High Gene Frequency of Factor XI (PTA) Deficiency in Ashkenazi Jews

By Uri Seligsohn

Factor XI deficiency has previously been observed mainly in Jews. For 34 of 36 probands with factor XI deficiency in Israel, reliable information on ethnic background was obtained. Of 34 probands 33 were of definite Ashkenazi Jewish origin; 1 was of probable Ashkenazi origin. From a survey of factor XI levels among 428 unrelated healthy Ashkenazi Jews, 35 had partial factor XI deficiency (factor XI levels 0.15–0.49 U/ml), 1 had severe deficiency (0.02 U/ml) and 392 had normal levels (0.5–2.1 U/ml). The calculated frequency of the mutant gene was 0.043; the 95% confidence limits for the frequency of homozygotes in the total population was 0.1%–0.3% and for heterozygotes 5.5%–11%. In 20 of 41 obligatory carriers of the mutant gene factor XI levels were in the normal range. Since in the survey only subjects with deficient factor XI levels were considered as carriers, the true frequency of the mutant gene may be even higher. Factor XI deficiency can therefore be added to the list of genetic disorders common to Ashkenazi Jews. Since patients with factor XI deficiency may bleed excessively following trauma, it is advisable to carry out the appropriate tests in any Ashkenazi Jewish patient undergoing surgery.

Since the time of the original report of hereditary factor XI deficiency by Rosenthal et al., this autosomal disorder has been observed mainly in Jews. Muir and Ratnoff estimated that the minimal prevalence of homozygotes among Jews was approximately 1:12,000. However, their estimate was based on a very small sample of six families, and as correctly pointed out this figure may be a gross underestimate, since a large fraction of the patients are known to remain asymptomatic unless surgical intervention or trauma occurs.

Over the last 11 yr we have encountered 36 unrelated probands with factor XI deficiency. Since 33 of them were Jews of definite Ashkenazi origin, a survey of factor XI levels among the normal Ashkenazi population was carried out, aiming to reach a more reliable estimate for the frequency of this mutant gene in the Ashkenazi Jewish community of Israel and to seek a possible focus of its origin in Eastern Europe.

Materials and Methods

Factor XI assays were performed by the method of Rapaport et al., using plasma of a patient with severe factor XI deficiency. Test plasma samples were kept in plastic tubes at –20°C for not more than 1 wk until assayed. Reference normal plasma was pooled from at least 20 normal subjects of various ethnic backgrounds. Three groups of subjects were studied:

Probands and family members. The records of all patients in whom the diagnosis of factor XI deficiency was established between January 1966 and January 1977 were reviewed. All probands, and whenever possible their close relatives, were invited to our institute for factor XI assays.

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The probands were questioned about parental consanguinity and about the exact place of birth of their grandparents.

Ashkenazi Jewish subjects. Factor XI was assayed in 428 healthy adult Ashkenazi subjects who participated between January and June 1976 in a Tay-Sachs disease screening program carried out at our medical center. These subjects were tested only once and were questioned about their grandparents' exact origin.

Control group. This group consisted of 46 healthy hospital employees of various ethnic backgrounds in whom factor XI was assayed.

RESULTS

From January 1966 to January 1977 the diagnosis of factor XI deficiency was established in 36 probands (12 females, 24 males) belonging to 36 unrelated families; 22 had severe factor XI deficiency (<0.15 U/ml) and 14 partial deficiency (0.15–0.49 U/ml). Nineteen patients were referred to us because of a bleeding tendency that presented in 14 after surgical trauma or tooth extraction and in 5 with either menorrhagia, epistaxis, or easy bruising. In 17 patients the diagnosis of factor XI deficiency was established following a prolonged partial thromboplastin time or had been measured before elective surgery or after a general physical examination.

Only 1 of 22 probands with severe factor XI deficiency was an offspring of a consanguineous marriage, her parents being first cousins. The other 21 probands denied parental consanguinity.

Factor XI levels in the probands, their 114 close relatives, and 46 control

![Factor XI levels in probands, obligatory carriers, and 73 other relatives](image-url)
FACTOR XI DEFICIENCY IN ASHKENAZI JEWS

subjects are shown in Fig. 1. Interestingly, 20 of 41 obligatory carriers had factor XI levels within the range of the normal controls, 0.5–2.1 U/ml. Five obligatory carriers, offspring or parents of severely deficient probands, had severe factor XI deficiency. This pseudodominant mode of inheritance was observed in three unrelated families whose pedigrees are shown in Fig. 2.

For 34 of 36 probands with severe or partial factor XI deficiency reliable information was obtained concerning the place of birth of their respective 136 grandparents: 133 of these possible carriers of the mutant gene were Ashkenazi Jews, originating in Eastern Europe; 2 grandparents of a homozygous proband were born in Turkey, and another grandfather of a homozygous patient was a Sephardic Jew born in Bulgaria, but his wife was an Ashkenazi Jew born in Austria.

Of the 428 healthy Ashkenazi Jewish subjects (372 males and 56 females) whose factor XI levels were assayed, 35 were found to have partial factor XI deficiency (0.15–0.49 U/ml), 1 had severe factor XI deficiency (0.02 U/ml), and 392 had factor XI levels within the normal range (0.5–2.1 U/ml). There was no significant difference in the frequency distributions of results between males and females. The accumulated frequency distribution of factor XI levels for all 428 Ashkenazi Jewish subjects is shown in Fig. 3. It can be seen that the population is quite homogeneous except for a small fraction with unusually high factor XI levels.

The minimal frequency of the mutant gene in the surveyed population was calculated by the formula:

\[ P = \frac{(b + 2a)}{2G} \]

\( P \) being the gene frequency, \( b \) the number of partial factor XI-deficient subjects (35), \( a \) the number of severely deficient subjects (1), and \( G \) the total number of tested subjects (428). Applying this formula to our figures yielded \( P = 0.043 \).

Fig. 2. Pedigrees of three unrelated families manifesting vertical transmission of severe factor XI deficiency (pseudodominance).
The 95% confidence limits of the mutant gene frequency, $P \pm 1.96\sqrt{P(1-P)/2G}$, are 0.030-0.057. Using the Hardy-Weinberg formula and the gene frequency data obtained, the 95% confidence limits of the expected frequency of homozygotes for factor XI deficiency are 0.1% - 0.3% for the general Ashkenazi Jewish population and 5.5% - 11.0% for heterozygotes.

For 32 of 36 subjects found in the survey to have factor XI deficiency, and for 289 of 392 subjects who had normal factor XI levels, reliable information was obtained concerning the place of birth of their respective grandparents. The countries of origin of the grandparents of all 66 factor XI-deficient individuals (34 probands and 32 observed in the survey), as well as of those of 289 normal subjects, are shown in Table 1. It can be seen that the proportion of grandparents coming from most countries was similar in the two groups, except for Romania, where fewer grandparents of factor XI-deficient patients were born. A further breakdown into provinces of birth did not disclose a particular area with a high concentration of possible carriers of the mutant gene.

### Table 1. Origin of Grandparents of Individuals With Factor XI Deficiency and With Normal Factor XI Levels

<table>
<thead>
<tr>
<th>Country of Origin</th>
<th>Grandparents of 289 Individuals With Normal Factor XI Levels</th>
<th>Grandparents of 66 Individuals With Deficient Factor XI Levels*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent of Total</td>
</tr>
<tr>
<td>Poland</td>
<td>597</td>
<td>51.6</td>
</tr>
<tr>
<td>U.S.S.R.</td>
<td>215</td>
<td>18.6</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>47</td>
<td>4.1</td>
</tr>
<tr>
<td>Hungary</td>
<td>44</td>
<td>3.8</td>
</tr>
<tr>
<td>Romania</td>
<td>180</td>
<td>15.6</td>
</tr>
<tr>
<td>All others</td>
<td>73</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>1156</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Thirty-four probands were being followed and 32 were detected in the survey.
†Present-day boundaries.
DISCUSSION

The survey of factor XI levels carried out in 428 healthy Ashkenazi Jewish subjects revealed that the frequency of the mutant gene is rather high in this population. This conclusion is supported by the observation that only one proband with severe factor XI deficiency was an offspring of a consanguineous marriage, and also by the observation of three unrelated nonconsanguineous families with a pseudodominant mode of severe factor XI-deficiency inheritance (Fig. 2).

It should be noted that the presented data on the gene frequency may still be an underestimation, since only subjects with factor XI levels below the lower limit of the normal range were considered as heterozygous carriers. It is known that obligatory carriers of factor XI deficiency may present with levels overlapping with the normal range. Thus of 41 obligatory carriers (parents or offspring of homozygous probands) 20 had factor XI levels above 0.5 U/ml (Fig. 1). Consequently, the number of heterozygous carriers of factor XI deficiency in the Ashkenazi Jewish population may be even higher than indicated.

In Israel, 48% of the Jewish population is of Ashkenazi origin, the rest being of Sephardic, Asian, and North African origin. None of the 44 probands with factor XI deficiency who have been encountered in our institute over the last 18 yr (including 10 previously reported) was found to be of definite non-Ashkenazi descent. One previously reported patient with factors XI deficiency was of Iraqi origin. However, this patient also had a prolonged bleeding time and a low factor VIII level. A recent reexamination showed that the patient suffered from von Willebrand disease, her factor XI level being 1.08 U/ml.

In this study, we observed that two grandparents of another homozygous patient with severe factor XI deficiency were born in Turkey and could therefore be of Sephardic origin, like most of the Jews coming from Turkey. However, they may have been of Ashkenazi origin, since it is well known that Ashkenazi Jews had settled in Turkey long before the Sephardic Jews. Furthermore, during the Khmelnitzki massacres in 1648-1649, numerous Jews from the cities around Kiev gave themselves up to the Tatars, who transported them to Istanbul, where they were ransomed by the local Jewish community.

About 18% of the world Jewry is Sephardic or of Asian or North African origin. We recently completed a 2-yr screening program for coagulation disorders in patients admitted to the department of urology. None of the 347 patients who were of Sephardic, Asian, or North African origin had a partial thromboplastin time (PTT) exceeding 60 sec [normal (mean ± 2SD) 43 ± 9 sec]. These observations make it unlikely that factor XI deficiency is prevalent in these communities. However, a very rare frequency of the mutant gene cannot definitely be ruled out, since no correlation between factor XI levels and PTT was made in the above-mentioned study and since heterozygous carriers may manifest neither factor XI deficiency nor a prolonged PTT.

Unlike Tay-Sachs disease, which originated in individuals coming mainly from provinces neighboring the Baltic sea, the origin of the possible carriers of factor XI deficiency was found to be widely dispersed over Eastern Europe (Table 1). Consequently, it is conceivable that the mutation of the Tay-Sachs
gene in Ashkenazi Jews occurred later in history than the mutation of the gene controlling synthesis of factor XI.

The observed high gene frequency of factor XI deficiency in Ashkenazi Jews has very practical implications, calling for greater awareness of physicians to the existence of this disorder in such patients, especially before surgery.

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