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Molecular genetic analysis of steroid resistant nephrotic syndrome: Detection of a novel mutation.

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ABSTRACT

Background: Nephrotic syndrome is a disorder of the glomerular filtration barrier, a highly specialized tri-layer structure with unique functional properties. Recent advances emanating from the field of molecular genetics have revealed the podocyte as probably the central player in the control of glomerular filtration. More specifically, the cell–cell junction between adjacent podocyte foot processes, namely, the slit diaphragm, has been revealed to be made up of a sophisticated multi-protein complex which dynamically controls foot process architecture via signaling to the actin cytoskeleton. Nephrotic Syndrome (NS) is one of the most common idiopathic primary diseases in childhood. Which is defined as presence of four main symptoms: proteinuria, hyperlipidemia, hypoalbuminemia and edema. According to the patient's response to the steroid therapy the disease divided into: resistant and sensitive groups. About 90% of patients are responsive to steroid therapy during four weeks who called steroid sensitive nephrotic syndrome (SSNS). Patients in whom proteinuria does not stop after about one month are classified as resistant which describe as steroid resistant nephrotic syndrome (SRNS).SRNS is considered as a poor prognostic disease, in which 30-40% of it progresses to end stage renal disease (ESRD), requiring dialysis and transplantation. The most frequent renal histological feature associated with SRNS is focal segmental glomerulosclerosis (FSGS). Moreover minimal change nephrotic syndrome (MCNS), and diffuse mesangial sclerosis (DMS) have been identified. Genetic forms of SRNS are classified as isolated kidney disease or syndromic disorder. The fenestrated endothelium, the glomerular basement membrane (GBM) and the podocytes form three layers of glomerular filtration barrier (GFB) which is impaired in NS and cause proteinuria.

2major proteins of podocytes including nephrin and podocin, coded by NPHS1 and NPHS2, are considered to play an important role in GFB. Mutations in these genes result in altering conformation and stability of podocytes and causing proteinuria and SRNS. Most cases of SRNS are considered as sporadic representing both AR and AD inheritance. NPHS1 and NPHS2 genes are the most common identified genes in AR form.

This study was aimed to screen mutations causing disease within NPHS1 and NPHS2, figuring out the most common mutations in Iranian children and comprising the prevalence of such mutations among different nations. Due to heterogeneity of this disease,

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WES was performed for 10 patients in pilot study to evaluate other related genes and exploring new potential mutations. Indeed, preventing of ineffective treatment with steroids and helping proper clinician prediction in post transplantation outcome may be facilitated via indicating the specific mutations.

Nephrotic syndrome is one of the most common kidney diseases in childhood. About 20% of children are steroid-resistant NS (SRNS) which progress to end-stage renal disease (ESRD). More than 53 genes are associated with SRNS which represent the genetic heterogeneity of SRNS. This study was aimed to screen disease causing mutations within NPHS1 and NPHS2 and evaluate new potential variants in other genes.

Method: In first phase of study, 25 patients with SRNS were analyzed for NPHS1 (exon 2, 26) and all exons of NPHS2 genes by Sanger sequencing. In the second phase, whole exome sequencing was performed on 10 patients with no mutations in NPHS1 and NPHS2.

Result: WES analysis revealed a novel mutation in FAT1 (c.10570C>A; Q3524K). We identified 4 pathogenic mutations, located in exon 4 and 5 of NPHS2 gene in 20% of patients (V180M, P118L, R168C and Leu156Phe). Also our study has contributed to the descriptions of previously known pathogenic mutations across WT1 (R205C) and SMARCAL1 (R764Q) and a novel polymorphism in CRB2.

Conclusion: In summary, this is the first and largest study among Iranian population with different ethnic origins that investigates causative variants associated with SRNS through screening both common genes (NPHS1 and NPHS2) and whole exome study. Among 25 patients who underwent for PCR sequencing for all exons of NPHS2, 5 patients carried a mutation causing disease, suggesting that NPHS2 especially exons 4 and 5 of this gene should be considered as the first step genetic approach in children with SRNS. For the first time in this country, 3 known variant were detected in WT1, SMARCAL1 and CRB2, significantly a novel variant were identified in FAT1 gene.Our study concludes that mutations of exon 4 and 5 NPHS2 gene are common in Iranian and some other ethnic groups. We suggest conducting WES after NPHS2 screening and further comprehensive studies to identify the most common genes in the development of SRNS, which might help in clinical impact on management in patients with SRNS.

Because of the heterogeneous clinical and pathological spectrum, a molecular diagnosis based on sequencing is required. Identification of mutations causing SRNS is of importance, not only for therapeutic considerations but also for genetic counseling.

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