A Novel Gene Affecting the Timing of Puberty

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Background - Puberty
• Puberty is the normal developmental stage when reproductive capacity is attained
• Disruptions of pubertal timing affect over 4% of the population
• Deranged pubertal timing has significance for public health in view of the association between early or late puberty and an adverse cardiovascular, metabolic and cancer risk profile1-4

Background – Puberty Genetics
• The timing of pubertal onset has high heritability; 60-80% of variation is determined by genetic factors5 – however, the majority of these factors remain elusive
• We hypothesise that low-frequency, high or intermediate-impact variants will be enriched in populations at the extremes of normal pubertal timing (Figure 1).

CDGP
• Familial Constitutional Delay in Growth and Puberty (CDGP) is a condition of healthy individuals with pubertal onset delayed by more than 2 standard deviations and has repeatedly been shown to cluster in families6
• Our cohort was collected from patients seen under specialist Paediatric care from Finland between 1982-2004
• Cohort contains 403 affecteds from 170 families and their unaffected relatives (total of 910 individuals)

Methods
Enriched sequencing (Namblagen V2 platforms of 52 individuals (7 families) and 37 with CDGP, 15 unafflicted

5 top candidate genes: Targeted sequencing in further 42 families (p=0.08)
1 gene with >1 variant present in up to 9 families
Variants not present in 210 controls
*Gene*

2,985,030 variants Filtered and annotated
64,064 variants Significantly with rare
158 variants (50 genes) V2 only with rare (24 families)
65 variants (22 genes) V2 only without rare (24 families)
64,064 variants
23 variants with >1 family with MAF>1%

References

Conclusions
• We describe a novel, in-house bioinformatic pipeline for identification of novel causal variants from next-generation sequencing data in common, complex traits
• We have identified an exciting new gene implicated in the timing of puberty, which appears to play a role in migration of GnRH neurons towards the hypothalamus during embryonic development.
• We demonstrate potential overlap between simple delayed puberty and hypogonadotropic hypogonadism/ Kallmann syndrome

Figure 3. Pedigrees of six of nine families with CDGP with Gene* variants segregating with trait. Phenotypic symbols listed in the key. Presence of Gene* variant indicated by solid black bar adjacent to individual. Statistical validation shown in blue box.

Figure 4. Schematic of the Gene* protein showing important functional domains with position of CDGP variants (blue) and GnRH deficiency variants (red)

Mouse embryo studies show expression of this gene in the nasal mesenchyme, in the region where GnRH neurons begin their migration to the hypothalamus (Figure 5)

Figure 5A&B. In situ hybridisation demonstrating staining for candidate gene probe (purple) within the nasal mesenchyme adjacent to the vomeronasal organ; 5A mouse E12.5, 5B mouse E14.5. VNO: vomeronasal organ; NS: nasal septum; NM: nasal mesenchyme; GnRH neurons labelled with black arrows

Figure 2. ‘Unbiased’ methodological approach to identify novel candidate genes associated with trait in our cohort of CDGP patients through next generation sequencing and filtering, via in house bioinformatic pipeline (M. Barnes unpublished) and pathway analysis.

Figure 1. Genetics of puberty(1). AAM, age at menarche; CDGP, constitutional delay of growth and puberty; IHH, idiopathic hypogonadotropic hypogonadism; GWAS, genome-wide association studies

Figure 6. Gene* variants with CDGP with six of nine families

Table 1. Variants demonstrating staining for candidate gene probe (purple) within the nasal mesenchyme adjacent to the vomeronasal organ; 5A mouse E12.5, 5B mouse E14.5. VNO: vomeronasal organ; NS: nasal septum; NM: nasal mesenchyme; GnRH neurons labelled with black arrows

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