Genetic Markers of Immunoglobulin G as Potential Risk Factors for IgG4-related Disease

To the Editor:

Immunoglobulin (Ig) G4-related disease is a relatively new fibroinflammatory systemic condition of unknown etiology. It is usually associated with elevated serum IgG4 concentrations[1]. Among the disease-initiating mechanisms, host genetic factors are thought to be important, but there is a paucity of genetic studies and to date only a few probable susceptibility factors have been described[1]. Our aim is to spur further genetic research by postulating Ig GM allotypes — highly polymorphic hereditary antigenic determinants expressed on γ chains — as possible risk factors for IgG4-related disease. GM (IgG marker) allotypes are encoded by 3 very closely linked genes on chromosome 14q32. They are localized on the constant region of γ1, γ2, and γ3 chains[2]. Ig γ4 chains do not express subclass-specific unique allotypes, but they do express isoallotypes — determinants that behave as alleles in one IgG subclass (allotypes) but are also expressed in all molecules of at least one other subclass (isotypes).

Several attributes of the GM genetic system make it a likely candidate for involvement in the etiopathogenesis of IgG4-related disease. Serum IgG4 concentration, which is usually elevated in this condition, has been shown to be associated with particular GM allotypes. GM allotype analyses of sera from related and unrelated subjects showed strong association of the GM 23/n allotype (expressed on γ2) with serum IgG4 concentration[3]. Moreover, the effect of the GM 23 allele appeared to be additive: of the 3 genotypes in this biallelic system, serum IgG4 concentration was highest in GM 23+/GM 23+ homozygotes, somewhat intermediate in GM 23+/GM 23− heterozygotes, and lowest in GM 23−/GM23− homozygotes.

Atopy and asthma may represent another link between GM allotypes and IgG4-related disease. Particular GM allotypes have been shown to be associated with these allergic features[4], which are commonly present in patients with IgG4-related disease[1]. It has been postulated that IgG4-related disease might have an infectious etiology[1]. Immunity to a large number of pathogens (bacteria, viruses, and parasites) is influenced by GM genes[2,5,6]. It follows that GM genes could act as potential effect modifiers of pathogen-IgG4-related disease association.

IgG4 antibodies — unlike those of other IgG subclasses — can swap their arms, a biological mechanism that has been suggested to provide the basis for the antiinflammatory activity of this molecule[7]. Interestingly, the arginine/lysine substitution at amino acid position 409 (R409/K409) in the CH3 domain of IgG4, crucial for the Fab-arms exchange, characterizes an isoallotype[8]. R409 and K409 behave as alleles on IgG4 (allotypes), but they are also present on all molecules of the other IgG subclasses (isotypes). R409 has been shown to be a molecular determinant for enabling, and K409 for blocking, the Fab-arms exchange[9].

Thus, examination of GM allotypes is likely to yield insights into the etiopathogenesis of IgG4-related disease. It might be relevant to add that a candidate gene approach would be necessary to delineate the role of GM genes in this disease, as these variants are not included in the widely used genotyping platforms and therefore are unlikely to be detected by genome-wide association studies of this condition[10,11]. IgG gene segments harboring GM alleles are highly homologous and apparently not amenable to the high-throughput genotyping technology; this attribute may have contributed to their exclusion from the genotyping panels.

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