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New developments in the genetics, pathogenesis, and therapy of IgA nephropathy

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Abstract

Recent years have brought notable progress in the field of IgA nephropathy. Here, we highlight important new directions and latest developments, including successful discovery of several genetic susceptibility loci, formulation of the multi-hit pathogenesis model that integrates findings from studies of galactose-deficient IgA1, anti-glycan response and immune complex-induced kidney injury, introduction of the Oxford pathology scoring system, and formalization of the Kidney Disease Improving Global Outcomes (KDIGO) consensus treatment guidelines. We focus on the latest genetic findings that confirm a strong contribution of inherited factors and explain some of the geo-ethnic disparities in disease susceptibility. Most IgA nephropathy susceptibility loci discovered to date encode genes involved in the maintenance of the intestinal epithelial barrier and response to mucosal pathogens. The concerted pattern of inter-population allelic differentiation across all Genome Wide Association Studies (GWAS) loci parallels the disease prevalence and correlates with variation in local pathogens, suggesting that multi-locus adaptation might have shaped the present-day landscape of IgA nephropathy. Importantly, the “Intestinal Immune Network for IgA Production” emerged as one of the new targets for potential therapeutic intervention. We place these findings in the context of the multi-hit pathogenesis model and existing knowledge of IgA immunobiology. Lastly, we provide our perspective on the existing treatment options, discuss areas of clinical uncertainty, and outline ongoing clinical trials and translational studies.

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URLs:

Genomics of IgA-related disorders in kids (GIGA-kids) Study: www.gigakids.org

Cure Glomerulonephropathy (CureGN) Study: www.curegn.org

STOP-IgAN Study: www.stop-igan-study.rwth-aachen.de

IgAN Progression Calculator: www.columbiamedicine.org/divisions/gharavi/calc_progression.php

IgAN Genetic Risk Calculator: www.columbiamedicine.org/divisions/gharavi/calc_genetic.php

Global Infectious Disease and Epidemiology Online Network (GIDEON): www.gideononline.com

Keywords

IgA nephropathy; *O*-glycosylation; GWAS; glomerulonephritis; adaptive immunity; innate immunity; complement system; treatment

Introduction

Since its description in 1968¹, IgA nephropathy (IgAN) has been recognized as the most common form of primary glomerulonephritis and an important cause of chronic kidney disease and end stage kidney failure. Recent years have brought remarkable progress in the field of IgAN, largely due to increased collaborative efforts that enabled execution of well-powered clinical and genetic studies. Landmark developments include the discovery of new genetic susceptibility loci, formulation of the multi-hit pathogenesis model based on the studies of IgA1 *O*-glycosylation and anti-glycan antibodies, introduction of the Oxford pathology scoring system, as well as formalization of IgAN treatment guidelines. In this review, we provide an update on these developments, give our perspective on the treatment guidelines, outline the remaining areas of uncertainty, and highlight important new directions in the field.

The Diagnosis of IgA Nephropathy

IgAN typically affects young adults, but can also occur in children and the elderly. The disease has a wide spectrum of clinical symptoms, ranging from asymptomatic microscopic hematuria to a more severe course characterized by sustained proteinuria and rapid deterioration of renal function. Definitive diagnosis of IgAN requires a kidney biopsy; the disease is defined immunohistologically by dominant or co-dominant glomerular deposits of IgA². According to recent consensus, the IgA should be at least 1+ in intensity³ and in most cases is 2+ or more⁴, and involves the glomeruli diffusely. Typically there is obvious dominant staining for IgA with weaker and more variable staining for IgG and/or IgM⁴. The deposits consist predominantly of polymeric IgA of the IgA1 subclass⁵. Among 2,249 cases of IgAN compiled from 13 published biopsy series, 100% of cases had positivity for IgA, 43% had positivity for IgG and 54% for IgM⁶. The stronger staining for lambda light chain than kappa light chain observed in most cases reflects the predominance of IgA1-lambda in the circulation⁷.

The histologic features of IgAN are diverse and span the gamut seen in most forms of immune complex-mediated proliferative glomerulonephritis (Figure 1). These include no or minimal abnormalities by light microscopy, mesangial hypercellularity (defined as 4 or more mesangial cells per mesangial area in a 3 µm-thick histologic section, Figure 1a), focal endocapillary proliferative (involving <50% glomeruli, Figure 1b), diffuse endocapillary proliferative (involving ≥50% glomeruli), necrotizing and crescentic lesions, and more rarely membranoproliferative patterns of injury^{3,8}. Red blood cell casts may be associated with acute tubular injury (Figure 1h). In the chronic stages, progression to focal or diffuse segmental and global glomerulosclerosis⁹ with attendant tubular atrophy and interstitial fibrosis occurs (Figure 1d and e).

By electron microscopy, the glomerular deposits in IgAN are primarily localized to the mesangium, with variable subendothelial and rare subepithelial deposits in the more severe forms. Mesangial deposits tend to cluster beneath the glomerular basement membrane reflection over the mesangium, a location referred to as paramesangial (Figure 1i). The glomerular basement membranes may manifest focal thinning, rupture and remodeling, which present sources for hematuria.

Henoch-Schönlein purpura nephritis (HSPN) is a systemic form of IgA vasculitis (IgAV) with renal manifestations that occurs predominantly in the pediatric age group¹⁰. This disease typically manifests with a tetrad of palpable purpura, arthralgia, abdominal pain, and renal disease. Although HSPN is frequently self-limiting in children, persistent proteinuria and chronic or progressive renal dysfunction are often observed in adult cases¹¹. The renal disease has a similar histologic spectrum as IgA nephropathy, but with greater frequency of severe lesions such as glomerular necrosis and crescents (Figure 1g)¹². Correspondingly, HSPN has a higher frequency of glomerular staining for fibrin than IgAN, but with an otherwise similar immunofluorescence profile.

Heuristic classification systems applied to IgAN in the past, including those by Lee et al.¹³ and Haas et al.⁸, were based on the pattern and severity of the proliferative and sclerosing lesions, similar to the WHO classification of lupus nephritis. The Oxford IgAN classification, devised by a working group of over 40 nephrologists and pathologists representing the International IgA Nephropathy Network and the Renal Pathology Society, is unique as the first evidence-based schema^{3,14}. It sought to identify reproducible histologic features that predict progression in a large disease cohort with known outcomes, and thus represents a scoring system, not a comprehensive classification. The discovery cohort included 265 cases of IgAN from Europe, North America and Asia, of which 78% were adults. Because the study excluded cases with proteinuria of <0.5 g/day, initial eGFR of <30 mL/min per 1.73 m² and progression to ESRD within 12 months of biopsy, patients with very mild disease, rapidly progressive glomerulonephritis, and advanced chronic disease were underrepresented¹⁴. Three reproducible histologic features correlated independently with both the rate of renal functional decline and renal survival endpoints (defined as 50% reduction in eGFR or ESRD), namely diffuse mesangial hypercellularity (M), segmental glomerulosclerosis (S) and tubular atrophy/interstitial fibrosis involving >25% of the cortical area (T)³. Tubular atrophy/interstitial fibrosis involving >50% (versus 26–50%) of the cortex was associated with even worse outcomes. Endocapillary hypercellularity (E) was associated with response to immunosuppressive therapy. The MEST score applies the designations M0 or M1 for mesangial hypercellularity involving 50% or >50% of glomeruli, respectively; E0 or E1 for endocapillary hypercellularity in 0 versus at least 1 glomerulus, S0 or S1 for segmental sclerosis in 0 versus at least 1 glomerulus, and T0, T1 and T2 for tubular atrophy/interstitial fibrosis involving 25%, 26–50%, and >50% of the cortical area, respectively³. The major limitation of the Oxford system is that the study design constrained its ability to fully address the impact of crescents and specific immunofluorescence features, such as the presence of peripheral capillary wall deposits of IgA and co-deposits of IgG.

A number of studies have attempted to validate the predictive value of the MEST lesions in independent cohorts from North America^{15,16}, Europe^{17–20} and Asia^{21–29}, including pediatric cases^{30,31}. These studies have generally confirmed the predictive value of various components by univariate and multivariate analyses, but with some differences^{32,33}. The largest meta-analysis based on 16 retrospective cohort studies and involving a total of 3,893 IgAN cases validated the predictive utility of the M, S, and T lesions, but did not confirm the prognostic value of the E score³³. While the E score exhibited some of the weakest and most heterogeneous associations with disease progression, the T score was consistently the most significant predictor of poor renal outcomes across all cohorts. In addition, five of 16 studies (4 Asian and 1 European with a total of 1,487 patients) examined the association of crescents with clinical outcomes; meta-analysis of these studies showed that the C score (defined as presence of any crescents) was strongly associated with progression to kidney failure³³. Lastly, the recently published VALIGA study of 1,147 patients from 13 European countries (not included in the above meta-analysis) provided an independent validation of the predictive value of the M, S and T lesions across a broader spectrum of the disease³¹. The E score, again, was not associated with outcomes. However, the relationship between some variables, such as the E score, and clinical outcomes might have been confounded by immunosuppressive treatment exposure, since all of the published validation studies have been based on retrospective observational data.

In summary, the Oxford scoring system represents an important step toward improved prognostication and standardization of diagnosis, but further refinements of the score may be needed to enhance its prognostic utility. A more definitive assessment of the scoring system would require a sizable randomized controlled trial in which decisions regarding therapy are not made on the basis of pathology. The TESTING study (see below) may present a unique opportunity to validate and refine this scoring system while removing inherent therapeutic biases.

The Epidemiology of IgA Nephropathy

Because the diagnosis of IgAN requires a kidney biopsy, the exact disease prevalence remains difficult to establish. The prevalence of mesangial IgA deposits assessed in necropsy studies is surprisingly high, ranging from 4% to 16% depending on the population studied^{34–36}. Similarly, the frequency of IgA deposition in protocol biopsies of living or cadaveric donor kidneys is reported to be as high as 16% in Japan³⁷. These studies suggest that subclinical IgA deposition is common and may be more prevalent in East Asian populations.

Another commonly reported metric of IgAN occurrence is a relative frequency of IgAN among all cases of primary glomerulonephritis in a biopsy registry. Depending on the geographic region, this number tends to be highly variable, ranging from 5% in the Middle East^{38,39}, 10–35% across Europe^{40–44} and up to 50% in Japan and China^{45,46}. This metric, however, can be affected by disparities in local biopsy practices⁴⁷ and local incidence of other glomerular diseases. An alternate approach to estimating the incidence of IgAN is to use data from national ESRD registries. These data still do not reflect true incidence as only the patients with progressive disease are captured. A subset of patients with “hypertension”

as the cause of ESRD may also represent patients with IgAN who never underwent kidney biopsy. In the US, depending on the state of residence, the incidence of ESRD due to IgAN ranges from 18 to 264 cases per million population (USRDS 2009)⁴⁸. The high level of variability between states may be attributable to regional differences in racial/ethnic composition and accessibility to healthcare, but it may also reflect a general lack of consensus among clinicians on the utility of biopsy in specific clinical settings, resulting in high degree of regional disparities in biopsy practices even within the US.

Despite these limitations, some important prevalence patterns have clearly emerged⁴⁹. Most notably, there is a clear West-to-East prevalence gradient, with the disease being most common in East Asia (32–54% of primary GN in China⁵⁰ and Japan⁵¹) compared to European countries (10–35% of primary GN)^{41,42,44,52–63}. Similar trends are observed when the incidence of ESRD due to IgAN is compared between ethnicities in the US. Asian-Americans have a 4-fold higher ESRD incidence due to IgAN compared to European-Americans, and a 7-fold higher incidence compared to African-Americans, further supporting a substantial role of genetic factors (USRDS data, 2009)⁴⁸. Additionally, a more subtle South-to-North prevalence gradient has also been described within Europe; Northern Europeans have up to 2.4-fold increased risk of ESRD due to IgAN compared to Southern Europeans⁴⁸. Lastly, IgAN occurrence has unequal gender distribution. In Europe and North America, the disease generally affects males more frequently than females, with male-to-female ratio as high as 3:1 in Europeans^{64,65}. In contrast, this ratio approximates 1:1 in East Asia^{66–68}, a pattern that may be shaped by differences in ancestry or local environments. These geographic differences also suggest that our existing definition of IgAN may encompass a number of distinct disease entities with differential distribution between Europe and Asia. Improved sub-classification of IgAN based on the underlying disease mechanism rather than descriptive pathology represents perhaps one of the greatest challenges for the IgAN research community. In this respect, some of the notable progress comes from genetic studies.

The Genetics of IgA Nephropathy

Multiple studies have recognized familial aggregation of IgAN^{69–74}. In most cases, the inheritance is suggestive of autosomal dominant pattern with variable penetrance; however, other more complex genetic models are also plausible. Although no large twin studies have been performed to formally estimate the heritability of IgAN, several cases of disease concordance in identical twins have been reported^{75–77}. The blood relatives of patients affected by IgAN also appear to be at a higher risk of urinary abnormalities⁷⁸ and have higher levels of galactose-deficient IgA1^{79,80}.

The first successful application of genome-wide linkage analysis to IgAN families identified the significant linkage peak on chromosome 6p22–23 under an autosomal dominant inheritance⁸¹. Follow-up linkage studies reported additional suggestive peaks at several other loci, providing evidence for significant locus heterogeneity^{73,82}. Confirmation of these loci in the setting of heterogeneity represents a major challenge; if each family carries a unique molecular defect in a different gene, hundreds of families will not suffice to provide linkage replication. Newer approaches using next generation sequencing face the

same limitation – considering significant genetic heterogeneity, finding an independent segregating mutation may require sequencing of thousands of probands. For this reason, the discovery of rare variants underlying familial IgAN has been challenging, and no causal mutations have been identified to date.

Genome-wide association studies (GWAS) represent an alternative approach to genetically complex traits, such as IgAN. In contrast to linkage studies, GWAS offer a powerful tool to identify susceptibility variants even in the setting of significant locus heterogeneity. The inherent limitations of GWAS include the ability to detect only common (frequency > 1–5%) variants, which typically exhibit relatively small effects; thus, GWAS tend to explain only a relatively small proportion of disease heritability⁸³. To date, GWAS has been successfully applied to IgAN in four large-scale studies that led to the identification of 15 distinct common risk variants at a genome wide significance (Table 1)^{84–87}. Cumulatively, the 15 new and replicated GWAS loci explain approximately 6–8% of the overall disease risk⁸⁷.

Although the overall disease risk explained by GWAS is relatively small, the hypothesis-free approach of GWAS provided novel and unbiased insights into human biology of IgAN. Most importantly, GWAS loci highlighted several pathogenic disease pathways and pointed to potential new therapeutic targets. The implicated pathways include antigen processing and presentation (*MHC* region), the complement system (*CFHR1/3* and *ITGAM-ITGAX* loci), regulation of mucosal IgA production (*TNFSF13* and *LIF/OSM* loci) and innate immunity against pathogens (*DEFA*, *CARD9*, *ITGAM-ITGAX* and *VAV3* loci). The cumulative burden of GWAS risk alleles has a strong inverse relationship with the age at disease onset, with up to a 20-year difference between the cases with highest and lowest numbers of risk alleles⁸⁷. These observations may be clinically relevant and suggest that pediatric patients have a different disease pathogenesis compared to a late-onset adult disease, and thus may also differ in their responsiveness to specific treatments.

In the geospatial analysis of 6,319 individuals representative of 85 worldwide populations, the IgAN genetic risk increases sharply with eastward distance from Africa (Figure 2, **top panel**)⁴⁸. This model parallels the known West-to-East gradient in disease prevalence, suggesting that variation in frequency of GWAS risk alleles may partially explain the geo-epidemiology of IgAN (see URL for an online genetic risk calculator). Moreover, higher resolution geo-genetic analysis of the European continent revealed additional South-to-North risk gradient, which subsequently led to the discovery of a parallel trend in disease incidence. Similar to IgAN, higher latitude has been associated with increased risk of other immune diseases, such as multiple sclerosis, type I diabetes or inflammatory bowel disease, all of which share common susceptibility loci with IgAN^{88–91}. Complex selective pressures likely underlie these gradients.

The inter-population differences in genetic risk become even more pronounced for the latest set of GWAS loci. Interestingly, the risk alleles with largest effects tend to have the greatest population differentiation and contribute most to the observed geo-genetic patterns. For example, the *ITGAM-ITGAX* risk alleles demonstrate nearly complete fixation in East Asian populations. Taken together, these findings suggest that local selective pressures might have

systematically increased the frequency of risk alleles in some populations through the process of multilocus adaptation. In the analysis of different ecological variables that could potentially provide a selective pressure that drives this adaptation, the diversity of endemic pathogens emerged as one of the strongest predictors of genetic risk. Among different pathogen classes, the strongest association was found for local helminth diversity (defined as a number of endemic helminthic species infecting humans in a given geographic area). Notably, worm infestations have been a major source of morbidity and mortality throughout human history, and even today helminthes infect nearly a quarter of the world population ⁹². The enhanced IgA response conferred by GWAS risk alleles is likely protective against these pathogens, but it can also explain the known association of mucosal infections as a common trigger for IgAN.

In aggregate, these findings gave rise to a novel hypothesis that higher genetic risk of IgAN in Asia represents an untoward consequence of protective adaptation to worm infections, the process that has likely occurred over thousands of years of human-parasite co-evolution. Despite recent amelioration of life conditions, availability of effective anti-helminthic therapies, and improvements in healthcare delivery, worm infections are far from being eradicated in these regions ^{92,93}. Even in the most developed Asian countries, humans continue to be exposed to a high diversity of worm species (Figure 2, **bottom panel**). Moreover, the time scale of recent developments would not have been sufficiently long to reverse the effect of genetic adaptation. For example, Japan has some of the largest number of helminthic species infecting humans, despite the fact that the overall incidence of parasitic infections has declined recently. In parallel, Japanese carry the greatest load of IgAN risk alleles (Figure 2, **top panel**) and consistently have some of the highest metrics of IgAN prevalence worldwide. Further studies will be needed to test this intriguing new hypothesis.

The Multi-hit Pathogenesis Model

The originally proposed multi-hit pathogenesis model integrates findings from studies of galactose-deficient IgA1, anti-glycan response, formation and deposition of IgA1-containing immune complexes, and mechanisms of immune complex-mediated tissue injury ⁹⁴ (Figure 3). Newer insights arising from GWAS contributed to the refinement of this model ^{95,96} and here we extend the model to incorporate the latest genetic data (Table 1). Abnormalities in the production of IgA1, leading to elevated levels of galactose-deficient IgA1 (Gd-IgA1), represent the first hit in the model. These IgA1 glycosylation defects have been shown to have high heritability ^{79,80}. However, family-based studies also demonstrate that an elevated level of Gd-IgA1 alone is not sufficient to produce IgAN and additional co-factors are required to trigger the formation of immune complexes ^{79,80}. More recent work suggests that elevated Gd-IgA1 elicits an autoimmune response, resulting in generation of anti-glycan antibodies that recognize N-acetylgalactosamine epitopes on Gd-IgA1 ⁹⁷. This anti-glycan response may represent a second hit in the model. The elevation of both Gd-IgA1 and anti-glycan antibodies leads to formation of immune complexes (Hit 3), which then deposit in the glomerular mesangium. This deposition activates the complement pathway, stimulates mesangial cells, and induces secretion of cytokines, chemokines, and extracellular matrix proteins resulting in inflammation and fibrosis (Hit 4). While this model likely

oversimplifies the sequence of pathogenic events, it provides a conceptual framework for focused functional studies and testing of candidate genes.

Defect in the regulation of IgA1 production and glycosylation (Hit 1)

Human IgA molecules are composed of two subclasses: IgA1 and IgA2; IgA1 is the predominant form in the circulation of healthy individuals and this subclass is also found in circulating immune complexes and mesangial immune deposits of patients with IgAN^{98,99}. The IgA1 molecule has a unique hinge segment between the first and second constant-region domains of the heavy chains that is the site of attachment of *O*-linked glycan moieties.

Multiple studies have shown that IgAN patients have significantly higher levels of circulating IgA1 with galactose-deficient *O*-linked glycans in the hinge region (Gd-IgA1), and this defect represents a risk factor for nephritis^{99–103} and more rapid progression of kidney disease¹⁰⁴. Moreover, serum levels of Gd-IgA1 are highly heritable among the relatives of adult patients with IgAN⁷⁹ as well as pediatric IgAN and HSP nephritis⁸⁰, and these findings are reproducible in different ethnicities¹⁰⁵. The enzymatic pathway responsible for the elongation of IgA1 glycan chains has been studied extensively: the key enzymes include N-acetyl-galactosaminyltransferases-2 and -14 (GalNAc-T2 and GalNAc-T14), which link N-acetylgalactosamine to Serine or Threonine residues of the hinge region, followed by core-1- β 1,3-galactosyltransferase-1 (C1GalT1) and its chaperone Cosmc, which add galactose to N-acetylgalactosamine, and a number of sialyltransferases^{96,99}. Interestingly, the pattern of *O*-glycosylation is normal for IgD in patients with IgAN, suggesting that these enzymes may be altered specifically in IgA1-producing cells secondary to their aberrant immunoregulation¹⁰⁶. Furthermore, IgA1-secreting cell lines from patients with IgAN demonstrated a decrease in C1GalT1 activity and an increase in α -N-acetylgalactosaminide- α -2,6-sialyltransferase 2 (ST6GalNAc-II) activity, which suggests that premature sialylation of N-acetylgalactosamine may be contributing to this defect¹⁰⁷.

The glycosylation defects involve predominantly polymeric IgA1, which is normally produced by mucosal IgA1-secreting cells¹⁰⁸. Presently, it is not clear how polymeric Gd-IgA1 finds its way to the circulation in patients with IgAN. An intriguing possibility is that mucosal IgA1-secreting cells may migrate to the bone marrow or other systemic sites and that this “mis-trafficking” may occur because of faulty expression of surface homing receptors^{109–111}. An alternative hypothesis is that upon antigenic stimulation of genetically-predisposed individuals, there is an enhanced mucosal IgA1 response that leads to a “spill-over” from mucosal sites, leading to increased circulating levels of polymeric Gd-IgA1. Clinical associations of macroscopic hematuria coinciding with mucosal infections (“synpharyngitic hematuria”) further suggest that enhanced mucosal IgA responsiveness to an antigenic challenge triggers IgAN. These hypotheses are not mutually exclusive; exaggerated mucosal IgA1 responsiveness may lead to a “spill-over” of polymeric Gd-IgA1 into the circulation, while overstimulation of IgA1-secreting cells may promote “mis-trafficking” of these cells.

The interplay between mucosal pathogens and IgA immunity is central to the disease process; the inherited propensity for enhanced mucosal IgA production in response to microbial antigens represents a common pathway for most of the GWAS loci discovered to

date (Figure 4, Table 1). For example, the *TNFSF13* locus encodes a proliferation inducing ligand (APRIL) involved in T cell-independent generation of IgA-secreting plasma cells^{112,113}. The risk variant is associated with a higher serum IgA levels among IgAN cases^{86,87}. Inactivation of *Tnfsf13* in mice produces reduced IgA antibody responses to mucosal immunization¹¹⁴. Conversely, over-expression of B cell activating factor (BAFF), a related molecule with overlapping functions and receptors with APRIL, results in autoimmune disease with commensal flora-dependent mesangial IgA deposits in mice¹¹⁵. Another GWAS locus on chromosome 22q12 encompasses several genes including the cytokine-encoding genes *LIF* and *OSM*⁸⁵. These cytokines are members of the IL-6 family, are expressed in mucosal tissues, and have immunoregulatory properties^{116–118}. The effects of LIF and OSM on mucosal production of IgA have not been well studied, but the IgAN risk allele at this locus has previously been associated with protection against Crohn's disease, pointing to its involvement in the regulation of intestinal inflammation^{119–121}. Critically, the IgAN risk allele is also associated with higher serum IgA levels among IgAN patients^{85,87}.

Additional GWAS loci that are likely involved in the regulation of mucosal responses to pathogens include the *DEFA* locus (encoding alpha-defensin antimicrobial peptides) and *CARD9* locus (encoding a pro-inflammatory adapter molecule implicated in the pathogenesis of inflammatory bowel disease and involved in the activation of NFκ-B signaling), as well as *ITGAM-ITGAX* locus (encoding leukocyte-specific alpha-integrins involved in the process of phagocytosis and regulation of IgA production). There is also a large set of suggestive IgAN loci that is dramatically enriched for additional genes participating in the “Intestinal Immune Network for IgA Production”, one of the pathways curated by the Kyoto Encyclopedia of Genes and Genomes database (Figure 4). This includes the *IL2RA-IL15RA* locus (encoding receptor components for IL2 and IL15), the *ICOS* and *ICOSLG* loci (encoding inducible T-cell co-stimulatory molecules) and the *TNFRSF13B* locus (encoding TACI, a receptor for both BAFF and APRIL). Genetic perturbations to the “Intestinal Immune Network for IgA Production” may also have an effect on the composition of the commensal gut microbiome, as suggested by early studies showing dramatic differences in fecal microbiota between IgAN cases and healthy controls¹²².

However, the hypothesis of intestinal IgA over-reactivity may not be so straightforward. For example, previous studies demonstrated a reduction in J-chain mRNA expression in duodenal IgA plasma cells in patients with IgAN¹²³ and lack of enhanced human IgA response to an immune challenge with mucosal tetanus toxoid immunization^{124–126}. Clearly, additional investigations of intestinal IgA responsiveness in IgAN are needed to clarify this issue. Follow-up studies are also needed to test if any of these candidate genes also affect the process of IgA1 O-glycosylation. Lastly, newer gene mapping approaches that utilize serum Gd-IgA1 levels as a quantitative endophenotype may offer further insights into the genetic architecture of this trait¹²⁷.

Anti-glycan antibodies (Hit 2)

The galactose-deficient hinge-region of IgA1 contains N-acetylgalactosamine (GalNac) residues with or without terminal sialic acid. Recent data suggest that exposed GalNac may represent an epitope recognized by specific anti-glycan antibodies, promoting formation of circulating immune complexes⁹⁷. Because some bacteria and viruses express GalNac on their surfaces, exposure to these pathogens could act as a trigger for the formation of cross-reacting antibodies. The presence of permissive MHC class II alleles may be required for this response. While very attractive, this “molecular mimicry” hypothesis will require experimental validation. The formation of immune complexes appears critical for the nephritogenic property of Gd-IgA1. In vitro studies of cultured human mesangial cells show activation with IgA1-IgG immune complexes, but absence of reactivity to isolated Gd-IgA1¹²⁸. Recent clinical studies also suggest that using elevated levels of circulating anti-glycan antibodies as a disease biomarker outperforms serum Gd-IgA1 levels¹²⁹. Furthermore, the presence of anti-glycan antibodies correlates with proteinuria⁹⁷, more severe histopathologic injury¹²⁹, and faster progression of kidney disease¹³⁰. These promising findings now require prospective validation.

Immune complex formation and deposition (Hit 3)

A complex series of molecular interactions that remain poorly characterized lead to the formation of circulating immune complexes. Circulating polymeric IgA1-containing immune complexes induce cleavage of the extracellular domain of FcαR (CD89), forming an IgA1-CD89 complex; mice expressing both human IgA1 and CD89 develop mesangial deposition of IgA1 resembling human disease¹³¹. These mice also overexpress transglutaminase-2 in the mesangium, while transglutaminase-2-deficient animals are protected from IgA1 deposition. Transglutaminase-2 is a multifunctional protein ubiquitously expressed in all tissues¹³²; the protein can be externalized, after which it cross-links with proteins of the extracellular matrix^{133,134}, but its role in human disease requires further study. Interestingly, one of the newly identified loci contains *ITGAM*, encoding integrin αM that is essential for interactions between CD89 and secretory IgA^{135,136}, but the dissection of its precise role also awaits additional studies. Several other molecules have been implicated in immune complex binding by mesangial cells¹³⁷, of which transferrin receptor (CD71) appears most promising^{138–141}.

Local activation of inflammatory pathways and the complement system (Hit 4)

Once deposited, IgA1-containing immune complexes stimulate mesangial proliferation and local production of cytokines, such as IL-6 and TGF-β^{142,143}. These molecules promote inflammatory responses by recruiting leukocytes and promote glomerular and tubulointerstitial fibrosis. Furthermore, glomerular inflammation is enhanced by the complement system; C3 glomerular staining (Figure 1f) is present in over 90–95% of IgAN biopsies^{2,4,12}. In general, C3 staining tends to be less intense and more granular than the staining for IgA. C1q is generally negative (in 90% of cases) with less than 10% of cases exhibiting scant C1q staining of low (<1+) mean intensity^{4,12}. Such positivity for C3 with negativity for C1q is consistent with activation of either the lectin or the alternative pathway. Lectin pathway activation is further suggested by glomerular staining for C4d in the absence

of C1q in approximately 40% of IgAN biopsies¹⁴⁴. Moreover, mesangial deposition of mannose-binding lectin (MBL) is reported in 25% of IgAN biopsies¹⁴⁵. All MBL-positive cases show glomerular co-deposition of L-ficolin, MBL-associated serine proteases and C4d, and these patients exhibit greater mesangial and extracapillary proliferation, glomerular sclerosis, interstitial infiltration, and proteinuria.

Support for alternative pathway activation in IgAN comes from GWAS. Inheritance of a common deletion in factor H-related genes 1 and 3 (*CFHR3,1-del*) provides additive protection from IgAN^{48,85,87}. *CFHR1* and *CFHR3* encode regulatory proteins that promote activation of the alternative pathway, likely through a competitive inhibition of factor H (FH)^{146,147}. Recent data suggests that *CFHR3,1-del* is associated with higher levels of circulating FH and lower levels of complement activation split products in IgAN. Higher FH levels are also positively associated with circulating C3 and negatively correlated with mesangial C3 deposition¹⁴⁸. Interestingly, a similar protective effect of *CFHR3,1-del* has been described for age-related macular degeneration, a common cause of retinal disease characterized by increased local overactivity of the alternative pathway¹⁴⁹. In contrast, *CFHR3,1-del* has been associated with increased risk of systemic lupus erythematosus and atypical hemolytic uremic syndrome^{150,151}. The mechanisms underlying these opposed pleiotropic effects of the deletion are presently not well understood.

The Treatment and Prognosis of IgA Nephropathy

The new Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis provide an evidence-based review and appraisal of the literature on treating IgAN (Table 2). Because these guidelines have been published recently, we refer interested readers to the original publication for detailed discussion of supporting evidence¹⁵². Here, we provide a brief synthesis of the recommended treatment plan and highlight specific areas of ongoing controversy.

The only KDIGO recommendation in IgAN based on unequivocal evidence is for blood pressure control and the use of ACE inhibitors or ARBs¹⁵². A target of <130/80 mm Hg is recommended for patients with proteinuria <1 g daily, and <125/75 is recommended for patients with proteinuria >1 g daily. Additionally, it is recommended that medication be up-titrated to achieve <1 g of proteinuria daily. A number of randomized controlled trials (RCTs) document reduction of proteinuria and delay of GFR deterioration with this treatment^{153,154,155,156}. However, it remains unclear at what level of proteinuria this therapy should be initiated. Moreover, although several small studies suggest a benefit in proteinuria reduction with combined ACE inhibition and ARB use¹⁵⁷, there are no data showing decreased rate of renal failure or mortality. Given the potential risks of such combinations, specifically in older and high-risk cardiovascular populations, the combination is generally not advised.

The KDIGO guidelines suggest the use of a 6-month trial of corticosteroids in patients with persistent proteinuria of >1g/day despite 3–6 months of optimal supportive care. This recommendation is based on three RCTs performed in patients with generally preserved renal function^{158–161} and a meta-analysis, concluding that steroids reduce kidney disease

progression in this setting ¹⁶². Presently, it is unclear at what level of reduced renal function this therapy becomes futile (i.e. “the point of no return”) and whether patients with lower levels of proteinuria should also be treated ¹⁶³.

For patients with crescents involving over 50% of glomeruli, the outcome is likely to be unfavorable ^{164,165}. Most nephrologists treat such patients aggressively with pulse solumedrol followed by oral corticosteroids and IV cyclophosphamide ¹⁶⁶. Rituximab has not yet been used in a significant enough number of patients to be recommended, however, data from studies on other crescentic diseases suggest a potential benefit ^{167,168}. Of note, the exact definition of crescentic IgAN remains somewhat controversial.

Except for crescentic forms, KDIGO does not recommend a routine use of cyclophosphamide in addition to corticosteroids. Similarly, the use of MMF and azathioprine are generally not recommended; the data for MMF are inadequate, while azathioprine offered no additional benefit in a recent well-designed RCT ¹⁶⁹. The benefits of other interventions, such as tonsillectomy or oral fish oils, also do not appear convincing ¹⁵². Overall, the evidence supporting these recommendations is of relatively poor quality.

The publication of KDIGO guidelines made it clear that the effectiveness of the existing therapies is limited and targeted treatments, more specific to the pathogenic process in IgAN, are still lacking. Despite the recommended treatment approach, IgAN remains a progressive disease in up to 50% of individuals ¹⁷⁰. Overall, it is estimated that 20–40% of IgAN cases develop end stage renal disease (ESRD) within 20 years from the time of diagnosis ^{171,172}. In the recent VALIGA cohort of 1,147 European patients, the annual rate of eGFR decline was 1.8 ± 7.5 ml/min and ESRD developed in 12% of the patients that were followed for an average period of 4.7 years from the time of diagnosis ¹⁷³. A number of retrospective studies pointed to several clinical risk factors for kidney disease progression, such as depressed baseline eGFR, low serum albumin and hemoglobin levels, severity of proteinuria, and elevated blood pressure at the time of biopsy ^{172,174–177}. New online clinical decision support tools are also being developed based on these data (see URL for the IgAN Progression Calculator). However, most of the progression studies are based on single-center cohorts and rely on retrospective data; well-powered prospective cohort studies are needed to validate these findings.

In summary, the prognosis of IgAN is quite variable and the outcome remains difficult to predict in individual patients ¹⁷⁸. The high level of inter-individual differences in disease course and inconsistent response to immunosuppressive therapies provide additional support for the hypothesis that our existing diagnostic criteria for IgAN likely encompass a more diverse set of disease entities. Further disease sub-classification, perhaps based on genetic and biomarker profiles specific to the underlying pathogenic process, is urgently needed to improve our treatment strategies.

Future Directions

There is a number of new important studies underway to address some of the most critical clinical questions outlined above. The CureGN Study (see URL) is a large prospective multicenter study of 2,400 patients with common forms of glomerular disease, including 600

patients with IgAN. This cohort will generate data on the natural history of IgAN, and provide means for a well-powered prospective validation of novel serum, urine, and tissue biomarkers for diagnosis, prognosis, and for tailoring treatments. Additionally, new clinical trials will soon clarify the role of immunosuppressive regimens in IgAN. The STOP IgAN Study (see URL) is a multicenter RCT of nearly 150 IgAN patients with persistent proteinuria of >0.75 g daily despite RAS inhibition and supportive therapy; the patients with a GFR of >60 cc/min are randomized to alternate day steroid treatment plus solumedrol pulses versus placebo, while those with a GFR of 30–60 cc/min are randomized to a regimen of cyclophosphamide for 3 months followed by azathioprine versus placebo. Lastly, the newly launched TESTING study will randomize $>1,000$ patients (proteinuria of >1.0 gm/day and an eGFR of >20 cc/min) to corticosteroids or placebo and is likely to provide definitive data on the utility of systemic glucocorticoids.

Moreover, GWAS findings have already stimulated investigations of promising treatment approaches that target the newly implicated pathways. Budesonide, a glucocorticoid locally released in the ileocecal region near the Peyer's patches, is being studied in a larger controlled trial after proving successful in a small pilot trial ¹⁷⁹. Other promising agents include Bortezomib (proteasome inhibitor), Fostamatinib (Syk inhibitor), Blisibimod (BAFF inhibitor), and Atacicept (humanized recombinant TACI-IgGfC fusion protein with anti-APRIL and anti-BAFF activity). In addition, the discovery of the protective effect of *CFHR1,3-del* suggests that pharmacologic suppression of the alternative complement pathway may be of potential benefit in IgAN.

Nevertheless, GWAS loci discovered to date explain less than 8% of the disease risk, suggesting contributions of additional, yet unidentified, genetic and environmental factors. Similar to other autoimmune diseases, IgAN is likely to have a highly complex genetic architecture with a large number of contributing risk alleles. For example, recent GWAS for inflammatory bowel disease (IBD) defined 193 independent risk loci, explaining over 25% of familial risk ¹²¹. Similarly, 110 GWAS risk alleles have been identified for multiple sclerosis (MS), explaining nearly 30% of sibling recurrence ¹⁸⁰. New biology arising from these studies allowed for identification of previously unrecognized pathways that are shared between different autoimmune disorders, shedding light on the common underlying mechanisms that could now be targeted pharmaceutically ¹⁸¹. This is highly relevant to IgAN, since many of the IgAN risk alleles have shared effects on the risk of IBD, MS, and other autoimmune traits. However, the sample size of the aforementioned IBD or MS studies is over 4-fold greater compared to the largest IgAN study. Thus, one could reasonably expect to discover more IgAN risk alleles with increased GWAS sample size. In addition, fine mapping or re-sequencing of risk loci can identify causal alleles and potentially explain a larger proportion of disease risk. Moreover, post-GWAS functional studies of the molecular mechanisms underlying the observed genetic effects are needed to effectively translate the GWAS findings into clinical applications.

The discovery of rare variants with large effect that underlie familial forms of IgAN would also be valuable, because such variants readily demonstrate the consequence of severe gain or loss of function, and can inform the therapeutic potential of encoded gene products. Moreover, studies of pediatric patients may be especially worthwhile, since early onset of

disease is correlated with genetic risk. In this regard, the newly established GIGA-kids Study (Genomics of IgA-related disorders in kids Study, see URL) aims to enroll >1,000 children for genetic, genomic, and biomarker discovery studies in IgAN and HSPN. Lastly, the ongoing studies aimed at refining the multi-hit model are likely to define new biomarkers and potential therapeutic targets. Integration of this model with additional genetic discoveries may finally lead to improved disease classification and novel personalized treatment strategies.

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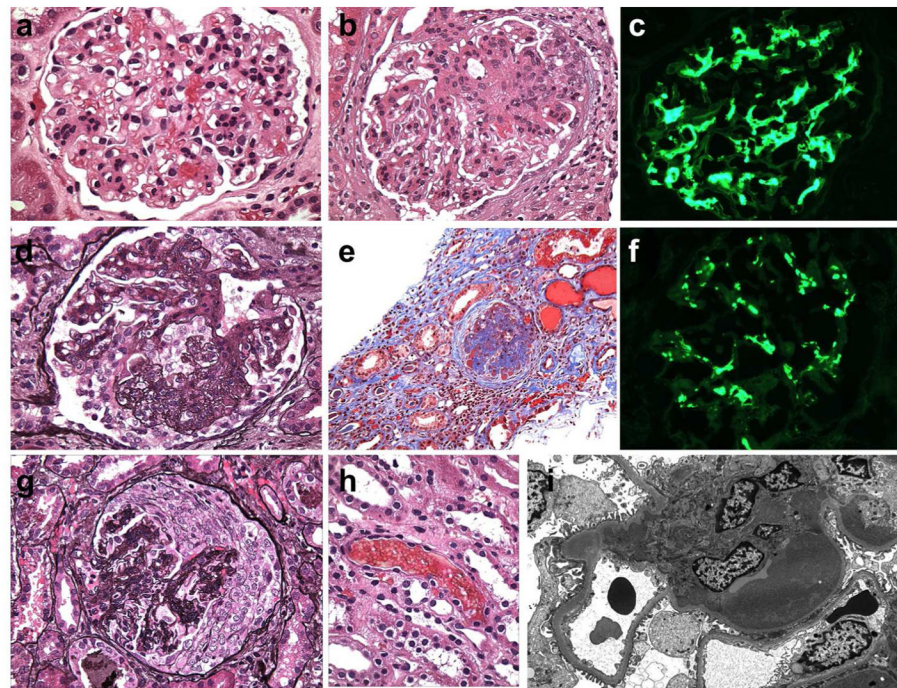


Figure 1. Pathologic features of IgA nephropathy by light microscopy, immunofluorescence and electron microscopy

(a) The glomerulus has global mesangial proliferation with at least 4 cells per mesangial area. When >50% of glomeruli exhibit mesangial hypercellularity, the biopsy receives a score of M1 according to the Oxford/IgA MEST system (H&E, x600).

(b) Segmental endocapillary proliferation obliterates capillary lumina (score E1 when a biopsy contains one or more such lesions). The adjacent glomerular segments have mild mesangial hypercellularity (H&E, x600).

(c) The stain for IgA is intense and globally outlines the mesangial framework of the glomerulus (immunofluorescence, x600).

(d) Segmental glomerular scarring develops as postinflammatory sclerosis, mimicking the changes in focal segmental glomerulosclerosis. (score S1 when a biopsy contains one or more such lesions), (Jones methenamine silver, x600).

(e) A case with high chronicity contains globally sclerotic glomeruli and exhibits more than 50% tubular atrophy/interstitial fibrosis (score T2), (Masson trichrome, x200).

(f) The immunofluorescence staining for C3 is similar in distribution as the mesangial staining for IgA (shown from the same glomerulus as in 1C) but exhibits weaker intensity and a more punctate, granular texture (immunofluorescence, x600).

(g) A severe example has a cellular crescent that compresses the glomerular tuft. Global mesangial expansion is present (Jones methenamine silver, x400).

(h) One or more red blood cell casts are commonly encountered at biopsy and may be numerous, especially in cases with gross hematuria and acute tubular injury (H&E, x600).

(i) By electron microscopy, large mesangial deposits elevate the glomerular basement membrane reflection over the mesangium, bulging towards the urinary space. This deposit involves the entire mesangium but is most prominent in the paramesangial region, beneath

the GBM reflection. The mesangial cellularity is increased but the capillary lumen is patent (electron micrograph, x5000).

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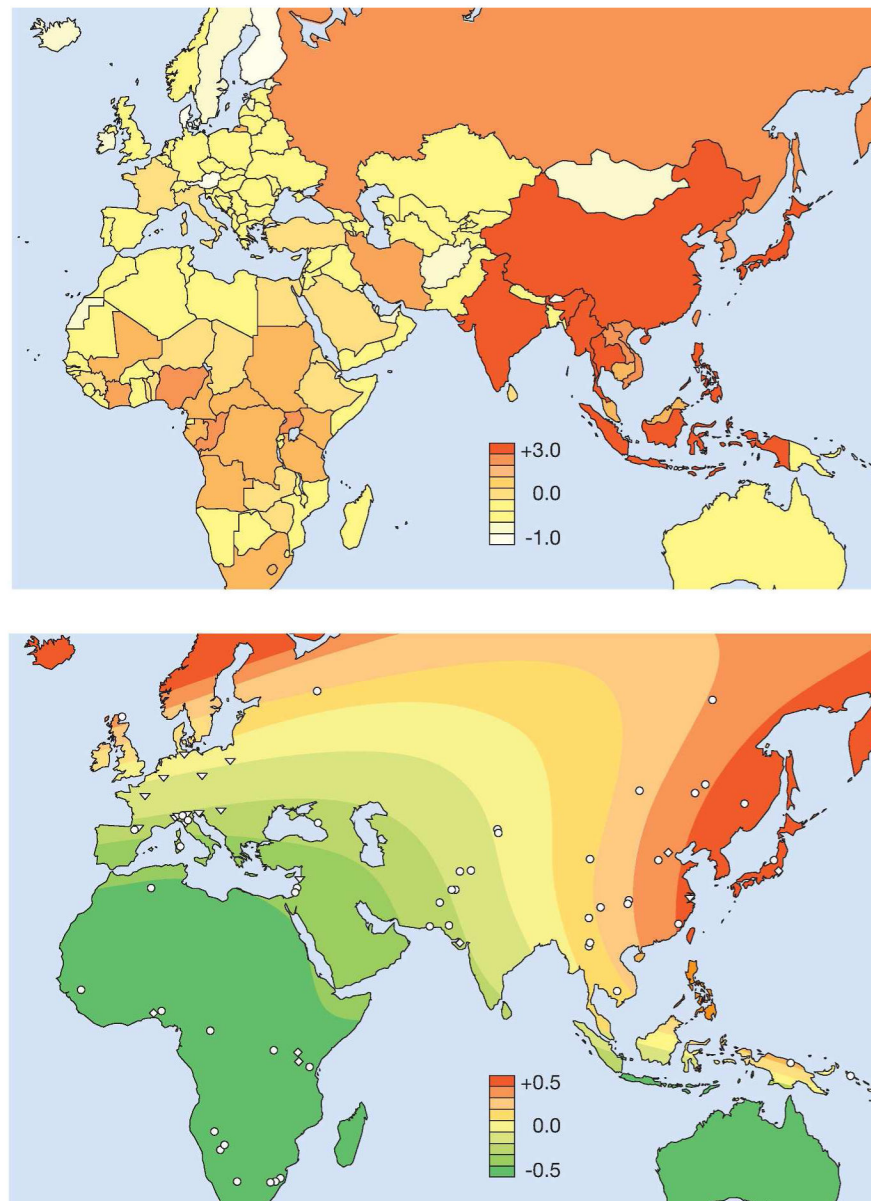


Figure 2. Geospatial Pattern of Genetic Risk for IgA Nephropathy and Worldwide Map of Helminth Diversity

Top Panel: Surface interpolation of the standardized genetic risk over Africa and Euroasia.

Symbols represent the locations of sampled populations: Human Genome Diversity Panel (HGDP; 1,050 individuals representative of 52 worldwide populations), HapMap III (1,184 individuals representative of 11 populations), other population samples (4,547 individuals representative of 25 populations); from Kiryluk et al. *PLoS Genetics* 2012;8(6):e1002765.

Bottom Panel: Standardized values for the diversity of helminth species infecting humans per country; data from the Global Infectious Disease and Epidemiology Online Network (GIDEON), see URL.

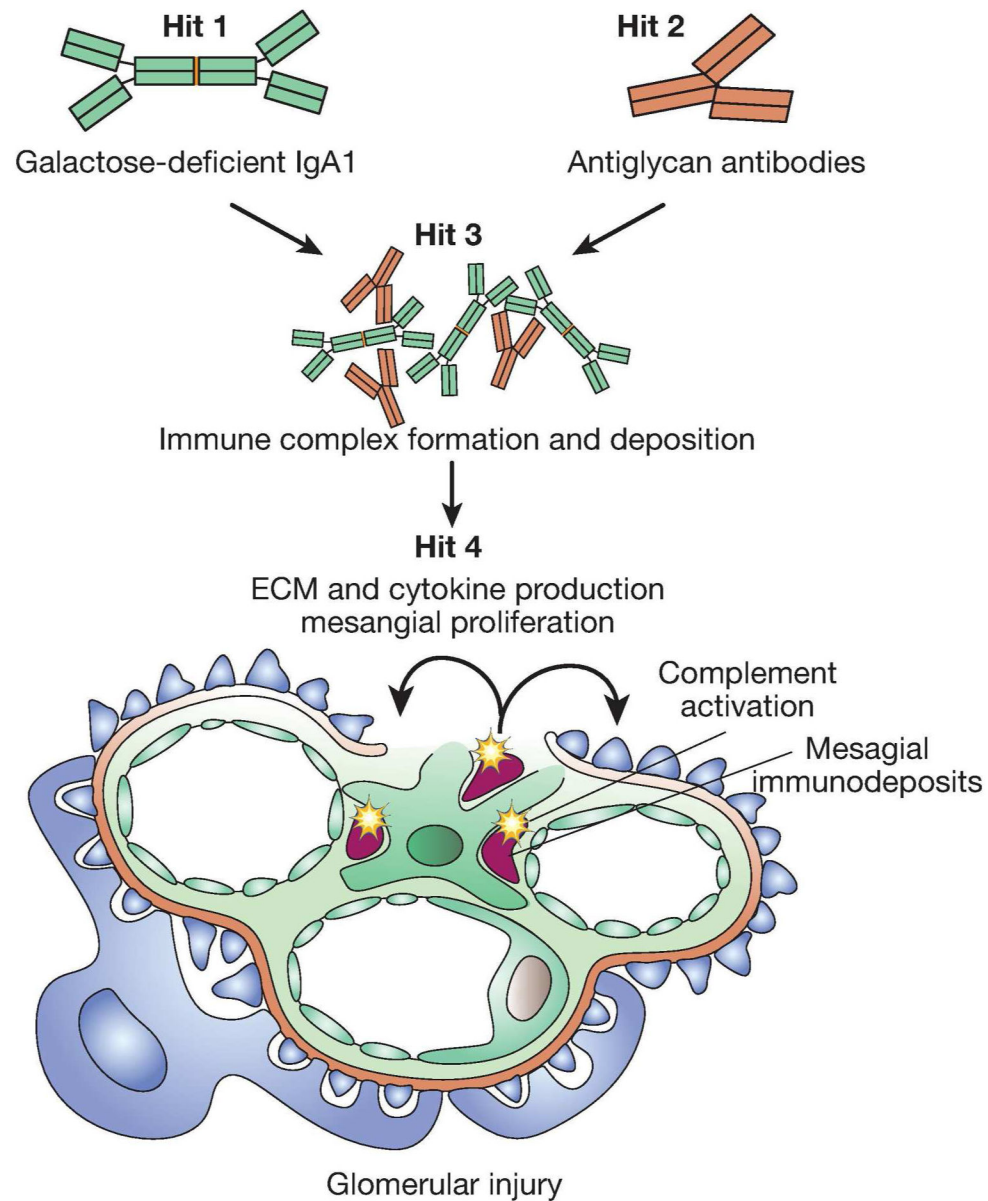


Figure 3.
The Multi-hit Pathogenesis Model of IgA Nephropathy.

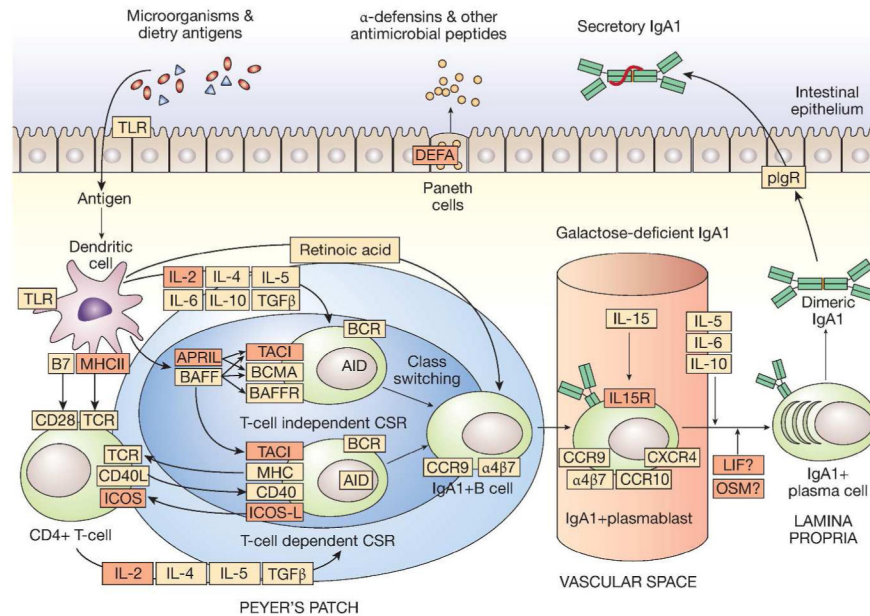


Figure 4. Genetic Hits to the “Intestinal Immune Network for IgA Production”

IgA is the most abundant antibody isotype in the body, with the majority of IgA found in mucosal secretions. Mucosal IgA production is induced by T cell-dependent and T cell-independent mechanisms. T cell-independent production of IgA is primarily stimulated by IL-6, IL-10, TGF- β , BAFF, and APRIL produced by intestinal epithelial, dendritic, and stromal cells. In this environment, intestinal B cells undergo class switching from IgM to IgA1. IgA-secreting plasma cells migrate to lamina propria, where they release dimeric IgA1. The dimers are formed through an interaction of two IgA1 molecules with a joining chain (J-chain), which is synthesized by plasma cells. IgA1 dimers can bind to the polymeric Ig receptor (pIgR) on the basolateral surface of the mucosal epithelium and undergo transcytosis to the apical surface, where they dissociate from pIgR and are secreted into the lumen carrying the secretory component of the receptor. The secretory component protects IgA molecules from proteolytic enzymes in the gut lumen. The bacteriostatic effects of secretory IgA1 are accompanied by antimicrobial peptides, such as defensins, secreted into the gut lumen by Paneth cells. The key molecules involved in the intestinal immune network for IgA production are indicated in orange; molecules implicated by GWAS are marked in red. The risk alleles generally lead to increased IgA1 responsiveness stimulating IgA1 production; increased levels of polymeric IgA1 in the circulation may represent a consequence of “spill-over” from mucosal sites and/or “mis-trafficking” of stimulated plasma cell to bone marrow sites.

Table 1

Summary of IgAN GWAS loci, their functions, pleiotropic effects, and potential role in the pathogenesis of IgAN.

GWAS Candidate Genes	Structure, Function, and Gene Expression	Potential Relationship to the Multi-hit Pathogenesis Model	Pleiotropic Effects and Links to Other Immune-mediated Diseases
<i>HLA-DQA1, HLA-DQB1, HLA-DRB1</i>	<ul style="list-style-type: none"> MHC class II molecules are critical for antigen presentation and adaptive immunity There are four independent classical HLA alleles associated with IgAN at this locus: two risk alleles (<i>DQA1*0101</i>, <i>DQB1*0301</i>) and two protective alleles (<i>DQA1*0102</i>, <i>DQB1*0201</i>). 	<ul style="list-style-type: none"> MHC-II molecules participate in the regulation of intestinal inflammation and IgA production (may contribute to Hit 1). Some class II alleles have a permissive role in autoimmunity, thus may be associated with a greater risk of anti-glycan response (Hit 2). 	<ul style="list-style-type: none"> Concordant effect on the risk of rheumatoid arthritis, systemic sclerosis, alopecia areata, Graves' disease, follicular lymphoma, type I diabetes, Celiac disease, and IgA deficiency. Opposed effect on the risk of SLE, multiple sclerosis, ulcerative colitis, and hepatocellular carcinoma.
<i>HLA-DP</i>	<ul style="list-style-type: none"> MHC class II molecules, less well studied compared to HLA-DQ and HLA-DR. 	<ul style="list-style-type: none"> May contribute to either Hit 1 or Hit 2, (similar to above). 	<ul style="list-style-type: none"> This locus has been previously associated with systemic sclerosis, ANCA vasculitis, Graves' disease and HBV infection, but it is not clear if the IgAN risk allele has any effect on these traits.
<i>TAP2, PSMB8, PSMB9</i>	<ul style="list-style-type: none"> The IgAN signal at this locus is specific to Asians. PSMB8 and PSMB9 are interferon-induced subunits of the immunoproteasome that mediate intestinal NF-κB activation in IBD¹⁸². PSMB8 is up regulated in intestinal tissue with active IBD lesions¹⁸³. Treatment with bortezomib (PSMB8 inhibitor) attenuates experimental colitis¹⁸⁴. 	<ul style="list-style-type: none"> The risk allele represents a cis-eQTL associated with increased peripheral blood expression of <i>TAP2</i>, <i>PSMB8</i> and <i>PSMB9</i>, which may result in a pro-inflammatory state modulating Hit 1 through up regulation of intestinal inflammation. 	<ul style="list-style-type: none"> This locus has been previously associated with Kawasaki disease, degenerative disc disease, and lymphoma, but it is not clear if the IgAN risk allele has any effect on these traits.
<i>CFHR1, CFHR3</i>	<ul style="list-style-type: none"> Common deletion of <i>CFHR1</i> and 3 genes 	<ul style="list-style-type: none"> Modulates local complement activation in 	<ul style="list-style-type: none"> Concordant (protective) effect on the risk of age-

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	<ul style="list-style-type: none"> has a protective effect against IgAN. <i>CFHR1</i> and 3 genes encode Factor H-related peptides that modulate the activity of the alternative complement pathway. FHR1 competes with FH for binding to surface-fixed C3b leading to increased activation of C3 convertase¹⁴⁶. 	<ul style="list-style-type: none"> the kidney (Hit 4); protective deletion of <i>CFHR1</i> and <i>CFHR3</i> is associated with higher circulating levels of Factor H and dampened local activation of the alternative complement pathway¹⁴⁸. 	<ul style="list-style-type: none"> related macular degeneration. Opposed (risk) effect on the risk of SLE and atypical HUS due to anti-FH antibodies.
<i>ITGAM, ITGAX</i>	<ul style="list-style-type: none"> <i>ITGAM</i> and <i>ITGAX</i> encode integrins αM and αX that combine with integrin β2 chain to form leukocyte-specific complement receptors 3 and 4 (CR3 and CR4, respectively). Intestinal dendritic cells that induce T-cell-independent IgA class-switch recombination express high levels of αM and αX integrins^{185,186}. <i>ITGAM</i> and <i>ITGAX</i> are also expressed in macrophages and participate in the process of phagocytosis. 	<ul style="list-style-type: none"> CR3 and CR4 may play a role in the regulation of glomerular inflammation (Hit 4), including phagocytosis of complement-coated immune complexes αM and αX integrins are involved in the regulation of intestinal inflammation and IgA production, thus may be involved in Hit 1. 	<ul style="list-style-type: none"> There are at least two independent risk alleles at this locus; one of the alleles is fixed in Asians. This allele has an opposed effect on the risk of SLE¹⁸⁷.
<i>CARD9</i>	<ul style="list-style-type: none"> <i>CARD9</i> encodes a molecular scaffold for the assembly of a BCL10 signaling complex that activates NF-κB, which is responsible for both innate and adaptive immune responses¹⁸⁸. <i>CARD9</i> is a pro-inflammatory molecule, and the IgAN risk allele is strongly associated with its increased expression (cis-eQTL effect). <i>CARD9</i> mediates intestinal repair, T-helper 17 responses, and control of bacterial infection after intestinal 	<ul style="list-style-type: none"> Potentially modulates Hit 1 through regulation of intestinal inflammation and IgA production. 	<ul style="list-style-type: none"> The IgAN risk allele increases <i>CARD9</i> expression and has a concordant effect on the risk of IBD. Conversely, a rare protein-truncating splice variant in <i>CARD9</i> confers additive protection from IBD^{190,191}, but its effect on the risk of IgAN has not been tested. Familial <i>CARD9</i> deficiency predisposes to invasive fungal infections¹⁹².

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	epithelial injury in mice ¹⁸⁹ .		
<i>VAV3</i>	<ul style="list-style-type: none"> VAV proteins are guanine nucleotide exchange factors essential for adaptive immune function and NF-κB activation in B-cells, a process that stimulates IgA production¹⁹³. VAV proteins are required for proper differentiation of colonic enterocytes and preventing spontaneous ulcerations of intestinal mucosa¹⁹⁴. VAV proteins are also expressed in macrophages and participate in phagocytosis. 	<ul style="list-style-type: none"> Potentially modulates Hit 1 through regulation of intestinal inflammation and IgA production. May also modulate Hit 4 through regulation of glomerular inflammation, phagocytosis, and clearance of immune complexes. 	<ul style="list-style-type: none"> <i>VAV3</i> is a positional candidate for QTL for mouse intestinal inflammation in a parasite-induced (Trichuris muris) model-of infection¹⁹⁵. A common variant in <i>VAV3</i> has previously been associated with autoimmune hypothyroidism¹⁹⁶, however, the IgAN signal represents an independent association.
<i>DEFA1, DEFA3, DEFA5, DEFA6</i>	<ul style="list-style-type: none"> α-defensins are antimicrobial peptides that provide innate defense against microbial pathogens. α-defensin 1 and 3 are synthesized in neutrophils. <i>DEFA1</i> and <i>DEFA3</i> genes are prone to complex copy number variation with a gene copy correlating with the expression level of these peptides. α-defensin 5 and 6 (<i>DEFA5</i> and <i>DEFA6</i>) are constitutively produced by the intestinal Paneth cells. 	<ul style="list-style-type: none"> It is not clear if the IgAN risk allele tags a risk haplotype carrying a specific copy number of <i>DEFA1/3</i> genes, or if the association is due to variants in the nearby intestinally-expressed <i>DEFA5</i> or <i>DEFA6</i> genes. This locus may potentially modulate Hit 1 through regulation of intestinal microbial pathogens and inflammation. 	<ul style="list-style-type: none"> Deficiencies in α-defensins-5 and -6 have been previously associated with Crohn's disease.
<i>TNFSF13</i>	<ul style="list-style-type: none"> <i>TNFSF13</i> encodes APRIL, a powerful B-cell stimulating cytokine that is induced by intestinal bacteria and promotes CD40-independent IgA class switching¹⁹⁷. APRIL levels are elevated in patients with IgAN¹¹⁵ and the IgAN risk allele is associated with 	<ul style="list-style-type: none"> Potentially modulates Hit 1 through direct up-regulation of intestinal IgA production. 	<ul style="list-style-type: none"> IgAN risk allele has been associated with elevated serum non-albumin protein and IgA levels¹⁹⁸. Mutations in the <i>TNFSF13</i> receptor (TACI) produce IgA deficiency or combined variable immunodeficiency, with increased propensity to

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	increased IgA levels ⁸⁶ .		mucosal infections ¹⁹⁹
<i>LIF, OSM, HORMAD2, MTMR3</i>	<ul style="list-style-type: none"> <i>LIF</i> and <i>OSM</i> represent the top positional candidates; both are IL-6 related cytokines that use gp130 for signal transduction and have been previously implicated in mucosal immunity. <i>LIF</i> is secreted by pericrypt fibroblasts and may be critical for proliferation and renewal of enterocytes²⁰⁰. Genetic disruption of gp130 signaling leads to gastrointestinal ulceration and inflammatory joint disease in mice²⁰¹. 	<ul style="list-style-type: none"> Potentially modulates Hit 1 through direct up-regulation of intestinal IgA production. 	<ul style="list-style-type: none"> The IgAN risk allele at this locus is protective against Crohn's disease and associated with increased serum IgA levels⁸⁵.

Table 2

Summary of the KDIGO treatment recommendations for IgAN.

Intervention	Recommendation	Grade	Comments and areas of uncertainty
Blood pressure control and use of ACE inhibitors or ARBs	Long-term use of ACE inhibitors or ARBs is recommended for patients with proteinuria > 1g/day, with up-titration of the drug depending on blood pressure to achieve proteinuria <1g/day.	1B	It is not clear at what level of proteinuria one should start ACE inhibitors or ARBs. Combined ACE inhibition and ARB use is generally not advised given potential risks of side effects of hyperkalemia and hypertension, especially in elderly.
Corticosteroids	A target blood pressure of <130/80 mm Hg is recommended for patients with proteinuria <1 g daily, and <125/75 for patients with proteinuria >1 g daily. A 6-month trial of corticosteroids is recommended in patients with persistent proteinuria of >1g/day despite 3–6 months of optimal supportive care and GFR > 50 ml/min per 1.73m ²	Not graded 2C	 Presently, it is unclear at what level of reduced GFR this therapy becomes futile (i.e. “the point of no return”), and whether patients with lower levels of proteinuria should also be treated.
Other immunosuppressive agents	Patients with crescentic IgAN involving over 50% of glomeruli and rapidly progressive course should be treated with steroids and cyclophosphamide. Not treating with corticosteroids combined with cyclophosphamide or azathioprine (unless crescentic forms with rapidly progressive course).	2D 2D	The definition of crescentic IgAN remains controversial. Rituximab has not yet been used in a significant enough number of patients to be recommended, however, data from studies on other crescentic diseases suggest a potential benefit. There is no convincing evidence for the use of combined immunosuppression in IgAN, except for crescentic forms.
	Not using immunosuppressive therapy in patients with GFR < 30 ml/min per 1.73 m ² (unless crescentic forms with rapidly progressive course).	2C	There is no convincing evidence for the use of immunosuppressive treatments in advanced stages of CKD due to IgAN.
	Not using MMF	2C	The data for MMF in IgAN is generally of poor quality
Fish oils	Fish oils may be potentially useful in patients with persistent proteinuria 1g/d, despite 3–6-months of optimized supportive care.	2D	RCTs give equivocal results on the benefit of fish oils. Given low side effect profile and over-the-counter availability, the use of fish oils can probably be left to the choice of individual patients. However, this treatment should not replace corticosteroids, for which the evidence is stronger.
Tonsillectomy	Not recommended	2C	No convincing evidence of benefit. Generally not recommended, unless specifically indicated by recurrent episodes of tonsillitis with suppurative disease flares.

Recommendation grading: Level 1 = “Recommended”, Level 2 = “Suggested”. Quality of evidence grading: A = “High”, B = “Moderate”, C = “Low”, D = “Very Low”.