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CLINICAL RESEARCH

Identification of a Locus on the X Chromosome Linked to Familial Membranous Nephropathy

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Introduction: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome (NS) in adults and is a leading cause of end-stage renal disease due to glomerulonephritis. Primary MN has a strong male predominance, accounting for approximately 65% of cases; yet, currently associated genetic loci are all located on autosomes. Previous reports of familial MN have suggested the existence of a potential X-linked susceptibility locus. Identification of such risk locus may provide clues to the etiology of MN.

Methods: We identified 3 families with 8 members affected by primary MN. Genotyping was performed using single-nucleotide polymorphism microarrays, and serum was sent for anti-phospholipase A2 receptor (PLA2R) antibody testing. All affected members were male and connected through the maternal line, consistent with X-linked inheritance. Genome-wide multipoint parametric linkage analysis using a model of X-linked recessive inheritance was conducted, and genetic risk scores (GRSs) based on known MN-associated variants were determined.

Results: Anti-PLA2R testing was negative in all affected family members. Linkage analysis revealed a significant logarithm of the odds score (3.260) on the short arm of the X chromosome at a locus of approximately 11 megabases (Mb). Haplotype reconstruction further uncovered a shared haplotype spanning 2 Mb present in all affected individuals from the 3 families. GRSs in familial MN were significantly lower than in anti-PLA2R–associated MN and were not different from controls.

Conclusions: Our study identifies linkage of familial membranous nephropathy to chromosome Xp11.3-11.22. Family members affected with MN have a significantly lower GRS than individuals with anti-PLA2R–associated MN, suggesting that X-linked familial MN represents a separate etiologic entity.

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MN is the most common cause of NS in adults and is a leading cause of end-stage kidney disease (ESKD) due to glomerular disease.[1] Although common in adults, MN is uncommon in children and usually accounts for less than 5% of pediatric patients undergoing biopsy for NS.[2] Across ages, MN demonstrates a 2:1 male predominance and is most often a sporadic disease.[3] Rare examples of familial MN have also been reported, usually presenting in siblings.[4] Although MN can occur in the context of systemic disease (secondary), primary (or idiopathic) MN accounts for 80% of cases in adults, of which approximately one-third progress to ESKD within 5 to 15years.[1,3,5]

Importantly, 85% of individuals with primary MN have IgG4 autoantibodies against the podocyte membrane antigen PLA2R, meaning that treatment tends to

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involve immunosuppressive therapy.[3] There remains a subset of patients with primary MN who have no identified autoantibodies and indeed have variable response to immunosuppression.[6] The etiology in this subset of patients is not yet understood, and genetic studies could provide important clues about disease mechanisms, especially in the context of familial clustering.

Although MN has a strong male predominance, currently associated alleles are all located on autosomes.[7] Genome-wide association studies implicate risk alleles in both *HLA-DQA1* and *PLA2R* genes, which contribute the highest proportion of disease risk, and in newly identified loci encoding *NFKB1* and *IRF4*, contributing a smaller proportion.[7–10] Identification of a risk locus (or loci) on the X chromosome could help explain why males are predominantly affected.

Our study investigates 3 families with idiopathic MN and negative anti-PLA2R antibodies with pedigrees suggestive of X-linked inheritance. We sought (i) to determine whether there is a risk locus on the X chromosome in these families, and (ii) to determine whether the known *HLA-DQA1*– and *PLA2R*-associated risk alleles contribute to their genetic risk.

METHODS

The study recruited 3 families of European ethnicity with 8 members affected by biopsy specimen-proven idiopathic MN. Affected members had serum tested for anti-PLA2R antibodies using the enzyme-linked immunosorbent assay.[11] Clinical features, such as age at presentation, response to immunosuppressive therapy, progression to renal failure, and renal transplant status, were also obtained from each individual's home institution, if available.

DNA was isolated from the 8 affected and 18 apparently unaffected family members from whole blood using standard procedures. Family 1 was genotyped *via* Omni-X-24 BeadChip (Illumina, San Diego, CA), with a total of 741,000 markers, and families 2 and 3 were genotyped *via* an Infinium Multi-Ethnic Global BeadChip (Illumina), with a total of 1,779,819 markers. Genotype files then underwent quality control checks as described previously.[12] Multipoint parametric linkage analysis, performed for families 1 to 3 using a model of X-linked recessive inheritance, was conducted in both Allegro (deCODE Genetics, Reykjavik, Iceland) and Merlin (University of Michigan, Ann Arbor, MI).[13,14] Alohomora (Max Delbruck Center (MDC) for Molecular Medicine Berlin-Buch, Germany) was used to generate input files for both linkage programs, and linkage output files were visualized using R 3.2.0 software (R Foundation for Statistical Computing, Vienna, Austria).[15] Haplotype reconstruction was performed and visualized in HaploForge (Free Software Foundation, Boston, MA),[16] with input files generated by Allegro. X-chromosomal regions were considered significant for linkage if the logarithm of the odds (LOD) score was >2.475 due to the lower number of recombination events on gonosomes.[17]

GRSs in our families with familial MN were calculated using the odds ratios at each autosomal risk loci, *HLA-DQA1* and *PLA2R*, determined from an independent historical genome-wide association studies analysis.[7] The GRS was computed by the sum of the natural logarithm of the odds ratio at each autosomal risk SNP multiplied by the number of risk alleles (0, 1, or 2), divided by the number of possible alleles.[18] The GRS was calculated for study individuals affected with familial MN (n = 8), unaffected (n = 18), and combined (n = 25). Scores were then compared against a European adult cohort of anti-PLA2R–positive MN patients (n = 410) and healthy European controls (n = 5642). Results were statistically compared using the χ^2 test with the Bonferroni correction for multiple comparisons. Statistical analysis and data visualization was performed in R 3.2.0 software.

RESULTS

Family Pedigrees

Pedigrees for each family are displayed in Figure 1. Pedigree analysis showed a pattern consistent with X-linked recessive inheritance in all families.

Clinical Details for Affected Family Members

All affected individuals included in the study had biopsy specimen-proven idiopathic MN and all had negative serologic test results for anti-PLA2R antibody. Histopathology images of family 1 have been published previously[4]; histopathology images for families 2 and 3 were unavailable. Histopathology features observed in the 3 families are detailed in Supplementary Table S1. No other autoimmune diseases were reported in any family member included in this study. Please refer to Figure 1 for pedigree position of each individual (identification numbers in bold) outlined in the family descriptions, below.

Family 1

Details of this British family have been reported previously.[4] Briefly:

61: Individual presented at age 3 years with NS, microscopic hematuria, and hypertension, which were initially responsive to combination therapy of corticosteroids and cyclophosphamide. Although this immunosuppression put him into remission at first, he went on to develop a relapsing course and eventually

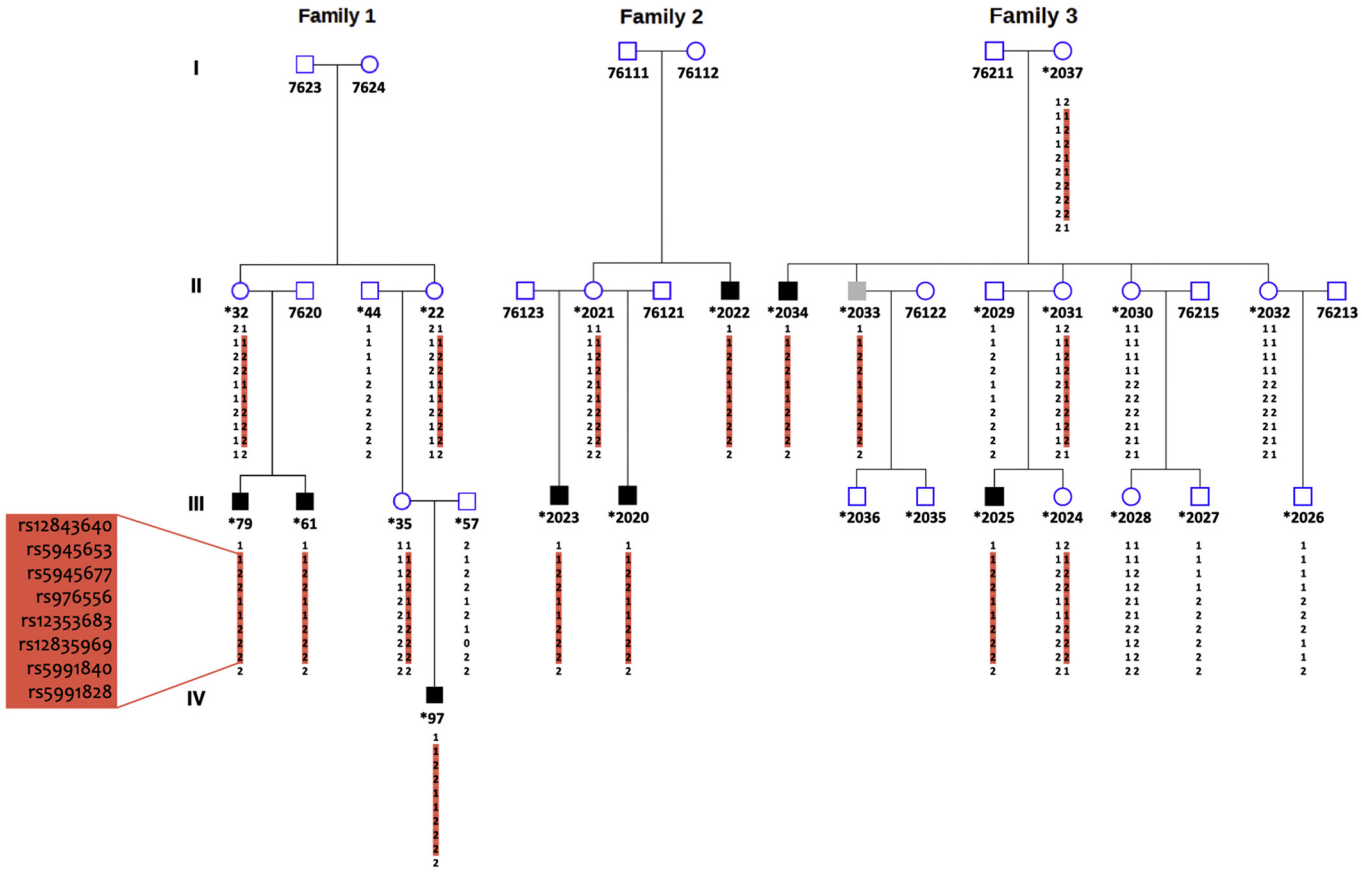

Figure 1. Pedigrees and haplotypes of families 1, 2, and 3 with familial membranous nephropathy. Squares indicate males and circles indicate females. A black symbol indicates that the individual is affected, a white symbol indicates the individual is unaffected, and a grey symbol indicates that the individual's affectation status is unknown. Asterisks indicate individuals who were genotyped and included in the study. Red boxes indicate the shared haplotype (rs12843640-rs5991828). Pedigree analysis in all 3 families showed a pattern consistent with X-linked recessive inheritance (i.e., only males are affected and inheritance is *via* the maternal line with no male-to-male transmission).

develop ESKD. He received a renal transplant at age 23 years and has not had subsequent recurrence of disease.

79: Individual presented at age 10 years with NS that was unresponsive to corticosteroids and a trial of azathioprine. He also had significant hypertension that led to a hypertensive crisis, seizures, and cerebral infarction, leaving him with permanent neurologic deficits. A spontaneous remission of NS occurred after 1 year, but it did eventually relapse. He was treated with cyclophosphamide and had some improvement. Like his brother, however, he went on to develop a relapsing disease course accompanied by declining glomerular filtration rate. At the last follow-up (age 31 years), he had chronic kidney disease stage 4.

97: Individual presented at age 1 year with NS, hematuria, and hypertension, which were unresponsive to steroids. He has had a relapsing disease course, with relapses occurring approximately every 3 months. At the last follow-up (age 16 years), he was in chronic kidney disease stage 3 and in partial remission and was being treated with mycophenolate mofetil, cyclosporin, and an angiotensin receptor blocker.

Family 2

This family resides in Canada.

2020: Individual presented at age 11 years with NS that eventually progressed to ESKD treated with a renal transplant. He then developed recurrence of disease post-transplant. Whether he had response to immunosuppression is unknown.

2023: Individual presented at age 6 years with NS that also progressed to ESKD, and like his half-brother, he developed disease recurrence after renal transplant.

2022: Individual presented in teenage period with kidney disease that progressed to ESKD. Whether he had features of NS or response to immunosuppression is unknown. He underwent 3 kidney transplants, all of which failed due to recurrence of disease.

Family 3

This family resides in Spain.

2025: Individual presented at age 5 years with NS that was treated with cyclosporine to induce full remission.

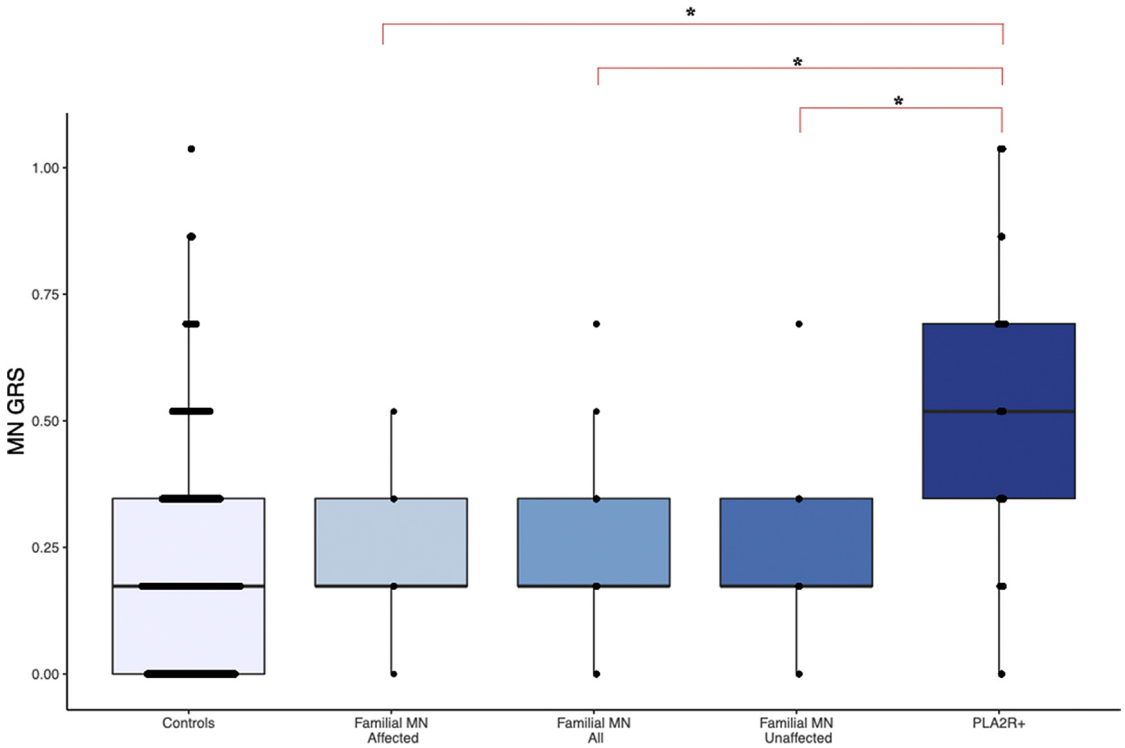

Figure 2. Box and whisker plot shows genetic risk scores (GRSs) in familial membranous nephropathy (MN). Median values (line inside the box) for each group with upper and lower quartiles (top and bottom) are represented by boxes, with whiskers delineating variability outside quartiles. Outliers are plotted as individual point beyond whisker limits. Asterisks indicate $P < 0.05$ using the χ^2 test with the Bonferroni correction.

2033: Individual was assessed at age 50 years. At that time, he had no clinical evidence of kidney disease. This family was lost to follow-up, and whether proteinuria has since developed is unknown.

2034: Individual is currently age 55 years and has a phenotype of NS. He presented with symptoms in adulthood, and whether he had any response to immunosuppression is unknown.

Genetic Risk Scores

GRSs in familial MN, calculated using risk estimates at *HLA-DQA1* and *PLA2R* loci, were found to be significantly lower than in individuals with MN associated with anti-PLA2R antibodies. GRSs in familial MN were not significantly different than controls (see Figure 2).

Linkage Analysis

Multipoint parametric linkage analysis for X-linked recessive inheritance in the 3 families initially revealed an 11-Mb region of linkage on the X chromosome. This region had a LOD score of 3.260 and had flanking markers of rs12014680 and rs2360739 (see Figure 3).

Haplotype reconstruction confirmed that the affected individuals within each family shared a haplotype that was also present as 1 allele in the unaffected "carrier" mothers. In families 1 and 2, this haplotype was not present in any other individuals; however, 1 adult man (aged 50 years) with unknown affectation status in family 3 shared the same haplotype across the linked region as the affected male individuals (see Figure 1 and Supplementary Figure S1). Because disease onset was observed in this family beyond the pediatric period (>18 years), we designated this individual as affectation status unknown so his data do not contribute to the LOD score.

Haplotype reconstruction showed flanking markers rs3027452 and rs2360739. A shared haplotype (i.e., identical alleles at all 8 markers) was further identified between all individuals carrying a risk allele, spanning a narrower region of 2 Mb (rs12843640–rs5991828), suggesting a shared distant common ancestor (founder effect).

This 11-Mb linked region on the X chromosome mapped to Xp11.3-p11.22, which contained 167 unique genes based on the Human Genome Organisation (HUGO) Official Gene Symbol listed in University of California Santa Cruz (UCSC) Genome Browser.[19] They represent a wide range of functionalities, including many ubiquitous proteins. Restricting the linked area to the 2-Mb region of the shared haplotype (Xp11.22) limited the list to 70 unique genes (see Table 1).

DISCUSSION

In this study, we present 3 families affected by renal biopsy specimen-proven idiopathic MN, mostly

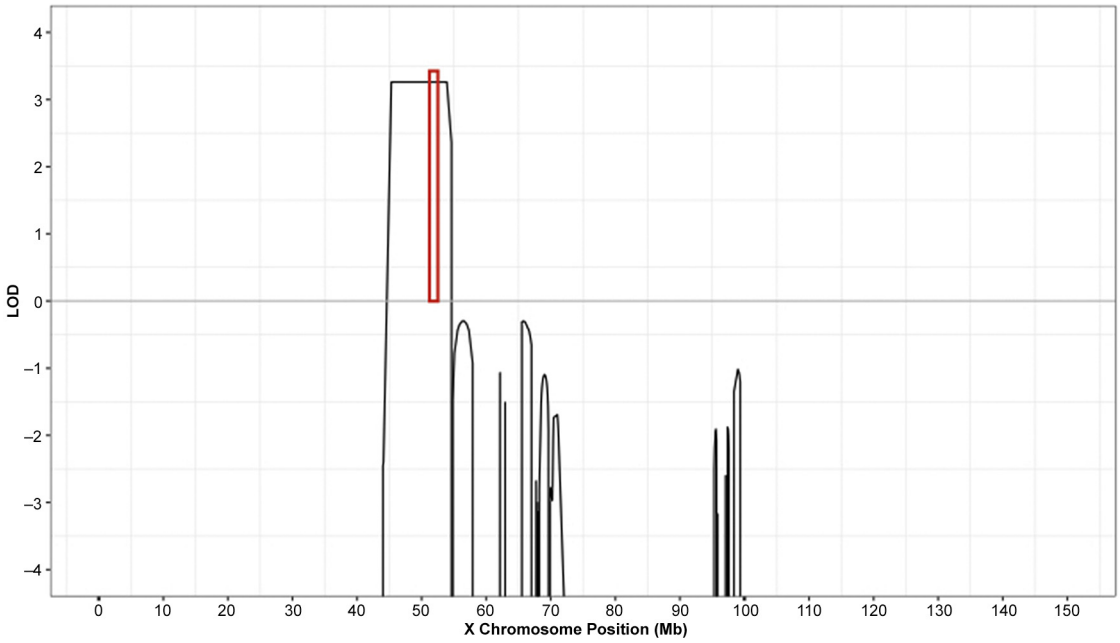

Figure 3. Multipoint parametric linkage analysis on chromosome X for families 1, 2, and 3. The *y* axis shows the logarithm of the odds (LOD) score, and the *x* axis gives the genomic position in megabases (Mb). Note significant linkage of 3.260 in the region of 43 to 54 Mb (reference genome: GRCh37). The red box indicates the area of shared identical haplotype in all 3 families (51–53 Mb).

presenting in childhood. All affected individuals were males connected through the maternal line, suggesting X-linked inheritance. By calculating GRSs in these families using risk allele counts at known autosomal risk loci, *HLA-DQA1* and *PLA2R*, we observed that the GRS was lower in familial MN compared with anti-PLA2R antibody-associated disease. Combined with the finding that all affected individuals also had negative serologic testing for anti-PLA2R antibodies, this suggested that the observed familial clustering was unlikely to be attributable to aggregation of known genetic risk factors and coincidental occurrence of the most prevalent cause of disease. In addition, although all of the families were of similar European ethnic background, they were recruited from 3 countries, and within each family, individuals from at least 2 different households were affected. These details imply that shared environmental exposures are unlikely to explain the observed familial clustering of disease.

Using X-linked recessive multipoint linkage analysis, we identified an 11-Mb region on the X chromosome (Xp11.3-p11.22) that is linked with MN in these families. This region can potentially be narrowed to a 2-Mb (Xp11.22) locus at which all marker alleles are identical-by-state if identical-by-decent inheritance from a common ancestor is inferred. These results suggest that familial MN represents a different genetic etiology than the more commonly associated sporadic PLA2R-positive MN and that perhaps the inheritance is derived from an X-linked susceptibility locus mapped to this newly identified X-linked region.

X-Linked Familial MN

There are several reasons why the linked region identified on the X chromosome is convincing to explain the pattern and predominance of primary MN in our 3 families. First, 7 of 8 of the affected individuals presented with nephrotic syndrome in childhood. We know that MN in childhood is rare, accounting for only 1.5% to 7% of children undergoing biopsy for NS.[20–22] However, because many children with steroid-sensitive NS do not undergo biopsy, the true prevalence remains unclear. The incidence of childhood MN is estimated at less than 1 per 1,000,000-child population per year.[23] If we consider this estimated incidence and calculate the likelihood of these affected family members presenting with MN by chance (given the absence of known genetic risk alleles in the families), we find that likelihood would be less than 10^{-18} in families 1 and 2, and less

Table 1. Unique genes within 2 megabases of shared haplotype (Xp11.22)

AC239367.3, LINC01284, AC233976.1, AC233976.2, NUDT10, AL158055.1, EZHIP, NUDT11, LINC01496, CENPVL3, CENPVL2
CENPVL1, GSPT2, MAGED1, AC241520.1, RNU6-504P, AL929410.1, IPO7P1, AL929410.2, TPMTP3, AC239585.1, AC239585.2, MAGED4B, SNORA11E, MAGED4, SNORA11D, AC231759.2, AC245177.1, AC231759.1, MIR8088, XAGE2, AC231532.1, AC231532.2, BX510359.1, BX510359.5, BX510359.8, BX510359.7, RBM22P6, XAGE1A, BX510359.6, BX510359.2, BX510359.4
BX510359.3, SSXP4, SSXP1, AL450023.2, SSX8P, SSX7
AL450023.1, RNA5SP504, SSXP5, AL450023.3, SSX2, AC244505.2, AC244505.3, AC244505.5, SSX2B, AC244505.7
AC244505.4, SPANXN5, AC244505.6, XAGE5, AC244505.1
EIF4A2P4, XAGE3, AC244505.1, EIF4A2P4, FAM156B
AC234031.1, FAM156A

than 10^{-12} in family 3. Therefore, it is highly likely that these families share a common basis for disease.

Furthermore, MN is known to have a 2:1 male predominance. Whether the biological factors that contribute to this are related to the X-linked mechanism associated with the disease in the 3 families presented here is unknown. Importantly, previous genome-wide association studies analyses in MN did not include the X chromosome due to its unique statistical challenges, so they would not have detected any common genetic variants located there that contribute to disease risk[7–10,24]

Shared Haplotypes

Haplotype reconstruction further identified a 2-Mb identical shared haplotype in all individuals who carried the risk allele. This suggests that all 3 families share a distant common ancestor, representing a founder effect. Extended family histories were not available. Comparison of haplotypes between the individuals who were (n = 9) and were not (n = 17) carrying the 11-Mb risk allele revealed that no non-carrying individuals harbored this 2-Mb region, suggesting that this result is highly unlikely to occur by chance. Furthermore, we looked at the 1000 Genomes Project phase 3 data set and found that this haplotype was not present in any of these control individuals (n =2504, of which 670 are of European ethnicity).[25] This result demonstrates that the haplotype is not a common haplotype in the population and implies identical by descent inheritance in the 3 families of the 2-Mb region.

Genes of Interest in Linked Regions on X Chromosome

The 11-Mb region of Xp11.3-p11.22 contains 167 genes that code for proteins with a wide range of physiologic functions. Focusing on the 2-Mb common haplotype (Xp11.22), however, further narrows this list to 70 potential genes. To hypothesize about which genes were implicated in disease, we dissected the types of genes/proteins represented within this region. We used the UCSC Human Gene Sorter, a data-mining tool, to narrow our list of regional genes.[26] Idiopathic MN is characterized by IgG4 deposition in the glomerular basement membrane, and IgG antibodies are synthesized exclusively by B cells.[27] Therefore, we restricted our UCSC search to genes/proteins implicated in immune function, including expression in B and T lymphocytes.

Using the UCSC Human Gene Sorter to visualize gene expression *via* Genotype-Tissue Expression (GTEx),[28] we identified *GSPT2*, the G1-to-S phase transition 2 protein that mediates translation termination of a large protein product,[29] and *MAGED1*, the melanoma antigen (MAGE) family member D1 gene that regulates transcription factor complex formation,[30] to both have above-average expression in lymphocytes and whole blood, respectively. Previous reports have associated an Xp11.22 deletion encompassing these genes to be associated with intellectual disability and developmental delay; however, the consequences of loss of function in either of these genes has not been elucidated in humans or mouse models to date.[31] Perhaps one of these genes has a role in mediating familial MN. For completion, we also searched in the Human Kidney Cell Atlas for gene expression in podocytes, but we found none.[32]

Lastly, within the UCSC Genome Browser, we used the Gene Ontology tool to identify whether any of the 70 genes were cell-membrane proteins that could possibly be implicated as presenting antigens to the immune system. *FAM156A* was the only gene labeled as such, but showed very low tissue specificity in the Human Protein Atlas.[33] Future work through whole-genome sequencing and including additional cases is needed to further unpack these hypotheses, in order to refine the locus and thereby limit the coding or noncoding shared rare variants among affected patients.

Disease Response to Immunosuppression in Families 1 and 3

We have demonstrated that the genetic region Xp11.3-p11.22 is linked to the development of familial MN and propose that this underlying genetic locus causes disease susceptibility rather than monogenic pathogenicity. This is suggested for 3 reasons: (i) affected family members in families 1 and 3 demonstrated varying response to immunosuppression; (ii) there were varying ages of presentation across all affected individuals (ages 1 to >18 years); and (iii) the absence of a history of further affected family members, which would be expected, if this locus had 100% penetrance. These clinical aspects raise the hypothesis that instead of having a causal genetic variant leading to disease, perhaps instead, these families have a genetically conferred susceptibility that predisposes them to disease but requires other triggers for them to fully develop MN.

Previous susceptibility genes have been described. Perhaps the best-known example is *APOL1*, in which specific genetic variations are found only in individuals of African descent that lead to increased risk of developing multiple types of kidney disease.[34] More importantly, polymorphisms in the *TNFA* gene have been associated with susceptibility to idiopathic MN in adults.[35] Indeed, further uncovering of the genes and

their function within this X-linked region will aid in this search.

CONCLUSIONS

In summary, our study shows significant linkage of familial MN to chromosome Xp11.3-11.22. MN family members have a significantly lower GRS than individuals with more typical MN associated with anti-PLA2R antibodies, suggesting that genetic risk in familial MN is distinct and that it encompasses an X-linked susceptibility locus mapped to this X-linked region.

DISCLOSURES

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Histopathology features in familial membranous nephropathy.

Figure S1. Haplotype reconstruction of 11-Mb-linked region (rs3027452-rs2360739) on chromosome X for families 1 to 3.

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