Membranous nephropathy (MN) is the leading cause of primary nephrotic syndrome in white adults and a major cause of nephrotic syndrome across global populations. In MN, circulating antibodies permeate the glomerular basement membrane and, in the subepithelial space, form immune complexes with antigens on podocyte membranes. Recently, PLA2R antibodies are detected in 60%–75% of idiopathic MN cases across many ethnicities.1,2 Additional podocyte autoantigens—mitochondrial SOD 2, aldose reductase, α-enolase, and neutral endopeptidase3,4—have likewise emerged as potential targets of MN-specific autoantibodies, potentially filling in the missing gaps in PLA2R antibody-negative disease. These breakthroughs have established MN as a disease of autoantibodies and, in many ways, challenge the continued use of the term idiopathic MN.5 Nonetheless, we still do not know why, exactly, such autoantibodies develop in MN. The identified podocyte antigens are endogenously expressed; only the autoantibodies against such antigens are detected in patients with MN.

Previous case reports of familial forms of MN have suggested a genetic predisposition to disease.6 In a recent genomewide 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 2q24.7 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,8 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).9 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 Korea10 and Taiwan11; 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 PLAR2I 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 PLAR2I 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 PLAR2I locus: 73% of individuals homozygous for risk alleles at this locus alone were antibody positive. Similar to most risk alleles underlying complex traits, the PLAR2I 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 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 by coming increasingly close to shedding the qualifier, “idiopathic.” Other glomerular diseases, such as FSGS,16 IgA nephropathy,17 and ANCA-associated vasculitis,18 have demonstrated a genetic predisposition to disease in studies similar to those by Stanescu et al. and Lv et al. However, the large odds ratio conferred by joint homozygosity for MN risk alleles suggests that genetic profiling may have some utility as a screening test for MN or for defining epidemiologic risk in the population. For example, based on published genotype frequencies in controls, as many as 0.14% of Asians and 0.54% of Europeans are homozygous for risk alleles at both loci and are therefore at highest risk for MN.7,9 Identification and prospective follow-up of these individuals in existing epidemiologic cohorts may help define the natural history of disease. Moreover, the PLA2R1 and HLA genotypes may serve as a method for defining subtypes of MN by pathogenetic mechanism, thereby enabling better analysis of disease progression, remission, and response to therapy. For example, genotypes could potentially explain why some patients with primary MN have spontaneous remissions whereas others display a frequently relapsing phenotype, and why recurrent MN does or does not occur in recipients of kidney transplants. This sort of risk stratification is desperately needed in MN, a disease with the broadest spectrum of natural history, ranging from spontaneous remission to unrelenting progression toward ESRD. Recent advances have moved us away from proteinuria and toward autoantibody titers in the search for a disease-specific risk assessment tool,19 but this may just be an intermediate 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.