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NPHS2 Gene Polymorphisms in Sporadic and Familial Focal Segmental Glomerulosclerosis

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Introduction

- NPHS2 gene variants are found in 5% to 30% of patients with Focal Segmental Glomerulosclerosis (FSGS), and are associated with corticosteroid-resistant nephrotic syndrome (SRNS).

Objectives

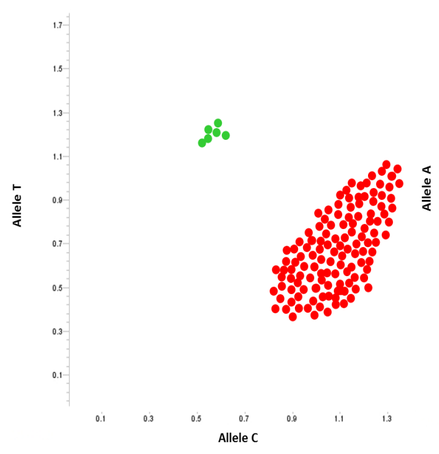
- The objective of this study was to determine the prevalence of NPHS2 variants in patients with FSGS in their familial and sporadic forms.

Methods

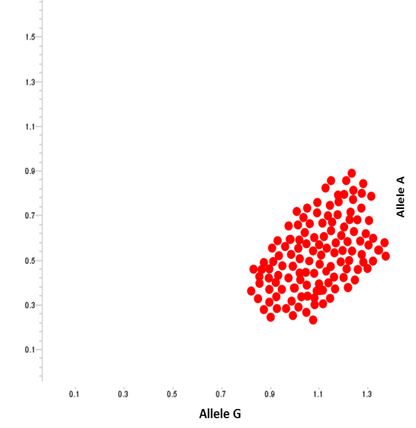
- The sample consisted of 40 children and 70 adults diagnosed with FSGS confirmed by renal biopsy. Age at disease onset, presenting renal syndrome, renal function, steroid resistance, and clinical outcomes were evaluated. Genotyping for the three single nucleotide polymorphisms (SNPs) was performed by real-time polymerase chain reaction (RT-PCR). Two polymorphisms were found in exon 5 - p.R229Q (rs61747728) and p.A242V (rs61747727), and one in exon 3 - p.R138Q (rs74315342). Gene variants were correlated with ethnicity, clinical presentation, treatment response, and renal outcomes.

Results

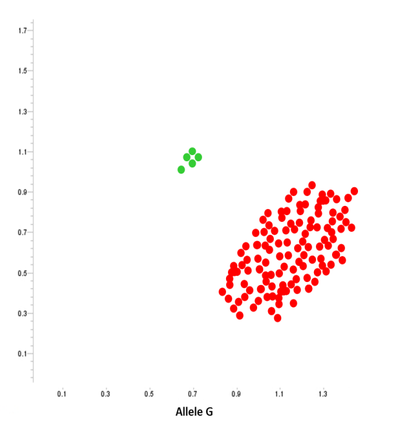
- Among children, variants were detected in only 2 (5%) with sporadic FSGS: p.R229Q in one and p.A242V in another. No children with familial FSGS carried variants. Among adults, variants were present in 9 patients (12.9%), all with sporadic FSGS: 4 had p.R229Q and 5 had p.A242V. No patient had the p.R138Q variant (Figure 1).
- Laboratory parameters at baseline and at the end of follow-up are presented in Table 1.
- All patients carrying the p.R229Q variant were white, while 67% of carriers of the p.A242V variant were black. Besides that, there was a tendency for higher proteinuria at the end of follow-up (p=0.06) in cases carrying a variants.
- In relation to ethnicity, 17% of African descendants had variants against 8% of Caucasian patients (p=0.184).
- Comparing prolonged cyclosporine use (> 3 years) between patients with variants (n=4, 36.4%) and those without variants (n=17, 17.2%), there was no statistical difference between the groups (p=0.124).



p.A242V variant Green samples, C/T heterozygous. Red samples, C/C homozygous.



p.R138Q variant. All samples have the homozygous G/G genotype.



p.R229Q variant Green samples, G/A heterozygous. Red samples, G/G homozygous.

Figure 1. Amplification plot of samples analyzed for the three variants.

Table 1. Laboratory parameters at baseline and at the end of follow-up

	Children (n=40)*		Adults (n=70)	
	Baseline	Final	Baseline	Final
Creatinine (mg/dL)	0.8(0.6-1.3)	0.83 (0.48-2.8)	1.3(0.9-2.0)	1.87(1.07-4.35)¶
Nadir creatinine	0.22	0.16	0.45	9.33
Peak creatinine	2.0	7.0	9.3	17.4
eGFR (ml/min/1.73m^2)	89(46-120)	88 (42-115)	62.5 (31.5-103)	37(14-76)#
Nadir eGFR	27	8	7	3.4
Peak eGFR	154	125	151	167
Urinary protein excretion, 24-hour (g), or PCR	6.0(4-13.7)	0.22(0.1-1.1)§	4.17(1.8-7.1)	0.97(0.12-2.1)§
Serum albumin (g/dL)	2.4(1.8-2.9)	4.2(3.5-4.5)§	3.3(2.2-4.0)	4.2(3.8-4.5)§

*Data refer to non-transplanted patients. Values expressed as median and interquartile range. eGFR: estimated glomerular filtration rate; PCR: protein/creatinine ratio in spot urine.
¶p=0.072 (baseline vs. final); #p<0.001 (baseline vs. final); §p<0.001 (baseline vs. final).

Conclusions

- In these patients with familial or sporadic FSGS, the prevalence of p.R229Q and p.A242V variants in children was 5% and in adults 12.9%; no patient presented the p.R138Q variant. There was no association between the presence of NPHS2 variants with ethnicity or dependence on immunosuppressive treatment with cyclosporine.