Racial and Genetic Factors in IgA Nephropathy

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Summary: Racial and ethnic variations in the incidence of IgA nephropathy (IgAN) could imply both genetic and environmental influences that exist in a complex and poorly understood interplay to modify the expression of the IgAN clinical phenotype. Progress in identifying genetic factors that influence either susceptibility to IgAN or its progression has been slow. Recent progress using family based approaches (genome-wide scan for linkage and family based genetic association studies) to study the genetic basis for susceptibility to familial and sporadic IgAN strongly point to clinical and genetic heterogeneity in the entity we presently call IgAN. The inconsistent findings reported from case-control genetic association studies may be explained by new understanding of the haplotype block structure of the human genome. Rapid improvements in available and developing technologies in the post-genomic era are needed and are expected to accelerate progress in understanding genetic factors underlying IgAN.

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Incidence and prevalence figures for primary IgA nephropathy (IgAN) suggest that, in general, it is the most common primary glomerulonephritis worldwide.[1-4] The true population incidence rates for primary IgAN are unknown because definitive diagnosis is dependent on policies governing renal biopsy, which vary considerably from country to country and within regions within the same country. For example, the high incidence figures reported for Singaporean Asian males undergoing renal biopsy probably reflect the practice of mandatory routine screening for urinary abnormalities of all army recruits.[5,6] In addition, a large proportion of clinically silent and undetected IgAN likely exists, as suggested by a control necropsy study of 200 consecutive patients who died from traumatic injuries and had no clinical history of renal disease or other organic disease discovered at the time of necropsy.[7]

Racial and ethnic differences in disease incidence have been advanced as support of a genetic basis for susceptibility to a number of renal diseases including the development of hypertensive nephrosclerosis and diabetic nephropathy among African Americans[8] and for susceptibility to end-stage renal disease among South Asians and African Caribbeans in the United Kingdom.[9] Recent retrospective studies have suggested that racial/ethnic differences also may exist for IgAN. The most dramatic example is the very low prevalence of IgAN and Henoch-Schönlein Purpura (HSP) reported in the 1980s for both African and American blacks that cannot readily be accounted for by differences in the racial distribution of hospital admissions or renal biopsy procedures performed.[10,11] More recent surveys have indicated that IgAN is not generally the most common primary glomerulonephritis in the United States, where focal segmental glomerulosclerosis is the most common biopsy diagnosis, especially among African Americans and Hispanics,[12-14] in whom IgAN continues be an infrequent biopsy diagnosis. One apparent

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exception is among young adults (age, ≤20 y), in whom IgAN has been reported to be the most common primary glomerulonephritis, at least among a biopsy cohort drawn from 24 Midwestern and Southern states in the United States, indicating the importance of taking into account age and regional distribution (perhaps reflecting differences in both ethnicity and environmental exposure) when assessing incidence/prevalence patterns of renal disease.[15] An apparent gradient of decreasing incidence of biopsy-proven IgAN from western (Italy and western France)[16,17] to central/eastern Europe (Czech Republic, Romania, and Republic of Macedonia)[18-20] also has been noted.

In contrast to the case of American and African blacks, Asian/South Asian cohorts and registries generally have reported that IgAN is the predominant biopsy diagnosis.[21-25] These findings provide indirect support for the existence of genetic factors that determine susceptibility to the development of IgAN. Because race and ethnicity are linked intricately, genetic and environmental factors cannot be dissociated clearly, and both may exert an influence on expression of the IgAN clinical phenotype.

OVERVIEW OF THE MOLECULAR GENETICS OF IgAN

The human IgAN phenotype does not show classic Mendelian inheritance patterns (ie, human IgAN is not a monogenic disorder).[26] The emerging model for the immunopathogenesis of IgAN involves the interplay of multiple discrete immunologic abnormalities related to the abnormal overproduction of mucosal type IgA1 (quantitative trait) in the systemic compartment (spatial trait) and possibly other protein functional abnormalities related to a propensity for mesangial deposition of polymeric IgA1 (functional trait). If this hypothesis is correct, then the disease-associated genetic variations at identified *IGAN* loci are less likely to be in the form of classic nonsense/missense/splice site mutations and deletions/insertions that affect protein structure and function, such as those shown in classic monogenic Mendelian podocytopathies (congenital nephrotic syndrome, steroid-resistant nephrotic syndrome, and focal segmental glomerulosclerosis) in which mutations occur in structural protein components of the slit diaphragm.[27] Rather, the molecular genetics of primary IgAN may more appropriately be considered to follow a paradigm recently shown for the genetically complex human autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and Crohn's disease,[28-30] for which multiple loci have been identified by family based genetic studies. Disease-associated genetic variations increasingly are being identified in these and other complex diseases as specific single-nucleotide polymorphism (SNP) alleles in noncoding regions or synonymous SNPs in coding regions, which function as *cis*-acting elements that alter the transcriptional activity of a disease gene and/or messenger RNA stability and therefore the expression level of the encoded protein. Indeed, recent studies have indicated that 30% to 50% of human genes with coding SNPs can present allelic variation in gene expression.[31,32]

A reasonable working model to describe the molecular genetic basis of IgAN may be that a small subset of genetic loci contributes strong effects (IgAN disease/susceptibility loci) that underlie the primary immunologic defects observed in IgAN (Fig. 1). Each locus may occur at a different prevalence rate in different racial/ethnic groups such that there may be a predominant disease locus responsible for disease among European Caucasians, whereas a distinct locus more commonly is responsible for disease among Asians, and a subset of disease loci may occur in combination in a single affected individual. These disease loci will be detectable by genome-wide scan for linkage, a methodology that has been used successfully to identify major disease/susceptibility genes, but that has limited power to detect genes of modest effect. Variations at these major genetic loci are necessary, but may not be sufficient for the development and/or progression of IgAN in the absence of the contributions from a potentially large number of modifier genes with modest genetic effects but high prevalence that are best identified using genetic association studies. When considered together in various allelic combinations, these loci that each contribute

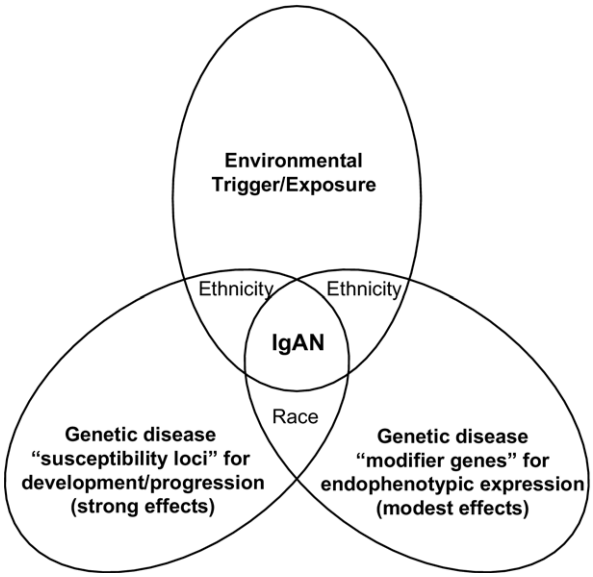

Figure 1. Genetic and environmental factors in the pathogenesis of IgAN. Proposed model illustrating the role of interactions between strong genetic susceptibility loci and modest genetic modifier effects with environmental triggers/exposures in the pathogenesis of IgAN. Racial factors may contribute to the genetic basis of disease, whereas ethnic factors may influence environmental triggers/exposures.

strong or modest effects may define distinct genetic bar codes or signatures for the numerous but finite number of disease phenotypes (development and/or progression of IgAN) and endophenotypes observed in human IgAN (eg, nephritic vs nephrotic clinical presentation, histopathologic subclass, severity of disease, responsiveness of proteinuria to angiotensin-converting enzyme [ACE] inhibitors, and/or angiotensin II receptor blockers). The expression of these phenotypes/endophenotypes in genetically susceptible individuals may require an environmental trigger/exposure (Fig. 1).

GENETIC STUDIES BASED ON LINKAGE ANALYSIS

Genome-Wide Scan for Linkage to Familial IgAN in Human Beings

The strongest evidence for the existence of genetic factors in the development and/or progression of IgAN comes from descriptions of familial IgAN, largely in Caucasian populations.[33-37] Familial IgAN initially was reported to be associated with a higher risk for progression to end-stage renal disease,[38] although a more recent study failed to confirm this finding and suggested that familial and sporadic IgAN may share a common pathogenic mechanism.[39] Although the prevalence rate among both Asian and Caucasian populations that undergo renal biopsy remains high,[24,40] IgAN rarely is reported in African or American blacks.[34]

Taking a family based approach, Gharavi et al[41] reported the successful identification by linkage analysis of a major disease locus designated *IGAN1* on chromosome 6q22-23 in a Caucasian cohort. Only 60% of the families in the study were linked to 6q22-23, suggesting the existence of genetic heterogeneity. Recently, this locus was excluded by linkage analysis in a single Japanese family consisting of 4 affected individuals, 7 unaffected individuals, and 2 individuals whose status was unknown.[42] To date, no specific genetic variation associated with disease/susceptibility has been identified at the gene-rich *IGAN1* locus.

As with all family based genetic studies, there is a high degree of dependency on access to sufficient numbers of clinically well-phenotyped and genetically informative cohorts. To address the paucity of cohorts with biopsy-proven IgAN available for the conduct of linkage-based, association-based, and sequence-based approaches, the European IgA nephropathy consortium has published the details of its IgAN Biobank resource.[43] The IgAN Biobank contains a minimum of 72 multiplex extended pedigrees, 159 trios, 1,068 cases, and 1,040 matched controls. All subjects enrolled were of Caucasian origin, belonging to various geographic areas in Germany, Italy, and Greece. By using a 2-stage genome-wide scan for linkage to IgAN in 22 new informative Italian families from the IgAN Biobank consisting of 59 affected and 127 unaffected subjects, Bisceglia et al[44] reported suggestive linkage for 2 novel IgAN loci on 4q26-31 and 17q12-22. Multipoint parametric analysis using an affected-only dominant model and allowance for the presence of genetic heterogeneity indicated that 50% and 65% of the families, respectively, were linked to the 2 loci, consistent with the existence of genetic heterogeneity.

Table 1. Susceptibility Loci Identified by Genome-Wide Scan for Linkage to Human IgAN

Susceptibility Locus*	NPL Score (*P* Value)	LOD Score	α Value†	Candidate Genes	Reference
6q22-23	5.1 (4.8×10^{-6})	5.6	.59	*SGK, VNN3*	41
4q26-31	? (.0025)	1.83	.50	*TRPC3, IL-2, IL-21*	44
17q12-22	? (.0045)	2.56	.65	*HD5*	
2q36	>2	3.5	-	*CCL20*	45

Abbreviations: NPL, multipoint nonparametric linkage analysis; IL, interleukin.
*Affected-only analysis.
†Admixture value that indicates percentage of families studied that were linked to the identified susceptibility locus when the presence of genetic heterogeneity has been determined by calculation of a multipoint heterogeneous LOD score. LOD (multipoint logarithm of odds) score for assumption of autosomal-dominant inheritance with incomplete penetrance.

Recently, a third genome-wide scan of a single, large, 4-generation Canadian family of German-Austrian descent with 14 affected subjects localized a novel IgAN susceptibility locus to a critical interval of approximately 9 cM on chromosome 2q36.[45] Methodologies, identified loci, and candidate genes reported in these studies are summarized in Table 1. It is remarkable that the genome-wide scans for linkage to IgAN reported to date in families of predominantly European Caucasian descent have reported nonidentical loci. Future studies of this kind that aim at molecular genetic dissection of increasingly homogeneous cohorts must consider the importance of defining distinct clinicopathologic subtypes of IgAN that may exist within the single pathologic ascertainment criterion currently used to diagnose IgAN: light microscopic evidence of mesangial deposits of IgA by immunofluorescence.

Genome-Wide Scan for Linkage to IgAN in Murine Models

A genome-wide association study conducted in the ddY spontaneous outbred model of murine IgAN identified 3 regions on chromosomes 1 ($\chi^2 = 16.5$, $P = .00054$, genome-wide significant $P = .0014$), 9 ($\chi^2 = 22.1$, $P = .0001$, genome-wide significant $P = .0001$), and 10 ($\chi^2 = 16.4$, $P = .00016$, genome-wide significant $P = .0054$) that were associated significantly with onset of glomerular injury.[46] Notably, the peak marker on murine chromosome 10 was found to be in a region syntenic to the human *IGAN1* locus on chromosome 6q22-34. In addition, the peak marker on chromosome 1 was located very close to the *L-selectin* gene locus, a candidate gene for human IgAN that encodes a well-characterized homing receptor for T cells, consistent with a role for genetic variations in the *L-selectin* gene as a mechanism underlying the proposed abnormal production of undergalactosylated mucosal IgA1 at systemic sites of IgA1 production in human IgAN. The peak marker for a final locus on chromosome 12 ($\chi^2 = 17.1$, $P = .00018$, genome-wide significant $P = .0014$) identified as a susceptibility locus for high serum IgA levels was noted to be very close to the IgA heavy chain (*Igh*) gene.

Quantitative trait loci (QTL) analysis of F2 animals generated by crossing the inbred high IgA (HIGA) mouse strain derived from the selective mating of ddY mice with BALB/c mice, also has proved to be a highly successful strategy for mapping multiple quantitative traits characteristic of the HIGA strain. Polymeric (trimeric) IgA dominance was mapped to the hinge region of the *Igh* gene on chromosome 12.[47] The DBA/2J strain of mice that shares the same amino acid sequence in the hinge region as the HIGA strain and that also shows a similar pattern of trimeric IgA dominance by size analysis of serum IgA is characterized by low levels of serum IgA,[47] suggesting that genetic variation in the hinge region located on the Cα1 exon of the IgA heavy chain plays a specific role in trimeric IgA formation in HIGA mice, but is distinct from the susceptibility locus for high serum IgA identified at the IgA heavy chain

Table 2. Susceptibility Loci Identified for Phenotypic Traits Associated With IgAN in Murine Models

Mouse Chromosome	χ^2 (*P* Value)	LOD Score	Phenotype	Candidate Genes	Reference
1	16.5 (.00054)		Glomerular injury	*L-Selectin*	46*
9	22.1 (.0001)		Glomerular injury	*?*	
10	16.4 (.00016)		Glomerular injury	*Syntenic* with *IGAN1*	
12	17.1 (.00018)		High serum IgA	*Igh*	
12			Trimeric IgA	*Igh*	47†
1		3.49	High serum IgA		48†
2		5.01	High serum IgA		
4		4.45	High serum IgA		
15		4.40	IgA deposition		
12			High serum IgA	*Igα*	49†
5			High serum IgA	*IgJ*	

*Genome-wide scan for linkage.
†Quantitative trait loci analysis.

locus in ddY mice as described earlier.[46] Indeed, QTL analysis mapped 2 loci to the quantitative trait of high serum IgA (hyperserum IgA) on chromosomes 2 (logarithm of odds [LOD], 5.01) and 4 (LOD, 4.45), with an additional suggestive locus on chromosome 1 (LOD, 3.49), whereas the quantitative trait of glomerular IgA deposition was mapped to chromosome 15 (LOD, 4.40).[48] Notably, although the serum IgA level was correlated weakly with the intensity of glomerular IgA deposition in 244 F2 mice, none of the QTLs identified for hyperserum IgA were associated significantly with glomerular IgA deposition.

A 350-kb region containing several Ig heavy chain genes and the Iα exon of the IgA (*Igα*) germline switch region on mouse chromosome 12, which is responsible for the natural 4-fold higher IgA levels in the inbred C3HeB/FeJ (C3H) mouse strain as compared with the C57Bl/6J (B6) strain, has been identified independently by a 1-step QTL mapping process along with a second independent, chemically induced mutation within the immunoglobulin joining (*IgJ*) gene on chromosome 5 that causes a 2-fold increase of IgA levels when transferred from C3H to B6.[49] In addition to independently confirming the importance of the IgA heavy chain gene region at map position 58.0 cM on mouse chromosome 12 in the regulation of the quantitative trait of hyperserum IgA, this study showed that interaction of 2 independent genetic loci was associated with a dramatic 40-fold up-regulation of serum IgA, suggesting that genetic control of both IgA expression and distribution contribute synergistically to the regulation of serum IgA levels. Susceptibility loci identified by either genome-wide scan for linkage or QTL analysis for phenotypic traits associated with IgAN in murine models are summarized in Table 2.

GENETIC CASE-CONTROL ASSOCIATION STUDIES

Pregenomic Era: Identification of At-Risk Alleles and Genotypes in Candidate Genes

There are many reports of small population-based, case-control, genetic association studies attempting to implicate various candidate genes (eg, components of the renin-angiotensin-aldosterone pathway, mediators of inflammation and/or vascular tone, components of the mesangial matrix, and various receptors for polymeric IgA1 expressed in mesangial cells) in the development and/or progression of IgAN. However, it is a characteristic of these studies that results are not replicated (the replication problem).[26,33,34] This has raised the question of the

validity of the methodologic framework that has been the foundation of hundreds of such studies in IgAN genetics research published since the 1990s.

The Replication Problem: The Case of the ACE Insertion/Deletion Polymorphism

A widely studied example of the replication problem is the case-control association studies of the angiotensin I-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism in the development and/or progression of IgAN, as well as in a number of other common human conditions including cardiovascular disease; complications of diabetes such as retinopathy and nephropathy; glomerular, tubulointerstitial, and renal cystic renal diseases; and even renal allograft survival.[33,34,50] The interest in studying the *ACE* I/D polymorphism is based on evidence for biological plausibility. Rigat et al[51] reported in 1990 that the *ACE* I/D polymorphism in intron 16 of the human *ACE* gene accounted for half of the variation in serum ACE levels in a Caucasian study cohort. This is a result of the presence of a transcriptional repressor element in the I allele.[52]

There have been numerous population-based studies that either supported or refuted an association between the D allele and progression of renal disease in these conditions.[33,34] Recent meta-analyses have concluded that the D allele is not associated with renal disease progression in patients with IgAN or diabetic nephropathy.[50,53] Despite more than a dozen generally small genetic case-control studies of the *ACE* I/D polymorphism in both Caucasian and Asian IgAN cohorts, no conclusions can be drawn confidently from these studies regarding the association between the D allele or DD genotype and development and/or progression of IgAN. Population-based genetic association studies of other genes encoding proteins in the renin-angiotensin-aldosterone system such as angiotensinogen and the angiotensin II type 1 receptor, as well as renin (*REN*) and aldosterone synthase (CYP11β2) also have generated conflicting results, as have similar studies of the expanded renin-angiotensin-aldosterone system that includes 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) and the mineralocorticoid receptor.[54] In general, the approach has been to genotype a single common polymorphism (typically a restriction fragment-length polymorphism) by polymerase chain in a single candidate gene. It is remarkable that, to date, the role of the renin-angiotensin-aldosterone system, whose components ACE and angiotensin II type 1 receptor are the targets of the important ACE inhibitor and angiotensin II receptor blocker classes of drugs, respectively, has not been shown convincingly by any genetic association study.

The Haplotype Block Structure of the Human Genome and Implications for Conducting Genetic Association Studies

In the postgenomic era, there has been renewed interest in conducting genetic association studies, especially SNP-based, whole-genome association studies, to identify genetic variations associated with the development and/or progression of a number of common human diseases. This renewed interest reflects the important finding that linkage disequilibrium (LD)—the phenomenon that particular alleles at nearby sites can co-occur on the same haplotype more often than expected by chance[55,56]—is highly structured into discrete blocks separated by hotspots for recombination.

The haplotype block model for LD has important implications for the way in which genetic association studies should now be conducted, and may explain at least in part the replication problem. Based on the haplotype block model of LD, the *ACE* I/D polymorphism is but a single marker variant in the *ACE* gene. Researchers have assumed that the D allele defines a single population of subjects at risk of disease. This assumption may prove incorrect because within the common SNP haplotype block that contains the *ACE* I/D polymorphism, more than one haplotype pattern may share the D allele, only one of which is associated with risk for disease. The lumping of such subgroups defined by haplotypes that share the D allele may explain at least in part the basis for discrepant reports of genetic association with disease.

Criteria for a Valid Genetic Case-Control Study

The *Journal of the American Society of Nephrology* recently has defined a set of minimum criteria for association studies using polymorphic genetic markers, indicating that the common SNP haplotype block model should be taken into account.[57] Based on these guidelines, only genetic association studies that use one or more methodologically valid approaches and satisfy the minimum rigorous conditions for a reliable genetic association study are discussed here. These elements include biological plausibility, haplotype relative risk analysis to identify statistically significant at risk haplotype(s) associated with small *P* values, use of family based methodologies such as the transmission equilibrium test (TDT/sib-TDT) or the family based association test to directly study trios/sib-trios and extended families or to verify the absence of significant population stratification bias (admixture) inherent in population-based case-control association studies, and the study of moderately large (ie, adequately powered) cohorts. Because admixture has not been ruled out in any published population-based association study of IgAN, only family based studies are reviewed.

Postgenomic Era: Family Based Association Studies to Identify At-Risk Haplotypes in Candidate Genes

Only 5 studies examining 3 candidate genes have used the family based TDT study methodology and/or analysis of at-risk haplotype. Three SNP polymorphisms in 2 contiguous genes at the *selectin* gene cluster at chromosome 1q24-25 (712C>T[P238S] in the coding region and −642A>G in the promoter region of the *L-selectin* gene; 1402C>T[H468Y] in the coding region of the *E-selectin gene*) were reported previously to be in tight LD and to occur in 2 haplotypes (IgAN-associated TGT and wild-type CAC).[58] Overexpression of an adenoviral construct expressing the disease-associated P238S substitution of the *L-selectin* gene is associated with significantly less rolling adhesion of stably transfected CHO cells perfused over interleukin-1β–activated human umbilical vein endothelial cells, as compared with wild-type and control adenovirus-expressing CHO cells.[59] The disease-associated −642A>G promoter variant is associated with significantly less transcriptional activity. In contrast, the H468Y substitution in the *E-selectin* gene did not show a functional difference in rolling adhesion. These findings suggest that in Japanese subjects, the disease-associated TGT haplotype in the *selectin* gene cluster can influence the quality and quantity of *L-selectin* gene products, and may play a potential role in inflammatory processes such as leukocyte-endothelial interactions, which may be important in the pathogenesis of IgAN. Notably, the *L-selectin* gene has been suggested previously as a candidate susceptibility gene based on the previously reported genome-wide scan of the ddY mouse model[46] and because of its well-known function as a T- and B-cell homing receptor.

A family and haplotype-based association study using the TDT methodology has shown that 2093C and 2180T SNP variants in the 3'-untranslated region of the *Megsin* gene were transmitted significantly more frequently from heterozygous parents to patients than expected in the extended TDT analysis (increased co-transmission in 232 Chinese families, $P < .001$), whereas haplotype relative risk (HRR) analyses showed that these same SNP alleles were transmitted more often to patients (HRR = 1.568, $P < .014$ for the 2093C allele; HRR = 2.114, $P < .001$ for the 2180T allele).[60] The same group, using a similar approach, recently reported that the *Megsin* 23167G SNP variant is associated with both susceptibility and progression of IgAN in 435 Chinese patients and their family members using TDT and HRR analysis.[61] The GG genotype was found to be associated with severe histologic lesions and disease progression. Megsin is a member of the serpin (serine proteinase inhibitor) superfamily that is up-regulated in the context of mesangial proliferation and extracellular matrix expansion in IgAN, and therefore represents a strong candidate gene for susceptibility to IgAN.

A haplotype of the *interferon-γ (IFNγ)* gene consisting of the 12-CA repeat allele in tight LD with the +874A SNP variant recently showed an association with susceptibility to IgAN with-

out influencing survival in a family based association test analysis of 53 Italian patients, 45 complete trios, 4 incomplete trios, and 36 discordant siblings from the collection of the European IgAN Consortium.[62] The +874T/A SNP lies within a putative nuclear factor-κB transcription factor binding site. Notably, the +874A variant is associated with transcriptional down-regulation of *IFN*γ gene promoter activity, consistent with the known role of nuclear factor-κB in the transcriptional regulation of the *IFN*γ gene.

FUTURE DIRECTIONS

Given the racial and ethnic variations in disease incidence and prevalence, the translational goal of IgAN studies will extend from bench to bedside to community. The data presented in this review support both clinical and genetic heterogeneity in the disease that we refer to collectively as *IgAN*; failure to detect disease-associated genetic variations in one racial/ethnic population or geographic group does not preclude the finding of novel racial/ethnic-specific gene polymorphisms in other populations.

With the recent findings from 3 independent genome scans for linkage to the development of human IgAN, paralleled by similar studies of molecular genetics in models of murine IgAN, there has been significant progress toward the identification of chromosomal loci containing genetic variations that exert major effects on the expression of the IgAN clinical phenotype. Notably, no specific disease susceptibility gene or polymorphism has been identified to date. The next phase of studies must take into account more precise clinicopathologic classification schemes for likely IgAN subtypes and use the opportunities given by increasingly powerful tools for the high-resolution mapping of genetic variations at putative disease susceptibility loci.

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