Previous case reports of familial forms of MN have suggested a genetic predisposition to disease. In a recent genome-wide association study (GWAS) in three European populations (French, Dutch, and British), Stanescu et al. described associations of MN with the HLA locus on chromosome 6p21 and the PLA2R1 locus (encoding PLA2R) on chromosome 2q24. The association with HLA was significant in all three patient samples, whereas the association with PLA2R1 was significant in the Dutch and British samples (as well as in joint analysis of all three populations). Strikingly, whereas the risk of disease was relatively modest in individuals with risk alleles at any one locus, the odds ratio for MN was an astronomical 78.5 (95% confidence interval [95% CI], 34.6 to 178.2) in individuals homozygous for risk alleles at both loci, indicative of strong genetic interaction. This GWAS was thus unusual because the effect sizes imparted by the combined risk alleles were very large, suggesting a potential role for genetics for noninvasive screening or risk stratification of MN. This study also provided an independent line of evidence implicating PLA2R1 in the pathogenesis of disease, suggesting that sequence variants within PLA2R1 may alter expression or function of PLA2R, potentially unmasking it as an autoantigen that, in conjunction with the right MHC haplotype, results in activation of T cells and stimulation of autoantibody production. Limitations of this GWAS included the relatively small sample size, which precluded precise localization of the risk alleles within each locus. Particularly, the origin of the signal within the MHC locus remained unclear, because this region has a very complicated structure, and class I and class II response loci may each contain multiple independent haplotypes with opposing effects on risk of disease. These findings thus required follow-up in larger cohorts and validation beyond European populations.

In this issue of JASN, Lv and colleagues genotyped 1112 Chinese patients with MN and 1020 healthy controls for the top single-nucleotide polymorphism (SNPs) in the European GWAS (three SNPs within the PLA2R1 locus and three SNPs within HLA genes). All three SNPs within PLA2R1 were highly associated with MN, and the strongest signal emerged from the same SNP (rs4664308) identified in the European GWAS. The HLA-DQA1 SNP (rs2187668) also showed association with MN, whereas two other HLA-located SNPs showed no such association with disease. Thus, this study robustly replicated the genetic signal demonstrated in a GWAS of European cohorts. However, in this Chinese population, the odds ratio for MN associated with homozygosity for both risk alleles was 9.9 (95% CI, 1.1 to 91.9), which is much lower than the odds ratio described for Europeans. Interestingly, the odds ratio rose to 11.1 (95% CI, 6.5 to 19.2) when looking at patients homozygous for the PLA2R1 risk allele but either homozygous or heterozygous for the HLA-DQA1 risk allele. Similar findings have been reported in replication studies from Korea and Taiwan; the lower odds ratio in Asians suggests true differences in effect size between different ethnicities but may also reflect convergence to the mean. Because
these SNPs are thought to represent “tag-SNPs” for the true causal alleles, differences in linkage disequilibrium structure between ethnicities may also account for this discrepancy in odds ratios. It is expected that fine mapping of these loci and more detailed analysis of haplotype structures across different populations will clarify the origin of the signals within each locus.

Among the most intriguing aspects of the report from Lv et al. is the subanalysis done in 71 patients with MN, subdivided into low risk versus high risk according to their PLA2R1 and HLA-DQA1 genotypes, looking at two increasingly important phenotypes of MN: whether anti-PLA2R antibodies are detectable in serum, and whether PLA2R can be detected in glomerular deposits by immunofluorescence.12 None of the 19 MN patients homozygous for low-risk PLA2R1 and HLA-DQA1 genotypes had detectable anti-PLA2R antibodies, whereas 36 of the 52 (65%) remaining patients with one or both high-risk genotypes demonstrated antibody positivity. Likewise, PLA2R staining of glomeruli was enhanced in none of the 19 patients with both low-risk genotypes compared with 36 of the 50 (65%) of the remaining patients with one or both high-risk genotypes and adequate biopsy tissue for analysis. Interestingly, the predictive power of genotypes was mostly attributable to the PLA2R1 locus: 73% of individuals homozygous for risk alleles at this locus alone were antibody positive. Similar to most risk alleles underlying complex traits, the PLA2R1 risk variants are located in noncoding regions, and the identity of the causal mutation is not known. One can speculate that the causal variant(s) exert a regulatory role, somehow altering the expression level or localization of the encoded protein. These results, linking genotype to phenotype, concur with a recent study by the investigators of the European GWAS in which the PLA2R1 gene was sequenced in 60 patients with PLA2R-related MN (by serology and/or histopathology) and six common sequence variants were significantly associated with disease.13 Lv et al. also report an association between risk genotypes of PLA2R1 and histopathologic stage of MN, although this classification scheme has not been found, in two recent MN cohorts, to correlate with disease outcomes.14,15

The last decade has witnessed remarkable progress in unraveling the genetic factors that influence the pathogenesis of virtually every glomerular disease. MN does not stand alone. It is increasingly recognized that understanding the genetic basis of MN may lead to novel therapeutic opportunities. In this regard, the current study by Lv et al. represents an important step as we get closer to decoding the genes that explain why such autoantibodies develop.

**DISCLOSURES**

None.

**REFERENCES**


See related article, “Interaction between PLA2R1 and HLA-DQA1 Variants Associates with Anti-PLA2R Antibodies and Membranous Nephropathy,” on pages 1323–1329.