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Homozygosity for the IgG2 Subclass Allotype G2M(n) Protects against Severe Infection in Hereditary C2 Deficiency

Göran Jönsson,²*† Vivi-Anne Oxelius,† Lennart Truedsson,‡ Jean Henrik Braconier,* Gunnar Sturfelt,§ and Anders G. Sjöholt¶

Homozygous C2 deficiency (C2D) is the most common deficiency of the classical complement pathway in Western countries. It is mostly found in patients with autoimmune disease or susceptibility to bacterial infections and in healthy persons. We wished to assess to what extent other immunological factors might explain differences of susceptibility to infections in C2D. For this reason, 44 Swedish patients with C2D were stratified with regard to the severity of documented infections. Investigations of IgG subclass levels, IgG subclass-specific GM allotypes, concentrations of factor B, properdin, and factor H, and polymorphisms of mannan-binding lectin and the Fc receptors FcγRIIa and FcγRIIb were performed. Homozygosity for the G2M(n) allele, which is known to promote Ab responses to polysaccharide Ags, was strongly associated with the absence of severe infections ($p < 0.001$) in the patients, suggesting a major protective role. The combination of mannan (or mannose)-binding lectin and C2 deficiency was found to be a minor susceptibility factor for invasive infection ($p = 0.03$). Low concentrations of IgG2 and factor B might sometimes contribute to susceptibility to infection. Other factors investigated did not appear to be important. In conclusion, the findings indicated that efficient Ab responses to polysaccharides are protective against severe infection in C2D. Implications with regard to vaccination should be considered.


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3 Abbreviations used in this paper: C2D, homozygous C2 deficiency; IGHG, immunoglobulin constant heavy G chain; MBL, mannan (or mannose)-binding lectin. Copyright © 2006 by The American Association of Immunologists, Inc.

S tudies of inherited immunodeficiency states have strongly contributed to the current knowledge of immunological in vivo functions (1). An aspect that has only been partly explored is the influence of the modifying effects that coincident genetic factors may have on disease expression. Homozygous C2 deficiency (C2D) is a well-defined deficiency of the complement system, with an estimated prevalence of ~1:20,000 in Western countries (2). C2D is associated with the susceptibility to infection caused by encapsulated bacteria and with the development of autoimmune conditions such as systemic lupus erythematosus, and it may also be a risk factor for atherosclerosis (2–4). Moreover, many persons with C2D are healthy (2–4). The phenotypic heterogeneity encountered in C2D probably indicates that other genes influence disease expression in the patients.

C2 supplies the catalytic moiety of the C3 convertase C4b2a, which can be generated through activation of the classical pathway, the principal mechanism for Ab-dependent recruitment of complement (5), or through the lectin pathway, which is an important constituent of innate immunity (6). The lectin pathway involves the recognition molecules mannan-binding lectin (MBL), L-ficolin, and H-ficolin, which form complexes with MBL-associated serine proteases and bind to microbial carbohydrates and other targets. Impaired functions of the classical pathway and the lectin pathway could both account for the clinical consequences of C2D. Complement-mediated defense in C2D mainly relies on the alternative pathway, C3 convertase C3bBb (5), the recruitment of which is usually intact in C2D.

In mice with experimental C1q deficiency, another classical pathway deficiency state, the expression of autoimmune disease, is strongly influenced by the genetic background (7). Most likely, the genetic background also influences susceptibility to infection. In patients with C2D and infections, individual case reports have described coincident findings of common variable immunodeficiency (8), low IgG2 concentrations combined with lack of the G2M(n) allotype (9, 10), and impaired alternative pathway function due to low factor B concentrations (11, 12) or properdin deficiency (13). Among the background genes in C2D, it is noteworthy that >90% of the cases are caused by the homozygous presence of a 28-bp deletion of the C2 gene in the MHC haplotype HLA-B*18,5042,DRB1*15 and closely related haplotypes (2, 4). This implies that immune functions determined by the MHC might be expected to be unusually uniform in C2D as compared with many other immunodeficiencies.

We recently described a cohort of 40 Swedish patients with C2D in which invasive infection was the predominant manifestation (4). To date, this is the largest comprehensive study of C2-deficient patients reported by a single center. In the present investigation, 44 patients with C2D were stratified with regard to severity of infections. Selected immunological factors with potential influence on susceptibility to infection in C2D were analyzed, including IgG subclasses and their GM allotypes, concentrations of the alternative pathway proteins factor B, properdin, and factor H, and polymorphisms of MBL and the Fc receptors FcγRIIa (CD32) and FcγRIIb (CD166).
GM allotypes are markers of the Ig constant heavy G chain (IGHG) (14, 15). The IgG subclass-specific GM allotypes of IGHG1, IGHG2, and IGHG3 are well characterized and have important immunological functions (14–17). The homozygous presence of the IgG2 allotype G2M(n) is known to be associated with efficient IgG2 Ab responses to polysaccharide Ags as well as with the absence of symptoms in C2D. The presence of the IgG2 allotype, by the presence of methionine instead of a valine residue at CH2 position S2 in the Fe part of the IgG2 molecule (20). Furthermore, the two IgG2 allotypes differ with regard to physicochemical properties, maturation during childhood, and catalebic rate (21–23).

Among IgG subclass-specific GM allotypes, G3M(b) and G3M(g) are alternative markers for IgG3, whereas G1M(f)/G1M(a) and G2M(n)/G2M(n–) are alternative markers for IgG1 and IgG2, respectively. The alleles are inherited as haplotypes in fixed combinations, of which there are four principal variants in northern Europe: GM*b;f;n, GM*b;f;n–, GM*g;an, and GM*g;an–. Due to allelic exclusion, each B cell line only expresses genes from one haplotype (14, 15).

MBL polymorphism was examined on the assumption that combined C2 and MBL deficiency might be associated with increased susceptibility to infection (24, 25). IgG receptors represent another group of factors involved in the defense against encapsulated bacteria. Homozygosity for the FcγRIIa-R131 allotype has been suggested to be a risk factor for pneumococcal infections in children and adults (26). Moreover, combined effects of FcγRIIa-R131/R131 and FcγRIIb-NA2/NA2 have been shown to influence susceptibility to Neisseria meningitidis in patients with terminal complement component deficiencies (27).

Among the immunological factors investigated, we found that homozygosity for G2M(n) is protective against severe infection in C2D, indicating that efficient Ab responses to polysaccharides is of crucial importance in the patients. The impact of IgG2 levels, MBL deficiency, and components of the alternative pathway was less pronounced. There was no evidence for correlation between FcγRIa or FcγRIIb polymorphisms and susceptibility to infection in C2D.

Materials and Methods

Patients

Between 1977 and 2002, 40 Swedish patients with C2D were identified. Demographics and clinical manifestations have been previously described (4). A history of invasive infection, mainly septicemia and meningitis, was obtained in 57% of the patients. The predominant pathogen was Streptococcus pneumoniae. A diagnosis of systemic lupus erythematosus was made in 25% of the patients, and another 18% had undifferentiated connective tissue disease or vasculitis. An increased rate of atherosclerotic disease was also found. Another four patients, an essentially healthy 49-year-old male, a 36-year-old woman with undifferentiated connective tissue disease and invasive infection, a 63-year-old man with systemic lupus erythematosus, and a 12-year-old boy with ethmoiditis and an intracranial epidural abscess, were added to the study. A summary of data with stratification of the patients into four groups with regard to severity of infections is given (Tables I and II). The investigation was approved by the Lund University Research Ethics Committee (protocol LU 513-01). Written informed consent was obtained for each patient.

IgG and complement proteins

Serum and EDTA plasma were stored in aliquots at −80°C. Analysis of GM allotypes and IgG subclasses was performed as described in detail elsewhere (22, 28). In short, the IgG subclass allotypes G1M(f), G1M(a), G2M(n), and G3M(b) were quantified by a sensitive competitive indirect ELISA, whereas homozygosity and heterozygosity for G2M(n) and G2M(n–) were established by double immunodiffusion (29). Concentrations of the IgG subclasses IgG1, IgG2, and IgG3 were determined by single radial immunodiffusion using age-related reference intervals (22) expressed as 2.5–97.5 percentiles. IgG4 levels were measured with a commercial ELISA (Bindzyme; The Binding Site). IgE was determined by fluoroenzyme-immunometric assay (UniCAP; Phadia). IgM, IgA, and IgA were previously determined by turbidimetry (Cobas Mira; Roche Diagnostic Systems) in most of the patients (4), and the same method was used for the new patients included in the study. Factor B, properdin, and factor H were determined by immununoassay (30). The pooled serum used for reference was assumed to contain factor B at 200 mg/L, factor H at 500 mg/L, and properdin at 25 mg/L (31). In four patients, concentrations of MBL were determined by sandwich ELISA (mAb 131-1; Immunolex) (32). Ten patients were deceased and, in four of these, very limited amounts of serum were available for analysis. This explains why the number of patients varies somewhat for the parameters investigated.

Gene nomenclature

General guidelines were followed (33). For IGHG and the FcγRs FcγRIla and FcγRIIIb, the HUGO Gene Nomenclature database was consulted (34), (www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl). For allotypes of FcγRIla and FcγRIIib, we adopted the designations used by van Sorge et al. (26). For the GM allotypes of IGHG1, IGHG2, and IGHG3 we used the International Immunogenetics Information System database (35) (http://imgt.cines.fr) using alphabetical designations. However, asterisks for indication of subspecificity groups of the IGHG3 allotypes G3M(b) and G3M(g) were omitted. Alleles, haplotypes, and genotypes were italicized with an asterisk between the gene symbol and the allele or haplotype designations (e.g., G3M*b, G3M*n–, G3M*b;f;n, GM*b;f;n–, G2M*n/G2M*n, G2M*n/G2M*n–, etc.). For MBL deficiency and MBL sufficiency genotypes, we used the simplified designations suggested by Kronborg et al. (36). Thus, MBL sufficiency genotypes were homozygous for the wild-type structural gene A (A/A). Genotypes containing a high or medium expression promoter haplotype together with a wild-type structural gene (A/A) and another haplotype with a structural mutation (b/b) were also classified as MBL deficiency genotypes (b/b). MBL deficiency genotypes were those that were homozygous for a structural mutation (b/b) or contained a low expression promoter haplotype with a wild-type structural gene (A/a) and another promoter haplotype associated with a structural mutation (A/a). DNA analysis

DNA was obtained from whole blood of 40 persons with C2D (37) and was not available in four of the deceased patients. A reference population of healthy blood donors (n = 200) was used for the polymorphisms investigated. MBL genotypes were analyzed as previously described (32, 38). The polymorphisms of FcγRIla and FcγRIIib were investigated according to Edberg et al. (39) with minor modifications. Primers for the FcγRIla and MBL variants were synthesized by MWG Biotech, and primers for FcγRIIib were synthesized by biomers.net. G2M*n and G2M*n– alleles were identified by PCR analysis combined with pyrosequencing (20, 40), confirming the results obtained by allelotyping of the proteins.

Statistical analysis

Most of the statistics were analyzed using the computer program SPSS, version 10.0. Fisher’s exact test, Mann-Whitney U test, and the Jonckheere-Terpstra test were used for analysis of statistical relations between patient groups and immunological markers. Distributions were compared with the CHI2 test. Binomial probability distribution was used to ascertain differences between medians of IgG subclass concentrations. Spearman rank correlation was used in conjunction with analysis of factor B, properdin, and factor H levels. All p values were two-tailed.

Results

Patients with C2D were stratified into four groups according to severity of infections (Table I). Patients with rheumatologic manifestations were fairly evenly distributed among the patient groups (Table II). The results of GM allotyping in relationship to severity of infections are given in Table III. The patients were classified with regard to homozygosity for G2M(n), heterozygosity for G2M(n) and G2M(n–), homozygosity for G2M(n–), and the associated GM haplotypes.

The G2M*n/G2M*n genotype was found in nine persons, seven of whom belonged to group 1, the patient group that only had minor infections (Table III). Two patients with this genotype had a history of repeated invasive infections. Statistical analysis with
was not found in the cohort. A Fisher’s exact test. Expression of concentrations was even more pronounced (range, investigated (Fig. 1). In adults, the range was 0.56 –5.1 g/L (median, 2.3
IgG2 concentrations were present in 15 of the 44 patients inves-
tations of IgE (410 IU/L; reference interval, 
were also normal in the new patients added to the study. A patient
levels of IgM, IgG, or IgA (4). The concentrations of these proteins
concentrations, considering that this might influence alternative
regard to the presence of G2M*n/G2M*n revealed a highly sign-
ificant difference between group 1 and groups 2–4 (relative
risk = 9.3; confidence interval (95%) = 2.2–38.8; p < 0.001; Fisher’s exact test). Expression of G2M*n was consistently asso-
ciated with the GM*b;f; haplotype. The rare GM*g;a;haplotype
was not found in the cohort. A G2M*n dose-dependent trend from
susceptibility to infection toward resistance to infection was dem-
onstrated in the patient groups 1–4 (p = 0.02; Jonkheere-Terpstra
test).

None of the patients in the cohort originally described had low
levels of IgM, IgG, or IgA (4). The concentrations of these proteins
were also normal in the new patients added to the study. A patient
with urticaria was the only patient with clearly raised concentrations
of IgE (410 IU/L; reference interval, <100 IU/L). IgG1 con-
centrations were slightly decreased in four patients. IgG3 levels
were essentially normal. In accordance with previous studies (41,
42), the levels of IgG2 and IgG4 were found to be low. Thus, low
IgG2 concentrations were present in 15 of the 44 patients inves-
tigated (Fig. 1). In adults, the range was 0.56–5.1 g/L (median, 2.3
g/L; reference interval, 1.7–6.1 g/L). The decrease of IgG4 con-
centrations was even more pronounced (range, <0.002–0.54 g/L
in adults; median, 0.02 g/L; reference interval, 0.06–1.2 g/L). When
distributed according to IgG2 allotypes, all medians for
IgG2 concentrations were below the medians of the age-related
reference interval (Fig. 1). In the largest group, adults with
G2M*n/G2M*n –, the difference was statistically significant (p <
0.001). The results also indicated a G2M*n dose-dependent effect
on IgG2 concentrations (Fig. 1), similar to that reported in com-
plement-sufficient persons (18, 19).

Eight adults had low IgG2 levels, and five of these had a history
of invasive infections (Fig. 1). Adults with invasive infections did
not differ from the other patients with regard to median IgG2 levels
(p = 0.11; Mann-Whitney U test). Among the children investig-
ated (n = 12), seven had moderately or slightly low IgG2 levels
as defined by age-related reference intervals (not shown). Seven
of the children had invasive infections, and four of these showed
normal IgG2 concentrations. In conclusion, no consistent correla-
tion was found between severity of the infections and the concen-
trations of IgG2. Similar conclusions were drawn with regard to
the other IgG subclass proteins.

Concentrations of factor B are known to be comparatively low
in C2D (41), as was also found in the present study (Fig. 2, A and
B). The concentrations of properdin and factor H showed normal
distribution. Factor B levels were moderately decreased in four
patients, three of whom had a history of repeated invasive infec-
tions. Moreover, patient groups 3–4 showed a median factor B
level (158 mg/L) that was somewhat lower than the median level
in groups 1 and 2 (190 mg/L; p = 0.02; Mann-Whitney U test). We
also examined the relationship between factor B and factor H
concentrations, considering that this might influence alternative

<table>
<thead>
<tr>
<th>Group 1: Minor Infections</th>
<th>Group 2: Pneumonia, Minor Infections</th>
<th>Group 3: Invasive Infection (1 Episode), Pneumonia, Other Infections</th>
<th>Group 4: Invasive Infections (2 Episodes or More), Other Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Episodes of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
<td>12</td>
<td>&gt;20b</td>
</tr>
<tr>
<td>Septicemiaa</td>
<td></td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Meningitisc</td>
<td></td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Other invasive infections</td>
<td></td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Total no. of invasive infections</td>
<td></td>
<td>15c</td>
<td>42c</td>
</tr>
</tbody>
</table>

* Major infections are specified with regard to the number of documented episodes.
* One patient showed 57 episodes of pneumonia.
* Seventy-nine percent of the meningitis episodes occurred before the age of 13, and 14% occurred after the age of 40.
* Severe headache was documented in the patient groups 1–4.
* One patient had two episodes of sepsis.

Table II. Demographic data of the CD2 patients

<table>
<thead>
<tr>
<th>Group 1</th>
<th>No Invasive Infections</th>
<th>Invasive Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 12 (27%)</td>
<td>Age at diagnosis of C2D (median) = 23</td>
<td>Age at diagnosis of C2D (median) = 40</td>
</tr>
<tr>
<td>Person-years = 485</td>
<td>Person-years = 520</td>
<td>Person-years = 520</td>
</tr>
<tr>
<td>Person-years (median) = 43</td>
<td>Patients that died during the observation period (n = 2)</td>
<td>Patients that died during the observation period (n = 1)</td>
</tr>
<tr>
<td>Rheumatologic disease (n = 5)</td>
<td>Rheumatologic disease (n = 5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>n = 7 (16%)</th>
<th>Age at diagnosis of C2D (median) = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years = 333</td>
<td>Person-years (median) = 49</td>
<td>Person-years (median) = 52</td>
</tr>
<tr>
<td>Patients that died during the observation period (n = 5)</td>
<td>Patients that died during the observation period (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Rheumatologic disease (n = 5)</td>
<td>Rheumatologic disease (n = 5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3</th>
<th>n = 12 (27%)</th>
<th>Age at diagnosis of C2D (median) = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years = 520</td>
<td>Person-years (median) = 52</td>
<td>Person-years (median) = 52</td>
</tr>
<tr>
<td>Patients that died during the observation period (n = 1)</td>
<td>Rheumatologic disease (n = 5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4</th>
<th>n = 13 (30%)</th>
<th>Age at diagnosis of C2D (median) = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years = 383</td>
<td>Person-years (median) = 22</td>
<td>Person-years (median) = 22</td>
</tr>
<tr>
<td>Patients that died during the observation period (n = 2)</td>
<td>Rheumatologic disease (n = 3)</td>
<td></td>
</tr>
</tbody>
</table>

* The patient groups are the same as those described in Table I.
pathway function in C2-deficient serum (43). However, factor B and factor H concentrations were fairly closely correlated in the patients (r = 0.64; confidence interval (95%) = 0.40–0.80; p < 0.0001) in accord with previous findings in complement-sufficient persons (44). No correlation was found between concentrations of factor B and properdin (p = 0.21; r = 0.20; Fig. 2B).

Based on MBL genotypes, 40 C2D patients were classified as being MBL-sufficient or MBL-deficient (36). The six patients with MBL deficiency genotypes all had a history of invasive infection (Table IV). However, the difference was not statistically significant (p = 0.06; Fisher’s exact test). The investigation was supplemented by measurements of MBL concentration in the sera of four patients, assuming MBL sufficiency at MBL concentrations >0.5 mg/L (45). The patients were clearly MBL-sufficient (range, 2.4–10.5 mg/L). With the inclusion of the four additional patients in the statistical analysis, the association between MBL deficiency and invasive infection in patients with C2D was found to be statistically significant (relative risk = 1.3; confidence interval (95%) = 1.1–1.6; p = 0.03; Fisher’s exact test). No patient with combined C2 and MBL deficiency had rheumatologic disease.

No correlation was found between FcγRIIa or FcγRIIib allotypes and severity of infections (Table V). The distribution of FcγR allotypes in C2D resembled that found in healthy controls. Combinations of FcγRIIa and FcγRIIib allotypes were not informative. In a study of meningococcal disease, Platonov et al. (46) reported that FcγRIIa polymorphism influenced outcome, but not in patients below the age of 5 years. In our study, the exclusion of nine children with invasive infections that occurred below this age did not change the results.

**Discussion**

The G2M*n/G2M*n genotype was found to be protective against severe infection in C2D, suggesting the involvement of an Ig-dependent mechanism capable of compensating for the impaired immunity caused by the complement deficiency. Judging from the history of patients without severe infections, the protective function of G2M*n/G2M*n was already operative at early age, which implies that it did not require a mature immune system and was sustained during prolonged observation. Of note, two patients with the genotype had repeated invasive infections, which shows that the protective effect of G2M*n/G2M*n is sometimes insufficient. One of the patients was a child who was homozygous for the FcγRIIa-R131 and FcγRIIib-N24 allotypes, considered to be an unfavorable combination of FcγR (27). However, the influence of FcγRIIa and FcγRIIib polymorphisms was found to be low in C2D.

Basic defense mechanisms against S. pneumoniae are known to include specific Abs and complement. Experiments in genetically engineered mice suggest that innate immunity to S. pneumoniae involves natural Ab and a functional classical pathway of complement (47). Earlier animal studies have emphasized a role of the alternative pathway (48). Splenic marginal zone B cells are a likely source of natural Abs and can respond rapidly to thymus-independent Ags (49) such as capsular polysaccharides that can induce protective Ab responses (50). Furthermore, a subset of circulating CD27+ memory B cells develops early in life and shares properties with splenic marginal zone B cells (51).

The strong impact of G2M(n) on immunity in C2D is difficult to fully understand. The most simple explanation is the established association between the homozygous presence of G2M(n) and the findings of quantitatively strong Ab responses to polysaccharide Ags (18, 19). Several mechanisms have been suggested through which G2M* and the associated GM*h/f/n haplotype might promote Ab responses, including involvement of haplotype-linked genes and slow processing of Ag by macrophages (17, 18, 52). Circulating CD27+ memory B cells account for Ab responses to polysaccharides and show evidence of Ab diversification at an early age before immune responses to Ag might be expected to

**FIGURE 1.** IgG2 levels in relationship to IgG2 allotypes (n.n, n.n+n−, n−n−) and invasive infection in 32 C2-deficient adults. Open symbols indicate patients with invasive infections (patient groups 3 and 4, Table I). The children are divided into three age groups, each with its own symbol and reference interval. Medians are indicated with horizontal bars.
have occurred (51). There are four variants of B cells as determined by GM haplotypes (16). The possibility that the GM*bzfn haplotype contributes to early Ab diversification in CD27+ memory B cells might perhaps be considered. Given the moderate size of the cohort investigated, statistically clear-cut results were expected for common variants of immunological factors with a strong impact on susceptibility to infection in C2D. The G2M*n/G2M*n genotype met these qualifications. We also assumed that the study would provide useful information concerning less frequent variants and factors with modest influence on disease expression. Based on previous reports (9, 10), we expected the G2M*n−/G2M*n− genotype to be associated with susceptibility to invasive infections (9, 10). A G2M*n− dose-dependent trend from susceptibility to infection toward resistance to infection was found that supports this assumption to some extent.

Concentrations of IgG2 and IgG4 are low in deficiencies of the classical pathway, which probably reflects impaired maturation of Ig production (41, 42). Because the GM*bzfn haplotype partly determines the concentrations of IgG2 (28), the question was asked of whether IgG2 levels might reflect susceptibility to infection in C2D. Indeed, low IgG2 levels were found in several patients with invasive infection, but correlations between IgG2 levels and patient groups were not statistically significant. In general accord with results of Alper et al. (41), IgG subclass concentrations did not predict the occurrence of infections in C2D.

With regard to other Igs, only one patient with C2D showed increased IgE concentrations. Considering the evidence for impaired isotype switching with very low IgG4 levels in C2D, it is conceivable that C2D might counteract development of atopic disease.

Table IV.  MBL polymorphisms in 40 C2D patients

<table>
<thead>
<tr>
<th>Severity of Infections</th>
<th>MBL Sufficiency Genotypes</th>
<th>MBL Deficiency Genotypes</th>
<th>MBL Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/A</td>
<td>YA/0</td>
<td>XA/0</td>
</tr>
<tr>
<td>Group 1 (n=12)</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 (n=7)</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Group 3 (n=12)</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Group 4 (n=13)</td>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total (n=44)</td>
<td>57.5%</td>
<td>27.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Controls (n=200)</td>
<td>58.0%</td>
<td>28.0%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

a Serum concentrations of MBL were determined by sandwich ELISA in four patients from whom DNA samples were not obtainable. The patients were divided into groups according to severity of infections (see Table I).

b All patients with MBL deficiency genotypes had invasive infections, but the difference was not statistically significant (p = 0.06; Fisher’s exact test).

c The four patients showed MBL concentrations at 10.5, 10.0, 2.75, and 2.4 mg/mL, respectively. Values >0.5 mg/L were considered to indicate MBL deficiency (46).

d Combined analysis, using results of MBL genotyping and MBL measurements, indicated that the association between MBL deficiency and invasive infections in C2D was statistically significant (relative risk = 1.3, confidence interval (95%) = 1.1-1.6; p = 0.03, Fisher’s exact test).

e Healthy blood donors.
Low factor B levels have been suggested to cause susceptibility to infection in C2D (11, 12). We found moderately low factor B concentrations in 15% of the patients with invasive infection and in 6% of the other patients, indicating that low factor B levels could be a minor susceptibility factor. Interestingly, a statistically significant association was found between combined C2 and MBL deficiency and the occurrence of invasive infections, suggesting that MBL has a C2-independent role in host defense (24, 25).

FcγRIIa-R131 and FcγRIIib polymorphisms are associated with increased susceptibility to meningococcal disease in deficiencies of the terminal complement components (27). Perhaps surprisingly, no such effect was found in C2D. Phagocytosis with ligand binding to receptors for Fc and C3b/iC3b is considered to be a major defense mechanism against S. pneumoniae (50). Phagocytic killing of N. meningitidis involving Abs and the alternative pathway of complement has been described in experiments with C2-deficient sera (53). It is not known if FcγRs were required in the assay system. Antibody-dependent opsonophagocytosis of S. pyogenes was recently shown to require involvement of iC3b receptors (CD18/CD11b), but not FcγRs (54). Moreover, results of animal experiments indicate that FcγRs might not always be of critical importance in defense against S. pneumoniae (55, 56).

Abs might also mediate protective effects through other complement-dependent mechanisms in C2D. Anticipatable IgM and IgG Abs may trigger immune adherence of S. pneumoniae to CR1 by recruitment of C4 (57, 58). Repeated severe infections in children with C2D usually cease after adolescence (3, 4) indicating by recruitment of C4 (57, 58). Repeated severe infections in children with C2D. MBL deficiency and impaired alternative pathway function due to low factor B concentrations may increase susceptibility to infections such as properdin deficiency (13) or common variable immunity. Moreover, results of an assay system. Antibody-dependent opsonophagocytosis of

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References

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