Genetic associations of variants of the high affinity receptor for immunoglobulin E in Wegener’s granulomatosis

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KEY WORDS
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ABSTRACT
Immunoglobulin E (IgE) and the high affinity IgE receptor (FcεRI) have been suggested to contribute to the pathogenesis of autoimmune disorders. Their role in Wegener’s granulomatosis (WG) are, however, poorly recognized. We sought a genetic association between laboratory markers for the disease, i.e. anti-proteinase 3 antibodies (anti-PR3), anti-myeloperoxidase antibodies, anti-cyclic citrullinated peptide antibodies, C-reactive protein (CRP), C3c and C4 complement components, and total serum IgE levels in WG subjects with common genetic variants of FcεRI subunits. Anti-PR3 and CRP and serum IgE levels showed significant associations, while complement components tended to be associated, with −18483A>C and/or −344C>T FCER1A (FcεRI α-subunit gene) polymorphisms. Moreover, a correlation between −109T>C FCER1B (FcεRI β-subunit gene) genotypes and serum IgE was observed. Both WG specific auto-antibodies and other blood inflammatory markers displayed correlations with serum total IgE levels and genetic variants of the high affinity receptor for this immunoglobulin. This observation suggests a functional relationship of FcεRI in the regulation of autoimmune response observed in WG.

INTRODUCTION W encer’s granulomatosis (WG) is a primary necrotizing vasculitis of unknown etiology, characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA). Genetic association studies have suggested that the variability of T-cell co-stimulatory molecule receptor cytotoxic T-lymphocyte antigen 4, interleukin-10 gene and human leukocyte antigens system may predispose to WG. Genetic association studies have suggested that the variability of T-cell co-stimulatory molecule receptor cytotoxic T-lymphocyte antigen 4, interleukin-10 gene and human leukocyte antigens system may predispose to WG, 2,3 Elevated serum immunoglobulin E (IgE) levels have also been reported among immunological alterations in WG patients, but their relevance to the vasculitis has not been established. Serum IgE represents only to a minute fraction of immunoglobulins, and is mostly bound to the high affinity receptor (FcεRI) present on mast cells, basophils and eosinophils. The receptor occupied by allergen-specific IgE molecules is responsible for anaphylaxis and possibly can also modulate the immunological response, because it is expressed on antigen presenting cells. Moreover, the gene encoding for IgE-binding α-subunit of the FcεRI (FCER1A) maps to chromosome 1q21-23, the region implicated in susceptibility to multiple autoimmune disorders and/or allergy. Interestingly, altered expression of FCER1A has been observed in patients with systemic lupus erythematosus.

Working hypothesis We investigated common genetic variants of genes coding for α- (FCER1A) and β-subunit (FCER1B) of FcεRI in WG. This genetic variability is located in the gene controlling region and was previously associated with elevated serum IgE in allergic subjects, however there were no studies performed in subjects with autoimmune diseases. We wondered if genetic variability of these loci is correlated to quantitative inflammatory features in a moderately numerous but well characterized group of WG patients.

MATERIALS AND METHODS 30 consecutive subjects diagnosed with WG were enrolled...
TABLE 1 Clinical and laboratory characteristics of the patients (n = 30)

| Parameter                        | Value |
|----------------------------------|-------|
| age (years)                      | 50.6 ±13.03 |
| sex (females/males)              | 15/15 |
| skin involvement                 | 11/n  |
| joint involvement                | 17/n  |
| urogenital involvement           | 19/n  |
| lower respiratory tract involvement | 18/n |
| upper respiratory tract and/or ear involvement | 18/n |
| eye involvement                  | 6/n   |
| gastrointestinal involvement     | 7/n   |
| cardiovascular involvement       | 8/n   |
| neurological involvement         | 9/n   |
| positive ANCA                    | 26/n  |
| positive ANCA currently or in the past | 30/n |
| positive anti-PR3                | 21/n  |
| anti-PR3 (RU/ml)                 | 37.6 (9.46–98.18) |
| positive anti-MPO                | 2/n   |
| positive ANA                     | 15/n  |
| positive aCCP                    | 1/n   |
| positive RF                      | 6/n   |
| CRP (mg/l)                       | 4.33 (3.08–8.77) |
| C3c complement component (g/l)   | 1.26 (1.12–1.56) |
| C4 complement component (g/l)    | 0.28 (0.237–0.333) |
| logarithm of total serum IgE     | 1.73 ±0.49 |

Age and log-transformed IgE are means ± standard deviations, other measurements are medians (25th–75th percentile)

In addition, –18483A>C polymorphism was associated with anti-PR3 levels. C3c and/or C4 complement components showed a statistical trend for a correlation with both FCERIA variants. Total serum IgE levels were also associated with –109T>C FCERIB polymorphism. None of the listed above genetic variants was associated with the severity of WG, assessed using a clinical symptoms scale. The FCERIA –95T>C genetic variant, which did not correlate with laboratory markers of WG, interestingly showed a significant association with cardiovascular manifestations of WG; 78.6% carriers of –95C variant (CC or TC) had cardiovascular symptoms, while in patients with –95TT genotype only 25% (p = 0.016).

RESULTS Genotypes for FCERIA and FCERIB were in Hardy-Weinberg equilibrium and their frequencies did not differ from those published for Caucasians. The following frequencies were observed for FCERIA: –18483A>C (10 AA, 18 AC, 2 CC), –344C>T (9 CC, 19 CT, 2 TT), –95T>C (13 TT, 16 TC, 1 CC), and for FCERIB –109T>C (12 TT, 13 TC, 5 CC).

Both, –18483A>C and –344C>T FCERIA polymorphisms were related to total serum IgE and CRP (TABLE 2). In addition, –18483A>C polymorphism was associated with anti-PR3 levels. C3c and/or C4 complement components showed a statistical trend for a correlation with both FCERIA variants. Total serum IgE levels were also associated with –109T>C FCERIB polymorphism. None of the listed above genetic variants was associated with the severity of WG, assessed using a clinical symptoms scale. The FCERIA –95T>C genetic variant, which did not correlate with laboratory markers of WG, interestingly showed a significant association with cardiovascular manifestations of WG; 78.6% carriers of –95C variant (CC or TC) had cardiovascular symptoms, while in patients with –95TT genotype only 25% (p = 0.016).

SUMMARY Elevated total serum IgE levels have been already described in WG patients, however, the specific role of IgE has not been discussed because increased biosynthesis of immunoglobulins commonly coexists autoimmune inflammation. In this preliminary report we confirmed that genetic variants of the high affinity receptor for IgE correlate with its levels, which was previously demonstrated in allergic subjects. Moreover, the same receptor variants seem to have an impact on WG specific laboratory markers and on inflammatory process of the disease.
TABLE 2 Correlations between the high affinity IgE receptor variants and the measured biomarkers

| Polymorphism | Quantitative trait | Values | p     |
|--------------|-------------------|--------|-------|
| FCER1A −344C>T | Total serum IgE<sub>a</sub> | 1.35 ±0.04 vs. 1.91 ±0.11 | 0.0001 |
|              | CRP               | 8.63 (5.72–16.75) vs. 3.08 (3.08–6.29) mg/l | 0.004 |
|              | Anti-PR3          | 98.18 (10.57–237.745) vs. 31.34 (29.21–78.80) RU/ml | NS     |
|              | C3c               | 1.42 (1.27–1.60) vs. 1.2 (1.03–1.45) g/l | 0.09   |
|              | C4                | 0.33 (0.25–0.42) vs. 0.26 (0.23–0.31) g/l | 0.06   |
| FCER1A −18483A>C | Total serum IgE<sub>a</sub> | 1.49 ±0.14 vs. 1.87 ±0.1 | 0.04   |
|              | CRP               | 8.46 (5.2–13.8) vs. 3.08 (3.08–6.91) mg/l | 0.005  |
|              | Anti-PR3          | 143.5 (10.94–283.78) vs. 28.8 (2.87–70.67) RU/ml | 0.049  |
|              | C3c               | 1.42 (1.31–1.59) vs. 1.19 (1.03–1.425) g/l | 0.06   |
|              | C4                | 0.32 (0.24–0.41) vs. 0.26 (0.23–0.316) g/l | NS     |
| FCER1B −109T>C | Total serum IgE<sub>a</sub> | 1.93 ±0.14 vs. 1.58 ±0.1 | 0.047  |

<sup>a</sup>log-transformed IgE: means ± standard deviations, other data: median (25th–75th percentile)

Abbreviations: anti-PR3 – anti-proteinase-3 antibodies, C3c – C3c complement component, C4 – C4 complement component, CRP – C-reactive protein, IgE – immunoglobulin E, NS – non-significant

Genetic variability of FCER1A was found to associate with chronic urticaria<sup>14</sup>, a disease with frequently an autoimmune background. However, finding the correlation between the levels of specific autoantibodies and non-specific inflammatory markers, and variants of the high affinity receptor for IgE in WG suggest that the underlying mechanism may be more complex than the receptor mediated control of IgE biosynthesis alone. One of plausible mechanisms is the activity of dendritic cells involved in the clearance of apoptotic neutrophils, which may be modulated by FcRI in WG.<sup>6</sup> Recently functional FcRII expression has been demonstrated on smooth muscle cells of the airways.<sup>15</sup> A potential induction of the receptor on vascular smooth muscle cells is another putative mechanism which requires further investigations. Furthermore, the alternative ANCA-mediated complement activation pathway was proposed to play a role in the pathogenesis of ANCA-associated diseases.<sup>16</sup> Therefore, relationships between FcRII genetic polymorphisms and complement components, and anti-PR3 or anti-MPO circulating ANCA which closely associate with WG<sup>17,18</sup>, appear particularly interesting. It could be supposed that also FCER1A may be hypothetically involved in the ANCA-dependent complement activation mechanism.

In summary, while in line with previous reports on allergic diseases<sup>9–13</sup>, the current study on associations between FCER1A/FCER1B genetic variants and total serum IgE levels extends these observations to the disease-specific and inflammatory markers in WG. These correlations are difficult to interpret based on current knowledge and suggest the presence of an immunological mechanism modulating the autoimmune inflammatory response by the high affinity IgE receptor pathway. If the presence of such a mechanism could be confirmed, new therapeutic modalities might be considered for WG, for example using anti-IgE neutralizing antibodies.

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