Nature Reviews Urology **11**, 540 (2014); published online 2 September 2014; doi:10.1038/nrurol.2014.231

PAEDIATRIC UROLOGY

GWAS IDENTIFIES HYPOSPADIAS LOCI

A genome-wide association study (GWAS) recently published in *Nature Genetics* has identified several genomic regions associated with the development of hypospadias, showing that genes with key roles in embryonic development might be implicated in the disorder.

Hypospadias is a common congenital condition, with an incidence of approximately 4.5 in 1,000 newborn boys in Denmark, where the study was conducted. The condition is thought to arise between weeks 8 and 16 of gestation, and manifests as an opening of the urethral meatus on the underside of the penis instead of the tip of the glans. Although surgical revision is the best treatment option, it does not always produce a satisfactory outcome and many patients experience long-term sequelae—including negative genital appraisal, sexual inhibition and erectile or ejaculatory dysfunction in adulthood.

This GWAS was performed on 1,006 patients with hypospadias and 5,486 controls. In the initial study, 12 loci were identified as reaching statistical significance ($P<5\times10^{-8}$). After replication genotyping was carried out on a further 1,972 patients with hypospadias and 1,812 control patients, 18 genomic regions were shown to be significantly associated with hypospadias. Further analysis revealed that these identified hypospadias-risk regions had been associated with tooth development, bone mineral density, blood pressure, prostate cancer and pulmonary function in previous genomic studies. Together, these loci were shown to confer 9% of the liability to develop hypospadias.

Four of the loci identified were close to homeobox genes (*HOXA* cluster, *IRX5*, *IRX6*, and *ZFHX3*), a class of regulatory genes with roles in embryonic morphogenesis and another risk locus was close to the *EYA1* gene, encoding a member of the eyes absent (EYA) family of proteins, which are also involved in embryogenesis. Assessment of the expression of five of the identified genes (*ADK*, *AHRR*, *EYA1*, *HOXA4* and *IRX5*) in the foreskin was carried out using quantitative RT-PCR, and showed a significant increase in the mRNA levels for *HOXA4*, dependent on the number of copies of the hypospadias risk allele at rs1801085 ($P=0.04$), but no other loci reached statistical significance.

Annette Fenner

Original article Geller, F. *et al.* Genome-wide association analyses identify variants in developmental genes associated with hypospadias. *Nat. Genet.* doi:10.1038/ng.3063