ORIGINAL ARTICLE

Risk HLA-DQA1 and PLA_2R1 Alleles in Idiopathic Membranous Nephropathy

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ABSTRACT

BACKGROUND

Idiopathic membranous nephropathy is a major cause of the nephrotic syndrome in adults, but its etiologic basis is not fully understood. We investigated the genetic basis of biopsy-proven cases of idiopathic membranous nephropathy in a white population.

METHODS

We performed independent genomewide association studies of single-nucleotide polymorphisms (SNPs) in patients with idiopathic membranous nephropathy from three populations of white ancestry (75 French, 146 Dutch, and 335 British patients). The patients were compared with racially matched control subjects; population stratification and quality controls were carried out according to standard criteria. Associations were calculated by means of a chi-square basic allele test; the threshold for significance was adjusted for multiple comparisons (with the Bonferroni method).

RESULTS

In a joint analysis of data from the 556 patients studied (398 men), we identified significant alleles at two genomic loci associated with idiopathic membranous nephropathy. Chromosome 2q24 contains the gene encoding M-type phospholipase A_2 receptor (PLA_2R1) (SNP rs4664308, $P=8.6\times10^{-29}$), previously shown to be the target of an autoimmune response. Chromosome 6p21 contains the gene encoding HLA complex class II HLA-DQ alpha chain 1 (HLA-DQA1) (SNP rs2187668, $P=8.0\times10^{-93}$). The association with HLA-DQA1 was significant in all three populations ($P=1.8\times10^{-9}$, $P=5.6\times10^{-27}$, and $P=5.2\times10^{-36}$ in the French, Dutch, and British groups, respectively). The odds ratio for idiopathic membranous nephropathy with homozygosity for both risk alleles was 78.5 (95% confidence interval, 34.6 to 178.2).

CONCLUSIONS

An HLA-DQA1 allele on chromosome 6p21 is most closely associated with idiopathic membranous nephropathy in persons of white ancestry. This allele may facilitate an autoimmune response against targets such as variants of *PLA2R1*. Our findings suggest a basis for understanding this disease and illuminate how adaptive immunity is regulated by HLA.

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Membranous nephropathy has an incidence of approximately 1 case per 100,000 persons per year,[1] and its phenotype has been clearly defined on the basis of histologic features, making it a good subject for genomewide association studies. Recognized as a clinicopathological entity in the 1950s,[2] membranous nephropathy is the most common diagnosis in adults with the nephrotic syndrome. Roughly one fourth of the biopsies performed in patients with the nephrotic syndrome show membranous nephropathy, which is among the glomerulonephritides that lead to end-stage renal disease.[3-6] One of its hallmarks is the presence of glomerular deposits that typically contain immunoglobulin and complement components. Two major antigens, both of which are membrane glycoproteins, have been identified in human membranous nephropathy. The first is neutral endopeptidase, the alloantigen involved in membranous nephropathy in neonates whose mothers have a deficiency of this enzyme.[7] The second is the M-type phospholipase A_2 receptor (PLA_2R1), the first antigen identified in adults with idiopathic membranous nephropathy, which is generally considered to be an autoimmune disease.[8] Furthermore, two autoantibodies against aldose reductase (aldo-keto-reductase family 1, member 1 [AKR1B1]) and mitochondrial superoxide dismutase 2 (SOD2) were recently discovered to be present in serum and glomeruli from patients with idiopathic membranous nephropathy.[9] It is not known why these autoantibodies develop.[10-13] Familial occurrence of idiopathic membranous nephropathy has been noted previously, suggesting a genetic contribution to the disease.[1,14] Identification of risk alleles or genetic alterations would be a key step in gaining a better understanding of the disease mechanism and thus the potential to develop specific treatments.[15] We performed genomewide association studies (discovery and independent replication studies) using single-nucleotide–polymorphism (SNP) technology to identify risk alleles in three separate populations of patients with idiopathic membranous nephropathy.

METHODS

PATIENTS

Participants were part of three separate national cohorts (French, Dutch, and British) comprising patients with idiopathic membranous nephropathy who were of self-reported white ancestry. The diagnosis of idiopathic membranous nephropathy was established by renal biopsy as part of the routine clinical workup for the investigation of proteinuria.[8] The studies were approved by the relevant institutional review boards in the three countries and were conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from participants in all three studies.

GENOTYPING

Isolation of DNA and genotyping were performed with the use of standard procedures. In the French study, DNA samples from 75 case patients (58 men) and 157 racially matched controls (66 men) were genotyped by Centre National de Génotypage, Evry, France; these samples were obtained from the GN-PROGRESS Study.[16] In the Dutch study, DNA samples from 146 case patients (109 men) were genotyped by University College London Genomics at the Institute of Child Health, London, and DNA samples from 1832 racially matched Dutch controls (906 men) were genotyped by deCODE Genetics, Reykjavik, Iceland; these samples were from the Nijmegen Biomedical Study.[17] In the British study, DNA samples from 335 case patients (231 men) and 349 racially matched controls (108 men) were genotyped by deCODE genetics (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

GENOMEWIDE ASSOCIATION STUDIES

All genotyping data sets underwent the same rigorous quality checks both before and after patients and control subjects were compared. SNPs were excluded from the analysis if they were out of Hardy–Weinberg equilibrium ($P<0.01$), had a call rate below 90%, or had an allele frequency below 1%. All analyses were carried out with the use of established procedures (see the Supplementary Appendix).[18-20]

Table 1. Characteristics of Patients in the Three Study Cohorts.*

Characteristic	French Cohort	Dutch Cohort	British Cohort
No. of patients	75	146	335
Sex (no.)			
Male	58	109	231
Female	17	37	104
Sex ratio (M:F)	3.4:1	2.9:1	2.2:1
Age at diagnosis (yr)	49.8±15.3	51.8±14.2	52.5±13.3

Table 2. Results of Genomewide Association Studies in the Three Study Groups and the Joint Study, According to Single-Nucleotide Polymorphism Characteristics.*

Variable	Single-Nucleotide Polymorphism Characteristics	
	Chromosome 6, rs2187668 (HLA-DQA1)	Chromosome 2, rs4664308 (*PLA2R1*)
French study		
Odds ratio (95% CI)	4.48 (2.68–7.50)	1.87 (1.20–2.92)
Minor allele frequency (%)		
Patients	31.3	23.3
Controls	9.2	36.3
P value	1.8×10^{-9}	5.1×10^{-3}
Dutch study		
Odds ratio (95% CI)	3.76 (2.92–4.86)	2.27 (1.73–2.97)
Minor allele frequency (%)		
Patients	37.0	26.0
Controls	13.5	44.4
P value	5.6×10^{-27}	1.0×10^{-9}
British study		
Odds ratio (95% CI)	5.33 (4.04–7.02)	2.10 (1.67–2.64)
Minor allele frequency (%)		
Patients	41.9	25.3
Controls	11.9	41.6
P value	5.2×10^{-36}	2.1×10^{-10}
Joint study		
Odds ratio (95% CI)	4.32 (3.73–5.01)	2.28 (1.96–2.64)
Minor allele frequency (%)		
Patients	39.2	25.2
Controls	13.0	43.4
P value	8.0×10^{-93}	8.6×10^{-29}

* The odds ratios are for the alleles most significantly associated with idiopathic membranous nephropathy on chromosomes 6 and 2 (risk allele modeled for both single-nucleotide polymorphisms [rs2187668:A, rs4664308:A]). CI denotes confidence interval.

STATISTICAL ANALYSIS

See the Supplementary Appendix for a description of the statistical analyses.

RESULTS

STUDY PARTICIPANTS

Characteristics of the participants in the three studies are shown in Table 1. The phenotype was remarkably similar among the three cohorts of patients with idiopathic membranous nephropathy, with regard to age at diagnosis and sex ratio. Two genomic loci appeared to confer a risk of the disease in these white participants (Tables 2 and 3).

FRENCH STUDY

This genomewide association study, which assessed 315,049 SNPs in 75 French patients with idiopathic membranous nephropathy and 157 racially matched controls, established a significant association with an HLA-DQA1 allele on chromosome 6 (Fig. 1). The study population appeared to be homogeneous (showed no relevant stratification) (Fig. 1 in the Supplementary Appendix). SNPs rs2187668 within HLA-DQA1, rs9273327, and rs9272192 were significantly associated with idiopathic membranous nephropathy ($P=1.8\times10^{-9}$, $P=1.7\times10^{-9}$, and $P=5.9\times10^{-10}$, respectively) (Fig. 2 and Table 1 in the Supplementary Appendix). No

Table 3. Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism (SNP) and Genotype Combinations.*

SNP rs2187668 (HLA-DQA1)	SNP rs4664308 (*PLA2R1*)		
	GG	GA	AA
GG			
No. of cases/total no. of subjects	14/354	79/944	97/659
Odds ratio (95% CI)	1.00	2.22 (1.24–3.97)	4.19 (2.36–7.46)
GA			
No. of cases/total no. of subjects	23/115	94/363	178/348
Odds ratio (95% CI)	6.07 (3.01–12.27)	8.49 (4.73–15.22)	25.43 (14.32–45.16)
AA			
No. of cases/total no. of subjects	5/11	23/41	42/55
Odds ratio (95% CI)	20.24 (5.51–74.38)	31.03 (13.72–70.19)	78.46 (34.55–178.17)

* Persons who were homozygous for the low-risk allele (GG) constituted the reference category. Numbers of cases and total numbers of subjects are from the joint analysis. OR denotes odds ratio.

other SNPs showed significant associations (Fig. 3 in the Supplementary Appendix).

DUTCH STUDY

This genomewide association study, which assessed 282,440 SNPs in 146 Dutch patients with idiopathic membranous nephropathy, as compared with 1832 racially matched controls, established a significant association with an HLA-DQA1 allele on chromosome 6 and a *PLA2R1* allele on chromosome 2 (Fig. 1). The study population showed no relevant stratification (Fig. 4 in the Supplementary Appendix). SNP rs2187668 within the HLA-DQA1 gene showed a significant association with idiopathic membranous nephropathy ($P=5.6\times10^{-27}$). Overall, 191 SNPs within the extended HLA locus showed significant associations with the disease (Fig. 5 and Table 2 in the Supplementary Appendix). SNP rs4664308 on chromosome 2 located within *PLA2R1* was significantly associated with idiopathic membranous nephropathy ($P=1.0\times10^{-9}$), and SNPs rs3749117, rs3792189, rs3792192, rs6722275, and rs1870102 at this locus also showed significant associations ($P=8.0\times10^{-11}$, $P=4.1\times10^{-11}$, $P=1.4\times10^{-10}$, $P=3.8\times10^{-10}$, and $P=1.2\times10^{-9}$, respectively) (Fig. 6 and Table 4 in the Supplementary Appendix).

BRITISH STUDY

This genomewide association study assessed 281,009 SNPs in 335 British patients with idiopathic membranous nephropathy, as compared with 349 racially matched controls, establishing a significant association with an HLA-DQA1 allele on chromosome 6 and a *PLA2R1* allele on chromosome 2 (Fig. 1). The study population showed no relevant stratification (Fig. 7 in the Supplementary Appendix). SNP rs2187668 within the HLA-DQA1 gene was significantly associated with idiopathic membranous nephropathy ($P=5.2\times10^{-36}$). Overall, 144 SNPs within the extended HLA locus on chromosome 6 showed significant associations (Fig. 8 and Table 3 in the Supplementary Appendix). As in the Dutch study, SNP rs4664308, located within *PLA2R1*, was significantly associated with the disease ($P=2.1\times10^{-10}$). SNP rs1870102 also showed a significant association ($P=8.2\times10^{-10}$) (Fig. 9 and Table 5 in the Supplementary Appendix).

JOINT GENOMEWIDE ASSOCIATION STUDIES

Because all the patients and controls were of white ancestry, it was possible to perform an unbiased joint analysis of all three independent genomewide association studies (Fig. 10 in the Supplementary Appendix). For the 556 patients with idiopathic membranous nephropathy and the 2338 controls, we examined 242,824 common SNPs and found the two most significant associations on chromosomes 6 and 2 for SNPs within HLA-DQA1 and *PLA2R1*, respectively (Fig. 2, and Tables 6 through 9 in the Supplementary Appendix). Both associations were independent of sex (data not shown). Significant associations were observed for SNP rs2187668 within HLA-DQA1 on chromosome 6 ($P=8.0\times10^{-93}$) (Fig. 11 and Table 9 in the Supplementary Appendix) and SNP rs4664308 within *PLA2R1* on chromosome 2, which was recently identified as a major target

antigen in idiopathic membranous nephropathy[8] ($P=8.6\times10^{-29}$) (Table 8 and Fig. 12 in the Supplementary Appendix). Subsequent reanalysis with the addition of 823 publicly available white HapMap controls increased the significance of the association with HLA-DQA1 ($P=1.8\times10^{-116}$), whereas the significance of the association with *PLA2R1* was decreased ($P=3.7\times10^{-19}$) (Fig. 13 in the Supplementary Appendix). This additional finding points to the uniqueness of the observed HLA-DQA1 association in white patients with idiopathic membranous nephropathy. There was no evidence of significant genetic associations with SNPs at other genetic loci.

Next we evaluated the effect of the combination of risk alleles at the two loci on the risk of idiopathic membranous nephropathy. The odds ratio for being homozygous for the risk allele in HLA-DQA1 was 20.2 (95% confidence interval [CI], 5.5 to 74.4), and the odds ratio for being homozygous for the risk allele in *PLA2R1* was 4.2 (95% CI, 2.4 to 7.5). As compared with the odds ratio for homozygosity for the protective allele at both loci, the odds ratio increased, in an additive fashion, with each additional copy of the risk allele at either locus and was 78.5 (95% CI, 34.6 to 178.2) for homozygosity for the risk alleles at both rs2187668 (chromosome 6, HLA-DQA1) and rs4664308 (chromosome 2, *PLA2R1*) (Table 3).

The SNP with the overall lowest P value (rs2187668) is located within the first intron of HLA-DQA1. HLA-DQA1 is an HLA class II alpha-chain paralogue gene (exon 1 encodes the leader peptide, exons 2 and 3 encode the two extracellular domains, exon 4 encodes the transmembrane domain and the cytoplasmic tail, and exon 5 is noncoding) that spans 6246 bp of genomic DNA on chromosome 6p21 and codes for a 255-amino-acid protein.

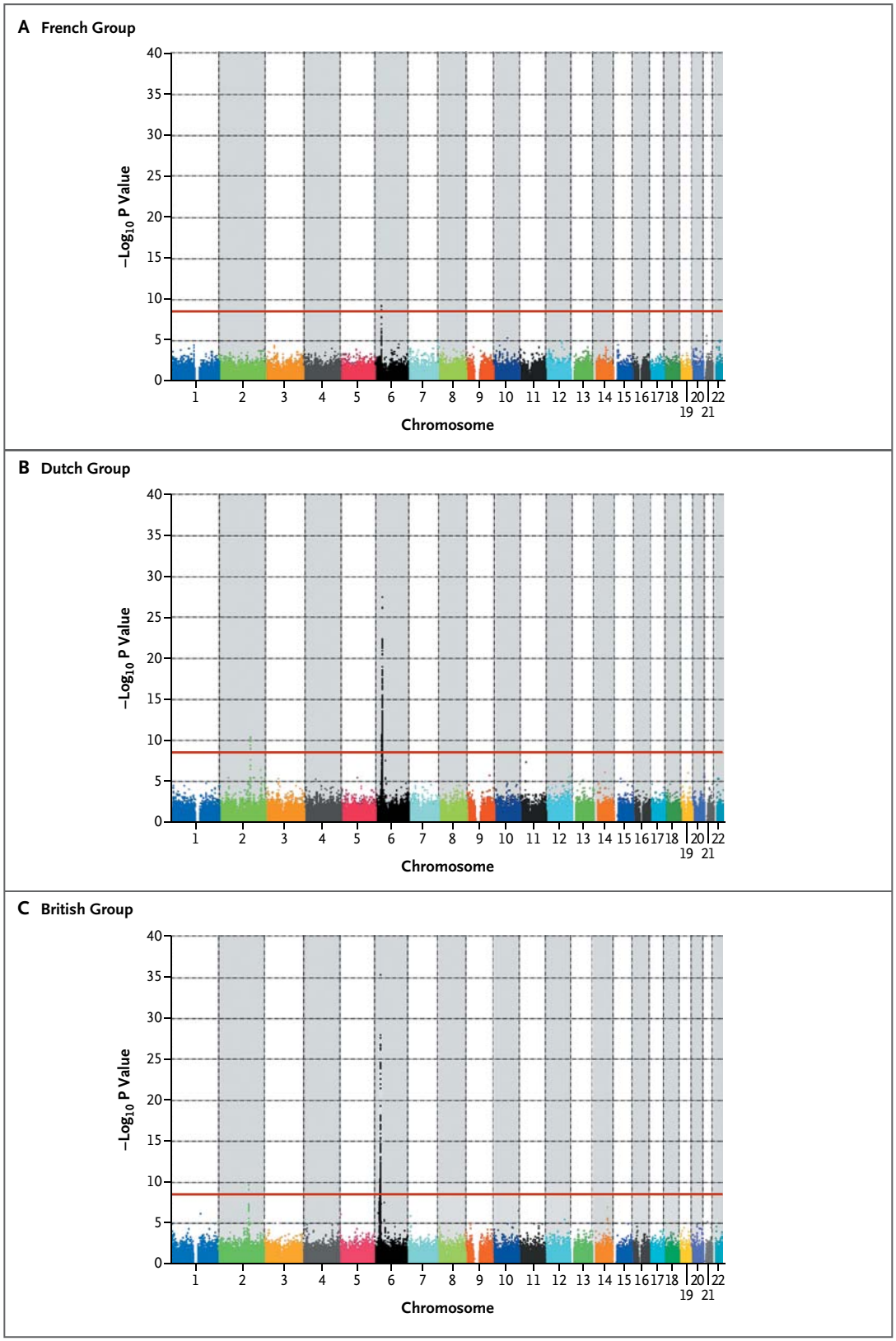
The SNP with the smallest P value on chromosome 2q24 (rs4664308) lies within the first intron of *PLA2R1*, the gene that encodes the phospholipase A_2 receptor 1 isoform 1. The gene spans 121,110 bp of genomic sequence and contains 30 exons (all of them coding). The *PLA2R1* protein has 1463 amino acids, with a single-pass transmembrane alpha-helix domain, and is a receptor for secretory phospholipase A_2.[21] Of note, rs4664308 is correlated with rs3749117 ($r^2=0.70$), encoding a nonsynonymous amino acid substitution in the extracellular C-type lectin domain 1 of PLA_2R1, M292V (Table 10 and Fig. 14 in the Supplementary Appendix). The finding that other significantly associated SNPs within this gene are not correlated or are only weakly correlated with rs4664308 provides circumstantial evidence for involvement of more than one risk allele in *PLA2R1* in idiopathic membranous nephropathy (Fig. 14 in the Supplementary Appendix). At present, 729 SNPs within the genomic region of *PLA2R1* are known (Table 11 in the Supplementary Appendix).

Figure 1 (facing page). Manhattan Plots for Genome-wide Association Studies of Idiopathic Membranous Nephropathy (IMN) in Three Groups of Patients and Racially Matched Controls.

The red horizontal lines indicate the genomewide significance level for the basic allele test, with the use of the chi-square test and the Bonferroni correction, with adjustment for the genomic inflation factor ($P<8.5\times10^{-8}$). Panel A shows the plot for 75 French patients with idiopathic membranous nephropathy and 157 racially matched controls, with the use of 315,049 single-nucleotide polymorphisms (SNPs). The genomic inflation factor was 1.02. The most significant association is with an allele on chromosome 6 (containing HLA-DQA1). Panel B shows the plot for 146 Dutch patients and 1832 controls, with the use of 282,440 SNPs. The genomic inflation factor was 1.12. There are significant associations with alleles on chromosome 6 (containing HLA-DQA1) and on chromosome 2 (containing *PLA2R1*). Panel C shows the plot for 335 British patients and 349 control subjects, with the use of 281,009 SNPs. The genomic inflation factor was 1.15. There are significant associations with alleles on chromosome 6 (containing HLA-DQA1) and on chromosome 2 (containing *PLA2R1*).

DISCUSSION

The association of HLA with idiopathic membranous nephropathy has been shown serologically and through molecular typing,[22] particularly with HLA-DR alleles in whites,[23-27] and our study defines this association in detail. We hypothesized that patients with idiopathic membranous nephropathy would have distinct similarities in the genetic makeup of their immune system best revealed with the use of current technology. Since idiopathic membranous nephropathy is a rare disease (with an estimated incidence of about 1 case per 100,000 persons per year), we further hypothesized that the disease would be reflected by alleles. In a given population such alleles should be recognizable with the use of current SNP chip technology and data analyses through classic ge-



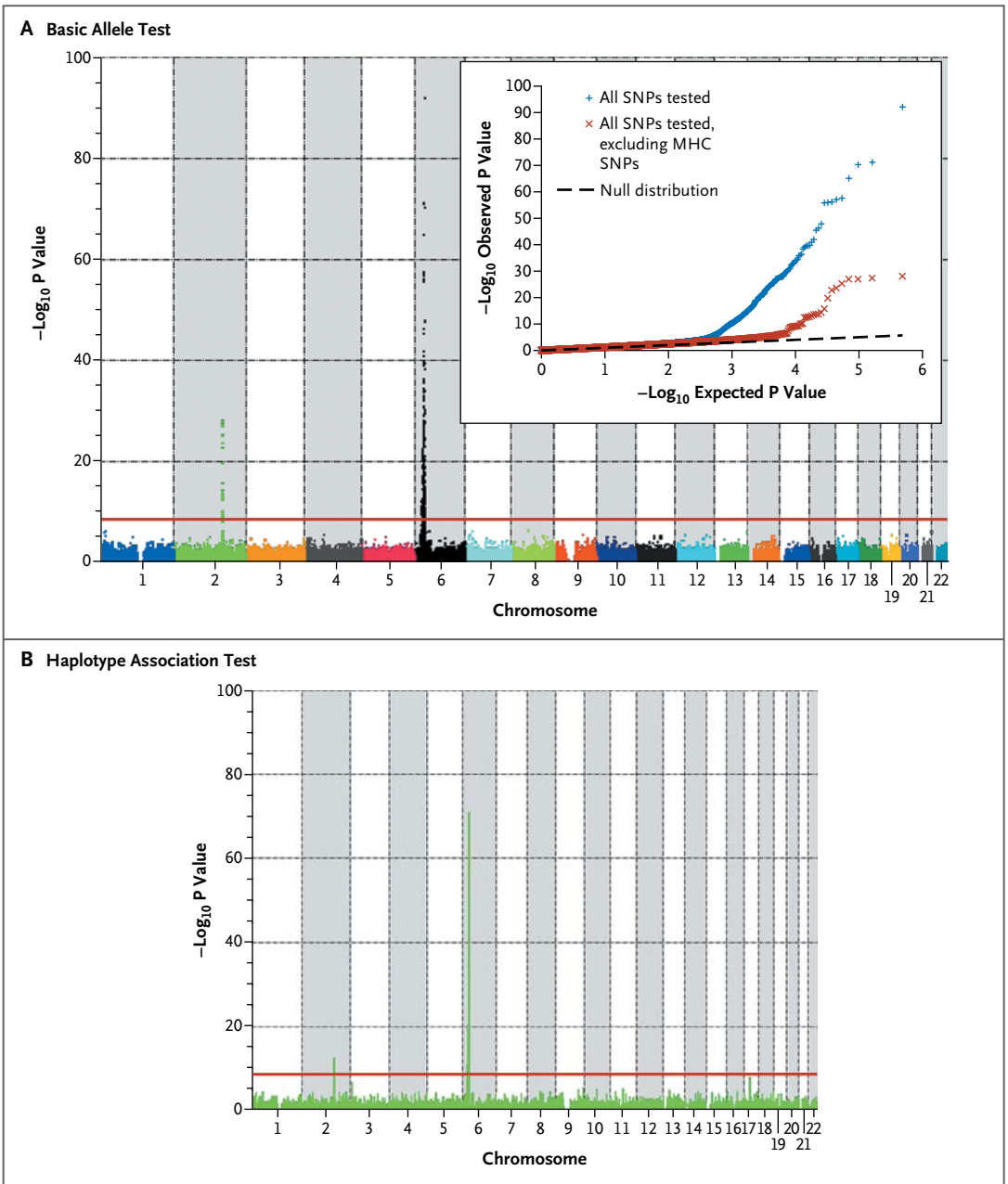


Figure 2. Manhattan Plots for the Joint Genomewide Association Study.

The joint analysis, which included 556 white patients with idiopathic membranous nephropathy and 2338 racially matched controls, used 242,824 single-nucleotide polymorphisms (SNPs). Panel A shows the genomewide significance level (red horizontal line) for the basic allele test, with the use of the chi-square test and the Bonferroni correction and with adjustment for the genomic inflation factor ($P<8.5\times10^{-8}$). The inset shows the quantile–quantile plot for observed versus expected $-\log_{10}$ P values with and without the extended HLA complex. There are highly significant associations with an allele on chromosome 6 (containing HLA-DQA1) and an allele on chromosome 2 (containing *PLA2R1*). Panel B shows the genomewide significance level (red horizontal line) for the haplotype association test with the use of the same data set. MHC denotes major histocompatibility complex.

nomewide association studies, which use common SNPs to map common risk variants as well as rare risk variants contained in common haplotypes. Our study shows that a relatively small number of cases is sufficient to establish significant findings for idiopathic membranous nephropathy in a given population (i.e., associations with HLA-DQA1 and *PLA2R1* alleles).

The data from the 75 French cases of idiopathic membranous nephropathy were sufficient to locate a significant association with an HLA-DQA1 allele. The data from the 146 Dutch cases were sufficient to establish significant associations with both HLA-DQA1 and *PLA2R1* alleles. The findings in the 335 British cases corroborated the associations with the HLA-DQA1 and *PLA2R1* alleles.

Differences between these findings and previously reported HLA associations are probably due to the progress in HLA typing technology — that is, the ability to define alleles at a much higher resolution within genes and to discriminate more precisely within the HLA locus. In fact, HLA-DQA1 is currently not part of any routine HLA typing procedure for renal transplantation in the United Kingdom.

The description of these genetic associations has important implications. First, our data point to the possibility that sequence variations within HLA and *PLA2R1* are responsible in part for the development of idiopathic membranous nephropathy in whites. Second, by adding genetic information in an unbiased manner, we provide support for the finding, reported by Beck and colleagues, that *PLA2R1* is associated with idiopathic membranous nephropathy.[8] However, our study shows a stronger association with HLA than with *PLA2R1*. Thus, it appears that the risk of idiopathic membranous nephropathy is higher with the HLA-DQA1 allele than with the *PLA2R1* allele, suggesting that the HLA-DQA1 allele might facilitate autoantibody development targeting not only PLA_2R1 but also other antigens. Two other such autoantigens in idiopathic membranous nephropathy have recently been identified.[9] However, no SNPs within these genes — that is, *AKR1B1* (chromosome 7q33) and *SOD2* (chromosome 6q25.3) — showed a significant association in our three individual or joint genomewide association studies of this disease.

In a study in mice, the susceptibility to anti–glomerular basement membrane disease was linked to the A beta–A alpha region, which corresponds to the human HLA-DQ region, supporting the importance of the HLA-DQA1 allele in immune-related glomerular disease.[28]

Our results show a highly significant association between idiopathic membranous nephropathy and risk alleles of HLA-DQA1 and *PLA2R1*. Although these findings do not establish causality, they strongly suggest that an interaction between genetic variants of immune-system proteins and glomerular components form the basis for the development of idiopathic membranous nephropathy, establishing a trigger (the immune system), a bullet (PLA_2R1 autoantibodies), and a target (glomerular antigen). However, the causative link between the presence of the HLA–DQA1 risk allele and PLA_2R1 autoantibodies remains unknown.

These findings are in agreement with current concepts of autoimmune disease: a recent genomewide association study of vitiligo established a similar trigger-and-target model by identifying significant associations with variants in the HLA locus (the trigger) and the gene encoding TYR (the target), which encodes a well-recognized autoantigen in vitiligo.[29] Similarly, variants within the HLA system appear to confer a predisposition to immunologic disorders such as alopecia areata through an intricate interplay between innate and adaptive immunity.[30]

The HLA locus, in its expanded form, covers a region of about 8 million bases on chromosome 6p21 and is considered the most complex locus in the human genome owing to extensive recombinatory events that occurred during evolution. Here, we describe 282 significant associations with idiopathic membranous nephropathy within HLA and, in particular, HLA-DQA1. Thirty-five different alleles in HLA-DQA1 have been documented (www.ebi.ac.uk/imgt/hla) and associated with various immune-related diseases, but so far, none have been linked to idiopathic membranous nephropathy.[31] However, a report on a previous study, in which a traditional method was used (restriction-fragment–length polymorphism analysis), pointed out that HLA-DQA1 alleles could be involved in idiopathic membranous nephropathy.[24] HLA-DQA1 is part of a heterodimer consisting of an alpha chain (DQA) and a beta chain (DQB), both anchored in the membrane and forming the antigen-presenting groove. This heterodimer plays

a central role in the immune system by presenting epitope peptides (9 to 15 amino acids in length) derived from extracellular antigenic proteins, which in idiopathic membranous nephropathy could, for example, be composed of extracellular PLA_2R1 fragments (i.e., an epitope containing the M292V variant in the C-type lectin domain 1). Class II molecules are expressed in antigen-presenting cells (e.g., B lymphocytes, dendritic cells, and macrophages). Within this class II molecule, both the alpha chain and the beta chain contain polymorphisms that determine peptide binding specificities. Sequence variants in HLA-DQA1 could therefore change its conformation and consequently control the shape of the peptide groove, altering the specificity of immunogen presentation,[32,33] although we cannot exclude the possibility that a causal variant underlying this association is located in one of the neighboring genes.

Our findings may also support an additional concept concerning the mechanism of autoantibody formation. *PLA2R1* encodes a protein that probably exists in both a transmembrane form and a soluble form. The transmembrane receptor may increase in the clearance of phospholipase A_2, thereby inhibiting its action. PLA_2R1 is present in normal podocytes and in immune deposits in patients with idiopathic membranous nephropathy. Sequence variations in *PLA2R1* that are related to idiopathic membranous nephropathy could control the pattern of antigen-peptide processing through conformational change.[34] For example, it is conceivable that the amino acid substitution M292V encoded by SNP rs3749117 could lead to a conformational change in PLA_2R1, resulting in its functioning as an antigen; there is precedence for such a scenario.[35] Furthermore, this or other sulfhydryl groups on the extracytoplasmic domains within this molecule could be modified owing to environmental, accidental, or therapy-related exposure to heavy metals (e.g., gold or mercury), a known cause of secondary membranous nephropathy.[36-39]

We speculate that sequence variants within HLA-DQA1 alleles that are unique to idiopathic membranous nephropathy lead to the presentation of such peptides to immunocompetent cells, resulting in autoantibody formation. Thus, the coexistence of risk alleles in HLA and *PLA2R1* in the same person may circumvent the tightly regulated adaptive immune system and allow for the development of idiopathic membranous nephropathy. Indeed, for persons who are homozygous for the risk alleles of both variants, the odds ratio for having this disease is almost 80, with additive increases in the odds ratio, depending on the combination of genotypes.

In persons of white ancestry, idiopathic membranous nephropathy is strongly associated with risk alleles within the HLA locus in general and with HLA-DQA1 in particular, as well as with *PLA2R1* alleles on chromosome 2. Among the 556 patients with idiopathic membranous nephropathy in our study, no other autosomal allele was significantly associated with this disease. Future studies are needed to determine whether the observed whole-genome associations are caused by a combination of our identified common variants (i.e., SNPs used for genomewide association studies), by rare genetic sequence variations within either the coding or noncoding regions of HLA-DQA1 and *PLA2R1* that are in linkage disequilibrium, or by both factors. Studies to assess sequence variations in the HLA-DQA1 and *PLA2R1* regions may therefore facilitate the diagnosis of idiopathic membranous nephropathy and improve our understanding of its pathophysiology.[40] Our results are consistent with the idea that the antibody response in this disease is related to the presentation of a "risk" PLA_2R1 epitope by an "idiopathic membranous nephropathy" HLA-DQA1 allele. Antigen presentation may depend on the presence of PLA_2R1 on dendritic cells or macrophages, and podocytes may be an innocent bystander. Our findings provide a basis for more in-depth research into the role of the immune system and PLA_2R1 in idiopathic membranous nephropathy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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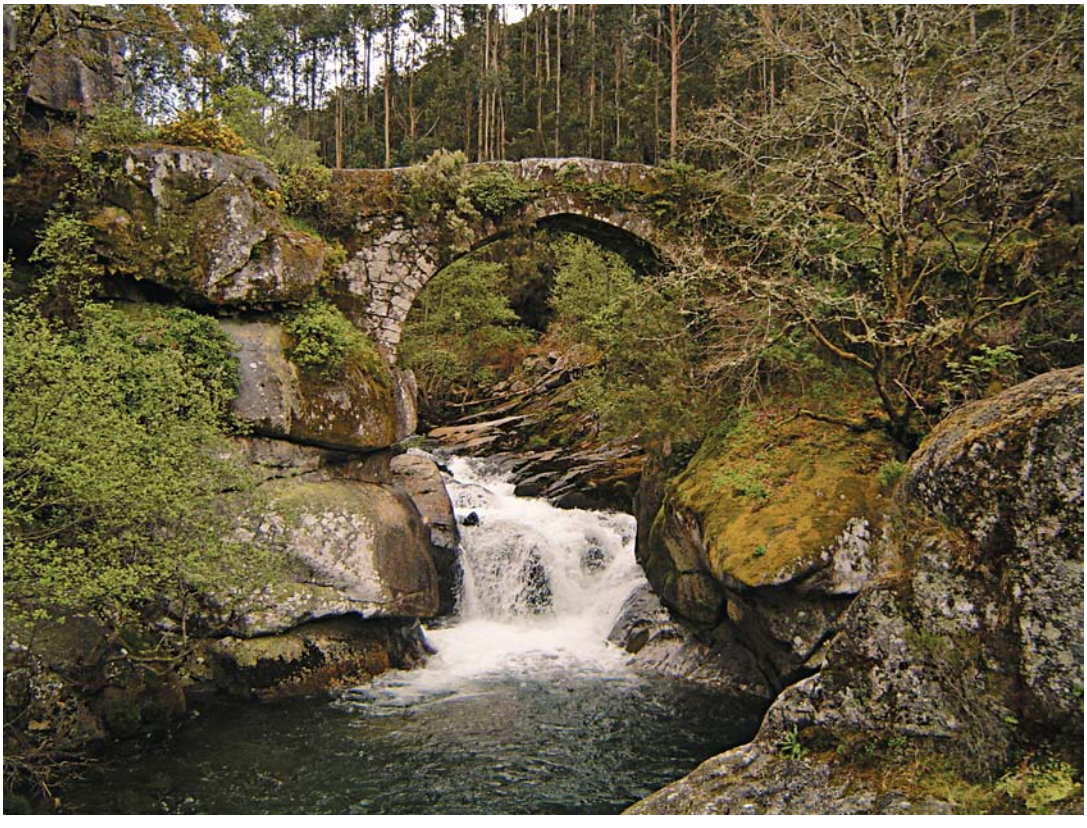

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