Genetics of Immunoglobulin A Nephropathy

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Abstract

***Introduction**: Immunoglobulin (Ig) A nephropathy is the most common primary glomerulonephritis in the world and about 20% to 50% of patients with it develop progressive renal failure. There is considerable evidence to show that IgA nephropathy is influenced by genetic factors. The purpose of this review is to provide useful information concerning genetics of IgA nephropathy. **Methods and Results**: Epidemiological, familial clustering, human leukocyte antigen and IgA immune system (immunoglobulin class switch gene, $I\alpha_1$ germ-line transcript regulatory region gene) studies have led to the hypothesis of genetic susceptibility to IgA nephropathy. Moreover, research on renin angiotensin system, platelet activating factor acetylhydrolase, neuropeptide Y Y1 receptor and others genes has demonstrated that genetic factors influence the pathological severity and natural course of IgA nephropathy. **Conclusions**: The evidence presented in this review strongly supports the role of genetic factors in IgA nephropathy. Detection of genetic risk factors for IgA nephropathy will allow us to study further the pathogenesis of IgA nephropathy and devise effective therapy.*

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Key words: Genetic factor, IgA immune system, Platelet activating factor acetylhydrolase, Renin angiotensin system

Introduction

Immunoglobulin (Ig) A nephropathy is the most common primary glomerulonephritis in various parts of the world, and it was detected in 25% of biopsy specimens taken from children in Kobe University Hospital.[1,2] IgA nephropathy was initially considered to be a benign disease with a favourable prognosis, but as data from a long-term follow up study became available, it was recognised that the disease progressed to renal failure in 20% to 50% of adult patients.[3] Accumulating data concerning geographical variations in the frequency of the disease, familial clustering, the association of the disease with human leukocyte antigen (HLA) and immune abnormalities in healthy relatives have led to the hypothesis of genetic susceptibility.[4] Moreover, it has been suggested that genetic factors may not only determine susceptibility to glomerulonephritis, but also influence the pathological severity and natural course of IgA nephropathy.[5,6] This article considers the evidence for genetic factors, i.e., some genes cording for products functionally related to the disease in the pathogenesis of IgA nephropathy.

Epidemiology

IgA nephropathy has been diagnosed all over the world, but its prevalence varies widely among countries. In Japan,[7] France,[8] Italy[9] and Australia,[10] it accounts for 18% to 40% of all primary glomerular disease, whereas in the United States,[11] the United Kingdom[12] and Canada,[13] it is responsible for only 2% to 10%. The explanation for this apparent variability in incidence is uncertain, but it may be related in part to differing indications for renal biopsy in different centres and genetic factors may be important in the pathogenesis of IgA nephropathy. Racial factors may also play a part in IgA nephropathy. IgA nephropathy has been reported to be uncommon in African Americans in the southern United States,[14] but high in Indians and Orientals.[15-17]

Familial Clustering

Evidence for genetic factors being important in IgA nephropathy is provided by family studies.[5,18-20] Rambausek et al[5] discovered that 9.6% of patients with mesangial IgA nephropathy in Germany had one or more siblings with

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glomerulonephritis. Julian et al[18] studied kindred from eastern Kentucky and found 6 patients with IgA nephropathy descended from one ancestor and that 8 others belonged to potentially related pedigrees. Moreover, their findings indicated that at least 48 (60%) of 80 IgA nephropathy patients who were born in same region were related to at least 1 other patient with the condition.[19] Recently, Scolari et al[20] reported that 26 (14%) of 185 patients with IgA nephropathy investigated in Italy were related to at least 1 other patient with the disease. These studies suggest that familial predisposition is a very common finding and genetic factors influence the pathogenesis of IgA nephropathy.

Human Leukocyte Antigen (HLA) Genes

Most efforts to study the genetics of IgA nephropathy have focused on the HLA system. Significant associations between the incidence of IgA nephropathy and some class I (HLA-B12, Bw35, B37) and II (HLA-DR1, DR4) major histocompatibility phenotypes have been reported.[21-25] Moreover, the recent application of HLA polymorphism techniques focused on three class II products, DP, DQ and DR, showed an association between the susceptibility to IgA nephropathy and the DQB1, DQw7 DQβ3b (DQ7) DQB (DQw4/8/9) and D-DR4 phenotypes.[26-29] However, none of these associations has been consistently confirmed and further investigations on a large number of informative families are needed before firm conclusions can be drawn.

Complement Factors

C4 is coded by two loci (C4A and C4B) within the major histocompatibility complex and its deficiency may affect the solubilisation and/or clearance of immune complexes. McLean et al[30] reported that the frequency of the homozygous null-C4 phenotype was significantly higher in patients with IgA nephropathy than normal subjects.

C3, together with factor B, plays a major role in the activation of the alternative pathway. The C3 gene is polymorphic with two main alleles: F and S. Rambausek et al[31] found a significant excess of the homozygous phenotype C3FF in patients with IgA nephropathy in comparison with normal subjects.

IgA Immune System

Several abnormal findings, such as high serum levels of IgA, high levels of IgA-bearing cells and increased production of IgA by peripheral blood mononuclear cells *in vitro* in patients with IgA nephropathy, have been described. Abnormalities in the IgA immune system have also been reported in some healthy relatives of patients with IgA nephropathy.[32,33] These results suggest that genetic background plays a crucial role in the pathogenesis of IgA nephropathy. In an attempt to determine the basic molecular mechanisms responsible for IgA synthesis in subjects with IgA nephropathy, polymorphisms of the switch region of the immunoglobulin heavy chain and $I\alpha_1$ germ-line transcript regulatory region genes have been studied:

1. Immunoglobulin Class Switch

The switch region of the immunoglobulin heavy chain is important for switching from one immunoglobulin class to another. Polymorphisms of the immunoglobulin heavy chain switch regions genes are associated with differences in the variable heavy chain regions and alterations in the Sμ and Sα gene regions probably influence the immunoglobulin heavy chain switch region. Demaine et al[34] reported increases in the frequency of homozygotes with either allele coding for the IgM switch regions (Sμ) in patients with IgA nephropathy. These findings suggest that immunoglobulin heavy chain loci play important roles in the pathogenesis of IgA nephropathy. However, these observations have not been confirmed in other studies. Our recent studies showed that the genotypic frequencies of the Sμ and Sα alleles in patients were similar to those in normal control subjects, but the frequency of the 2.6/2.1 kb Sμ heterozygous region in patients with diffuse mesangial proliferation was lower than that in controls and patients with minimal/focal mesangial proliferation. Our results suggest that immunoglobulin heavy chain switch region genes do not influence susceptibility to IgA nephropathy, but may influence the pathological expression of IgA nephropathy.[35]

2. $I\alpha_1$ Germ-line Transcript Regulatory Region Gene

Germ-line transcript, another characteristic molecular event in Ig class switching, has recently attracted attention. Yano et al[36] observed that structural and functional changes in the $I\alpha_1$ germ-line transcript regulatory region gene in patients with IgA nephropathy and described polymorphism of this gene. Polymorphism of the $I\alpha_1$ germ-line transcript regulatory region gene was observed more frequently in patients with IgA nephropathy than in control subjects. Patients with mutations had higher levels of serum IgA than normal subjects, and *in vitro* IgA synthesis by their peripheral blood mononuclear cells in patients was higher than that in normal subjects. Therefore, this gene may play an important role as the disease-causing gene in IgA nephropathy.

3. IgA1 O-galactosylation

The IgA subclass prominent in IgA nephropathy is generally considered to be IgA1. IgA1 is unique among all immunoglobulins in that it possesses a hinge region that is rich in proline, serine and threonine and characterised by 5 O-glycosylation sites which consist of N-acetylgalactosamine O linked to the serine residues of the hinge region. Abnormal galactosylated IgA1 showed higher

affinity for glomerular fibronection, laminin and collagen Iv than normal IgA1,[37] and may lead to accumulation of IgA in the mesangium. Preliminary data indicate that deficient galactosylation of hinge region glycans may be detected even in family members of patients with IgA nephropathy.[38] Alteration of the aminoacid sequence of the IgA1 hinge region is a possible mechanism responsible for abnormal galactosylation of IgA1. However, the hinge region is a highly conserved region of the IgA1 molecule and, to date, there is no evidence for any nucleotide sequence alteration or transcriptional abnormality of the hinge region in patients with IgA nephropathy.[39] It has also been postulated that altered galactosylated IgA1 in IgA nephropathy may be due to a deficiency of structural modification of β1, 3-galactosyltransferase, the enzyme responsible for the terminal galactosylation of GalNAc on O-linked glycans.[40] This structural or functional deficiency may be genetically determined. Now that β1, 3-galactosyltransferase has been sequenced, our understanding of the basis of genetic abnormalities of this enzyme should improve.[41,42]

Genes of the Renin Angiotensin System

Recent studies on IgA nephropathy have demonstrated intrarenal angiotensin II hyperreactivity in patients with progressive disease,[43] whereas angiotensin I-converting enzyme (ACE) inhibitors have been shown to reduce proteinuria and attenuate the progressive decline in renal function associated with IgA nephropathy.[44] These studies suggest that activation of the renin-angiotensin system plays an important role in the progression of IgA nephropathy. Moreover, some investigators have reported that genetic variability of the renin-angiotensin system modifies the progression of renal failure in patients with IgA nephropathy.

1. Angiotensin I-converting Enzyme Gene

An insertion (I)/deletion (D) polymorphism in intron 16 of the ACE gene is associated with variations in circulating levels of ACE.[45] Thus, the II genotype is associated with low serum levels of ACE, whereas the DD genotype is associated with high levels, and subjects with the ID genotypes have intermediate levels. Several recent studies have shown a significant association between ACE gene polymorphism and progression to chronic renal failure in IgA nephropathy.[46-48] Although no difference between the genotype distributions of patients with IgA nephropathy and a control population were found, the rate of progression of renal failure was significantly higher in patients with the DD genotype. Moreover, we investigated whether there was any association between ACE gene polymorphism and clinicopathological findings in 97 Japanese patients with IgA nephropathy. Our results showed that ACE gene polymorphism may not influence the extent of mesangial proliferation and crescents that are acute lesions, but the ID/DD genotypes are associated with chronic lesions, such as capsular adhesions, glomerulosclerosis and urinary protein excretion. Thus, polymorphism of this gene may not determine susceptibility to IgA nephropathy, but influence the pathologic severity and natural course of childhood IgA nephropathy.[49]

2. Angiotensinogen Gene

The M235T polymorphism of the angiotensinogen gene has been demonstrated in patients with essential hypertension.[50] Recently, Pei et al[51] reported 168 Caucasian patients with IgA nephropathy who had one or both copies of the angiotensinogen T235 alleles. They had a faster rate of decline in their renal function than patients with homozygous for the M235 allele. However, this association has not been replicated constantly in patients with IgA nephropathy.

3. Angiotensin II Type I Receptor Gene

The A1166C polymorphism of the angiotensin II type I receptor gene has been found to be associated with essential hypertension,[52] and thus, has been examined in patients with IgA nephropathy. However, in two studies by Yoshida et al[47] and Hunley et al,[48] the genotype frequency distributions of those with and without the progression of renal failure did not differ significantly.

Platelet Activating Factor (PAF) Acetylhydrolase Gene

PAF is a potent mediator of inflammatory injury associated with renal diseases. It is degraded to inactive products by PAF acetylhydrolase. A point mutation (G to T transversion) of the PAF acetylhydrolase gene was observed at position 994 and this mutation was found to contribute to the variability in plasma PAF levels, with undetectable plasma PAF acetylhydrolase activity occurring in homozygous patients (TT genotype) and reduced levels of activity in heterozygous patients (GT genotype).[53] We investigated the effect of this PAF acetylhydrolase gene mutation on the pathogenesis and progression of IgA nephropathy by analysing genomic DNA obtained from 89 children with IgA nephropathy and 100 controls. We found no significant difference between the genotypic frequencies of the two groups. However, urinary protein excretion at the time of biopsy was significantly higher in patients with the GT/TT genotypes than in those with the GG genotype. The percentage of glomeruli with mesangial cell proliferation was significantly higher in patients with the GT/TT genotypes than in those with the GG genotype.[54] These results indicate that the PAF acetylhydrolase gene mutation may influence the degree of proteinuria and the

extent of mesangial proliferation during the early stage of childhood IgA nephropathy. However, our most recent study has not enabled us to determine whether the PAF acetylhydrolase gene mutation in patients with IgA nephropathy has prognostic significance. Because most of our patients with severe IgA nephropathy were given combined therapy with prednisolone, azathioprine, heparin/warfarin and dipyridamole. Recently, Yoshikawa et al[55] demonstrated that such therapy led to clinical and histological recovery in patients with early-stage childhood severe IgA nephropathy. Further study is necessary to clarify the association between the PAF acetylhydrolase gene mutation and the progression to chronic renal failure in patients with IgA nephropathy.

Other Genes

1. Neuropeptide Y Y1 Receptor (NPYY1R) Gene

NPYY1R is found predominantly at sympathetic postjunctional site in blood vessels, especially arterioles, and it is considered to be related to vascular smooth muscle cell constriction and increased blood pressure. Herzog et al[56] cloned a 14-kilo base pair region of genomic DNA encoding the NPYY1R gene and also found a single point mutation in the first intron of this gene.[57] Ito et al[58] reported that the distributions of the NPYY1R genotypes, which were defined as YY, Yy and yy of 68 patients with IgA nephropathy and 60 normal control subjects did not differ. However, in patients with IgA nephropathy, the rate of urinary protein excretion was higher in the non-YY genotype than in the YY genotype group. The reciprocal of the serum creatinine level was lower in the non-YY genotype than in the YY genotype group. They proposed that the NPYY1R gene polymorphism might be a novel prognostic predictor in patients with IgA nephropathy.

2. T-cell Receptor (TCR) Constant Alpha Chain Gene

Changes of the TCR constant alpha chain gene may alter the interaction with CD3 and/or the function of the TCR-CD3 complex and could evoke immunologic abnormalities that lead to the progression of IgA nephropathy. Deenitchina et al[59] reported that the genotype distributions of the TCR constant alpha chain gene polymorphism in 213 Japanese patients with IgA nephropathy and 73 normal control subjects did not differ. However, it appeared the T allele might foreshadow a poor renal prognosis, conferring a potential risk for developing renal failure with time. On the other hand, a TCR constant alpha chain gene polymorphism was associated with development of IgA nephropathy in Chinese patients, but there was no link with progression of the disease.[60] Some of the discrepancies between these two studies may due to the different sample sizes and different geographical regions, and these findings need to be confirmed.

Conclusion

Numerous genes play important roles in the pathogenesis of IgA nephropathy and it is possible that the observations described above have therapeutic implications for patients with IgA nephropathy. ACE inhibition has already been shown to reduce urinary protein excretion and attenuate the progressive decline in renal function associated with IgA nephropathy.[44] Moreover, Yoshida et al[47] reported that the presence of the ACE gene DD polymorphism was associated with increased ACE inhibitor efficacy against proteinuria in patients with IgA nephropathy. Thus, the search for genes that contribute to IgA nephropathy may enable therapy to be targeted at patients at risk. However, it is crucial that more large collaborative and prospective studies are conducted to determine which genetic factors are involved in the pathogenesis of IgA nephropathy.

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