ISTOCK

DISEASE GENETICS

Insights into monogenic disease

Pathogenicity in autosomal recessive disease has been classically characterized by the presence of two copies of a mutant allele, which do not influence each other. Now, Tory *et al.* reveal that in steroid-resistant nephrotic syndrome (SRNS), the common variant of the podocin-encoding *NPHS2* gene, p.Arg229Gln, can be pathogenic depending on the presence of specific 3′ mutations in the other *NPHS2* allele.

Individuals who are homozygous for the p.Arg229Gln polymorphism of *NPHS2* do not develop SRNS. By contrast, individuals who carry p.Arg229Gln in addition to a mutation in the other allele of *NPHS2* are affected; however, this genotype (denoted as p.[Arg229Gln];[mut]) is associated with a less severe and later disease onset than that of individuals who are carriers of other known disease-causing variants of both alleles.

As the p.Arg229Gln variant is present at 15× higher frequency than the cumulative frequency of all other known SRNS-related *NPHS2* variants, late-onset disease should be more prevalent than early-onset disease. However, late-onset disease is actually 3.5× less frequent than early-onset disease, which led the authors to ask whether the p.[Arg229Gln];[mut] genotype is disease causing in all carriers.

The authors sequenced the *NPHS2* gene in 129 unaffected parents of affected children and found that 4.7% of the parents were compound heterozygotes for p.Arg229Gln and a mutant allele. This indicates incomplete penetrance of the p.[Arg229Gln];[mut] genotype, which is a rare characteristic in autosomal recessive disorders. In parallel, the researchers also determined which specific mutations in the other allele of *NPHS2* were carried by affected individuals who expressed the p.Arg229Gln variant. In this way, they showed that carboxy-terminal substitutions encoded by the last two exons of *NPHS2*, together with the p.Arg229Gln variant, are exclusively associated with SRNS.

Tory and colleagues also provide a mechanism for their results by showing that correct membrane localization of podocin is abolished when the p.Arg229Gln mutant protein is co-expressed with one of the associated C-terminal mutant proteins. This mislocalization is due to altered dimerization of p.Arg229Gln with the specific C-terminal mutant forms. Conversely, p.Arg229Gln can form functional heterodimers with the wild-type protein with correct subcellular localization, which is consistent with the genetic data.

This study has direct implications on genetic counselling for SRNS and potential implications for other monogenic disorders — the authors suggested that it is “very likely that other polymorphisms may become pathogenic in a very similar mutation-dependent fashion”.

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ORIGINAL RESEARCH PAPER Tory, K. *et al.* Mutation-dependent recessive inheritance of *NPHS2*-associated steroid-resistant nephrotic syndrome. *Nature Genet.* **46**, 299–304 (2014)