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Editorial

Next Generation Sequencing and Kidney Disease: The New Era

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The decreased cost and increased speed of sequencing has made it possible to use large-scale genomic analysis as a clinical tool. Most of the known diseases–causing mutations occur in exons, which are the coding sequences for functional proteins. This sequencing has facilitated an accurate diagnosis in individuals with disorders that present with atypical manifestations, which are difficult to confirm using clinical or laboratory criteria alone or otherwise require extensive or costly evaluation. Next generation sequencing (NGS) not only enables the detection of new genes and single-nucleotide polymorphisms (SNPs), which have important roles in human disease, but also provides a variety of information about what kinds of functions are associated with genes in these conditions. Genome and exome sequencing is currently indicated for the detection of rare variants in patients with a phenotype suspected to be due to a mendelian (single gene) genetic disorder.

The NGS technology area has helped to discover new genes in a great number of kidney diseases: in autosomal recessive childhood steroid resistant nephrotic syndrome, genes MYO1E (encoding Myosin 1E), CUBN (cubilin), and ARHGDIA (RhoGDI alpha) have been identified [1-3] and variants were found in known or news genes [4], adding to the already listed mutations.

In the large spectrum of the congenital abnormalities of the kidney and the urinary tract (CAKUT), the recessive mutation TRAP1 (in two families with isolated CAKUT and three families with VACTERL association) published in 2013 [5], then thirty three novel heterozygous mutations published in 2014, have been discovered in coding exons of the 17 known dominant CAKUT-causing genes in a cohort of 749 individuals from 650 families [6].The same team found also recessive mutations ingenes involved in the Fraser syndrome or Fraser-related spectrum: FRAS1, FREM2, GRIP1, FREM1, ITGA8, and GREM1, giving phenotypes (some have only isolated CAKUT), according to different mutations (biallelic missense, truncating, etc) [7].

Identifying these genetics abnormalities with these technologies will be in the near future tools to classify, predict, treat and avoid most pathologies: it can determine who will respond to treatment (steroid or cyclosporine for example), predict recurrence of the disease after transplantation, select living donors, help prenatal diagnosis, or make the diagnosis forrelatives. The difficulty is to give a clinical validity to these analytic results: variants can be falsely attributed, as there are thousands of genes tested simultaneously. Variant pathogenicity can be predicted by models that consider a protein's structure and by functional assays. Phenotype may not easily predict genotype and screening all known genes is clinically relevantand may provide useful information. Confirmation or comparison with conventional Sanger sequencing is still needed but willsoon no longer be required. Applications will be everywhere: a new era is opening up.

References

1. Ovunc B, Otto EA, Vega-Warner V, Saisawat P, Ashraf S et al. Exome sequencing reveals cubilin mutation as a single-gene cause of proteinuria. J Am Soc Nephrol. 2011, 22: 1815–1820.

2. Mele C, Iatropoulos P, Donadelli R, Calabria A, Maranta R et al. MYO1E mutations and childhood familial focal segmental glomerulosclerosis. N Engl J Med. 2011, 365: 295–306.

3. Gupta IR, Baldwin C, Auguste D, Ha KC, El Andalousi J et al. ARHGDIA: a novel gene implicated in nephrotic syndrome. J Med Genet. 2013, 50: 330–338.

4. McCarthy HJ, Bierzynska A, Wherlock M, Ognjanovic M, Kerecuk L et al. Simultaneous Sequencing of 24 Genes Associated with Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. 2013, 8: 637–648.

5. Saisawat P, Kohl S, Hilger AC, Hwang DY, Yung Gee H et al. Whole-exome resequencing reveals recessive mutations in TRAP1 in individuals with CAKUT and VACTERL association. Kidney Int. 2013, 85: 1310-1317.

6. Hwang DY, Dworschak GC, Kohl S, Saisawat P, Vivante A et al. Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. Kidney Int. 2014, 85: 1429-1433.

7. Kohl S, Hwang DY, Dworschak GC, Hilger AC, Saisawat P et al. Mild Recessive Mutations in Six Fraser Syndrome–Related Genes Cause Isolated Congenital Anomalies of the Kidney and Urinary Tract. J Am Soc Nephrol. 2014, 25: 1-6.