

# **COMPLEMENT GENE VARIANTS DETERMINE THE RISK OF PROGRESSION TO KIDNEY FAILURE IN C3 GLOMERULOPATHY**



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## **INTRODUCTION AND AIMS**

C3 glomerulopathy (C3GP) is a recently described disease with a high risk of progression to end stage renal disease<sup>1</sup>. There is insufficient translation of genetic findings into the daily care of patients with C3GP. Our aim is to detect novel genotype-phenotype correlations in patients with C3GP.

#### METHODS

A total of 67 patients [36 male, 31 female, mean age: 36±15 years, median follow-up time of 24 (IQR: 14-56) months] with kidney biopsies that fulfilled criteria for C3GP were enrolled in the study. Genetic studies to search for mutations in the genes coding for complement factor H (CFH) and I (CFI) were performed in 17 of these 67 patients. Of the 67 patients with C3GP, 27 were assigned to mycophenolate mofetil (MMF)-based treatment, 23 to non-MMF-based treatment (prednisolone or cyclophosphamide) and 17 to conservative care. The study groups were similar regarding age, sex, follow-up time, blood pressure, hemoglobin, serum creatinine, C3-, C4- complement levels, and eGFR at the time of diagnosis, and were compared with regard to primary endpoints defined as: 1) kidney failure (category G5 CKD); 2) eGFR decline  $\geq$ 50% from the baseline value.

RESULTS					
$C_{\text{opt}} = b_{\text{opt}} = b_{$	His402Tyr (384)	FH	YNQNHGRKF Disease Risk		

Genetic abnormalities of CFH and CFI genes were detected in 16 (94%) and 4

(24%) out of 17 patients, respectively. We observed a higher frequency of the Y402H (MAF: 0.32) and V62I (MAF: 0.21) CFH alleles in C3GP patients compared

with controls from the ExAC data set. Overall, 18 (27%) patients reached the

primary endpoint after a median time of 24 months. The number of patients,

who reached primary endpoint were similar among the treatment groups [MMFbased group: 8/27 (29.6%), non-MMF-based group: 4/23 (17.4%), and conservative care group: 6/17 (35.3%) (p= 0.413)]. C3GP patients with CFI mutations (c.907G>A; c.913G>T) primary endpoint (75% vs 23%) and kidney

failure (75% vs 15%) were observed in significantly higher rates compared to

patients without CFI mutations (p=0.05 and p=0.02, respectively). The [c.907G 4

A;c.913G 4 T] mutation involves the substitution of Glu303Lys followed by the

Nucleotide:	c.1204C>T	Mutation Type:	Disease Risk Polymorphism		
Alternative Syntax:	Tyr405His T1277C 1277C>T 1277C>T	Condition:	AMD		
Domain:	SCR 7	Phenotype:	U		
Position:	C ()	Ref Type:	Full		
Comments:	(Neumann 2003). (Caprioli 2003). This polymorphism has been strongly associated with AMD (Age-Related Macular Degeneration). The Major allele (tyrosine) is seen in normal populations at 54%. 94% of patients with AMD were found to have the histidine allele. (Haines et al 2005). (Edwards et al 2005). (Klien et al 2005). (Hageman et al, 2005). This has also been associated with MPGN linkage studies (Abrera-Abeleda et al, 2006).				
<b>Val62Ile</b> (44)	FH SLGNVIMVC				
Nucleotide:	c.184G>A	Mutation Type:	Disease Risk Polymorphism		
Alternative Syntax:	Val44Ile G257A G257A	Condition:	AMD		
Domain:	SCR 1	Phenotype:	U		
Position:	S ()	Ref Type:	Full		
Comments:	Associated with AMD <u>(Hageman et al, 2005)</u> . Associated with MPGN (Abrera-Abeleda et al, 2006).				
F 0070 4					
[c.907G>A; c.913G>T]		FI	VAQEETEIL		
Nucleotide:	[c.907G>A; c.913G>T]	Mutation Type:	Missense		
Alternative Syntax	:	Condition:	FI Deficiency		
Domain:	Linker Region 5	Phenotype:	I		
Position:	-	Ref Type:	Full		

change from Glu305 to a premature stop codon.

Comments:

Glu303Lys substitution and Glu305Stop substitution on the s ame alelle

#### CONCLUSIONS

Immunosuppressive treatment was not superior to conservative care in delaying the progression of C3GP. However, patients with

CFI mutations have a higher risk of disease progression suggesting the existence of different pathogenetic mechanisms that lead to kidney failure. This CFI [c.907G 4 A;c.913G 4 T] mutation may produce a truncated polypeptide without the SP domain that is not detected in patient plasma.<sup>2</sup>

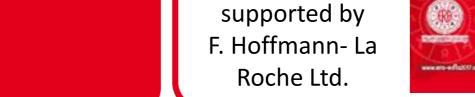
### REFERENCES

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DOI: 10.3252/pso.eu.54ERA.2017





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