1	Leukodystrophy 4H Sy N=2
Age at diagnosis (average, range)	**17.2** 16-22	**23.3 *** 15-50	**16**	**18**	**20**
Age at follow-up (average, range)	**26.5** 19-41	**33.9** 19-79	**19**		**28** 20-32
Familial cases	**1 family**: 2 brothers	**2 families**: brother & sister 5 brothers & sister	**-**	**-**	**-**
Cryptorchidism	4	4	***NR0B1* mutation**	**-**	***POLR3A* mutation**
Cleft palate	-	1	**-**	**-**	**-**

- **Sy CHARGE:** Coloboma / Heart defects / Atresia of choanae / Retarded growth / Genital anomalies / Ear defects
- **Sy 4H:** Hypomyelination / Hypodontia / Hypogonadotropic Hypogonadism

- Renal agenesis, dental agenesis, bimanual synkinesis and hearing loss NOT PRESENT in our group
- Achalasia in one male with reversible nCHH

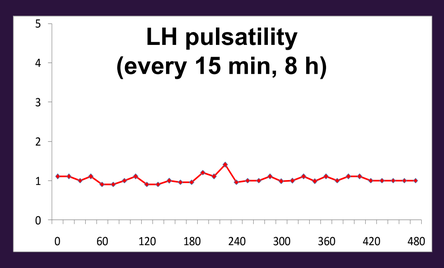
Family1: two brothers with KS and a novel mutation in *FGFR1* gene (heterozygote c-570G>A; *Tuttelmann, Human Genetics, Munster, Germany*). The older brother reversed hypogonadotropic hypogonadism and at age 42 was diagnosed with a pituitary tumor-macroprolactinoma (MRI). Their father had delayed puberty.

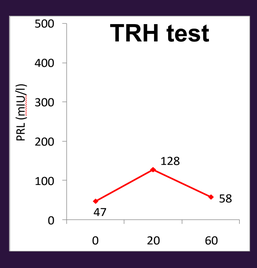


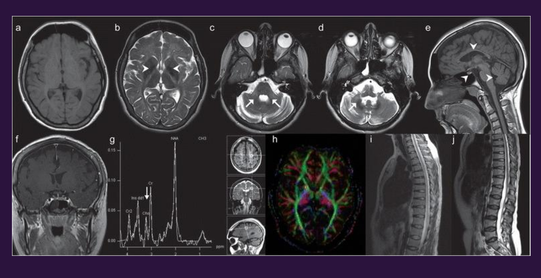
Family 3: a large family with 8 children (5 brothers and 1 sister with nHH and a novel mutation in *FGFR1 g*ene (heterozygote c-1552+1G>A; *Tuttelmann, Germany*). Their mother was the carrier of the same mutation. Two members from this family had cleft palate.

Family 2: brother and sister with nHH. Brother has periodic hypokalemic paralysis and agenesis of septum pellucidum. Exome sequencing revealed **oligogenicity** in brother (heterozygous mutations in ***FGFR1*, *GNRH1*, and *LEP)*** and he is the only patient with oligogenicity (1/11 tested patients). Genetic analysis in sister revealed heterozygous mutation in ***FGFR1***.

Leukodystrophy 4H Syndrome: Additional observations: hypoprolactinemia, thinned corpus callosum, small pituitary gland







MRI scans of the brain of a 20-year-old male patient with 4H Sy

Genetic studies revealed mutations in 11 different loci in 12/15 (80%) unrelated probands

Gene mutation	CHH / nCHH	Associated comorbidities
FGFR1	1 / 2	+ cleft palate; periodic hypokalemic paralysis (*FGFR1+GNRH1+LEP*)
TACR3	0 / 1	+ achalasia
PROKR2	0 / 1	-
SEMA7A	0 / 1	-
SOX10	1 / 0	-
PNPLA6	0 / 1	-
HS6ST1	0 / 1	-
NROB1	0 / 1	+ congenital adrenal hypoplasia
POLR3 A	0 / 2	+ Leukodystrophy 4H Syndrome

REVERSIBLE CHH: Three male reversal cases were noted among the 33 KS/nCHH (10%). Two of three reversal cases were found to carry heterozygous mutations (*FGFR1* and *TACR3,* respectively)

HYPOTHALAMIC-PITUITARY IMAGING (MRI): in 11 patients pituitary MRI scans were normal, while some abnormalities were described in others: pituitary microadenoma (n=5), pineal cyst (n=1), agenesis of septum pellucidum (n=1), agenesis of corpus callosum (n=1), empty sella (n=1), pituitary hypoplasia (n=3), and macroprolactiinoma (n=1, at age 42)

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