Two Common Mutations Causing Factor XI Deficiency in Ashkenazi Jews May Point to a European Origin

To the Editor:

Shpilberg et al.1 suggest that the occurrence of type II mutation in the factor XI gene in both Ashkenazi and Iraqi Jews attests to its presence in Jews already 2,500 years ago. They ignore the fact that both type II and type III mutations, which are common in Ashkenazi Jews, are also common in northwest England.2 A Pst+ polymorphism in the HEXA gene was also found in both Ashkenazi and Scots-Irish chromosomes.3 A Celtic origin for all these polymorphisms is a possibility. According to the factor XI gene, Ashkenazi Jews and northwest English, who share two mutations, should be considered more ethnically similar than Ashkenazi Jews and Iraqi Jews, who share only one.

The origin of the Jewish communities is a question not yet resolved. Thus, there is no justification to assume that a mutation common to two Jewish communities has existed in Jews since ancient times. The claim that Ashkenazi Jews are descendants of Jews exiled from Israel by the Romans has not been proven historically. In fact, the origin of Ashkenazi Jews is known to us only since their appearance as Franco-German Jewry in the ninth century.4,5 Shpilberg et al6 also state that "the Iraqi Jews represent the original gene pool of Jews who have lived in isolation in the Middle East since Babylonian times, 2,500 years ago." None of these statements is substantiated. Evidence exists showing that there were very many proselytes in Babylonia.6-9 Rapaport10 and Feldmann11 stress that the large Jewish population of Babylonia could only have developed as a result of a great proselytic movement. Babylonian Jews did not live in isolation. On the contrary, they were fully integrated into Babylonian society.12 The history of Babylonian Jews is not known to us since the Babylonian exile in the sixth century BC, but only since the Talmudic period, which began in the third century.12

It seems that the suggestion that type II mutation was present in Jews already 2,500 years ago cannot be substantiated. Haplotypes can support this claim only if it is shown that the Ashkenazi and Iraqi type II chromosomes bear the same haplotype and that the non-Jewish type II chromosomes do not.

Two other queries arise when one compares the findings of Shpilberg et al1 with those of Asakai et al13 from 1991. Did not the discovery of an Arab patient, homozygous for the type II mutation, justify a survey for factor XI mutations among Arabs? Type II mutation might have been discovered as a mutation also common in other populations in the Middle East. The second query concerns the discrepancy between the two articles about the rarer mutations for factor XI deficiency in Ashkenazi Jews. Forty-three homozygous Ashkenazi probands were screened.13 No type I mutations were observed. 82 genes contained type II or type III mutations, 3 genes contained an unidentified mutation (type IV), and 1 gene contained "a nonsense mutation identical to that found in a Japanese patient (Osaka-I)." In the updated survey1 among 125 Ashkenazi probands, 246 genes contained type II or type III mutations, 3 contained type I, and 1 contained type IV. What happened then to the 3 unidentified mutations and to the Osaka-I mutation? What happened to the fourth type I allele mentioned in an abstract in 1993?14

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8. Braude WG: Jewish Proselytism in the First Five Centuries of the Common Era, the Age of the Tannaim and Amoraim. Menasha, WI, George Banta, 1940
England. To the best of our knowledge, no survey of the type II and type III mutations on the common European origin of the type II and type III mutations on the common by the Romans in 70 AD. Middle East at about the time of the destruction of the second Temple and factor XI gene and bear the type II and or the type III mutation (personal communication, June 1995). In collaboration with Bolton-Maggs et al, we are currently performing haplotype analysis of chromosomes bearing the type II mutation in Ashkenazi and in Iraqi Jews. Complete identity of a different haplotype was also found in chromosomes bearing the type III mutation, a mutation that so far has not been identified in any Jewish community except for Ashkenazi Jews (manuscript in preparation). These data provide conclusive evidence for a common ancestry of the type II mutation found with a similar frequency among Ashkenazi and Iraqi Jews and suggest that the type III mutation frequently observed in Ashkenazi Jews (and absent in Iraqi Jews) stems from a founder who probably lived at a time when the Ashkenazi Jews had already separated from their original roots. Our consultant, Prof Yehuda Nini from the Tel Aviv University, who is a well-known authority in Jewish history, assured us that there is unequivocal evidence that Jews already lived in France and Germany during the time of the Roman Empire. This finding contrasts with the view cited by Zoossmann-Diskin that only in the ninth century AD did Jews settle in Europe and supports the notion that the Ashkenazi Jews diverged from the Jews who stayed in the Middle East at about the time of the destruction of the second Temple by the Romans in 70 AD.

Dr Zoossmann-Diskin based his assumption about a possible European origin of the type II and type III mutations on the common occurrence of these mutations in the population residing in northwest England. To the best of our knowledge, no survey of the type II and type III mutations has been performed in northwest England. What Bolton-Maggs et al.4 did find were 17 non-Jewish kindreds from northwest England with members affected by a bleeding tendency and factor XI deficiency. Ten of these kindreds bear unrelated mutations of the factor XI gene and 7 bear the type II and/or the type III mutation (personal communication, June 1995). In collaboration with Bolton-Maggs et al, we are currently performing haplotype analysis of the English patients in an attempt to address the interesting question of whether haplotypes bearing the type II mutation in non-Jews are identical with the Ashkenazi and Iraqi Jewish haplotypes and whether chromosomes bearing the type III mutation in the English patients are identical with the respective Ashkenazi Jewish chromosomes. If an identity is found, it might suggest that chromosomes bearing the type II and type III mutations have been transferred from Jews who assimilated in the English population since their settlement in England early in this millennium. Alternatively, if nonidentity is found, it would be consistent with both mutations having different founders in Jews and in non-Jews.

Dr Zoossmann-Diskin also argues that the Iraqi Jews are "im-pure," because proselytism was common in Babylonia (Iraq) and, consequently, in contrast to the common assumption,2 they do not represent the original gene pool of the Jews who have lived in Babylonia since the destruction of the first Temple in 586 BC. We certainly agree that none of the Jewish communities could have been in total genetic isolation during the last 2.5 millennia. This is self-evident when one looks at the variable external features of Jews of different ethnic backgrounds. However, Prof Nini informs us that no evidence exists regarding the extent and significance of proselytism in the population that resided in Babylon; thus, one cannot draw the conclusion reached by Zoossmann-Diskin.

Finally, the apparent discrepancy between our reports1,6 about the rarer mutations causing factor XI deficiency in Jews is easy to explain. The 3 patients mentioned in our report6 as bearing unidentified mutations have been re-examined or characterized since 1991 as follows. One is a compound heterozygote for the type II and type IV mutation. The second patient turned out to be a type III homozygote rather than bearing the Osaka I mutation. The third patient turned out to be a compound heterozygote for the type II and III mutations. Regarding the rare type I mutation, to date, 4 individuals bearing the type I mutation have been defined: 3 by us1 and one by Asakai et al.6 This was the figure mentioned in our abstract in 1993.6

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A Zoossmann-Diskin