Review

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Genetic Study of Nephrotic Syndrome in Iranian Children- Systematic Review

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Idiopathic nephrotic syndrome is a heterogeneous disease with a spectrum of age at presentation, phenotype, renal pathology, and response to treatment. Many mutations are recognized to be implicated in sporadic or hereditary forms. The aim of this review was to summarize the results of the genetic studies which have already been carried out in Iran considering their limitations.
A literature search was conducted from March 1970 to September 2015 through MEDLINE, EMBASE, Google Scholar, Google, Iran Medex, Magiran, and SID. Eleven studies were relevant. Three articles were excluded due to insufficient data, duplicated case, and a syndromic nephrotic case without genetic studies. Our results showed that in the southwest of Iran, 80% of the patients had mutations in NPHS1 while in Fars Province, one third showed mutations in NPHS2 when all exons were assessed. In two different studies conducted in one center in Tehran, no mutation was detected in exon 5 but when all exons were studied, more than 65% had hot spot mutation in exon 8 of NPHS2. Interestingly, none of adolescents with FSGS showed mutation in p.R229Q (NPHS2, exon 5). This review revealed that both NPHS1 and NPHS2 were prevalent in Iranian children with SRNS. No mutation of p.R229Q was reported in Iranian adolescent with SRNS.

Keywords: Nephrin; NPHS2 protein; Nephrotic Syndrome; Glomerulosclerosis; Focal Segmental.

Running Title: Genetic Study of Nephrotic Syndrome

Introduction

Nephrotic syndrome is diagnosed via heavy proteinuria, hyperlipidemia, hypoalbuminemia, and edema. The annual incidence is estimated to be 1-3 per 100000 in Europe and USA. The prevalence of steroid resistant nephrotic syndrome in Australia and New Zealand is 10.7 per million children. It is one of the most frequent genetic kidney diseases [1].

The majority of nephrotic children respond to steroid; however, the relapse rate is not low. Almost one third of children who are resistant to steroid progress to the end stage kidney disease after a decade.

Between 1972 and 2011, 20% of 1036 children that presented with nephrotic syndrome in Iran were steroid resistant. Out of the 1036 children

with NS, 604 (~ 60%) underwent renal biopsy. The histopathologic results included focal segmental glomerulosclerosis (42.5%), minimal change (40%), mesangioproliferative glomerulonephritis (10%), membranoproliferative glomerulonephritis (8%), and membranous glomerulonephritis (4%).

Thirty-five out of 1036 patients had congenital nephrotic syndrome while 42.5% of them had diffuse mesangial sclerosis on pathology. The aim of this review was to summarize the results of the genetic studies already done in Iran considering their limitations [2-14].

Genetic study is the cornerstone of decision making for steroid resistant or frequent relapse nephrotic patients. Genetic study is expensive; therefore, a systematic approach is suggested by considering the age at presentation of nephrotic syndrome, associated anomalies, renal pathology, family history, response to steroid, and finally ethnicity to keep specific gene study in priority [15].

Nephrin, podocin, and CD2AP are the main elements of slit diaphragm encoded by NPHS1, NPHS2, and CD2AP, respectively. Moreover, PLCε1, recently called NPHS3 and encoded by PLCE1, is a phospholipase that initiates second messenger regulating cell growth and differentiation.

There is a more complex algorithm for assessment of nephrotic syndrome according to the age at presentation, the pattern of inheritance, being syndromic or non-syndromic, and the renal pathology. If the nephrotic syndrome presents during the neonatal period and renal biopsy reveals radial dilation of the proximal tubules, *NPHS1* must be first assessed. However, in renal pathologies of MCNS or FSGS occurring from birth until childhood, *NPHS2* should be first evaluated, followed by *NPHS1*.

A nephrotic child with diffuse mesangial sclerosis (DMS) must be evaluated for WT1 and PCLE1. The cases of late onset FSGS in adolescents and adults, as well as steroid resistant congenital nephrotic syndrome should be evaluate for *NPHS2* (p.R229Q) in the case of autosomal recessive. Furthermore, in sporadic and autosomal dominant forms of nephrotic syndrome, TRPC6, ACTN4, and INF2 genes should be assessed [15-19].

If the nephrotic patient is syndromic, the following main genes are responsible: transcriptional factors (WT1, LMX1B), glomerular basement membrane components (LAMB2, ITGB4), lysosomal (SCARB2), mitochondrial (COQ2, PDSS2, MTTL1) proteins, and DNA-nucleosome restructuring mediator (SMARCAL1) [19-25].

The aim of this review was to summarize the genetic studies already done in Iran considering their limitations.

Material and Methods

A literature search was conducted from March 1970 to September 2015 through MEDLINE, EMBASE, Google Scholar, Google, Iran Medex, Magiran, and SID. Theses in Iranian medical universities, the abstract books of congresses (international and regional), and even unpublished studies collected from Iranian investigators in English and Persian were also included in this systematic review. Equivalent keywords for nephrotic syndrome, nephrosis, congenital nephrotic syndrome, genetic, and inherited were used. The definition of nephrotic syndrome was nephrotic range proteinuria either more than 2g/day or 40mg/m^2/h, a protein to creatinine ratio more than 1, hypoalbuminemia (serum albumin < 2.5 g/dl), and hyperlipidemia (cholesterol and triglyceride >200 mg/dl). Case reports related to genetic studies were also included. The databases were searched for the mentioned keywords that yielded 50 results in search engines. Then, the search was modified through using the subheading of genetic for children or adolescents. Eleven studies were relevant. Three articles were excluded due to insufficient data, duplicated case, and a syndromic nephrotic case without genetic studies.

Results

Despite the high rate of consanguinity marriages, there is little information about the inheritance pattern of nephrotic syndrome in Iranian children. Table 1 shows a summary of genetic studies already done in different parts of Iran. There was heterogeneity in the studied exons in SRNS.

In the southwest of Iran, 80% of the patients had mutation in NPHS1 while in Fars Province, one third showed mutation in NPHS2 when all exons were assessed. In two different studies conducted in one center in Tehran, no mutation was detected in exon 5 but when all exons were studied, more than 65% had hot spot mutation in exon 8 of NPHS2. Interestingly, none of adolescents with FSGS showed a mutation in p.R229Q (NPHS2, exon5).

Table 1. A summary of genetic study in Iranian children-adolescent with nephrotic syndrome

Authors	Population	NPHS1	NPHS2	others	Method	Exons
Behbahani et al [19] East Azarbijan N=20	SRNS (n=10) Age:30.7m	**8** **5 Hom** **c.1234G>T** (G421C-2) c.512T>A (I171N) c.2126T>G (V709G) c.3478C>T (R1160X) **1 C Hom** **c.1234G>T** **c.3243_3250insG** (G412C V1094fsx1095) **2 Het** c.2548del10 (A8506X87 V1094fsx1095)			PCR South Korea Macrogen Company	All exons of NPHS1
	SSNS (n=10) Age:58.7m	**6** **3 Hom,** G412C V1094fsx1095 **3 Het** c.2126T>G (V709G) c.2548del10) (A850FsX87) V1094fsX1095				
Basiratnia et al [20] Fars N=99 Age= 6.82yrs	SRNS (n=49)		**15** **9 Hom** 353C>T(P118L) 479A>G (D160G) 538G>A(V180M) 555delT(F185fsX186) 714G>T(R238S) **6 Het** 864G>A(A288T) 502C>T(R168C)		PCR	1,2,3,4,5,6,7,8
	SSNS(n=5)		**2 Het** 966C>G(R322G)			
Otukesh et al [21] Tehran N=20	SRNS Age=6.4 yrs		No mutation		PCR	5,7
Fotouhi et al [22] Tabriz	Late-onset FSGS Age=26.6yr	FSGS(n=25) Control(n=35)	No mutation		PCR	5 p.R229Q
Kariminejad et al [23] Tehran N=1	Pierson syndrome			(Hom) Exon 4 C.416TC (LAMB2)		4
Amoli et al [24] Tehran N=1	DMS		**Exon 4** **c.503G>A** **(p.R168H)**			All exons
Behnam et al (unpublished) Tehran	SRNS N=22		**> 65% in Exon 8** **(Hom); (Hot Spot)**			
Basiratnia et al [25] N=1 Fars	Schimke Immuno-Osseous Dysplasia			SMARCAL1 Missense Hom c.1682G>A (R561H)	NA	

FSGS: Focal Segmental Glomerulosclerosis; DMS: Diffuse Mesangial Sclerosis; SRNS: Steroid Resistance Nephrotic Syndrome; SSNS: Steroid Sensitive Nephrotic Syndrome; Hom: Homozygot; Het: Heterozygote

Discussion

This review revealed that both NPHS1 and NPHS2 were prevalent in Iranian children with SRNS. No mutation of p.R229Q was reported in Iranian adolescents with SRNS. In a 10-year survey of genetic renal diseases in New Zealand and Australia, steroid resistant nephrotic syndrome was the second most common congenital renal disease with a prevalence of 10.7 per one million children [1].

The study of NPHS2 in 338 patients revealed heterogeneity with a 43% mutation rate for familial and 10.5% for sporadic SRNS. Double mutation was associated with early onset SRNS and the heterozygote presented late. Pathogenic *NPHS2* mutations are restricted to severe early-onset SRNS and lack of recurrence of proteinuria after renal transplantation. Heterozygous NPHS2 mutations, sequence variants, and polymorphisms may play a role in atypical cases of SRNS with a later onset, mild clinical course, and recurring disease after renal transplantation [16].

A study by Abid et al on 145 children with nephrotic syndrome showed a low mutation rate in NPHS1 and NPHS2 in Pakistan [26].

An unpublished study by Behnam et al revealed hot spot mutation in exon 8 of NPHS2 in children with SRNS.

The importance of genetic study in those who are either frequent replacer or resistant is to avoid unnecessary immunosuppressive drugs that have short and long term side effects. Up to now, it has been shown that immunosuppressive therapy is of no value in patients with *NPHS1, NPHS2, WT1, and TRPC6 mutations.* Utilizing new generations of gene sequencing would improve the investigation and make the results more valid.

Some known players, such as *NPHS1* and *NPHS2,* with important roles in molecular mechanisms of nephrotic syndrome are subject to molecular analysis worldwide. On the other hand, improving access to updated nephrologists at reasonable costs and the inconvenience associated with traditional face-to-face comprehensive genetic and clinical consultations may be considered as a golden goal. There is limited published literature on genetic bases and variations in patients with nephrotic syndrome, including the congenital form, and in adults with focal segmental glomerulosclerosis (FSGS). The reports indicate that genomics in renal clinic is an effective modality in translating nephrogenetics for clinical practice [27]. To our knowledge, there are only eight pediatric studies in Iran reporting some genetic variations associated with nephrology consultations for the patients and their families. However, parallel to the increasing number of known genes involved in nephrotic syndrome, the results of our study also showed an increasing number of genetic studies for comprehensive pediatric nephrology and genetic consultations in Iran. With regard to the diagnosis, a wide spectrum of kidney problems including all subtypes of nephrotic syndrome has been covered in these recent studies. The children with corticosteroid-resistant congenital nephrotic syndrome comprised the majority of the patients who mostly benefited from nephrogenetic studies. Our recent unpublished data has revealed variations in the *NPHS2* gene as a hot spot in its exon 8 detected in > 65% of consanguineous cortico-steroid resistant CNS and FSGS cases.

Limitations

Emerging clinical genetics and research on highly prevalent complex illnesses (e.g., nephrotic syndrome) has been promising wider diffusion of genomic medicine in the past decade which has also been in need of educating physicians in this discipline. Moreover, molecular genetic tests are unavailable, expensive, and unaffordable for patients. Fortunately, a complete panel of Next Generation Sequencing (NGS) is available nowadays in 2016 to cover a full sequence of Nephrin, Podocin, ACT4, etc. in any child suspicious to have nephrotic syndrome.

Conflict of Interest

None declared

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None declared

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