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GLOMERULAR DISEASE

TRPC6 AND NPHS1 MEDIATE FSGS RISK

Mutations in podocyte genes, such as *NPHS1* and *TRPC6*, have known associations with focal segmental glomerulosclerosis (FSGS) and can elicit variable phenotypes in carriers. Findings from Kar-Hui Ng and colleagues now indicate that interactions between *TRPC6* and *NPHS1* variants account for such variable disease expression and can modify the risk of post-transplantation FSGS.

The researchers sequenced podocyte genes in patients with nephrotic syndrome and identified a *TRPC6* mutation (p.R68W) in one family with hereditary disease. "A kidney transplantation had taken place in this family nearly two decades ago, between a sibling pair both with the *TRPC6* mutation," explains Ng. "There was, however, no indication of FSGS in either the donor or recipient after so long."

The researchers performed patch-clamp experiments in human embryonic kidney (HEK) cells to study the effect of the p.R68W mutation on TRPC6 current amplitudes, which showed it to be a gain-of-function mutation. The effect of this mutation was also verified in immortalized podocytes lacking *TRPC6*. "We later detected two polymorphisms in *NPHS1*—c.294C>T and c.2289C>T—that segregated in the family members with end-stage renal disease," says Ng. "We therefore co-transfected the *NPHS1* polymorphisms with the mutated *TRPC6* in HEK cells to again see the effect on TRPC6 currents." Wild-type *NPHS1* suppressed TRPC6 channel currents independently of the p.R68W mutation but this suppression was lost in the presence of the c.294C>T *NPHS1* polymorphism. The *NPHS1* and *TRPC6* variants were then transfected into HEK cells according to the family members' genotypes, such that each genotype was represented *in vitro*. A notable difference in TRPC6 currents was identified between the transplant donor and recipient. "The difference in TRPC6 currents as a result of *NPHS1* variants might explain the lack of FSGS recurrence in this kidney transplant," proposes Ng. "We now plan to use next-generation sequencing in patients with glomerular disease to identify more genetic variants and to study the interactions between genes using *TRPC6*$^{-/-}$ conditionally immortalized podocytes."

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