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Fibrillary Glomerulonephritis Is Associated With HLA-DR7 and HLA-B35 Antigens

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Fibrillary glomerulonephritis (FGN) is a rare immune-mediated glomerulonephritis with an incompletely understood pathogenesis, characterized by glomerular deposits of randomly oriented fibrils (12−24 nm in diameter). The majority of FGN cases are Congo red negative and composed of polyclonal IgG.[1−3] DNAJB9 is a novel biomarker for FGN; expression of DNAJB9 in glomeruli is highly sensitive and specific for FGN,[4,5] and elevated serum levels of DNAJB9 have been observed in patients with FGN.[6] Because of the association with hepatitis C virus and autoimmune diseases, FGN has been linked to chronic immune stimulation in some patients. Most commonly, FGN is encountered in Caucasians.[1] Although only exceptional cases of familial FGN have been reported,[1,7−9] this is at least partially related to the rarity of FGN. In the United States, FGN is diagnosed in 1% of native kidney biopsy specimens compared with approximately 7% showing IgA nephropathy.[S1] Taken together, we hypothesized that genetic background plays a role in the pathogenesis of FGN. Because human leukocyte antigens (HLAs) have emerged as important inherited risk factors in most immune-mediated renal diseases,[S2] we examined the association of FGN with different HLAs.

We retrospectively identified a multi-institutional cohort of patients with FGN and available HLA typing (n = 26; Columbia University [n = 18], Oregon Health & Science University [n = 6], University of Washington [n = 2]). The cases comprised transplant recipients with end-stage kidney disease secondary to FGN (n = 23), *de novo* FGN in allograft (n = 2), and donor with FGN (n = 1). The HLA serotyping in this cohort was compared to internal controls from deceased kidney donors (DKDs, n = 96) and external controls of US residents of European descent from the National Marrow Donor Program (n = 15,740), as described in Supplementary Methods.

We initially identified the most frequent class I and class II antigens in FGN patients (Table 1). These

Table 1. HLA typing of patients with fibrillary GN and end-stage kidney disease

Patient	HLA-A	HLA-B	HLA-DR	HLA-DQ
1	A26, A66	B41, B51	DR11, DR13	NA
2	A2, A24	B35, B50	DR7, DR11	NA
3	A1, A11	B8, B51	DR11, DR15	DQ5, DQ7
4	A2, A32	B7, B35	DR4, DR7	DQ2, DQ8
5	A2, A11	B35, B44	DR7, DR14	DQ2, DQ5
6	A24, A30	B44, B45	DR7, DR10	DQ2, DQ5
7	A2, A29	B44, B49	DR7, DR11	DQ2, DQ7
8	A3, A24	B18, B51	DR11, DR17	DQ2, DQ7
9	A24, A30	B13, B35	DR7, DR15	DQ2, DQ6
10	A1, A11	B8, B35	DR103, DR17	DQ2, DQ5
11	A1, A2	B35, B35	DR13, DR14	DQ5, DQ7
12	A11, A24	B13, B44	DR7, DR11	DQ2, DQ7
13	A1, A68	B44, B50	DR7, DR8	DQ2, DQ4
14[a]	A2, A23	B35, B49	DR9, DR13	DQ2, DQ7
15[a]	A23, A29	B49, B49	DR9, DR11	DQ2, DQ6
16	A2, A3	B51, B71	DR11, DR17	DQ2, DQ7
17[b]	A2, A23	B41, B45	DR7, DR13	NA
18	A30, A32	B41, B51	DR7, DR13	DQ2, DQ7
19	A1, A30	B8, B13	DR17, DR7	DQ2, DQ3
20	A1, A3	B35, B37	DR13, DR14	DQ5, DQ6
21	A2, A3	B7, B57	DR15, DR7	DQ3, DQ6
22	A11, A11	B38, B61	DR11, DR11	DQ7, DQ9
23	A2, A3	B7, B64	DR7, DR15	DQ2, DQ6
24	A1	B8	DR17	NA
25[b]	A1, A1	B8, B35	DR1	DQ6
26	A3,A11	B39,B35	DR2	NA

HLA, human leukocyte antigen; GN, glomerulonephritis.
[a]Familial.
[b]*De novo* fibrillary glomerulonephritis in an allograft.

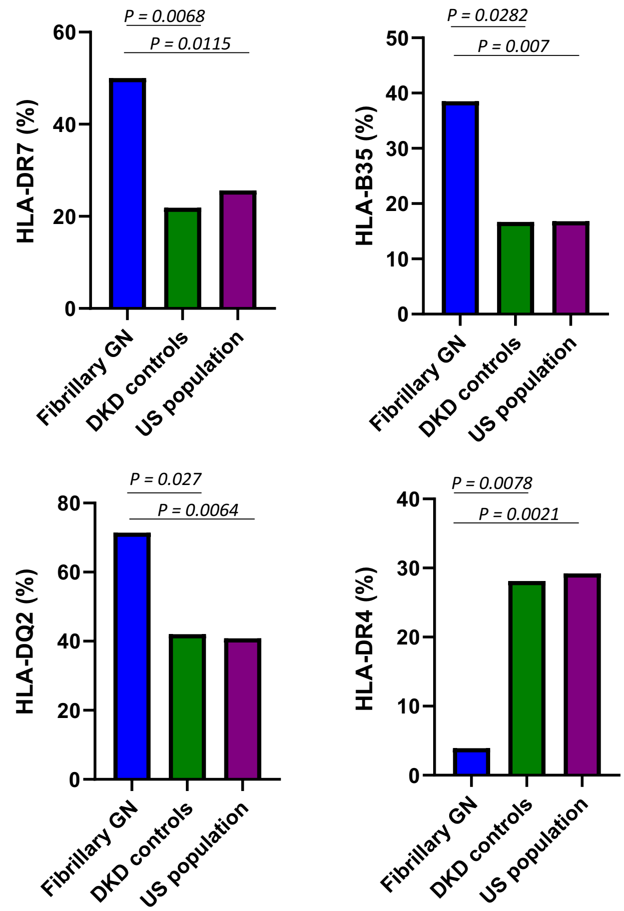

Figure 1. Human leukocyte antigens in fibrillary glomerulonephritis (GN; n = 26), compared with deceased kidney donors (DKD; internal controls, n = 96), and US Caucasian population (external controls, n = 15,740). Only significant results are shown.

included A2 (10 of 26; 38%), B35 (10 of 26; 38%), DR7 (13 of 26; 50%), and DQ2 (15 of 21; 71%). Compared with both internal and external controls (Figure 1), FGN was significantly associated with a higher prevalence of B35, DR7, and DQ2 antigens but lower frequency of DR4 antigen. Notably, there were no significant differences between FGN and controls with regard to 1 versus 2 loci for these antigens; therefore, a cumulative antigen effect was not identified.

To identify the antigen(s) with the strongest association with FGN, we performed multivariable logistic regression using the combined cohort of FGN cases and internal controls (n = 122). We assessed the interaction between DR7 and DQ2, which are known to be in linkage disequilibrium to form DQ2.2 complex. Nearly all subjects (30 of 31; 97%) with DR7 antigen who had available typing for DQ had detectable DQ2 antigens. In contrast, only 30 of 52 subjects (58%) with a DQ2 had a DR7. In the absence of DR7, DQ2 was not significantly associated with FGN ($P = 0.11$). Both DR7 (adjusted odds ratio [aOR] = 7.4, CI = 1.99–27.8, $P = 0.003$], and B35 (aOR = 5.4, CI = 1.59–18.1, $P = 0.007$) were significantly associated with FGN. After accounting for the effects of DR7 and B35 on multivariable analyses, there remained a nonsignificant trend (aOR = 0.12, CI = 0.014–1.162, $P = 0.07$) for DR4 to be underrepresented in patients with FGN.

The HLAs associated with FGN have been described in other kidney diseases: namely, HLA-DQ2 and HLA-DR7 have been associated with steroid-sensitive nephrotic syndrome, whereas HLA-B35 has occasionally been associated with IgA nephropathy/Henoch–Schönlein purpura.[S2]

Our findings should be interpreted in light of our small sample size, and the results need to be confirmed by larger studies. This series nonetheless represents the first study of HLA antigens associated with FGN, and benefits from a multi-institutional effort and adequate internal and external control subjects. Our cohort included mainly patients with FGN who developed end-stage kidney disease and underwent kidney transplantation. Although this may raise the possibility of selection bias (these antigens may have worse prognostic implications in FGN), it should be noted that the majority of patients with FGN have poor prognosis[1] and that a consistent association between specific HLA alleles and end-stage kidney disease has not been identified.[S2]

In conclusion, we identified an association between FGN and specific HLAs, namely DR7 and B35. This novel association will advance our understanding of the genetic background and potential pathogenesis of FGN, and lays groundwork for more comprehensive genomic studies for a precise assessment of FGN inherited risk factors in the future.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods and References

Supplementary information is available at KI Report's website.

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A Randomized Trial of Liposomal Prednisolone (LIPMAT) to Enhance Radiocephalic Fistula Maturation: A Pilot Study

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