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Genetic Epidemiology of Steroid-Resistant Nephrotic Syndrome in Japanese Children

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The majority of children with idiopathic nephrotic syndrome (INS) have minimal change disease (MCD), which is generally responsive to steroid therapy (steroid-sensitive nephrotic syndrome; SSNS). In contrast, approximately 10 to 20 percent of patients fail to respond to steroid, those who constitute a subgroup of steroid-resistant nephrotic syndrome (SRNS). SRNS children often show a renal histology of focal segmental glomerulosclerosis (FSGS), a pattern of glomerular injury representing a final common pathway arising from various etiologies.

Recent genetic studies with childhood to young-adult onset SRNS have shown that approximately one-third is a monogenic disorder, in which SRNS is caused by the defects in one of the 30 SRNS genes. Most of single gene mutations affect glomerular podocyte differentiation and function, thereby suggesting that genetic form of FSGS can be regarded as a “podocytopathy”. However, the molecular causes of other 70-80% of SRNS remain unknown.

To understand the molecular basis of SRNS in Asians, we studied 18 familial childhood-onset SRNS (17 Japanese and 1 Korean), in which NS generally develop at age 2 to 3 years and reach ESRD by age 10. The whole-exome sequencing revealed that five families have novel biallelic mutations in NUP107, a member of nucleoporins (NUP) that constitute the outer scaffold for nuclear pore complexes. Interestingly, all patients shared the identical missense variant of c.2492A>C (p.Asp831Ala). Haplotype analysis revealed that a 412-kb haplotype commonly shared by all five families (four Japan, one Korea), suggesting that c.2492A>C represents a founder mutation in East Asians.

Our results indicate that structure and function of the nuclear pore may be crucial for the development and maintenance of glomerular podocytes. The NUP defects may account for about 30% of Asian children with familial SRNS. Given that nuclear pore complexes are composed of more than 30 distinct subunits and are associated with many regulators and cytoskeletal elements, these nuclear membrane proteins may be more widely implicated in the pathogenesis of SRNS as well as other human genetic disorders than we thought.