Studying Congenital Human Malformations Caused By Too Many Genes

Dr Heiko Reutter

Scientia
As more is known about copy number variations (CNV), more diseases are found to be associated with abnormally large areas of CNV in one or more genes. Dr Reutter and his co-workers have found that CNV may, in fact, be associated with a variety of birth defects.
and related defects. He connected with the German and Austrian Bladder Exstrophy Support Group and with the Association for the Bladder Exstrophy Community in U.S. and Canada, and reported in new families with bladder birth defects. He reviewed these families’ histories and the literature, and determined that there was a significant genetic predisposition for susceptibility to this defect. He published this research in the American Journal of Medical Genetics in 2003. While continuing to deal with this defect from a clinical standpoint – he’s a paediatrician, after all – Dr Reutter continued to search for a genetic cause. In 2006 Dr Reutter reported in the Journal of Urology an epidemiologic of 238 European families with affected babies. His analysis showed that the problem must be genetic, since such things as paternal age, reproductive history and other exogenic factors seemed to be unrelated to the risk of exstrophy.

For example, in 2011, Dr Reutter and some colleagues published a report in the Journal of Pediatrics of several hundred U.S. and European patients with bladder exstrophy and related abnormalities that correlated various maternal characteristics and the severity of the defect in the baby. It turned out that taking folic acid during pregnancy was related to less severe disease. While exstrophy might be genetic in origin, it looks like there is still something that can be done to positively influence it or prevent it.

He and his co-workers published a number of other clinical papers on families affected with exstrophy, but Dr Reutter decided to expand his research in the American Journal of Medical Genetics in 2003. While continuing to deal with this defect from a clinical standpoint at the centre for rare disease of the University of Bonn. In 1998, he co-founded the German support group for those affected with the exstrophy-epispadias complex.

Looking for Causes of Other Defects… and Finding CNVs

Like bladder exstrophy and its associated conditions, oesophageal atresia with or without tracheoesophageal fistula are anatomical congenital malformations believed to be caused by multiple genetic and environmental factors. These congenital anomalies are rare, but potentially serious. As Dr Reutter investigated exstrophy, he became interested in oesophageal atresia. Sometimes it occurred in patients with exstrophy. Many of the same techniques, both laboratory and clinical, that he uses for exstrophy can be applied to oesophageal atresia. In fact, he and his colleagues recently reported on 375 patients in a combined Dutch, American and German cohort who were investigated with DNA microarray studies. Researchers compared the CNV profiles of the affected individuals with their unaffected parents and published controls and identified 167 rare CNVs containing genes. One CNV had been previously associated with oesophageal disease. There was an association with chromosomes 15, 16 and 22. They published this study this year in the European Journal of Human Genetics, concluding that CNVs could indeed be a cause or contributor to these types of defects. But there is more.

In a report submitted to the Journal of Neurodevelopmental Disorders for publication, Dr Reutter and his group employed molecular karyotyping and genetic analysis on 35 terminated fetuses with isolated central nervous system (CNS) malformations. They detected five disease-causing CNVs in four fetuses involving regions of chromosome 6, 16 and the X chromosome. They also detected a probably disease-causing CNV involving a region of chromosome 3 in one fetus. The conclusion? CNVs are related to CNS malformations, too, adding to data they published last year showing similar findings in patients with CNS abnormalities as well as aneuploid malformations.

So Close Yet So Far

Dr Reutter and his colleagues have made a lot of headway in the last decade unravelling the genetics in a number of birth defects. A promising candidate for some of their questions are CNVs. But there’s more work to be done and more puzzles to be solved. What is certain is, genetics is more than just a 23 chromosomes from each parent. That’s just the start. Be assured, though, that Dr Reutter’s dedication to this important field will lead to more answers as babies continue to be born.

Meet the researcher

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Dr Heiko Reutter was awarded his M.D. from the University of Tübingen in Tübingen, Germany, in 2000. After graduation, Dr Reutter did his residency in Paediatrics and Human Genetics and Fellowship in Neonatology at the University of Bonn in Bonn, Germany. In 2013 he joined the faculty of the University of Bonn in the Department of Neonatology and Paediatric Intensive Care, as well as becoming a Senior Researcher at the Institute of Human Genetics there.

Dr Reutter’s research interests initially included the genetic and non-genetic causes of the exstrophy-epispadias complex. From 2004 until 2010 he had that research turned to research on the genetic causes of oral-clefts. Since 2008 he had expanded his research to anorectal malformations. From 2009 until 2012 he coordinated the European Network for Congenital Uro-Renal Malformations. Since 2011 he is the spokesman of the research centre for rare uro-rectal malformations at the centre for rare disease of the University of Bonn. In 1998, he co-founded the German support group for those affected with the exstrophy-epispadias complex.

REFERENCES


