GENETIC PREDICTORS OF RENAL SURVIVAL IN ALTERNATIVE COMPLEMENT PATHWAY ASSOCIATED GLOMERULOPATHIES

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INTRODUCTION AND AIMS

C3 glomerulopathy (C3GP) and atypical hemolytic uremic syndrome (aHUS) are the main alternative complement pathway associated glomerular diseases (ACPAG). The aim of this study is to detect disease-causing variations and their correlation with phenotype in patients with ACPAG.

METHODS

Patients were screened for genetic variations encoding sequences of complement factor H (CFH) and I (CFI) genes. Mutations were sought by Sanger sequencing. Baseline platelet, serum creatinine, LDH and proteinuria (g/day) levels and change of these levels during the follow up were evaluated. Complete remission was defined as proteinuria <0.5 g/24h and an eGFR of ≥60 mL/min per 1.73 m^2 (or a return to ±15% of baseline values in those with eGFR <60 mL/min per 1.73m^2). Partial remission was defined as a proteinuria reduction of >50% (and a proteinuria value of <3.5 g/day in patients with nephrotic range proteinuria at baseline), plus stabilization (±25%) or improvement in renal function. In addition to these criteria, aHUS patients in remission were required to achieve normalization of both platelet count and LDH which was sustained for at least 2 consecutive measurements that span a period of at least 4 weeks.

RESULTS

Genetic abnormalities of CFH were detected in 17 of 19 (89%) patients and 22 of 23 (96%) patients with C3GP and aHUS, respectively. CFI genetic abnormalities were detected in 4 (21%) and 7 (30%) patients with C3GP and aHUS, respectively. Y402H CFH allele was the most common variation and the frequencies of this allele in C3GP (MAF: 0.32) and aHUS (MAF: 0.39) patients were similar to controls from the ExAC data set. Complete and partial remission rates were 16% (n=3) and 26% (n=5) in C3GP, and 35% (n=8) and 13% (n=3) in aHUS groups, respectively (p=0.29). During the follow up, 6 (31%) patients with C3GP and 12 (52%) patients with aHUS progressed to ESRD (p=0.18). Genetic variations in CFH gene did not significantly affect the progression to ESRD in all patients. In C3GP group, patients with E303K CFI allele progressed to ESRD more frequently (75% vs 20%, p=0.03).

His402Tyr (384)		FH	YNQN**H**GRKF
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).		

[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
Comments:	Glu303Lys substitution and Glu305Stop substitution on the s ame alelle		

CONCLUSIONS

Complement related genetic variations were frequently detected in patients with ACPAG. Regarding genotype-phenotype correlations, CFI mutations in C3GP could be of help to monitor disease activity and personalize treatment.

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