A Molecular Genetic Study of Factor XI Deficiency

By John F. Hancock, Kerstin Wieland, Roy E. Pugh, Uri Martinowitz, Sam Schulman, Vijay V. Kakkar, Peter B.A. Kernoff, and David N. Cooper

Factor XI deficiency is a rare bleeding diathesis found predominantly in Ashkenazi Jewish kindreds. A recent study of six Jewish patients identified three distinct mutations (Types I, II, and III) in the factor XI gene that were sufficient to fully define the genotypes of the patients. We have investigated 63 patients with factor XI deficiency and find overall allele frequencies of 44% for the type II mutation, 31% for the type III mutation, and 0% for the type I mutation. Therefore, 25% of the mutant factor XI alleles in our sample remain undefined. However, the distribution of mutant alleles is significantly different between Jewish and non-Jewish populations.

Factor XI is a serine protease zymogen that links the contact phase of blood coagulation with the intrinsic pathway via the activation of factor IX. Factor XI, a 160-Kd glycoprotein, circulates as a homodimer that is cleaved by factor XIIa between Arg369 and Ile370 in each monomer to generate factor Xla. The activated protease thus comprises two N-terminal heavy chains and two C-terminal light chains that are held together by disulphide bonds. In vitro, the activation of factor XI requires high molecular weight kininogen (HMWK) and a negatively charged surface. Factor Xla remains bound to the surface through the binding of HMWK to a site (Phe56 → Ser86) in the factor Xla heavy chain. The sequence of a factor XI cDNA cloned from human liver predicts that the protein is synthesized with an 18 amino acid N-terminal leader sequence. The catalytic triad of the protease active site is located in each of the two C-terminal light chains of the protein. The human factor XI gene spans 23 kb, comprises 15 exons, and is located on chromosome 4q35.

A recent study by Asakai et al identified three distinct factor XI gene mutations in six Ashkenazi Jewish patients homozygous for factor XI deficiency. A point mutation in the 5’ splice donor site (GT → AT) of the last intron, found in one of 12 alleles, probably results in aberrant mRNA processing. A second point mutation, introducing a novel termination codon into exon 5 (Glu117 → Ter), accounted for 5 of 12 mutant alleles. Finally, a third point mutation in exon 9, resulting in the amino acid substitution Phe283 → Leu, was found in six of 12 alleles. This amino acid change occurs at a site that is conserved between factor XI and human plasma prekallikrein. These three mutations, called type I, II, and III, respectively, therefore fully define the genotypes of the six patients examined. However, it should be noted that a causative role for the type III mutation has not yet been formally established by in vitro expression studies. While no correlation between genotype and clinical phenotype was found, the number of patients studied was too small for this observation to be conclusive.

We have investigated a large number of patients with factor XI deficiency, both Jewish and non-Jewish, to address three specific questions. First, do the previously described mutations account for all cases of factor XI deficiency? Second, is there any evidence of a correlation between genotype and clinical phenotype among a larger group of patients? Third, do the documented mutations described in Ashkenazi Jews also occur in non-Jewish populations?
kindreds, and if so, are the frequencies of the mutant alleles similar in both populations?

MATERIALS AND METHODS

Patients

Patients attending the Royal Free Hospital, London, UK, formed the major group for this study. Factor XI levels and detailed clinical histories were available from a previous study of inheritance and bleeding in factor XI deficiency. Additional patients from Israel, Sweden, and other UK centers were also included; factor XI:C levels and clinical histories of these patients were provided by their attending physicians.

Analysis of Mutant Alleles

High molecular weight genomic DNA was extracted from peripheral blood leukocytes. DNA (200 ng) was used in a polymerase chain reaction (PCR) of 40 cycles with 100 pmol of each oligonucleotide primer following the method of Saiki et al. The primers for the type I analysis were 5' AGTGACCAACGAAAGAGTGCCCA (5' end of exon 14) and 5' TTGCATATATCCATTGGCTAAGA (5' end of intron N), annealing at 55°C; the primers for the type II analysis were 5' GAATCTCGGAAGTAC-TCATGTC (3' end of intron D) and 5' ATCGACCACCTGAAATGTCCTCG (5' end of intron E), annealing at 60°C: the primers for the type III analysis were 5' ACTTACITTTCTCAATGGTGCTGT (3' end of intron G) and 5' ACGGTCTGAGTGTAGGTATGAA (5' end of intron I), annealing at 60°C. Denaturation was performed at 94°C for 30 seconds, annealing at the specified temperature for 15 seconds and extension at 72°C for 5 minutes. After 40 cycles the reactions were held at 72°C for 10 minutes. PCR products were digested with Mae I, Bsm I, and Sau3AI, respectively, and the digested products electrophoresed in 2.5% agarose gels containing ethidium bromide and visualised under UV light. After 40 cycles the reactions were held at 72°C for 10 minutes. PCR products were digested with Mae I, Sau3AI, and Sau3AI, respectively, and the digested products electrophoresed in 2.5% agarose gels containing ethidium bromide and visualised under UV light. Where appropriate (see Results), the validity of this restriction analysis was confirmed by direct sequencing of the PCR products using one or both of the amplification oligonucleotides as sequencing primers in dideoxy chain termination reactions using modified T7 DNA polymerase (Sequenase; US Biochemical Corp, Cleveland, OH).

Statistical Analysis

Analysis of variance and F-tests were used to test the null hypothesis of equality of multiple (more than two) means, t-tests used to test for equality of two means, and X²-tests used to compare predicted population frequencies. The analyses were performed according to established methods. Abbreviations used in reporting these tests are: SEM, standard error of the mean; DF, degrees of freedom.

RESULTS

Patient Pedigrees

Patients were designated homozygous or heterozygous deficient according to their plasma factor XI:C levels. Of the 28 homozygous patients (0% to 20% FXI:C), 16 were unrelated sporadic cases and 12 were drawn from seven unrelated kindreds. The 35 heterozygotes (25% to 70% FXI:C) comprised six unrelated sporadic cases and 29 cases drawn from 11 unrelated kindreds. Thus, a total of 22 unrelated patients and 41 patients from 13 unrelated kindreds were included in the study. The pedigrees of each of these 13 kindreds are presented in the Appendix.

The clinical histories of 61 patients were assessed from available case notes by two physicians and the bleeding symptoms classified into one of three groups:

None/trivial. No bleeding despite hemostatic challenge as a result of surgery, dental extraction, or trauma; or, very occasional trivial bleeding episodes not requiring clinical intervention.


Moderate. Recurrent bleeding in response to hemostatic challenges requiring specific treatment and/or blood transfusion; or one or more episodes of spontaneous hemorrhage.

Table 1. Plasma Factor XI:C Levels in Homozygous and Heterozygous Deficient Patients Classified According to Clinical Severity

<table>
<thead>
<tr>
<th>Factor XI:C Level (U/dL)</th>
<th>Clinical Severity</th>
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<tbody>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>0-20</td>
<td>0.45 ± 0.45</td>
</tr>
<tr>
<td>n = 2</td>
<td></td>
</tr>
<tr>
<td>25-70</td>
<td>53.1 ± 3.5</td>
</tr>
<tr>
<td>n = 17</td>
<td></td>
</tr>
</tbody>
</table>

SUMMARY

The clinical classification used to group patients is described in the text. Homozygous patients have plasma factor XI:C levels of 0 to 20 U/dL, while heterozygous patients have levels of 25 to 70 U/dL. Mean factor XI:C levels (±SEM) are given for each clinical group together with the number of patients (n) in each group. The plasma factor XI:C levels do not differ significantly between the clinical groups of homozygous patients (F = 0.77, DF = 3,24; P > .05) or heterozygous patients (t = 0.76, DF = 33; P > .06).
A Type I Mutation

Maelll

EXON 14

GAATC

pcd

pcu

A

Fig 1. Type I analysis. (A) The PCR product obtained using the 5′ (pcu) and 3′ (pcd) primers described in Materials and Methods. The type I, G → A point mutation is indicated and a Maelll restriction map given for a wild-type and mutant PCR product. (B) An agarose gel analysis of four patients. We found no examples of the type I mutation and so all the patients shown have a wild-type restriction pattern. Lanes have been loaded in pairs with an uncut PCR product (odd lanes) run alongside a digested PCR product (even lanes). The position of a 100-bp marker is indicated alongside the gel. The fastest migrating band in each lane comprises excess oligonucleotide primers (21 bp and 24 bp) that obscure the 33-bp fragment released from the digested PCR product.

PCR product of 706 bp and digested with Sau3AI. In the wild-type product, a single Sau3AI site in exon 10 gives two fragments of 578 bp and 128 bp, but the presence of the T → C mutation in exon 9 creates a new Sau3AI site resulting in three fragments of 328 bp, 251 bp, and 128 bp (Fig 3). Figures 1, 2, and 3 illustrate these analyses, which follow a similar strategy to that devised by Asakai et al.13

The restriction analysis was validated by direct sequencing of certain PCR products. For example, in every case where the restriction analysis failed to identify a known mutation, sequencing of all three PCR products from that patient was performed to confirm that one of the previously defined mutations had not been missed. In addition, a random 10% of PCR products that scored positive for type II or type III mutations on restriction analysis were also sequenced to confirm the presence of the predicted point mutations. In no case was any discrepancy found between the restriction and sequencing analyses.

Table 2 shows that of the 91 mutant alleles expected in this group of patients, 37 had a type II mutation and 31 had a type III mutation. No example of a type I mutation was found. Therefore, 23 mutant factor XI alleles (25%) in our sample did not contain one of the previously described mutations. Among the non-Jewish patients, only two of the 19 expected mutant alleles contained a defined mutation, indicating that the majority of mutant factor XI alleles in this group were other than the three previously described.
MOLECULAR GENETICS OF FACTOR XI DEFICIENCY

A

Type III Mutation

\[
\begin{array}{c|c|c}
\text{Sau3A1} & \text{Sau3A1} \\
\hline
\text{C} & \text{C} \\
\hline
\text{GAAT} & \text{GAAT} \\
\end{array}
\]

pcu "pcu + pcr product

Normal I 1 578bp 128bp
Mutant I 1 328bp 251bp 128bp

-600 -250 -100

Fig 3. Type III analysis. (A) The PCR product obtained using the 5′ (pcu) and 3′ (pcd) primers described in Materials and Methods. The type III, T → C point mutation is indicated and a Sau3A1 restriction map given for a wild-type and mutant PCR product. (B) An agarose gel analysis of three patients. One patient has a wild-type pattern (lanes 1 and 2), one is homozygous for the type III mutation (lanes 3 and 4), and one is heterozygous for the type III mutation (lanes 5 and 6). In each case an undigested aliquot of the PCR reaction (even lanes) has been loaded alongside an aliquot digested with Sau3A1 (odd lanes). The positions of 100-bp, 250-bp, and 600-bp markers are indicated alongside the gel.

To obtain an unbiased estimate of these allele frequencies, the genotypes of all unrelated sporadic cases and the index case of each family group were analyzed. In two kindreds (groups 6 and 10), a mutation not present in the index case was identified in another family member. These two alleles were also included in the analysis. Of the 62 evaluable alleles analyzed in this manner, 16 (25.9%) contained undefined mutations (Table 3). Among the remainder, type II mutations were slightly more common than type III mutations. The analysis presented in Table 3 also shows that the distribution of mutations is significantly different between Jewish and non-Jewish populations (\(\chi^2 = 61.98; P < .001\)). In the latter, 84% alleles contained undefined mutations compared with 12% among Jewish patients.

Correlation of Genotype and Phenotype

We then investigated whether the measured plasma factor XI:C level correlated with factor XI genotype (Table 4). We found that the mean factor XI:C levels associated with the homozygous and compound heterozygous genotypes differed significantly (F = 4.69; P < .01). The statistical analysis was therefore taken further with those genotypes containing defined mutations (ie, II/III, 11/11, and III/III). The differences between mean plasma factor XI levels in this subset of genotypes were highly significant (F = 11.12; P < .005). The plasma factor XI:C levels associated with a II/II genotype were very low (range 0 U/dL to 1.5 U/dL, mean 0.62 U/dL), whereas those associated with the III/III genotype were the highest of this subset (range 3

Table 2. Factor XI Gene Mutations

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Type of Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>All patients</td>
<td>0</td>
</tr>
<tr>
<td>Jewish</td>
<td>0</td>
</tr>
<tr>
<td>Non-Jewish</td>
<td>0</td>
</tr>
</tbody>
</table>

Summary of the factor XI gene mutations found in 28 homozygous and 35 heterozygous patients. The total number of expected mutations is therefore 91. Type I, II, and III mutations are those described previously by Asakai et al5 and are detailed in the text. Mutant alleles that were found not to contain any one of these three mutations are designated undefined (UND).

Table 3. Estimation of Mutant Factor XI Allele Frequencies

<table>
<thead>
<tr>
<th>Patients</th>
<th>Type of Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>All sporadic cases</td>
<td>0</td>
</tr>
<tr>
<td>All index cases</td>
<td>0</td>
</tr>
<tr>
<td>All cases</td>
<td>0</td>
</tr>
<tr>
<td>Allele frequency (%)</td>
<td>43.5</td>
</tr>
</tbody>
</table>

To obtain an estimate of gene frequencies, the mutations occurring in all sporadic cases plus the index cases of each family were analyzed. The upper part of the table gives the numbers of evaluable alleles and overall gene frequencies. The lower part of the table divides patients into Jewish and non-Jewish groups and gives gene frequencies for each group. The observed non-Jewish allele frequencies are significantly different from those expected for the alleles analyzed (\(\chi^2 = 61.98, DF = 1, P < .001\)). The Jewish allele frequencies were used to calculate the expected frequencies.
types (F = 1946 specific genotypes. Mean plasma factor XI:C levels differ significantly between the different homozygous and compound heterozygous genotypes (F = 5.22; P < .001) but not between the different heterozygous genotypes (F = 0.33; DF = 2.32; P > .05). The mean plasma factor XI:C levels in patients with homozygous and compound heterozygous genotypes containing defined mutations (II/II, II/III, and II/III) were analyzed further. The differences between the mean factor XI:C levels in patients with homozygous and compound genotypes we had established for each patient and the clinical severity of their factor XI deficiency was compared with the distribution of clinical phenotypes in patients with the II/III genotype.

A summary of the plasma factor XI:C levels found in patients with specific genotypes. Mean plasma factor XI:C levels differ significantly between the different homozygous and compound heterozygous genotypes (F = 4.69; DF = 5.22; P < .01) but not between the different heterozygous genotypes (F = 0.33; DF = 2.32; P > .05). The mean plasma factor XI:C levels in patients with homozygous and compound heterozygous genotypes containing defined mutations (II/II, II/III, and II/III) were analyzed further. The differences between the mean factor XI:C levels in this subset of genotypes were highly significant (F = 11.12, DF = 2.18; P < .005).

Abbreviation: WT, wild type.

There was no significant difference in plasma factor XI levels among the three homozygote genotypes (Table 4).

We next attempted to determine whether there was any correlation between the genotypes we had established for each patient and the clinical severity of their factor XI deficiency. Table 5 shows the distribution of clinical phenotypes for each homozygous and heterozygous genotype. It is clear that among heterozygotes no one particular mutation carries an increased likelihood of increased bleeding. However, the analysis presented in Table 5 does show that, among homozygous and compound heterozygous patients, the inheritance of a II/III genotype carries a greater risk of a moderate bleeding tendency than any other genotype ($\chi^2 = 27.45; P < .001$).

**DISCUSSION**

This study sought to determine the incidence of three previously identified factor XI gene mutations in a large group of factor XI-deficient patients and to investigate whether the factor XI genotype correlated with the clinical severity of the bleeding diathesis. Three main conclusions can be drawn from the data presented here.

First, a significant proportion (25%) of the mutant alleles causing factor XI deficiency in our patient sample remain to be identified. It is interesting that none of our patients possessed the type I (splice donor) mutation described by Asakai et al. These investigators identified the mutation in only one of 12 alleles studied. One interpretation of these observations is that whereas the type II (premature termination) and type III (amino acid substitution) factor XI gene mutations clearly predominate in Jewish populations, a number of individually uncommon mutations (eg, type I) account for the remaining 25% of disease alleles found mainly in non-Jews. We are currently sequencing the factor XI genes of patients with undefined mutations to address this hypothesis. It is also possible that one or more of these undefined mutations may be non-allelic, ie, they occur at other loci whose gene products are required for normal expression of the factor XI gene.

Second, as mentioned above, the frequencies of the two common factor XI gene mutations differ significantly between Jewish and non-Jewish patients. Indeed, the majority (84%) of the disease alleles in non-Jews remain undefined. These differences are probably not surprising in view of the early finding that non-Jewish homozygotes and heterozygotes possessed lower plasma factor XI levels than their Jewish counterparts. The high incidence of factor XI deficiency among Ashkenazi Jews was initially attributed to a founder effect. The results of our study are in part consistent with this hypothesis in that two distinct mutations account for 88% of all factor XI gene defects in this ethnic group. Our observation that these same mutations are rare in non-Jewish patients is also consistent with this interpretation, especially if several undefined mutations exist, rather than just a single mutation. The high frequency of factor XI deficiency among Ashkenazi Jews due to a minimum of four distinct mutations is nevertheless intriguing. Some selective advantage may well have accrued to heterozygous carriers of the mutant alleles to account for their high frequency in this ethnic group.

Third, the comparative analysis of phenotype and genotype presented here suggests that patients with a II/III genotype are significantly more likely to experience moderate bleeding than patients with other genotypes. Of the patients with a II/III genotype, approximately 50% had a moderate bleeding tendency and 50% had a mild clinical picture. Indeed, six of seven of the patients who had a moderate bleeding tendency possessed this genotype. This result indicates that a knowledge of a factor XI-deficient patient's genotype may be of some use in predicting the bleeding tendency of these patients.

### Table 4. Comparison of Plasma Factor XI:C Levels With Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency (n)</th>
<th>Range</th>
<th>Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>II/II</td>
<td>13</td>
<td>0-6</td>
<td>2.87 ± 0.49</td>
</tr>
<tr>
<td>II/III</td>
<td>3</td>
<td>3-20</td>
<td>11.0 ± 4.9</td>
</tr>
<tr>
<td>II/II</td>
<td>5</td>
<td>0-1.5</td>
<td>0.62 ± 0.29</td>
</tr>
<tr>
<td>UND/UND</td>
<td>4</td>
<td>1-3</td>
<td>1.75 ± 0.42</td>
</tr>
<tr>
<td>UND/UND</td>
<td>2</td>
<td>1.6-10</td>
<td>5.8 ± 4.2</td>
</tr>
<tr>
<td>II/UND</td>
<td>1</td>
<td>3-3</td>
<td>3.0</td>
</tr>
<tr>
<td>II/WT</td>
<td>13</td>
<td>34-65</td>
<td>52.5 ± 3.2</td>
</tr>
<tr>
<td>II/WT</td>
<td>10</td>
<td>30-70</td>
<td>52.7 ± 4.3</td>
</tr>
<tr>
<td>UND/WT</td>
<td>12</td>
<td>31-68</td>
<td>48.4 ± 5.2</td>
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</table>

### Table 5. Comparison of Factor XI Genotype With Clinical Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Unknown</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>II/II</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>II/III</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
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<tr>
<td>II/II</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>UND/UND</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>II/UND</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>II/UND</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>II/WT</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>II/WT</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>UND/WT</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
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</table>

The genotype of all 63 patients in this study was compared with the clinical assessment of the severity of their bleeding tendency. Clinical histories were not available on two patients. The upper part of the table lists homozygous and compound heterozygous genotypes and the lower part of the table lists heterozygous genotypes. The observed distribution of clinical phenotypes in patients with the II/II genotype differs significantly from that expected from the distribution of phenotypes among patients with all the other homozygous and compound heterozygous genotypes ($\chi^2 = 27.45; DF = 1; P < .001$).
Fig 4. Eleven patient pedigrees. The plasma factor XI:C level is recorded in the patients' box or circle. Underneath each patient, in parentheses, is given their genotype followed, after a comma, by their bleeding phenotype according to the key given below. For example, (I1 III.2) indicates a double heterozygote I/I III genotype with a moderate bleeding diathesis. If a single mutation is recorded, the patient is a heterozygote. All kindreds are Jewish except for groups 9 and 11, which are non-Jewish. U, undefined mutation; 0, none/trivial bleeding; 1, mild bleeding tendency; 2, moderate bleeding tendency; -, data not available.
likely outcome to an elective hemostatic challenge. Our data also show that there is an association between plasma factor XI:C levels and a patient’s genotype. In other words, the mean factor XI:C levels associated with individual homozygous and compound heterozygous genotypes differ significantly. We speculate that, for the three genotypes containing only defined mutations, the associated factor XI:C levels may be rationalized as follows. Dimers of a completely truncated factor XI molecule lack the catalytic site and are probably also unstable. This inactivity and instability would be reflected in the very low factor XI levels associated with the II/II genotype. Conversely, the missense mutation associated with the III mutation would not be expected to alter the stability of the protein because a bulky hydrophobic residue is merely replaced by a smaller aliphatic amino acid. In this case, stable dimers of a III/III protein should be produced that have limited activity. Although we do not as yet have confirmatory factor XI:Ag data, the observed higher factor XI:C level of type III homozygotes (11 U/dL) compared with that of type II homozygotes (0.6 U/dL) is consistent with this interpretation. Coexpression of type II and type III polypeptides in the same cell will result in the formation of II/II and II/III homodimers plus heterodimers of II/III protein. The amount of III/III protein secreted from heterozygous II/III liver cells would, therefore, be approximately 25% of that secreted by a homozygous III/III liver cell. This hypothesis fits with the observed mean factor XI:C level associated with the II/III genotype (2.9 U/dL). The question then arises as to whether II/III dimers are formed and secreted in II/III heterozygotes. The formation of such dimers may serve to stabilize the type II truncated chain resulting in a molecule that, despite lacking significant coagulant activity, can still bind HMWK because both binding sites for this molecule (Phe 56-Ser 86) would be present. The greater phenotypic severity associated with the II/III genotype might, therefore, be explained by a combination of HMWK depletion, due to sequestration by inactive II/III molecules, and a reduced production (relative to the II/III genotype) of the weakly active II/III homodimer.

APPENDIX

Eleven patient pedigrees are listed (Fig 4).

ACKNOWLEDGMENT

We thank Angus McCraw for preparing DNA from the Royal Free patients, Dr Sabri Kemahli for help in compiling certain of the clinical data, and Dr Atul Mehta for helpful advice. We also acknowledge Drs B.T. Colvin, R. Vaughan Jones, G.L. Scott, A. Copplestone, B. Zoll, and P.H.B. Bolton-Maggs, who kindly contributed patient material for inclusion in this study.

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