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Pathogenesis of Immunoglobulin A Nephropathy: Recent Insight from Genetic Studies

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Abstract

Recent genome-wide association studies (GWAS) have identified multiple susceptibility loci for immunoglobulin A nephropathy (IgAN), the most common form of glomerulonephritis, implicating independent defects in adaptive immunity (three loci on chromosome 6p21 in the MHC region), innate immunity (8p23 *DEFA* locus, 17p23 *TNFSF13* locus, 22q12 *HORMAD2* locus), and the alternative complement pathway (1q32 *CFH/CFHR* locus). In geospatial analysis of 85 populations, a genetic risk score based on the replicated GWAS loci is highest in Asians, intermediate in Europeans, and lowest in Africans, capturing the known difference in prevalence among world populations. The genetic risk score also uncovered a previously unsuspected increased prevalence of IgAN-attributable kidney failure in Northern Europe. The IgAN risk alleles have opposing effects on many immune-mediated diseases, suggesting that selection has contributed to variation in risk allele frequencies among different populations. Incorporating genetic, immunologic, and biochemical data, we present a multistep pathogenesis model that provides testable hypotheses for dissecting the mechanisms of disease.

Keywords

adaptive immunity; innate immunity; alternative complement system; IgA glycosylation; GWAS; IgA nephropathy

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common type of glomerulonephritis worldwide. It was recognized as a separate category of glomerulonephritis when Berger applied the immunofluorescence staining technique to renal biopsy in 1968 (1). Much progress has occurred in understanding immunologic and biochemical defects underlying IgAN (most recently reviewed in Reference 2). This review focuses on recent genetic studies of IgAN, which have enabled reinterpretation of classic clinical and epidemiologic findings and have led to the formulation of a new pathogenesis model.

DISCLOSURE STATEMENT

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CLINICAL FEATURES

IgAN manifests with recurrent episodes of gross hematuria, microscopic hematuria, or acute nephritic syndrome, which often coincide with mucosal infections (3). The peak incidence is in the second and third decades of life. A kidney biopsy is required for diagnosis and is characterized by mesangial immunodeposits of IgA1 with C3 and occasionally IgG or IgM (4). The alternative pathway components C3 and properdin (P) and the membrane attack complex (C5b--9) are generally detected in the mesangial deposits, whereas the classical pathway components C1q and C4 are usually absent. Serum concentrations of C3 and other complement proteins are typically normal, suggesting an alternative pathway is activated in situ in the kidney (5).

Hematuria is typical and often includes episodes of macroscopic bleeding that coincide with mucosal infections, including those of the upper respiratory tract or digestive system. Proliferation of mesangial cells and expansion of extracellular matrix are found in patients with mild clinical disease, but progressive glomerular and interstitial sclerosis leads to end-stage kidney failure in 20%--40% of patients within 20 years after diagnosis (6). The predictors of poor renal outcome in IgAN include higher levels of proteinuria, histology grade, systolic blood pressure, and degree of renal function impairment at diagnosis, as well as lower albumin and hemoglobin levels at the time of biopsy (7--10). Interestingly, IgAN recurs in up to 50% of renal allografts (11); however, immune deposits in a kidney transplanted from a donor with subclinical IgAN into a patient with non-IgAN renal disease clear within several weeks (12). These findings suggest that the cause of IgAN is extrarenal and is most likely due to abnormalities in the circulation.

IgA1 GLYCOSYLATION DEFECTS

New insight into pathogenesis emerged from the analysis of the glycosylation of IgA1 (13, 14). Owing to significant differences between the human and rodent IgA systems, human studies were critical in elucidating the role of IgA1 glycosylation defects. Whereas rodents express only one type of IgA, humans and hominoid primates have two IgA subclasses, IgA1 and IgA2 (15). IgA1 is the predominant subclass in circulation while IgA2 is more abundant in mucosal sites. IgA1 has a unique hinge region between the first and second constant-region domains that has multiple serine and threonine residues. This segment is the site of attachment of up to six *O*-linked glycan chains consisting of *N*-acetylgalactosamine (GalNAc) and a β 1,3-linked galactose, both of which may be sialylated (16--19). *O*-linked glycans are synthesized in a step-wise manner, beginning with attachment of GalNAc to serine or threonine. The carbohydrate composition of the *O*-linked glycans on normal human circulatory IgA1 is variable, with the largest glycan being a tetrasaccharide consisting of GalNAc, Gal, and two sialic acid residues. In patients with IgAN, immune complexes in circulation and in kidney deposits contain IgA1 with galactose-deficient *O*-linked glycans (Gd-IgA1) (20--23). Aberrant glycosylation in IgAN affects only IgA1 and not other glycoproteins with *O*-linked glycans, suggesting a specific defect (14, 24). The pathogenicity of Gd-IgA1 is further supported by the finding that among patients with IgA1 myeloma, only those with Gd-IgA1 develop IgA1-associated immune-complex glomerulonephritis (25, 26). Moreover, our studies have demonstrated that IgA1-producing cells are the source of the abnormal IgA1 glycoforms (27). IgA1-producing cells from IgAN patients have multiple enzymatic defects that shift the IgA1 glycosylation pathway toward production of Gd-IgA1, in which some of the *O*-glycans are galactose deficient (27). These data imply regulatory defects upstream of the glycosylation enzymes in IgAN.

The measurement of Gd-IgA1 has been facilitated by the development of a sensitive enzyme-linked immunosorbent *assay* with a GalNAc-specific lectin that can establish

normative values in large populations (28). Studies using this assay have shown that levels of Gd-IgA1 in supernatant of IgA1-producing cells and in serum of the matching donors are highly correlated, and 50%--78% of IgAN patients have serum Gd-IgA1 levels above the 95th percentile of healthy controls (28). This finding has been reproduced in European, African-American, and Asian populations, identifying abnormal IgA1 glycosylation as a common defect underlying the development of disease (29--31).

FAMILY STUDIES

Prior studies have demonstrated a range of immunologic defects in asymptomatic family members of IgAN patients, including increased production of IgA1, IgM, and cytokines at baseline and after antigenic stimulation (32, 33). More recently, systematic family studies have shown that elevated Gd-IgA1 levels are heritable, with 25%--33% of asymptomatic family members displaying levels that are just as elevated as the patients' (34, 35). These findings have been replicated, implicating abnormal IgA1 glycosylation as a consistent inherited risk factor across major ethnicities (29, 30). The heritability of Gd-IgA1 is >50% and is not explained by total IgA1 levels, indicating independent genetic control (34).

Gd-IgA1 is usually detected in complex with IgG or IgA1 antibodies specific for the aberrantly glycosylated hinge regions (36), suggesting that a second hit (viral or somatic) leads to production of antiglycan antibodies and results in formation of immune complexes that ultimately deposit in the kidney. IgAN patients also have a more pronounced IgG responses to mucosal antigens (37), perhaps enhancing the antiglycan IgG response.

Finally, although most cases of IgAN occur as sporadic disease, familial aggregation of biopsy-proven IgAN has been widely reported (38, 39). Studies have also shown increased prevalence of IgAN in isolated populations, implicating founder effects leading to disease (40, 41). Linkage studies have found multiple susceptibility loci for familial disease, but underlying genes have not been identified to date, likely owing to genetic heterogeneity and small family size (42, 43).

GENOME-WIDE ASSOCIATION STUDIES

There are three published genome-wide association studies (GWAS) of IgAN. The first GWAS, performed in 533 European cases and 4,980 public controls, identified a significant association at the major histocompatibility (MHC) locus (44). We performed a GWAS in 3,144 cases and 2,822 controls, with discovery in Han Chinese and follow-up in Asian and European cohorts, in which we identified five susceptibility loci for IgAN. These included three distinct loci in the MHC region as well as the *CFH/CFHR* locus and the *HORMAD2* locus (45). We have now extensively replicated these findings in 12 Asian and European cohorts including a total of 10,755 individuals (46). Another recent GWAS in Han Chinese cohorts of 4,137 cases and 7,734 controls identified two additional loci, *DEFA* and *TNFSFR13* (47). A summary of the GWAS loci discovered to date, including each one's approximate effect size, population frequency, and potential role in IgAN pathogenesis, is provided in Table 1. Although for many of these loci, the underlying causal variants are yet to be identified, the GWAS findings have generated new insight into the pathogenesis of IgAN.

The MHC Loci (Chromosome 6p21)

All three GWAS have identified multiple signals within the MHC region. Owing to the complexity of the MHC haplotype structure, its significant variability among world populations, and the relatively sparse coverage provided by standard GWAS SNP-chips, the

origin of the signals has not been precisely localized and will require higher-resolution mapping.

In our study, the strongest association was observed in the region that included the *HLA-DQB1*, *-DQA1*, and *-DRB1* genes. The association was supported by a large cluster of single-nucleotide polymorphisms (SNPs) in high linkage disequilibrium (LD) with the top SNP (rs9275596). Imputation of classical human leukocyte antigen (HLA) alleles identified a highly protective effect conferred by the *DQB1*0602-DRB1*1501* haplotype (45). However, this region harbors some of the most polymorphic genes in the human genome and has a complicated haplotype structure. Not surprisingly, conditional analyses in larger cohorts have identified at least two other independent risk haplotypes within this region (46). The third GWAS, conducted exclusively in the Han Chinese cohorts, confirmed the strongest signal in this region, also represented by at least three SNPs. The presence of multiple modest-sized signals explains why prior association studies with older HLA typing methods had yielded contradictory results (48--50).

This interval has been implicated in many immune-mediated disorders that show clinical overlap with IgAN, such as celiac disease (51), IgA deficiency (52), and inflammatory bowel disease (53), but the IgAN-associated SNPs are distinct from (in equilibrium with) those associated with these disorders. The *DRB1*1501-DQB1*0602* haplotype is common in the European and Asian populations and has been implicated in the risk of multiple disorders of immunity and response to environment: it has been associated with increased risk of multiple sclerosis (54), systemic lupus erythematosus (55), narcolepsy (56), and hepatotoxicity from COX2 inhibitors (57). The same haplotype is highly protective from type 1 diabetes mellitus (58).

The second independent locus within MHC contains the *TAP1*, *TAP2*, *PSMB8*, and *PSMB9* genes and the *PPP1R2P1* pseudogene. One of the top-scoring SNPs, rs2071543, is a missense variant (Q49K) in exon 2 of *PSMB8*. Interestingly, decreased *PSMB8* expression has been detected in peripheral blood mononuclear leukocytes in IgAN, providing independent evidence that this may be the causal gene (59). The *TAP2* and *PSMSB8/PSMB9* genes have been implicated in antigen processing and presentation and play an important role in modulation of cytokine production and cytotoxic T cell response. Nonetheless, our recent replication study detected heterogeneity at this locus, likely due to a recombination hotspot directly centered over the *TAP2* gene, which may perturb LD patterns between tag-SNPs and causal variants (46). Therefore, higher density of SNP coverage on either side of the recombination hotspot will be needed to guide future replication and fine mapping efforts.

The third independent locus within MHC is centered over the region of the *HLA-DPA1*, *-DPB1*, *-DPB2*, and *COL11A2* genes. This region has been associated with increased risk of systemic sclerosis stratified for anti-DNA topoisomerase I or anticentromere autoantibodies (60), but the risk alleles associated with this phenotype are not in LD with any of the IgAN risk alleles. Presently, the involvement of this region in the pathogenesis of IgAN is not clear.

The *CFH* and *CFHR* Gene Cluster (Chromosome 1q32)

The association region identified on chromosome 1q32 encodes critical regulators of the complement system and has a complex genomic organization; it contains *CFH* and five *CFH*-related genes that have a high level of sequence similarity to *CFH* (61). Factor H (FH), encoded by the *CFH* gene, is the key inhibitor of the alternative complement pathway. It accelerates the decay of C3 convertase by binding C3b and targeting it for Factor I--mediated degradation. Structurally, FH is composed of 20 domains encoded by highly

repetitive short consensus repeats (SCRs). The C terminus of the molecule (recognition domain) is responsible for binding to cellular surfaces, and the N terminus (regulatory domain) mediates C3b binding and inhibition. In healthy individuals, FH is active both in the fluid phase (as a circulating molecule in the serum) and in the surface-bound form (coating endothelial cells to prevent complement-mediated damage). Similar to *CFH*, the *CFH*-related genes are composed of a variable number of SCRs and have related binding properties. These genes likely arose by segmental duplications of *CFH* during evolution. Notably, the presence of highly repetitive sequences makes this area particularly prone to copy-number variation (CNV) due to nonallelic homologous recombination with intra- and intergenic breakpoints. Because each SCR unit is encoded by a single exon, duplications, insertions, and deletions of individual exons (a process described as exon shuffling) likely contributed to the final organization of this gene cluster.

The loss-of-function mutations in *CFH* have been well studied and generally result in increased activation of the alternative pathway (62). Because microvascular structures are particularly prone to complement-mediated injury, FH defects frequently result in either glomerular or retinal disease. Mutations of the N terminus (regulatory domain) result in complement-mediated mesangioproliferative glomerulonephritis, such as C3 glomerulonephritis (C3GN), or dense-deposit disease (63). Mutations of the C terminus (surface-binding domain) result in the clinical picture of atypical hemolytic uremic syndrome, a systemic thrombotic disorder of endothelial injury with renal and hematologic manifestations. Because such deleterious alleles cause serious renal and systemic disease, they negatively impact reproductive fitness and thus are quickly eliminated from the population by purifying selection. Accordingly, their frequency is extremely low in human populations. However, several common variants in *CFH* have also been associated with human disease. The best example is the Y402H variant in SCR-7 of FH, which predisposes to age-related macular degeneration (AMD) (64). AMD is characterized by excessive complement activation with retinal deposition of alternative pathway proteins such as FH, C3, C5, and membrane attack complex (MAC), manifesting as drusen on fundoscopic eye exam. The harmful effect of Y402H variant in AMD is substantial, yet this variant is maintained at high frequency in human populations, implying this phenotype has a low impact on reproductive fitness.

The top SNP associated with IgAN, rs6677604, resides in intron 12 of the *CFH* gene. However, the minor allele of this SNP is in perfect LD with a common inherited CNV in this area: a deletion of two contiguous genes, *CFHR3* and *CFHR1* (*CFHR3,1-del*). Heterozygous individuals carrying *CFHR3,1-del* have a >40% reduction in the risk of IgAN. Interestingly, *CFHR3,1-del* has previously been associated with decreased risk of AMD (65), although defining its protective effect has been complicated by the strong effect of nearby Y402H (66). In contrast, this deletion accounts for all of the IgAN GWAS signal on chromosome 1q32, and Y402H has practically no effect on disease risk. More recently, a rare partial duplication of *CFHR3* and *CFHR1* leading to formation of a *CFHR3-1* hybrid gene has also been reported to cause an inherited form of C3GN (67). These findings support the hypothesis of a dosage effect of *CFHR1* and *CFHR3*: whereas lower copy number is associated with renal protection, additional copies increase the risk of complement-mediated glomerular disease. Nevertheless, *CFHR3,1-del* may represent a double-edged sword: though protective against AMD and IgAN, *CFHR3,1-del* has been associated with anti-FH antibody formation causing rare acquired forms of atypical hemolytic uremic syndrome (68, 69).

The above disease associations clearly imply an important functional role of the *CFHR3* and *CFHR1* genes. Unfortunately, not much is known about the mechanism of action for these peptides. From the genetic standpoint, dissociating the copy-number effect of *CFHR3* from

that of *CFHR1* has been difficult, because single gene deletions are extremely rare in humans, and specific mouse knockout models have not yet been developed. The available antibodies against CFHR3 and CFHR1 cross-react with FH and other CFHR peptides, precluding accurate quantification of serum levels of these proteins. Based on limited in vitro functional studies, the effects of CFHR3 and CFHR1 appear to be independent of FH. CFHR1 has been found to inhibit the terminal complement pathway by dampening C5 convertase activity and inhibition of MAC assembly (70). Similar to CFHR1, but unlike FH, CFHR3 also inhibits the C5 convertase. In addition, CFHR3 has been found to act with Factor I to promote degradation of C3b in the absence of FH (71). These actions, however, do not explain the protective effect of lower copy number of *CFHR3* and *CFHR1*. One plausible hypothesis is that CFHR3 and CFHR1 compete with FH for C3b binding but are less effective than FH at accelerating the decay of C3-convertase (71). As a result, the protective effect of FH is enhanced with lower levels of these peptides, but further studies are clearly needed to refine this possibility.

The genetic association at the *CFH* locus is consistent with prior immunofluorescence studies demonstrating the involvement of the alternative pathway in IgAN: renal tissue staining is typically negative for C1q (classical pathway) and variable for C4d and mannan-binding lectin (lectin pathway) but consistently positive for C3, P, and MAC (5, 72--75). Moreover, circulating levels of activated C3 products are elevated in IgAN (76, 77), and the urinary MAC, FH, and P levels are higher in patients with IgAN than in healthy controls (78). Based on these data, we speculate that the renoprotective effect of *CFHR3,1-del* may be related to the relatively unopposed inhibitory effect of FH on C3 convertase, overall leading to the suppression of the alternative pathway. These findings open avenues for novel therapeutic approaches for IgAN. For example, targeted depletion of CFHR3 and CFHR1, treatment with recombinant FH, or suppression of the terminal complement pathway with anti-C5 antibodies may be of benefit in IgAN.

The *HORMAD2* Locus (Chromosome 22q12)

The fifth GWAS signal was found in a gene-rich area on chromosome 22q12 containing *HORMAD2*, *MTMR3*, *LIF*, *OSM*, and several other genes. In our study, the association was strongest at rs2412971, an intronic SNP in the *HORMAD2* gene, whereas in the Chinese GWAS, the signal peaked at rs12537, which is located in the 3' untranslated region of the *MTMR3* gene. Both of these SNPs are in strong LD ($r^2 = 0.64$, $D' = 0.96$) and presumably tag the same causal variant. Among the genes in this locus, both *OSM* and *LIF* encode cytokines that have been implicated in mucosal immunity and inflammation. In particular, inactivation of *OSM* produces thymic atrophy and autoimmune glomerulonephritis in the mouse (79). The functions of other genes within this interval have not been as well characterized. *HORMAD2* is part of a HORMA-domain-containing gene family implicated in DNA double-stranded break repair (80), and *MTMR3* (encoding myotubularin-related phosphatase 3) is implicated in autophagy (81). Interestingly, the rs2412973 allele (in LD with rs2412971 and rs12537), which is protective against IgAN, has also been associated with increased risk of early-onset inflammatory bowel disease (82).

In our GWAS, protective alleles at this locus were associated with lower serum IgA levels among cases, suggesting that this locus may be involved in the control of IgA production or regulation of mucosal immune response. Moreover, in the larger follow-up study, we observed a genetic interaction of this locus with *CFHR3,1-del*: the protective effect of rs2412971-A (*HORMAD2*) allele is reversed among *CFHR3,1-del* homozygotes. This interaction was most evident in the European cohorts, mainly because of power limitations because the protective alleles at both loci are considerably less frequent in Chinese. The biological basis of this statistical finding remains unknown.

The *DEFA* Locus (Chromosome 8p23)

The GWAS in the Han Chinese cohort identified a significant signal at rs2738048, centered on the alpha defensin (*DEFA*) gene cluster. The defensins are microbicidal peptides that are an important component of innate immunity (83, 84). Their positive charge enables electrostatic binding to pathogen cell surfaces, increasing membrane permeability. Defensins also modulate the inflammatory response and have chemoattractant properties. The *DEFA* gene family is present only in mammals and marsupials. Humans have six *DEFA* genes: *DEFA1--4* are expressed in neutrophils, dendritic cells, and natural killer cells, and *DEFA5* and *-6* are expressed in Paneth cells of the gut, supporting their role in mucosal immunity. Notably, a low level of alpha-defensin expression by intestinal Paneth cells is associated with susceptibility to Crohn's disease (85).

Similar to *CFHR* genes, *DEFA* genes likely arose by segmental duplications during evolution. Owing to high sequence homology in the *DEFA* gene family, it has been difficult to determine if these genes have similar or unique specialized functions. Studies are further complicated by the significant copy number variation in *DEFA1* and *DEFA3* genes, which are located in tandem, 4--14 copies per genome (86). High-resolution analysis of this locus is required to determine if the top SNP signal in the IgAN GWAS originates from a specific *DEFA* gene or is in LD with CNVs at this locus. Nonetheless, these findings provide another connection between inflammatory bowel disease and IgAN, and further implicate mucosal innate immunity in the pathogenesis of these disorders.

The *TNFSF13* Locus (Chromosome 17p13)

The IgAN locus containing *TNFSF13* and *TNFSF12*, which encode tumor necrosis factor ligands, was detected in the Han Chinese GWAS. *TNFSF13*, also known as APRIL ("a proliferation-inducing ligand"), is secreted by dendritic cells, monocytes, activated T cells, or intestinal epithelial cells and is important for T cell--independent generation of IgA-positive B cells, as well as IgA1-to-IgA2 class switching (87, 88). Inactivation of *Tnfsf13* in mice produces partial IgA deficiency and reduced IgA antibody responses to mucosal immunization (89). Conversely, overexpression of BAFF (*TNFSF13B*, a related tumor necrosis factor ligand that has overlapping functions and receptors with APRIL) results in autoimmune disease with commensal flora-dependent deposits of IgA in the renal mesangium (90). Serum levels of APRIL are elevated in many rheumatologic diseases, such as systemic lupus erythematosus and rheumatoid arthritis, and also in patients with IgA nephropathy (90). Inactivating mutations in *TNFRSF13B* (receptor for both APRIL and BAFF, also known as TACI) produce selective IgA deficiency and common variable immunodeficiency syndrome in humans (91).

Interestingly, the IgAN risk variant in *TNFSF13* is associated with increased total IgA levels in IgAN patients (47) but decreased levels in non-IgAN subjects (92). This may be consistent with prior findings that the effects of APRIL on class switching are dependent on the cytokine milieu (93). Although the exact functional consequence of the *TNFSF13* risk alleles and its effect on the levels of the IgA1/IgA2 subclasses remain to be determined, these data implicate defects in mucosal immunity and IgA class switching in the pathogenesis of IgAN and suggest an interplay with commensal flora as an important modifier of disease.

GENETIC RISK AND GEOEPIDEMIOLOGY OF IGA NEPHROPATHY

We noted a consistent shift in the cumulative distribution of GWAS risk alleles between major ethnicities: the burden of risk alleles was relatively low in Africans, intermediate for Europeans, and highest for Asians (45). Furthermore, the ethnic differences in allelic

frequencies were more pronounced for loci with larger effect sizes, such as *HLA-DRB1/DQB1*, *CHFR3,1-del*, and *HORMAD2* (Table 1). We therefore formulated a genetic risk score for IgAN (46) based on the number of risk alleles and their corresponding effect size. The most recent refinement of the score also incorporates the nonadditive interaction effect of the *CHFR3,1-del* and *HORMAD2* loci. Accordingly, the ethnic differences in genetic risk were even more striking when the risk score was considered instead of simple allele counts. In aggregate, this risk score explained nearly 5% of disease variance across 12 multiethnic cohorts examined (46). One standard-deviation increase in the score was associated with nearly 50% increase in the risk of disease. This translates into a fivefold increase in risk between individuals from the opposing extremes of the risk score distribution. We have recently implemented an online risk calculator that estimates an individual's genetic susceptibility in relation to the worldwide average using genotype data. This calculator can be found at the following link: <http://www.columbiamedicine.org/divisions/gharavi/resources>. Of note, the contribution of the two most recently described loci (*DEFA* and *TNFSF13*) has not yet been studied. Their addition in the risk score calculation will likely improve the score's predictive properties, provided these loci are validated in non-Asian populations.

We also examined the geographic variation in the genetic risk for IgAN across 85 worldwide populations, including individuals sampled by HapMap-III and the Human Genome Diversity Panel as well as our own control datasets. We built a geospatial risk model that confirmed lowest median scores for Africans, intermediate for Middle Easterners and Europeans, and highest for East Asians and Native Americans (Figure 1).

We next examined if variation in genetic risk is also reflected in differences in the prevalence of IgAN. Because the requirement for kidney biopsy diagnosis of IgAN makes determination of population prevalence difficult, we examined the numbers of cases of IgAN reported to the national end-stage renal disease (ESRD) registries. In the analysis of the most recent U.S. Renal Data System dataset, we observed dramatic differences in the prevalence of IgAN-ESRD among the four major U.S. ethnicities (Figure 2). The percentage of ESRD attributable to IgAN was fivefold greater for European-Americans and 15-fold greater for Asian-Americans when compared to African-Americans. Because these individuals represent immigrant populations and the disease prevalence closely reflects the genetic risk of ancestral populations, our data argue against environmental factors as major contributors to disease risk in North America. Interestingly, both the prevalence and genetic risk of Native Americans were considerably higher compared to European-Americans. This is consistent with previous reports of high IgAN occurrence among Native American tribes (94, 95) and comes as no surprise given the genetic relatedness of these populations to their East Asian ancestors.

Unexpectedly, higher-resolution geospatial analysis of the European continent revealed an additional south-to-north genetic risk gradient (Figure 3). As predicted by the genetic risk score, analysis of 13 countries reporting to the ERA-EDTA (European Renal Association - European Dialysis and Transplant Association) registry demonstrated the lowest prevalence in the South of Europe (Greece, Italy, Spain) and the highest prevalence in the Northern European countries (Sweden, Finland, Iceland). The analysis of both metrics resulted in concordant results, even after we controlled for potential detection bias due to regional differences in kidney biopsy practices or variability in survival. Findings were robust when we also normalized our data by prevalent counts of ESRD cases, as well as by ESRD due to biopsy-confirmed primary glomerulonephritis. The south-to-north cline in prevalence and genetic risk has not been previously appreciated. Interestingly, higher latitude has previously been associated with increased risk of many other immune diseases, such as multiple sclerosis, type 1 diabetes, and inflammatory bowel disease, all of which share common

susceptibility loci with IgAN (96--99), suggesting that complex selective pressures, rather than genetic drift alone, have shaped the geospatial distribution of IgAN risk alleles.

Finally, we have previously reported high prevalence of primary glomerulonephritis in an isolated population from the Valtrompia valley in Northern Italy. The Alpine villagers in this region have a 3.5-fold higher prevalence of ESRD attributable to primary glomerulonephritis, largely due to IgAN, when compared to the national average (40). Our previous genealogic investigations indicated that the affected individuals have a limited number of ancestors, implying genetic causation and the existence of a founder effect. We included healthy individuals from this region in the geospatial risk analysis of North Italian populations (Figure 3b). Consistent with the prevalence data, the average score in this population was comparable to some of the Northern European countries and ranked first among the 17 Italian populations sampled in our study (46). Thus, we discovered yet another example of covariation of genetic risk score and IgAN prevalence. The high endogamy rates may have maintained risk alleles at high frequency in this region. Unfortunately, the ancestral history of Valtrompia founders is not clear. The founders might have derived from a Northern European gene pool, perhaps during Celtic invasions of Northern Italy around 500--600 BCE, or from Asian ancestry, possibly during Mongol campaigns of the twelfth century. A genome-wide SNP analysis of this isolate may help to better define its ancestral origin.

A NEW PATHOGENESIS MODEL

By combining genetic and biochemical data, we have proposed a model of IgAN pathogenesis that describes sequential hits in innate and adaptive immunity (Figure 4). Our data indicate that IgAN results from a primary, inherited defect in IgA1-producing cells that leads to preferential production of Gd-IgA1. Gd-IgA1 production is likely influenced by variants in cytokine genes such as *LIF*, *OSM* (22q12) or *TNFSF13* (17p23) that influence IgA1 production and class switching. This glycosylation defect alone is usually benign, as evidenced by the finding that over a quarter of first-degree relatives have elevated Gd-IgA1 levels but no disease. However, in conjunction with inheritance of permissive MHC haplotypes (the strongest signals in GWAS), this genetically elevated Gd-IgA1 elicits production of antiglycan autoantibodies, leading to formation of immune complexes that deposit in the kidney. The pathogenicity of antiglycan antibodies may be enhanced by the presence of specific CDR3 sequences in the heavy-chain antigen-binding domains that enhance binding to Gd-IgA1 (36). Dysregulated mucosal immune response, influenced by variants in *TNFSF13* and *DEFA* loci, and perhaps also affected by the toll-like receptor system (100), may further enhance inflammatory signals, increasing Gd-IgA1 and/or antiglycan antibody production. Tissue injury is modulated by the alternative complement pathway, with variants in the *CFHR1* and/or *CFHR3* genes, modifying the risk of renal inflammation locally. This model undoubtedly simplifies the pathogenesis of disease, but it provides a rational start for hypothesis testing.

CONCLUSIONS AND FUTURE DIRECTIONS

Genetic studies of IgAN have provided a glimpse into pathogenesis and identified molecular candidates for disease. Nonetheless, the risk loci discovered to date explain only a small fraction of genetic risk, suggesting there are additional genetic and environmental risk factors. Fine mapping or resequencing of risk loci can identify culprit genes and potentially reveal additional independent risk alleles that can explain a larger proportion of disease variance. Additional genome-wide studies, using the GWAS approach in sporadic cases or exome sequencing in multiplex families, are expected to identify additional molecular pathways that can refine the model presented above and reveal common pathogenetic links

between IgAN and other immunologic disorders. In particular, discovery of rare mutations with large effect will be valuable, because such variants readily demonstrate the consequences of severe gain or loss of function for organismal physiology and can inform about the therapeutic potential of gene products. Finally, analysis of immunologic and clinical profiles in patients with differing genotypes may also provide clues to selection forces and environmental factors that have driven major differences in risk allele frequency among world populations and shaped the epidemiology of disease.

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Figure 1.

Worldwide geospatial analysis of genetic risk for immunoglobulin A nephropathy (IgAN). Surface interpolation of the standardized risk score over continents reveals increasing genetic risk with increasing distance from Africa. The risk score is derived from seven SNPs representing replicated IgAN susceptibility loci. Symbols represent the locations of 85 sampled populations: the Human Genome Diversity Panel sample (*circles*), the HapMap-III sample (*diamonds*), and healthy controls (*triangles*). Adapted from Reference 46 with permission.

Figure 2.

Ethnic differences in the prevalence of IgAN in the United States. IgAN-ESRD prevalence by ethnicity is expressed as a proportion of biopsy-diagnosed IgAN in all ESRD (*green*) and all biopsy-diagnosed primary glomerulonephritis (*red*). The data were obtained from the USRDS report and reflect disease prevalence as of December 31, 2009. Abbreviations: IgAN, immunoglobulin A nephropathy; ESRD, end-stage renal disease; USRDS, United States Renal Data System.

Figure 3.

Geoepidemiology of IgAN in Europe. (a) Country-specific IgAN-ESRD prevalence ordered by latitude demonstrates a trend for increased risk in Nordic countries (ERA-EDTA, December 31, 2009). The prevalence of IgAN-ESRD is expressed as a proportion of biopsy-diagnosed IgAN in all ESRD (*green*) and all biopsy-diagnosed primary glomerulonephritis (*red*). (b) High-resolution geospatial analysis highlights the area of increased risk in Northern Italy centered over Brescia, Valtrompia, and Cremona. Abbreviations: IgAN, immunoglobulin A nephropathy; ERA-EDTA, European Renal Association - European Dialysis and Transplant Association; ESRD, end-stage renal disease; USRDS, United States Renal Data System. Adapted from Reference 46 with permission.

Figure 4.
New pathogenesis model for immunoglobulin A nephropathy based on findings from genetic and biochemical studies.

Table 1

New immunoglobulin A nephropathy (IgAN) susceptibility loci discovered in genome-wide association studies (GWAS)

SNPs independently associated with IgAN (ancestral allele) ^a	Risk allele: approximated effect size ^{bb}	Risk allele frequencies (Africans--Europeans--Asians) ^c	Genes in the region	Potential role in IgAN pathogenesis
<i>Within the MHC region</i>				
6p21: rs9275596 (T)	T: ~50% risk increase	63%–67%–87%	<i>HLA-DRB1 DQA1, -DQB1</i>	This region contains some of the most polymorphic MHC-II molecules involved in antigen presentation. Based on conditional GWAS analyses, this region harbors at least three genome-wide significant haplotypes independently associated with IgAN, implying causal associations of several classical <i>HLA-DR</i> or <i>-DQ</i> alleles. The <i>DRB1*1501-DQB1*602</i> haplotype exhibits the strongest protective effect against IgAN; notably, this haplotype is also strongly protective against type 1 diabetes.
6p21: rs9275224 (A)	G: ~40% risk increase	47%–52%–62%		
6p21: rs2856717 (C)	C: ~30% risk increase	69%–63%–81%		
6p21: rs9357155 (G)	G: ~20% risk increase	94%–83%–85%	<i>PSMB8, PSMB9, TAP1 TAP2</i>	<i>TAP2, TAP1, PSMB8, and PSMB9</i> are interferon-regulated genes involved in antigen digestion and processing for presentation by MHC-I molecules; <i>PSMB8</i> expression is increased in peripheral blood mononuclear cells from individuals with IgAN.
6p21: rs1883414 (T)	C: ~20% risk increase	85%–67%–80%	<i>HLA-DPB2, -DPB1, -DPA1, and COL11A2</i>	This region contains MHC-II molecules involved in antigen presentation. The exact involvement in the pathogenesis of IgAN is presently not clear.
<i>Outside the MHC region</i>				
1q32: rs6677604 (G)	G: ~40% risk increase	53%–77%–91%	<i>CFH</i> and <i>CFHR</i> gene cluster	The derived allele (A) is a perfect proxy for a common deletion of <i>CFHR1</i> and <i>CFHR3</i> genes. This deletion is protective against IgAN and AMD and promotes suppression of the alternative complement pathway. The inhibitory effect on the complement system likely confers protection against glomerular inflammation from the deposited immune complexes.
8p23: rs2738048 (T) ^d	C: ~30% risk increase	19%–29%–35%	<i>DEFA</i> gene cluster	<i>DEFA</i> genes encode α-defensins, which are natural antimicrobials. Involved in the innate immune defense against infections, α-defensins have variable copy numbers that are related to the level of protein expression. The relationship of <i>DEFA</i> copy numbers to the risk of IgAN is not clear.
22q12: rs2412971 (A)	G: ~30% risk increase	21%–62%–70%	<i>HORMAD2, MTMR3 LIF, OSM, GATSL3 SF3A1</i>	The derived allele (G) conveys increased risk of IgAN but protection against inflammatory bowel disease and is also associated with higher serum IgA levels in IgAN. The two nearby cytokines, LIF and OSM, may promote IgA production by stimulated B cells. Not much is known about the structure and function of the <i>HORMAD2</i> and <i>MTMR3</i> genes in this region.
17p13: rs3803800 (A) ^d	A: ~20% risk increase	79%–22%–28%	<i>TNFSF13, MPDU1 EIF4A1, CD68, TP53 SOX15</i>	<i>TNFSF13</i> encodes APRIL, a TNF ligand involved in B cell development, response

SNPs independently associated with IgAN (ancestral allele) ^a	Risk allele: approximated effect size ^{bb}	Risk allele frequencies (Africans--Europeans--Asians) ^c	Genes in the region	Potential role in IgAN pathogenesis
				to mucosal antigens, and production of IgA in the gut-associated mucosal lymphoid tissues. Patients with IgAN have elevated serum levels of APRIL and higher IgA levels.
Gene × gene interactions				
1q32 × 22q12 interaction	--	--	--	The protective effect of the ancestral allele at chromosome 22q12 is reversed among homozygotes for the <i>CFHR3/1</i> deletion (1q32). The biological basis of this interaction is presently not clear.

Abbreviations: AMD, age-related macular degeneration; APRIL, a proliferation-inducing ligand; MHC, major histocompatibility complex; TNF, tumor necrosis factor

^a Ancestral allele defined by comparison of human to chimpanzee sequence.

^b Approximate effect sizes based on the largest available analyses of GWAS discovery and replication cohorts combined.

^c Allelic frequencies expressed as percentages, based on the HapMap-III data. Notably, all risk alleles with larger effect sizes (ORs 1.3–1.5) are most frequent in Asians and least frequent in Africans.

^d These loci have not yet been replicated in European cohorts (not included in the genetic risk score).