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Prevalence of Monogenic Causes in Children with Steroid-Resistant Nephrotic Syndrome

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Objectives : Steroid-resistant nephrotic syndrome (SRNS) is the second most common cause of end stage renal disease (ESRD) in children and mostly associated with focal segmental glomerulosclerosis (FSGS). FSGS/SRNS are highly heterogeneous disease both phenotypically and genetically. To date, multiple monogenic causes of FSGS and/or SRNS have been identified. However, the prevalence of each monogenic gene in a pediatric FSGS and/or SRNS cohort has not yet been extensively studied.

Methods : To figure out the prevalence of monogenic SRNS/FSGS, we conducted a high-throughput exon sequencing analysis for 57 known genes in a Korean pediatric cohort a total of 100 (M:F=53:47) unrelated Korean children, who met one of the following inclusion criteria: 1) steroid non-responsiveness, 2) progression to ESRD and 3) congenital or infantile onset. Patients in whom genetic diagnosis was confirmed previously were excluded in this study. The nucleotide variations detected in the patients were judged to be pathogenic when the variations were 1) previously reported as pathogenic, 2) frame-shifting variations, 3) predicted as disease-causing by in silico analyses.

Results : Pathogenic mutations were detected in 31 patients in 18 genes. Eighteen patients had autosomal or X-linked dominant mutations (PAX2 in 4, COL4A5 in 3, WT1 in 2, MYH9 in 2, INF2 in 2, ACTN4 in 1, TRPC6 in 1, ANLN in 1, ARHGAP24 in 1, and LMX1B in 1), and 13 patients had recessive mutations (ADCK4 in 3, NPHS1 in 2, NPHS2 in 2, CAPN12 in 2, COQ6 in 1, NUP107 in 1, CUBN in 1 and COL4A4 in 1). Mutations were detected in 3 of 16 patients with congenital (n=5) or infantile (n=11) onset. Among 84 patients with onset > 1 year, recessive mutations were detected more frequently in younger children than dominant mutations. In addition, dominant mutations were detected more frequently in patients with proteinuria than in patients with nephrotic syndrome, while recessive mutations showed no difference between two groups.

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Conclusions : Pathogenic mutations were detected in 18 genes in 31 patients, including dominant mutation in 10 genes in 18 patients and recessive ones in 8 genes in 13 patients. The incidence of mutations may not be accurate in children with onset < 1 year because of the exclusion of many of those patients with previous genetic diagnosis by traditional Sanger sequencing method. High incidence of PAX2 mutations and 2 patients with NPHS2 mutations were unexpected findings. Dominant mutations were detected more frequently in patients with older age than recessive ones and those manifesting as isolated proteinuria without nephrotic syndrome. Progression to CKD/ESRD did not correlate with higher detection rate of mutations.

Keywords : Steroid-resistant nephrotic syndrome, Focal segmental glomerulosclerosis