Genetic Determinants of IgA Nephropathy: Eastern Perspective

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Summary: IgA nephropathy (IgAN) is one of the most common primary glomerulonephritides throughout the world and a major cause of end-stage renal disease among the East Asian population. It is widely considered that genetic factors play an important role in the pathogenesis of IgAN. This article summarizes the recent achievements in the genetic studies of IgAN, focusing mainly on studies performed in East Asia, from the early association studies of candidate genes and family based designs, to the recent genome-wide association studies. There have been five large genome-wide association studies performed that have identified multiple susceptibility loci for IgAN, especially some novel loci identified in the Chinese population. Genes within these loci have provided important insights into the potential biological mechanisms and pathways that influence genetic risk to IgAN. In susceptibility loci/genes, the study of genetic interaction and structural variants (such as copy number variation) was conducted to identify more variants associated with IgAN and disease progression. Genetic studies of IgAN from East Asia have made great achievements over the years. Most susceptibility loci discovered to date encode genes involved in the response to mucosal pathogens, suggesting that an intestinal-immune network for IgA production may be involved in the pathogenesis of IgAN. Although genetic studies of the complex diseases are challenging, for future genetic studies in IgAN, new genetic techniques and methods of analysis, especially next-generation sequencing, need to be applied to push the genetic studies forward.

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IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide since described by Berger in 1968.[1] The diagnosis of IgAN is based on a renal biopsy that shows deposition of IgA-containing immune complexes in the mesangial area of glomeruli and histopathologic lesions such as mesangial cell proliferation and accumulation of extracellular matrix.[2] It leads to progressive loss of kidney function, and between 20% and 40% of cases will progress to end-stage renal disease within 20 years of disease onset.[3-6]

There is substantial variation in the prevalence of IgA nephropathy globally, with the highest frequency in some Asian populations (40%-50%), moderate frequency in the European population (20%-30%), and the lowest frequency in the African population (<5%), and there was a clear west-to-east gradient of ascending prevalence.[7-10] However, whether this geographic variation may be influenced by differences in policies and techniques for performing renal biopsies is debatable.

Nonetheless, the difference in the prevalence of IgAN between ethnic groups, together with evidence of familial clustering[11-13] and renal abnormalities among relatives of cases, strongly suggest the presence of a substantial genetic contribution to IgAN.

GENETIC STUDY OF IgAN IN THE EAST

Because of the variable prevalence of IgAN among different ethnicities and high familial aggregation of IgAN, a genetic factor is considered an important part of the disease. To identify susceptibility genes of IgAN, family based analysis and population-based analysis were used, and to find common risk genes in large populations, several genome-wide association studies (GWAS) have been performed since 2011.

LINKAGE STUDY AND CANDIDATE-GENE ASSOCIATION STUDY

Both linkage and association studies have been performed to identify genetic risk factors for IgAN. The first application of a genome-wide linkage study of familial IgAN identified a significant linkage peak on chromosome 6q22-23,[14] under an autosomal-dominant mode of inheritance with incomplete penetrance. Another two linkage studies of IgAN families reported additional suggestive peaks at 4q26-31 and 17q12-22.[12,15] However, in exploring the causative genes at these loci, no disease genes were identified, which partly may be owing to the genetic heterogeneity and called for distinction based on genetic/biomarker data.

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Candidate gene association studies were conducted more widely in East Asia during the past 3 decades compared with linkage studies. Many encoding proteins involved in adaptive and innate immunity, glycosylation of IgA1, and the renin-angiotensin system have been investigated,[16] including the HLA molecules of *HLA-DQ* and *HLA-DR* alleles.[17-19] For the family based association studies, using a "transmission disequilibrium test"[20] design in a Chinese population, the *Megsin* gene was shown to confer susceptibility and disease progression of IgAN.[21-22] However, most of these studies were limited by small sample sizes, insufficient methodologies, and lack of validation in independent samples.

GENE-GENE INTERACTION STUDY IN IgAN

Because the effect of a single gene is relatively weak in a polygenic disorder, studies focusing on combining the effect of genes on disease were performed. To detect gene-gene interaction, 24 candidate genes associated with the pathogenesis of IgAN were selected and analyzed using the multifactor dimensionality reduction method. The interaction between *C1GALT1*-330G/T and *IL5RA*31t197A/G was discovered to affect the pathogenesis of IgAN,[23] and the combination of *P-selectin*-2441A/G and *CD14*-159C/T was associated with macroscopic hematuria in IgAN patients. In addition, the interaction of *TGF-β1* 509T/C, *P-selectin*-2441A/G, and *MCP-1* 2518A/G had an integrated effect on crescent formation.[24] Another study on the interaction between two key susceptibility genes, *C1GALT1* and *ST6GALNAC2*, was analyzed and showed that these two genes may have an additive effect on IgAN predisposition and disease progression.[25]

GWAS IN IgAN

GWAS have identified common variants within several loci (chromosomal regions) associated with the risk of developing IgAN. A GWAS was conducted in a British cohort composed of 431 cases and 4,980 public controls and identified a significant association at the major histocompatibility complex (MHC) region.[26] The second GWAS was performed in 3,144 cases and 2,822 controls which involved Han Chinese in discovery and follow-up validation in Chinese and European cohorts, in which five susceptibility loci for IgAN were identified. These included three distinct loci in the MHC region as well as the 1q32 (*CFH/CFHR*) locus and the 22q12 (*HORMAD2*) locus.[27]

In 2014, a large GWAS by Kiryluk et al[28] analyzed 7,658 cases and 12,954 controls, of which 3,685 cases and 2,682 controls were East Asians and the rest were Europeans. The study identified six novel genome-wide significant associations, four in *ITGAM-ITGAX*, *VAV3*, and *CARD9*, and two new independent signals at *HLA-DQB1* and *DEFA*. A further study also implicated that most of these loci are associated with the risk of inflammatory bowel disease or maintenance of the intestinal epithelial barrier and response to mucosal pathogens.

Because of the difference in prevalence and genetic heterogeneity, a GWAS of a Chinese population was performed in our group since 2011. We performed a two-stage GWAS study of IgAN in Han Chinese, with 1,434 IgAN patients and 4,270 controls in the discovery phase, and follow-up evaluation of the top 61 SNPs in an additional 2,703 cases and 3,464 controls. We identified associations at 17p13 and 8p23 that implicated the genes encoding tumor necrosis factor (*TNFSF13*) and α-defensin (*DEFA*) as susceptibility genes. In addition, we found multiple associations in the MHC region. We also found that rs660895 was associated with clinical subtypes of IgAN, proteinuria, and serum IgA levels. Our findings show that IgAN is associated with variants near genes involved in innate immunity and inflammation.[29]

By adding more samples in the discovery and validation stage, and using the imputation analysis for deep mining the GWAS data, we conducted an extended GWAS, analyzing a total of 8,313 cases and 19,680 controls from the Han Chinese population across four stages.[30]

In this large study of IgAN, we discovered novel associations at *ST6GAL1* on 3q27.3, *ACCS* on 11p11.2, and *ODF1-KLF10* on 8q22.3, validated the recently reported association at *ITGAX-ITGAM* (16p11.2), and moderately replicated the reported associations at *VAV3* (1p13) and *CARD9* (9q34). Most of these loci, including two of our newly discovered ones (*ST6GAL1* and *UBR5*), implicate genes involved in innate immunity and IgA production, in particular mucosal immunity in the gut. Several loci are shared with a variety of other autoimmune diseases. In addition, variants at several loci including *ST6GAL1*, *ACCS*, and *ITGAX* showed a trend of increasing risk allele frequencies from the African, European, to Asian samples of the HapMap project, suggesting that they may contribute cumulatively to geographic differences in genetic susceptibility and thus disease prevalence of IgAN. We estimate that these novel association signals explain approximately 1.7% of the disease variance and 5.5% of the variance in combination with previously published loci.

Collectively, these GWAS have identified 11 new loci (Table 1), providing initial insight into the genetic architecture of IgAN.

COPY NUMBER VARIATION IN IgAN

Structural variants, including copy number variant (CNV), reversion, and deletion/insertion, are the important contributors to human genome variation, which have been considered to be involved in the pathogenesis of many common diseases.

Although multiple susceptibility variants have been identified by GWAS in IgAN, these loci typically have