Genetic insights to vesicoureteric reflux

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UCD researchers in the National Centre for Medical Genetics have carried out a genome scan of 225 Irish families to locate causative mutations in vesicoureteric reflux. Their work, published recently in *Molecular Genetics & Genomic Medicine*, indicates that the condition is even more genetically heterogeneous than previously thought while also highlighting various genes already implicated in urinary tract development.

Vesicoureteric reflux (VUR) is the reverse flow of urine from the bladder towards the kidneys that results from a developmental anomaly in the associated valve mechanism. It is a very common in children but often not detected. It may stop happening as the child grows but can result in kidney damage and ultimately in kidney failure.

The research group, which includes Conway Fellows, Professors Andrew Green and Prem Puri, set out to identify the genes involved in this condition and pinpoint the different mutations that can affect each gene.

By matching the genetic with the clinical presentation (or genotype with phenotype), the team can discover which mutations lead to VUR that clears up spontaneously without medical problems and which ones predispose to the development of reflux nephropathy or kidney damage.

This genetic linkage and association scan used 900,000 markers. The large number of suggestive linkage peaks indicates that VUR is even more genetically heterogeneous that previously imagined.

Several candidate genes are suggested by the results of the study. A peak of dominant linkage was found on chromosome 10q that was also present in a scan of UK and Slovenian families. A recessive linkage peak relating to just three families corresponds precisely to one previously found in a single Somali family and centred on the gene KHDRBS3. There was one association result that stood out because there were 23 adjacent minimally significant markers suggesting involvement of the gene SHOX2.

Describing the results, first author and postdoctoral researcher Dr John Darlow said, "We have already started to capitalise on this study by running nine whole-genome sequences on members of one of these extended families, through which we have identified novel non-coding genetic variants in a homeobox gene cluster that are currently under investigation.

Ultimately, through this study, we hope to better understand the processes by which genetic changes lead to reflux nephropathy so that clinicians can be prevent or alleviate the condition."

More information: J. M. Darlow, M. G. Dobson, R. Darlay, C. M. Molony, M. Hunziker, A. J. Green, H. J. Cordell, P. Puri and D. E. Barton. "A new genome scan for primary nonsyndromic vesicoureteric reflux emphasizes high genetic heterogeneity and shows linkage and association with various genes already implicated in urinary tract development." *Molecular Genetics & Genomic Medicine* 2014, 2(1) 7-29.

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