Is progression of IgA nephropathy conditioned by genes regulating atherosclerotic damage?

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Progress has been slow in identifying genetic factors that influence either susceptibility to IgA nephropathy (IgAN) or its progression to end-stage renal disease (ESRD) (1). Studies of both familial and sporadic IgAN strongly point to clinical and genetic heterogeneity in the entity we presently call IgAN. The human IgAN phenotype does not exhibit classic Mendelian inheritance patterns, but is better considered using the paradigm for genetically complex human autoimmune diseases, for which multiple loci have been identified by family-based genetic studies. In these complex diseases many different types of genetic variations contribute to the final phenotype. Among the many potential mechanisms involved, interest has recently been focused on specific single-nucleotide polymorphism (SNP) alleles which alter the transcriptional activity of genes involved in the pathogenesis. Recently it has been said that 30%-50% of human genes with coding SNPs can present allelic variation in gene expression (2).

In IgAN it can be assumed that there are multiple disease/susceptibility loci that regulate mechanisms of IgA deposition, injury and progression. These disease loci will be detectable by genome/wide scan for linkage, however this method has limited power to detect genes of small effect. Variation at these loci may be further influenced by a potentially large number of modifier genes with small genetic effect which lead to the final IgAN phenotypes.

Careful analysis of kindreds in which IgAN has high phenotypic expression has also supported disease heterogeneity (3,4,5). Linkage-based approaches to the study of familial forms of the disease have identified significant or suggestive loci on chromosomes 6q22-23, 2q36, 4q26-31, 17q12-22 and 3p24-23, but no causal gene has yet been identified despite thorough analysis of these loci.

Case-control genetic association studies have yielded inconsistent results in IgAN. Gene polymorphisms have sometimes been pursued even when there were no data for a biologically plausible functional effect of the polymorphism. Even within ethnically uniform populations successive studies of the same candidate have often been contradictory; this is now realised to be explicable at least in part by hidden ancestral differences between subgroups of the same ethnic group (6) and use of haplotype block-based methods for SNP selection (7).

In view of the altered O-glycosylation identified as a key element in the pathogenesis of IgAN (8), genetic variation in the relevant glycosylating enzymes has been studied as a possible disease mechanism. However available data again emphasise the heterogeneity of IgAN; there are conflicting data for C1GALT1, the gene encoding the key enzyme β1,3 Gal transferase [on chromosome 7p14-p13] and C1GALT1C1 [on chromosome Xq24] encoding its chaperone protein, Cosmc (C1GALT specific molecular chaperone). Whereas in a Chinese population with IgAN three SNPs of C1GALT1 have been reported in significantly different frequency in IgAN and healthy controls without differences in C1GALT1C1 (9), no association for C1GALT1 SNPs and IgAN was found in French patients (Berthoux et al communication at the 2009 IgAN Symposium, Stresa, Italy), and the lack of differences for C1GALT1C1 was confirmed in Caucasians (10).

As well as modifying IgA1 glycosylation, other genetic influences in the pathogenesis of IgAN could render IgA1 molecules more phlogistic, by increasing the synthesis of IgG autoantibody leading to formation of macromolecular IgA1-IgG immune complexes (11), or by increasing complement activation by such complexes (12), or by modifying the affinity for IgA receptors on mesangial cells (13). Thus far no candidacies have been established in these pathways.

Besides the search for genetic factors favouring the development of IgAN, interest has focused on genes conditioning the progression of IgAN, some of them likely common to the progression of other renal diseases. Such genes could influence the many pathways which decide the capacity of the kidney to respond to the initial IgA-mediated injury by resolution of inflammation or with progressive scarring, and may modify the vascular injury associated with hypertension and atherosclerosis which contributes to progression in many renal diseases.

Among genes influencing vascular responses, the polymorphisms regulating insertion/deletion (I/D) of intron 16 of the angiotensin-converting enzyme (*ACE)* gene have been most studied. This is supposed to be particularly relevant in IgAN, a renal disease with local angiotensin hyperactivity (14). Once more the heterogeneity of IgAN emerges in a meta-analysis, which indicates that an association between the I/D ACE gene polymorphism and progression of IgAN is only seen in Asian patients (15). There are also some data that the prognosis of IgAN is influenced by polymorphisms of other genes related to vascular response and atherosclerosis, including angiotensinogen *AGT* (16) and plasminogen activator inhibitor-1 *PAI-1* (17). A role for atherosclerosis in the progression of IgAN is supported by the association of progression of IgAN with metabolic factors involved in atherosclerosis, including obesity, hypertriglyceridemia and hyperuricemia (18,19). These observations gave the rationale of the study published in this issue of NDT by Yamamoto *et al*, reporting the results of a multicenter retrospective observational study in Japan (PREDICT-IgAN) which investigated associations between disease progression and 100 atherosclerosis-related gene polymorphisms in 320 proteinuric patients with IgAN. The scale of this study deserves attention since the majority of previous reports in IgAN have tested only a few genes

of potential interest. There was a substantial period of follow-up (8.3 ± 4.2 years) during which 25.9% reached the end point of a 50% increase in serum creatinine. Using the Cox proportional-hazards model, three polymorphisms - glycoprotein Ia *GPIa* C807T and G873A and intercellular adhesion molecule-1 *ICAM-1* A1548G (K469E) - were identified as independent genetic predictors of disease progression, along with conventional clinical prognostic factors, such as eGFR, urinary protein, and use of antihypertensives at diagnosis. *ACE* ID and DD had no predictive value in multivariate analysis. Patients with the minor homozygotes *GPIa* C807T/G873A and *ICAM-1* A1548G had significantly higher IgAN progression rates than those with the major homozygotes, and the authors concluded that these gene polymorphisms are associated with IgAN progression in a recessive model.

These genes have some biological plausibility as candidates. Glycoprotein Ia (integrin α_2 chain) is a transmembrane protein that forms dimers exclusively with glycoprotein IIa (integrin β_1 chain), to form the glycoprotein Ia/IIa, also known as $\alpha_2\beta_1$ integrin. This integrin, a member of adhesion molecule family, is selectively expressed on the surface of platelets, and conditions platelet adhesiveness to collagens. *GPIa* polymorphisms have been associated with cardiovascular diseases (20). Glycoprotein IIa (β_1) is expressed in glomeruli in IgAN and in healthy subjects (~~19~~21). Although the authors speculate on a possible expression of $\alpha_2\beta_1$ on mesangial cells influencing mesangial cell proliferation, this seems improbable. In mesangial cells β_1 colocalizes with α_3, forming an integrin specific for collagen IV (22), while $\alpha_2\beta_1$ dimer is exclusively expressed on the surface of platelets. Indeed $\alpha_3\beta_1$ has been detected in cultured human mesangial cells, and another integrin, $\alpha_v\beta_3$, is regulated by coincubation of mesangial cells with aberrantly glycosylated IgA either prepared *in vitro* or isolated from patients with IgAN (23). Rather, the Authors' findings focus attention on the role of intracapillary factors governing the progression toward sclerosis of IgAN. The other gene polymorphism which the Authors report in association with IgAN progression is ICAM-1, a cell surface glycoprotein of the immunoglobulin superfamily which mediates adhesion of circulating leukocytes to vascular endothelium. The *ICAM-1* polymorphism

associated with disease progression in patients with IgAN (A1548G) regulates an increased expression of *ICAM-1* on the surface of endothelial cells, and leukocytes adhesion (24). This polymorphism is also associated with chronic inflammatory disorders in various organs, and cardiovascular disease (25). In patients with histopathologically advanced IgAN, glomerular and tubulointerstitial expression of *ICAM-1* was particularly evident (26,27).

As the Authors pointed out, functional genomic studies are needed to confirm any role for these polymorphisms in progression of IgAN. However, as well as the interpretation provided by the authors, that these polymorphisms might favour accelerated atherosclerosis which could contribute to accelerated progression in IgAN, we see in this study an additional point of interest. In the recently published Oxford Classification of IgAN, we identified endothelial hypercellularity as an independent risk factor for IgAN progression, even when clinical data at renal biopsy and at follow-up were considered (28,29). An endocapillary inflammatory process might be regulated by polymorphisms leading to altered ICAM1 expression which may favour an intracapillary hypercellular response to circulating macromolecular IgA reaching the glomerulus on the way to mesangial deposition.

While the approach taken in this study to investigate a substantial number of genes relating to a particular disease modifying pathway represents an advance on the many previous studies of very small numbers of candidates, it still lacks some of the power needed to speed progress in our genetic understanding of the heterogeneous complex trait disorder known as IgAN. Genome wide association studies represent a new avenue likely to provide major new information provided cohorts of sufficient size are available for analysis. A number of collaborative research groups around the world are establishing such cohorts in IgAN, and important new findings may soon emerge.

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Conflict of interest statement

The material presented in this paper has not been published previously in whole or part, except in abstract format.