Elevated factor H-related protein 1 and factor H pathogenic variants decrease complement regulation in IgA nephropathy

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IgA nephropathy (IgAN), a frequent cause of chronic kidney disease worldwide, is characterized by mesangial deposition of galactose-deficient IgA1-containing immune complexes. Complement involvement in IgAN pathogenesis is suggested by the glomerular deposition of complement components and the strong protection from IgAN development conferred by the deletion of the *CFHR3* and *CFHR1* genes ($\Delta_{CFHR3\text{-}CFHR1}$). Here we searched for correlations between clinical progression and levels of factor H (FH) and FH-related protein 1 (FHR-1) using well-characterized patient cohorts consisting of 112 patients with IgAN, 46 with non-complement-related autosomal dominant polycystic kidney disease (ADPKD), and 76 control individuals. Patients with either IgAN or ADPKD presented normal FH but abnormally elevated FHR-1 levels and FHR-1/FH ratios compared to control individuals. Highest FHR-1 levels and FHR-1/FH ratios are found in patients with IgAN with disease progression and in patients with ADPKD who have reached chronic kidney disease, suggesting that renal function impairment elevates the FHR-1/FH ratio, which may increase FHR-1/FH competition for activated C3 fragments. Interestingly, $\Delta_{CFHR3\text{-}CFHR1}$ homozygotes are protected from IgAN, but not from ADPKD, and we found five IgAN patients with low FH carrying *CFH* or *CFI* pathogenic variants. These data support a decreased FH activity in IgAN due to increased FHR-1/FH competition or pathogenic *CFH* variants. They also suggest that alternative pathway complement activation in patients with IgAN, initially triggered by galactose-deficient IgA1-containing immune complexes, may exacerbate in a vicious circle as renal function deterioration increase FHR-1 levels. Thus, a role of FHR-1 in IgAN pathogenesis is to compete with complement regulation by FH.

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IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. The hallmark of IgAN is the deposition of immune complexes containing galactose-deficient IgA1 (Gd-IgA1) in the glomerular mesangium of the kidney.[1,2] IgAN is a slow, progressive disease in which 15% to 40% of patients progress to chronic kidney disease (CKD) and require renal replacement therapies.[3–5] In addition to Gd-IgA1 deposition, IgAN is characterized by glomerular deposits of C3, properdin, C4 (C4d), mannose-binding lectin, and terminal complement components but not C1q.[6–10] These findings support the view that the activation of the lectin pathway and alternative pathway (AP) plays a role in IgAN pathogenesis.[10,11] Roos *et al.*[10] classified IgAN patients into 2 groups according to glomerular staining for complement proteins; C4d-negative IgAN patients tended to have a more benign renal disease. Espinosa *et al.*[7] also showed that the presence of mesangial C4d deposition could be used to identify IgAN patients with a poor long-term prognosis. Consistent with these findings, mesangial C3 deposition correlated with severe histologic lesions and worse renal outcomes,[12,13] and plasma levels of C3 activation fragments were elevated

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in IgAN patients with declining renal function.[11] These data support the relevant contribution of complement activation to renal injury in IgAN patients and its potential value as a prognostic marker.

The involvement of complement activation in IgAN pathogenesis is further supported by genome-wide association studies that demonstrates that the deletion of *CFHR3* and *CFHR1* genes ($\Delta_{CFHR3\text{-}CFHR1}$), which encode the complement factor H-related proteins (FHRs) FHR-3 and FHR-1, respectively, strongly protects from IgAN in multiple populations.[14,15] Factor H (FH) is the main regulator of AP, both in fluids and on cellular surfaces. FH is a relatively abundant plasma protein that is essential for restricting the action of complement to activating surfaces. FH binds to C3b, accelerates the decay of AP-related C3 convertase, and acts as a cofactor for the factor I-mediated proteolytic degradation of C3b.[16] The complement regulatory activities of FH on self and non-self surfaces are modulated by FHR.[17] These proteins lack the complement regulatory domains of FH but have conserved FH surface recognition domains that enable competitive binding of FH to complement-activating surfaces. In contrast to FH binding to surfaces, which prevents further C3b generation and deposition (negative regulation), FHR binding competes with FH binding and enables C3b amplification to proceed unhindered. Thus, the relative levels of FH and FHRs, established by their expression or activity levels, are critical for modulating complement regulation and may determine susceptibility to complement-mediated injury.[17] The capacity of FHRs to deregulate complement activation by competing with FH binding to surfaces explains the association of $\Delta_{CFHR3\text{-}CFHR1}$ with a lower risk of IgAN.[14] Interestingly, $\Delta_{CFHR3\text{-}CFHR1}$ is in strong linkage disequilibrium with a particular *CFH* haplotype associated with increased plasma FH levels,[18] further supporting that an excess of FH in relation to FHR-1 and FHR-3 accounts for the strong association of the extended *CFH-CFHR3-CFHR1* haplotype with protection from IgAN.

We measured the plasma levels of FH and FHR-1 proteins of IgAN patients, noncomplement-related autosomal dominant polycystic kidney disease (ADPKD) patients, and control individuals. IgAN patients with disease progression and ADPKD patients with CKD had elevated FHR-1 levels and FHR-1:FH ratios, which likely compromise FH function by competing for binding to C3 opsonized surfaces. In addition, 5 IgAN patients with progressive renal function decline had decreased FH levels because of pathogenic variants in *CFH* or *CFI*. Our data support that an impaired regulation of complement activation by FH plays a relevant role in IgAN pathogenesis.

RESULTS

Baseline characteristics of IgAN patients

The main clinical and histologic characteristics of IgAN patients at diagnosis are shown in Table 1. Forty-nine patients (43.8%) had an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2. Positive C4d staining in renal biopsy was observed in 47 patients (44.8%).

Table 1 | Clinical and histologic characteristics of IgA nephropathy patients (n = 112) at time of diagnosis and at the time of blood sampling

Variable	Time of diagnosis (mean [SD])	Blood sampling (mean [SD])	*P* value
Age (yr)	33.5 (12.9)	40.6 (13.2)	>0.001
Sex, number (%), female	39 (34.8%)	-	-
Serum creatinine (mg/dl)	1.5 (1.8)	2 (2.2)	>0.001
eGFR[a] (ml/min per 1.73 m^2)	77.1 (34.7)	61 (34.7)	>0.001
Proteinuria (g/d)	1.7 (1.3)	1.5 (1.2)	0.1
C4d+ in renal biopsy, number (%)	47 (44.8%)	-	-
Oxford MEST classification of renal biopsy			
M1, number (%)		72 (65.5%)	
E1, number (%)		16 (14.5%)	
S1, number (%)		58 (52.7%)	
T0 (<25%), number (%)		65 (59.1%)	
T1 (25%–50%), number (%)		25 (22.7%)	
T2 (>50%), number (%)		20 (18.2%)	

E, endocapillary hypercellularity; eGFR, estimated glomerular filtration rate; *M*, mesangial hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis.
[a]eGFR was calculated by the CKD-EPI equation.

$\Delta_{CFHR3\text{-}CFHR1}$ allelic frequency is significantly decreased in Spanish IgAN patients. We performed a multiplex ligation-dependent probe amplification analysis in 106 IgAN patients, 46 ADPKD patients, and 188 control individuals. As reported in other populations, the frequency of the $\Delta_{CFHR3\text{-}CFHR1}$ allele in our Spanish IgAN cohort was significantly different from the control population (0.151 vs. 0.229, odds ratio = 0.60, 95% confidence interval = 0.38–0.94, P = 0.025) (Figure 1). Importantly, we found no significant

a

	$\Delta_{CFHR3\text{-}CFHR1}$ Hom.	Het.	No
Control (n = 188)	**11** 5.9%	**64** 34.0%	**113** 60.1%
IgAN (n = 106)	**1** 0.9%	**30** 28%	**75** 71%
ADPKD (n = 46)	**3** 6.5%	**18** 39.1%	**25** 54.3%

b

	Control	ADPKD		IgAN		
	Freq.	Freq.	*Pvalue*	Freq.	*Pvalue*	OR (95% CI)
$\Delta_{CFHR3\text{-}CFHR1}$	0.229	0.261	0.58	0.150	0.025	0.60 (0.38–0.94)

Figure 1 | $\Delta_{CFHR3\text{-}CFHR1}$ association with IgA nephropathy (IgAN) in the Spanish population. (**a**) The number and proportion of IgAN, autosomal dominant polycystic kidney disease (ADPKD), and control individuals having each of the 3 $\Delta_{CFHR3\text{-}CFHR1}$ genotypes. (**b**) Comparison of the frequencies of the $\Delta_{CFHR3\text{-}CFHR1}$ allele in IgAN and ADPKD patients and control individuals. 95% CI, confidence interval; Freq., frequency; Het., $\Delta_{CFHR3\text{-}CFHR1}$ heterozygotes; Hom., $\Delta_{CFHR3\text{-}CFHR1}$ homozygotes; No, non-carriers of $\Delta_{CFHR3\text{-}CFHR1}$; OR, odds ratio.

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