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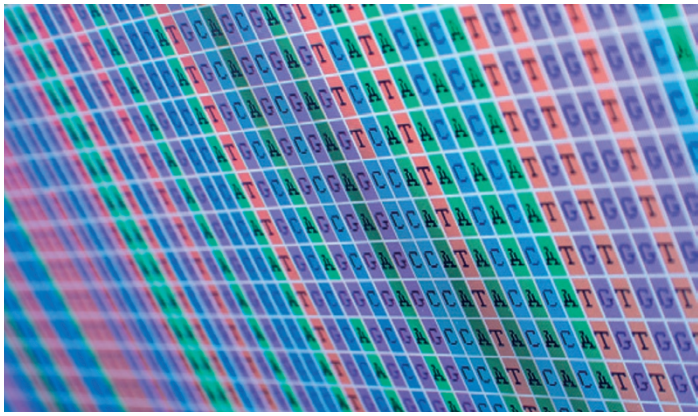
GENETICS

Causative genes identified in rare renal ciliopathies



Carlo Taccari

Renal disease in children is frequently caused by an inherited recessive gene. However, in over 50% of cases, the causative gene has not been identified, meaning that the disease pathogenesis can not be elucidated. Now, a team led by Friedhelm Hildebrant has developed a novel technique to identify these mutations. Using this technique, they identified causative mutations in seven out of ten families diagnosed with nephronophthisis-related ciliopathies.

This project has been in development for some time. More than 5 years ago, the team started to use the whole-exome sequencing approach to identify these recessive genes. "We knew that whole-exome sequencing is a very powerful technique," explains Hildebrandt, "however, whole-exome sequencing carries the severe limitation that, when comparing exome sequence with normal reference sequence, we obtain thousands of genetic variants, although we know that only one single mutation will be the causative one. To overcome this limitation, we have since combined whole-exome sequencing with genetic mapping."

Over 500 families diagnosed with nephronophthisis-related ciliopathies were referred to the team for participation in the study. Of these, sibling pairs with no known primary mutations from ten different families were selected for analysis using the whole-exome squencing technique.

In five of the selected families, recessive mutations in the known ciliopathy genes (*INVS/NPHP2, NPHP4, BBS1, BBS9* and *ALMS1*) were identified. In two of the families, however, the results of the genetic analysis revealed that they had been misdiagnosed. These families had mutations in the known chronic kidney disease-causing genes *SLC4A1* and *AGXT1*, resulting in a change of diagnosis to distal renal tubular acidosis and hyperoxaluria type 1, respectively.

For the other three families, no causative genetic mutation or rearrangement could be identified. Despite this limitation, the technique could have a considerable impact on families such as the ones studied, as Hildebrandt explains: "whole-exome sequencing now allows us to directly arrive at the specific aetiological diagnosis by detecting the causative gene mutation rapidly. This will often save families and patients multiple rounds of diagnostics and a prolonged odyssey in trying to obtain a second and third opinion on the cause of disease."

The techniques used to identify the genetic causes of renal disease in 70% of the families in this study have now been applied to identify novel single-gene causes of chronic kidney disease. Indeed, the team are offering the technique to a wide range of eligible families. "To families worldwide we now offer mutation analysis (and whole-exome sequencing) in causative genes for individuals who manifest with chronic kidney disease in the first two decades of life", says Hildebrandt.

Rebecca Kirk

Original article Gee, H. Y. *et al.* Whole-exome resequencing distinguishes cystic kidney diseases from phenocopies in renal ciliopathies. *Kidney Int.* doi:10.1038/ki.2013.450

Further reading Renal Genes. *A web site coordinating mutational analysis in selected monogenic renal disorders* [online], www.renalgenes.org (2013)