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GLOMERULAR DISEASE

Frequency of podocyte-related gene mutations in FSGS

Researchers report that genetic testing for *NPHS2* has clinical utility in children with sporadic focal-segmental glomerulosclerosis (FSGS). To determine the frequency of podocyte-related gene mutations in a heterogeneous cohort of patients with biopsy-proven sporadic FSGS ($n = 65$), Karen Weck and colleagues analysed genomic DNA samples for germline mutations in *APOL1, NPHS2*, *TRPC6*, *ACTN4*, *INF2* and *PLCE1*, targeting coding exons in which mutations had previously been reported. "This approach allowed us to interrogate known mutations for all of the genes of interest using efficient state-of-the-art methodology," explains Weck.

The researchers identified known pathogenic *NPHS2* mutations, consistent with autosomal recessive steroid-resistant nephrotic syndrome (SRNS), in two of 27 white children with no clear family history of kidney disease. *APOL1* G1 and/or G2 risk alleles were found in 34 patients (79.5% of African American and 4.8% of white participants). No known pathogenic mutations in *TRPC6*, *ACTN4*, *INF2* or *PLCE1* were identified. However, several nonsynonymous genetic variants of unknown significance (VUS)—including a novel, potentially pathogenic *INF2* variant in an African American adult with late-onset FSGS—were detected.

> "Identifying children with *NPHS2*-related FSGS or SRNS has potential implications for treatment response..."

"As *NPHS2* is associated with autosomal-recessive FSGS, a proportion (likely ~5–15%) of children with apparently sporadic FSGS will actually have an inherited form of the disease," concludes Weck. "Identifying children with *NPHS2*-related FSGS or SRNS has potential implications for treatment response as well as for risk assessment in relatives. By contrast, our results indicate limited clinical utility for testing for autosomal dominant genes (*TRPC6* and *ACTN4*) in patients with sporadic FSGS without a family history." These findings are in contrast to those of previous studies, which suggested a role for systematic genetic testing in adults and children with SRNS without a family history of the disease.

"This study highlights the role of systematic mutation screening in children with biopsy-proven sporadic FSGS, but how this can translate into changes in clinical practice remains undefined," says Weck. She notes that as genomic sequencing becomes widespread, a proportional increase in the detection of VUS will occur, and cautions that the uncertainty of genetic test results must always be considered because a tendency exists to overstate the importance of these variants.

Ellen F. Carney

Original article Laurin, L.-P *et al*. Podocyte-associated gene mutation screening in a heterogeneous cohort of patients with sporadic focal segmental glomerulosclerosis. *Nephrol. Dial. Transplant*. doi:10.1093/ndt/gft532