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Genetic studies of IgA nephropathy: what have we learned from GWAS

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Abstract

Primary IgA Nephropathy is the most common glomerulonephritis in the world. It is most common in Asian populations, followed by Caucasians, yet relatively infrequent amongst African populations. The striking difference in the prevalence of IgAN between world populations, together with the known familial aggregation of disease, suggests an inherited mechanism. Recently three Genome-wide association studies (GWAS) of IgAN have identified seven susceptibility loci, providing initial insight into the genetic architecture of this complex trait. While genetic studies of complex traits are challenging, applying new genetic techniques and methods of analysis, especially Next-Generation Sequencing, will push the genetic studies of IgAN forward.

Primary IgA Nephropathy (IgAN) is the most common glomerulonephritis in the world, and is especially prevalent in Asia, where it accounts for up to 45% of primary glomerulonephritis. Additionally, IgAN is one of the most common causes of end-stage renal disease (ESRD), with 15–40% of patients progressing to ESRD [1]. There is strong epidemiological and now molecular evidence for involvement of genetic factors in the pathogenesis of the disease[2,3]. In an effort to identify the susceptibility loci involved in sporadic cases of IgAN, genome wide association studies (GWAS) have been undertaken. GWAS have heralded a breakthrough in understanding the genetic basis of many complex diseases, enabling the discovery of common disease-causing alleles that have only a small effect on disease phenotype.

Pathogenesis

IgA Nephropathy manifests as recurrent episodes of hematuria and is defined on renal biopsy by the presence of mesangial proliferation with the deposition of IgA1 containing immune-complexes. Humans have two IgA subtypes, IgA1 and IgA2. In evolutionary terms, IgA1 is relatively new, found only in humans and hominid primates. It presumably arose from a duplication of the IgA heavy constant-region genes. The main structural difference between the IgA1 and IgA2 molecules is at the hinge region between the two Fab fragments.

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The hinge region of IgA1 contains multiple serine and threonine residues, each of which can be O-glycosylated by the addition of N-acetyl-galactosamine (GalNAc); these GalNAc moieties are subsequently galactosylated and sialylated. In a majority of IgAN patients, the GalNAc moiety on IgA1 is galactose-deficient. This exposed GalNAc moiety can be recognized as an antigen, stimulating production of anti-glycan antibodies and ultimately leading to the formation of immune complexes. Mesangial deposition of immune-complexes containing galactose-deficient IgA1 (Gd-IgA1) and subsequent complement activation are likely responsible for glomerular injury seen in IgAN.

It is now known that serum Gd-IgA1 levels are elevated most patients with both familial and sporadic IgAN regardless of ethnicity or age [4]. Recent studies suggest that an inherited defect in IgA1-producing cells leads to the preferential production of Gd-IgA1 [3]. More recent studies, in Caucasian, Asian, and African-American cohorts, have also demonstrated that 25–33% of first-degree relatives of patients with IgAN also have elevated levels of serum Gd-IgA1, despite having no clinical manifestation of renal injury [4]. Serum Gd-IgA1 levels appear to be heritable in a dominant pattern and appear to co-segregate with IgAN susceptibility alleles [4]. Of note, a recent study demonstrated that pediatric patients with Henoch–Schönlein purpura Nephritis (HSPN) and a large fraction of their first-degree relatives also have significantly higher Gd-IgA1 levels compared with age- and ethnicity-matched controls. This provides evidence of a shared pathogenesis between IgAN and HSPN [5].

Genetics of IgAN: before the GWAS era

Prior to the GWAS era, candidate-gene association studies and linkage analysis were the methods used to identify susceptibility genes or loci for IgAN. Genome-wide linkage scans identified significant and suggestive susceptibility loci, but no causative genes have been identified [6–8]. Linkage analysis did demonstrate significant genetic heterogeneity, such that different genes account for disease in different families [6–8]. Additionally, there have been over 100 candidate-gene studies for IgAN, the majority of which focus on genes involved in adaptive immunity (HLA, IgAFc receptor), cytokine signaling (TGF-β1, TNF), and the glycosylation pathways (C1GALT1 and ST6GALNAC2, cosmc)[9]. While many of these studies had positive results, virtually none of these findings have been replicated, suggesting a publication bias. In general these older studies suffered from inadequate sample sizes and general methodological problems.

Genetics of IgAN: GWAS era

Recent advances in high-density genotyping technology allow simultaneous analysis of several million SNPs. By using a large number of common SNPs to screen the entire genome, GWAS enable the discovery of common alleles that confer low risk of developing complex polygenic diseases. Since the first GWAS was published in 2005, identifying *complement factor H* (*CFH*) as a susceptibility gene for age-related macular degeneration [10], numerous investigators have used GWAS to study complex diseases in populations worldwide. At this point, over 1100 susceptibility loci have been identified and confirmed in diseases such as type 2 diabetes, schizophrenia, and IgAN.

To date, GWAS have identified 7 susceptibility loci for IgAN in European and Asian populations [11–13]. The first IgAN GWAS was conducted by Feehally et al. in a British cohort composed of 431 cases and 4980 controls [11]. This study used 286,200 SNPs for analysis and identified association signals at the major histocompatibility (MHC) locus, specifically across the HLA-B, DRB1, DQA, and DQB loci. The second IgAN GWAS was performed in a Chinese cohort that consisted of 1194 cases and 902 controls. It was subsequently replicated in two additional independent cohorts, a Chinese cohort of 712 cases and 748 controls and an Italian cohort of 1238 cases and 1172 controls [12]. This GWAS identified five susceptibility loci for IgAN: 3 loci on chromosome 6p21 in the MHC region, one on chromosome 22q12 called the *HORMAD2* locus, and one on chromosome 1q32 containing the *CFH* gene cluster. The most recent GWAS, conducted with discovery in an independent Chinese cohort of 1434 cases and 4270 controls, replicated four of the previously identified IgAN susceptibility loci and identified two novel loci, on chromosome 17p13 and 8q23 [13]. Table 1 summarizes the seven IgAN susceptibility loci identified in the three GWAS.

The strongest signal in all three IgAN GWAS was at the MHC locus on Chr. 6p21, although there is still uncertainty about the precise origin of the signal. The HLA locus has been the subject of multiple candidate-gene and linkage studies, but these studies yielded contradictory results. In retrospect, multiple factors contributed to the conflicting results of the candidate gene studies, including the high degree of polymorphism intrinsic to this region, the lack of resolution inherent in older genotyping technology, and small cohort size. Moreover the risk imparted by the MHC locus is modest, and there are at least three independent loci within this region, as well as multiple risk alleles within these loci. These factors complicate the identification of specific causal alleles. In fact, all three GWAS identify broad regions on Chr. 6p21, indicating that high-resolution mapping will be required to resolve the signals in the region. Conditional analysis has identified three distinct loci on Chr. 6p21 [12], and these will be discussed in more detail below.

6p21(top SNPs: rs9275596, rs9275224, rs2856717) (Candidate Genes: *HLA-DRB1, -DQA1, -DQB1*)

The GWAS conducted by Gharavi et al. identified three independent loci in the MHC region. The locus with the strongest association signal encompassed *HLA-DRB1*, *-DQA1*, *-DQB1* [12]. These three genes code for alpha and beta subunits of MHC II molecules. The strength of this signal is mediated by the multiple independent risk alleles within this locus. At least the three independent SNPs were demonstrated in a large replication (rs9275596, rs9275224 and rs2856717) [14]. Interestingly, the risk haplotype, *DQB1*0602-DQA1*0102-DRB1*1501m* has been associated with an increased risk of multiple sclerosis, systemic lupus erythematous, narcolepsy (DQB1), and liver injury from COX2 inhibitors, but is thought to be highly protective from type 1 diabetes mellitus[1,15]. This region is associated with variation in serum IgA levels in the GWAS by Yu et al. [13].

6p21(top SNPs: rs1883414) (Candidate Genes: *HLA-DPB2, -DPB1, -DPA1, and COL11A2*)

A second locus in the MHC region was found to harbor *HLA-DPA1, -DPB1, -DPB2*, which also code for alpha and beta chains of MHC class II molecules. Of note, these genes are paralogs of *HLA-DRB1, -DQA1, -DQB1*. Genetic polymorphisms of *HLA-DPB1* are associated with chronic berylliosis, graft-versus-host disease, juvenile rheumatoid arthritis, insulin dependent diabetes mellitus and sarcoidosis [16]. This region has also been associated with increased risk of systemic sclerosis, but the risk alleles associated with this phenotype are not in LD with any of the IgAN risk alleles [1]. This locus also contains *COL11A2*, coding of a component of type XI collagen.

6p21 (top SNPs: rs9357155) (Candidate Genes: *PSMB8, PSMB9, TAP1, TAP2*)

A third independent locus found within the MHC region contains *TAP2*, *TAP1*, *PSMB8*, and *PSMB9*, which are interferon-regulated genes involved in the degradation and processing of antigens for presentation by MHC-I molecules. *PSMB8* codes for an immunoproteasome involved in processing class I MHC peptides, and its expression is increased in peripheral blood mononuclear cells of some IgAN patients [17]. *TAP1* and *TAP2* code for proteins that are involved in the transport of peptides from the cytoplasm to the endoplasmic reticulum where they can be loaded onto MHC molecules; they have also been associated with ankylosing spondylitis [18], type I DM [19], and celiac disease [20]. In the replication of the second IgAN GWAS, four of the original five loci were replicated. The *TAP2/PSMB9* locus, however, displayed heterogeneity across cohorts and the full replication cohort did not support this association. The heterogeneity may be explained by the presence of a recombination hotspot in this region, which may result in differing linkage disequilibrium patterns across populations [1].

1q32 (top SNPs: rs6677604) (Candidate Genes: *CFH* and *CFHR* gene cluster)

The region of Chromosome 1 associated with IgAN contains *CFH* (complement factor H) and five *CFH*-related genes (*CFHR3, CFHR1, CFHR4, CFHR2 and CFHR5*) [1]. *CFH* codes for Factor H, a key inhibitor of the alternative complement pathway. The complement system is involved in opsonizing and lysing pathogenic cells, as well as modulating the adaptive immune response. Inappropriate complement activation leads to self-injury. Factor H prevents uncontrolled complement-activation by binding C3b and targeting it for Factor I–mediated degradation; this prevents the formation and accelerates the decay of C3/C5 convertase [21].

Factor H is composed of 20 short consensus repeat domains and has two main functional regions, located at the opposite ends of the protein. The C-terminus mediates binding to cell surfaces, while the N-terminus, the regulatory site, mediates the decay of the C3 convertase [21]. The function of the *CFH*-related proteins is unknown but a high degree of homology

exists between them and FH, especially at the C- and N-terminus, indicating that these proteins may bind the same ligands [21].

The top SNP associated with the *CFH* locus, rs6677604, is in strong linkage disequilibrium with a deletion of *CFHR3* and *CFHR1*, and imparts a decreased risk of developing IgAN (OR=0.68) [12]. Of interest, the *CFHR3,1*-del is rare in the Chinese, explaining why this locus was not discerned in the GWAS exclusively conducted in this population [13]. It is theorized that the protective effect of the *CFHR3,1*-del may be the result of competition between FH and CFHR1, such that a loss of CFHR1 enhances the effect of FH, leading to decreased complement activation. Although the *CFHR3,1*-del has a protective effect in age related macular degeneration (AMD) and IgAN[1], it is associated with an increased risk of developing systemic lupus erythematous [22] and atypical acquired forms of hemolytic uremic syndrome, the latter further mediated by the formation of anti-FH antibodies[23]. Additionally, it has recently been shown that specific variants of *CFH* and *CFHR5* are associated with membranoproliferative glomerulonephritis type II (Dense deposit disease) [1]. These data clearly implicate modulation of the alternative complement pathway in the pathogenesis of IgAN and other glomerular diseases.

22q12 (top SNPs: rs2412971) (Candidate Genes: *HORMAD2, MTMR3, LIF, OSM, GATSL3, SF3A1*)

The fifth locus, located on chromosome 22q12, contains *HORMAD2*, *MTMR3*, *LIF*, and *OSM*. The strongest signal from this locus, rs2412971, is located in an intron of *HORMAD2*. Among the genes in this locus, both *OSM* and *LIF* encode cytokines and are involved in mucosal immunity and inflammation. In particular, inactivation of *OSM* produces thymic atrophy and autoimmune glomerulonephritis in the mouse [24]. The functions of other genes within this interval have not been as well characterized. *HORMAD2* is involved in DNA double-stranded break repair [25], and *MTMR3* (encoding myotubularin-related protein 3) is a phosphatase implicated in autophagy[26]. Interestingly, the rs2412973 allele is protective against IgAN, and is associated with lower serum IgA levels among patients. Despite its protective effect on IgAN, this SNP is associated with an increased risk of inflammatory bowel disease [27]. 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*) is reversed among *CFHR3,1-del* homozygotes [14]. The biological basis of this statistical finding remains unknown. The GWAS performed by Yu et al. confirmed the association of this locus but in that study the strongest signal came from rs12537, which is located in the 3' UTR of the *MTMR3* gene. These two SNPs are in strong LD (r2 = 0.64, D' = 0.96) and most likely signal the same causal variant.

8p23 (top SNPs: rs2738048) (Candidate Genes: *DEFA* gene cluster)

The most recent GWAS, conducted by Yu et al., identified a significant signal at rs2738048, centered on the alpha-defensin (*DEFA*) gene cluster on chromosome 8p23. Defensins are short, cysteine-rich, cationic peptides found in vertebrates, invertebrates and plants. They are natural antimicrobials, and as such, they play an important role in the innate immune system. Mammalian defensins are predominantly produced by the epithelium of mucosal surfaces

(the skin, respiratory airways, gastrointestinal and genitourinary tracts) and by leukocytes (mostly neutrophils) [28]. Humans have six *DEFA* genes: DEFA1–4 are expressed in neutrophils, dendritic cells, and natural killer cells, while DEFA5-6 are expressed in Paneth cells of the gut. Interestingly, reduced expression of alpha-defensins in Paneth cells has been associated with an increased risk of Crohn's disease [1].

17p13 (top SNPs: rs3803800) (Candidate Genes: *TNFSF13, MPDU1, EIF4A1, CD68, TP53, SOX15*)

The seventh locus, containing *TNFSF13* and *TNFSF12*, was also detected in the GWAS conducted by Yu et al. The protein encoded by *TNFSF13*, also known as APRIL, is a tumor necrosis factor ligand, expressed primarily on monocytes/macrophages, and is important for B-cell homeostasis and immunoglobulin production. Specifically, APRIL is involved in T cell–independent generation of IgA-positive B cells, as well as IgA1-to-IgA2 class switching [29]. Of note, the top SNP in this locus, rs3803800, is a missense variant that may affect post-translational processing of APRIL. Recent studies have shown that serum levels of APRIL are elevated in patients with IgA nephropathy, and also in patients with systemic lupus erythematous and rheumatoid arthritis [1]. Additionally, the IgAN risk variant of *TNFSF13* has been associated with increased IgA levels in IgAN patients but decreased levels in controls[1]. Another recent study on BAFF (B cell activation factor), a member of the TNF superfamily that is closely related to APRIL, showed that mice overexpressing BAFF produce high levels of aberrantly glycosylated IgA and subsequently develop fatal nephritis with mesangial deposits of IgA [30].

Risk Score and Geospatial Model

Each of the IgAN susceptibility alleles can additively affect an individual's risk of developing disease. Kiryluk et al. created a genetic risk score based on the 7 loci identified in their GWAS, which accurately predicted the relative risk of disease between all replication cohorts[12,14]. Subsequently, the geographic variation of the susceptibility loci, and thus the genetic risk score, was investigated using genomes of over 6,000 healthy individuals, as well as genomes from HapMap-III and the Human Genome Diversity Project. The results accurately reflected current IgAN prevalence data, predicting the greatest burden of disease in Asians and the lowest in African-Americans. A geospatial model of IgAN genetic risk accurately reflected the known East-West decline in disease prevalence. In general, the genetic risk score increased with distance from Africa, including increased risk in Northern Europe. The predicted North-South gradient was validated within Europe by using published prevalence data of IgAN-attributable kidney failure. Thus the genetic data uncovered a novel aspect of IgAN epidemiology.

A new pathogenesis model

The results of the GWAS provide new insights into the pathogenesis of IgAN and have resulted in molecular candidates for the multi-hit hypothesis [1]. In this new pathogenesis model, the first hit is the inherited defect in IgA1 glycosylation in IgA1 producing cells. The production of Gd-IgA1 may be influenced by variants of *LIF*, *OSM*, or *TNFSF13*, which

influence IgA1 production and class switching. Gd-IgA1 is not automatically pathogenic but may lead to IgAN in the presence of additional susceptibility factors. The second hit is defective allorecognition, namely the production of anti-Gd-IgA1 antibodies, which is likely mediated by MHC-II alleles in susceptible individuals. This is followed by the formation of immune-complexes that deposit in the kidney. In this setting, variants in the *TNFSF13* and *DEFA* loci may promote inflammation or increase the production of the anti-glycan antibodies. Finally an overly active alternative complement pathway, mediated by variants in the *CFH* locus, may increase glomerular injury, initiated by immune-complex deposition.

Summary

During the past decade, the developments of new genetic tools have enabled novel insight into the pathogenesis of IgAN. The GWAS have identified common variants with modest effect on the risk of disease, presenting molecular candidates for disease. However much remains to be discovered. Only ~5% of IgAN variance is explained by the genetic risk score based on seven IgAN susceptibility loci [14]. Larger GWAS cohorts can undoubtedly uncover additional loci, increasing the catalog of candidates. Moreover, susceptibility loci likely harbor multiple risk alleles, some of which probably impart a large effect on disease. Thus high-resolution mapping or comprehensive sequencing of these intervals will likely identify variants underlying the GWAS signals and uncover additional independent risk alleles. Moreover, the availability of cost-effective Next-Gen sequencing will enable direct interrogation of whole genome and provide further insight into pathogenesis.

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Table 1

Genetic loci associated with IgAN

Locus	Marker (minor allele)	Chr	Chr position (37.3)	Type of SNP	Risk allele frequency			Disease associations	Effect size odds ratio (95%CI)	Function
					HapMap (HCB)	HapMap (CEU)	HapMap (YRI)			
HLA-DRB1 HLA-DQA1 HLA-DQB1	rs9275596 (C)	6p21	32789609	Noncoding	0.13	0.33	0.37	MS, narcolepsy, liver injury from COX2 inhibitors, SLE, T1DM	0.60 (0.52, 0.69)	antigen presentation
	rs9275224 (A)		32681631	Noncoding	0.38	0.48	0.53		0.73 (0.67, 0.80)	
	rs2856717 (T)		32670308	Noncoding	0.19	0.37	0.39		1.53 (1.31, 1.78)	
HLA-DPB2 HLA-DPB1 HLA-DPA1 COL11A2	rs1883414 (T)	6p21	33086448	Noncoding	0.2	0.33	0.15	Chronic berylliosis, GVHD, JRA, T1DM, sarcoidosis	0.83 (0.78, 0.90)	antigen presentation
PSMB8 PSMB9 TAP1 TAP2	rs9357155 (A)	6p21	32809848	Noncoding	0.15	0.17	0.06	AS, T1DM, celiac disease	0.75 (0.69, 0.82)	antigen digestion and processing
CFH CFHR1-5	rs6677604 (A)	1q32	196686918	Noncoding	0.09	0.23	0.47	HUS, C3GN, AMD	0.61 (0.53, 0.71)	innate immunity (alternative complement pathway)
HORMAD2 MTMR3 LIF OSM GATSL3 SF3A1	rs2412971 (A)	22q12	30494371	Noncoding	0.39	0.39	0.79	Thymic atrophy, autoimmune glomerulonephritis, IBD	0.75 (0.70, 0.81)	Involved in mucosal immunity and inflammation
DEFA gene cluster	rs2738048 (C)	8p23	6822785	Noncoding	0.26	0.29	0.19	Crohn's Disease	0.79 (0.74, 0.84)	innate immune system (antimicrobial)
TNFSF13 MPDU1 EIF4A1 CD68 TP53 SOX15	rs3803800 (A)	17p13	7462969	Coding	0.28	0.22	0.79	CVID, SLE, celiac disease, RA	1.21 (1.14, 1.28)	B cell homeostasis and immunoglobulin class switching

HCB: Han Chinese in Beijing; CEU: Utah residents with Northern and Eastern European ancestry from the CEPH collection; YRI: Yoruba in Ibadan, Nigeria

T1DM: type 1 diabetes; MS: multiple sclerosis; SLE: systemic lupus erythematous; AS: ankylosing spondylitis; GVHD: graft-vs.-host disease; JRA: juvenile rheumatoid arthritis; SS: systemic sclerosis; AMD: age related macular degeneration; HUS: hemolytic uremic syndrome; C3GN: C3 glomerulonephritis; IBD: inflammatory bowel disease; CVID: common variable immunodeficiency; RA: rheumatoid arthritis