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ORIGINAL ARTICLE

Genetic mutation in Egyptian children with steroid-resistant nephrotic syndrome

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KEYWORDS

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Abstract *Background/Purpose:* Nephrotic syndrome is the commonest etiology of proteinuria in children. Steroid-resistant nephrotic syndrome (SRNS) is defined by resistance to standard steroid therapy, and it continues to be one of the most intractable etiologies of renal failure. Molecular studies discovered specialized molecules in podocytes that play a role in proteinuria. Mutations in *NPHS2* that encodes for podocin constitute a frequent cause of SRNS worldwide. This study aimed to screen for podocin mutations in SRNS Egyptian children and their parents.

Methods: Our study included patients from 10 unrelated Egyptian families diagnosed with SRNS. Mutational analysis of the *NPHS2* gene was performed by polymerase chain reaction amplification of the whole coding region of the gene and direct sequencing.

Results: Positive consanguinity was detected in five cases, and four of them had a positive family history of SRNS in a family member. Mutational analysis of *NPHS2* revealed pathogenic mutations in four cases (40%) including a novel missense in one patient (c.1A>T; p.M1L).

Conclusion: Our study concludes that mutations of *NPHS2* gene are common among Egyptian children with SRNS. We support a model where ethnicity plays an important role in specific *NPHS2* mutations, since a novel mutation was found in one patient in this study. Future study on a large number of Egyptian patients with SRNS is warranted to identify the actual genetic

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contribution of this gene in the development of SRNS in our population, which might help in patients' prognosis and management.

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Introduction

Nephrotic syndrome (NS) is one of the commonest primary kidney diseases, and its progressive forms can end up in chronic kidney disease.¹

NS is the result of an injury to the glomerular filtration barrier and presents clinically with heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Most patients with NS show a good response to steroid therapy and have a good prognosis. On the contrary, approximately 10% of children and 40% of adults are steroid resistant [steroid-resistant nephrotic syndrome (SRNS)], showing no response to steroid therapy and having a poor prognosis.²

The progressive fate of SRNS to end-stage renal disease (ESRD) is seen in 50–70% of patients.³ Inherited structural defects of the glomerular filtration barrier have been detected in isolated as well as familial cases of SRNS.⁴

The pathological picture of focal segmental glomerulosclerosis (FSGS) is revealed in approximately 63–73% of patients with childhood-onset SRNS.⁵

Recent molecular studies involving children with sporadic primary SRNS have described mutations in many genes encoding proteins responsible for the integrity of the glomerular filtration barrier.⁶ These genes include nephrin (*NPHS1*), podocin (*NPHS2*), alpha-actinin 4 (*ACTN4*), CD2-associated protein (*CD2AP*), Wilms' tumor 1 gene (*WT1*), transient receptor potential cation channel 6 (*TRPC6*), and Laminin-beta-2 (*LAMB2*). Proteins encoded by these genes (nephrin, podocin, alpha-actinin-4, an adapter protein anchoring CD2, and others) alter the function of the podocytes.⁷

Mutations of *NPHS1*, *NPHS2*, or *WT1* may be the cause of severe forms of NS in children, progressing to ESRD. Of them, *NPHS2* mutations are considered the most common and are observed in 10–30% of sporadic cases of SRNS with FSGS.⁸ The clinical scope of *NPHS2* mutations has widened, with the proof that mutations in the corresponding gene podocin may lead to NS at birth, in childhood, or in adulthood.^{8,9}

It is recommended to check for *NPHS2* mutations in parallel or prior to starting steroid therapy in NS patients to judge treatment benefits.¹⁰ *NPHS2* mutations were first identified in children with SRNS diagnosed before the age of 6 years who reached ESRD during the first decade of life.¹¹

This study aims to screen for podocin mutations in Egyptian patients with SRNS and compare it with other published series.

Patients and Methods

This study was approved by the Ethical Scientific Committee in the Cairo University Hospital, Giza, Egypt and was conducted in accordance with the university bylaws for

human research. It conforms to the provisions of the Declaration of Helsinki in 2000. All caretakers have given their informed consent.

This study was conducted in the Pediatric Nephrology Clinic, Cairo University Children's Hospital and Genetics Department, National Research Centre. Ten Egyptian children diagnosed with SRNS were included in the study. This study was approved by the Research Ethics Committee of Cairo University Hospital according to the "World Medical Association Declaration of Helsinki", and written informed consent was obtained from the guardians of all patients.

Primary resistance to steroid treatment was defined as the absence of remission to less than a trace of proteinuria on dipstick analysis or <4 mg/m² per hour within the initial 6 weeks of standard steroid therapy.¹²

Patients were included in the study if they fulfilled the following criteria: age group of the patients between 6 years and 16 years, laboratory investigations consistent with SRNS, and patients regularly attending periodic visits and taking prescribed medications. Patients with congenital NS (NS occurring before 3 months of age), cases with secondary NS, and patients with any other medical illness were excluded from the study.

Patients were subjected to detailed history (including demographic data, age at the onset, detailed pedigree construction and analysis with special emphasis on parental consanguinity, similar disease in the family, treatment modalities and response to them, and progression to chronic kidney disease) and careful clinical evaluation (including anthropometric measurements, vital signs, presence of edema or hypertension, and presence of complications).

Information regarding biochemical investigations and, if present, histological diagnosis of NS (renal biopsy) was recorded from the files.

Methods

Genomic DNA was extracted from peripheral blood lymphocytes of the patients and their parents using a standard extraction procedure. The coding region of the *NPHS2* gene (8 exons) were amplified using eight pairs of primers, and the sequence of primers is available upon request from the corresponding author. The primers were designed using PRIMER 3 INPUT SOFTWARE version 0.4.0 (Boston, USA). The coding regions and their exon/intron boundaries of approximately 50 bp sequence were investigated to identify any splice site variation as well. Our standard polymerase chain reaction cycling conditions were as follows: initial denaturation at 96°C for 5 minutes, 30 cycles of denaturation at 96°C for 30 seconds, annealing at 60°C for 30 seconds, extension at 72°C for 30 minutes, and an additional extension at 72°C for 5 minutes. The polymerase chain reaction

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