# New genetic region responsible for testicle development found

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New research presented today at the European Society for Paediatric Endocrinology meeting has found a genetic region, which may control testicle development in the foetus.

Men have XY sex chromosomes, and the development of testes is thought to occur after upregulation of the testicular SOX9 gene pathway, in the presence of factor SRY on the Y chromosome. However, the mechanism by which this testicular SOX9 upregulation occurs has so far been unclear.

In this study, Dr Jacqueline Hewitt and colleagues from the Royal Children's Hospital Melbourne, Australia, used whole genome mircoarray, and subsequently fluorescence in-situ hybridisation and bioinformatic analyses, to examine the genomes of 30 children with disorders of sex development (DSD). Nine patients had 46,XX testicular DSD (meaning that although they had XX chromosomes, they had developed as males with testicles), while 21 patients had 46,XY gonadal dysgenesis (meaning that although they had XY chromosomes, they had developed as females, without testicles).

In two of the patients with 46,XX testicular DSD, the researchers found a small region, outside of the SOX9 gene, which was duplicated. Bioinformatic analysis of this duplicated region indicated that it contained an SRY/SOX binding motif, meaning the region may be a regulator of SOX9 gene activity and thus involved in testicle formation. The tandem arrangement (i.e. one after another) of the duplications

implies they have either a dosage-related or structural effect on the SOX9 gene. The position of these duplications ties in with previous research in patients with a similar condition, familial 46,XX testicular DSD, which also showed that this chromosome region may be involved in testes development.

These findings address key issues in the complex gene regulation system that controls human sex development, in particular the mechanism by which the SOX9 gene is upregulated and testicles are formed in the embryo. This new gene regulatory region appears to be a missing link in the testis development system, and it is significant that duplications in this region can initiate the development of testicles in a person who has XX chromosomes. Further studies are now needed to ascertain if testis development can be initiated by switching on this region in growing cells and in developmental animal models.

Researcher Dr Jacqueline Hewitt, from the Royal Children's Hospital Melbourne, Australia, said:

"We have known for a while that for testes to form in the embryo, a key gene called SOX9 needs to be activated. However, until now, the mechanism by which this activation occurs has been unclear.

"Our research indicates that there is a gene regulatory region on chromosome 17, upstream of the SOX9 gene, which is involved in the initiation of testicle development in the foetus. This regulatory region is sited a distance away from the SOX9 gene itself, but functions to switch the gene on, allowing the formation of testicles. This illustrates the fundamental importance of not just the actual genes, but also of gene regulation systems in human development. We are only now beginning to understand the mechanisms of gene regulation, which are essential for the development of a complex organism such as a human child. This research significantly advances our understanding of how the testes

develop in the human body."

Provided by European Society for Paediatric Endocrinology