Is E148Q a Benign Polymorphism or a Disease-causing Mutation?

To the Editor:

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent episodes of fever accompanied by sterile peritonitis, arthritis, pleuritis, and a typical inflammatory rash termed erysipelas-like erythema. The development of renal amyloidosis type AA is the most devastating manifestation of the disease, and prior to colchicine treatment was a major cause of morbidity and mortality. The disease is very prevalent among North African and Iraqi Jews, Middle Eastern Arabs, Turks, and Armenians, but rare in other populations. FMF is caused by mutations in the *MEFV* gene, which is composed of 10 exons and encodes a protein of 781 amino acids[1,2]. To date more than 50 mutations have been identified, most of which are extremely rare (Infevers database, http://fmf.igh.cnrs.fr/infevers). The association between FMF and mutations such as M694V, M694I, and V726A has been clearly established; however, controversy exists as to the role of the amino acid substitution E148Q, where glutamine (Q) substitutes for glutamic acid (E). Initially this sequence variation was described as a disease-causing mutation with low penetrance and mild symptoms, but in more recent studies some investigators found a similar frequency of E148Q among patients and controls and therefore suggested that it is no more than a benign polymorphism[3,4]. We hypothesized that if E148Q is a low-penetrance mutation, the difference in allele frequency between patients and controls may not be evident if the study groups are too small. We therefore compared the frequency of the E148Q allele in a large cohort of Israeli patients with FMF and controls.

All data used in this analysis was taken from 4 published studies, 3 that estimated the frequencies of the 3 most prevalent FMF sequence variations M694V, V726A, and E148Q in an Israeli control population[5-7], and one study that described the prevalence of these 3 mutations in a group of 412 Israeli patients[8], all with definite FMF according to the Tel Hashomer criteria[9]. The results are presented in Table 1. The E148Q allele was found in 58 (7.0%) of 824 FMF alleles compared to 163 (5.8%) of 2802 control alleles, a small difference but not statistically significant ($p = 0.23$). Using the same data sources a much larger difference was found for the M694V mutation (391 of 824 FMF alleles versus 82 of 4188 control alleles; $p = 0.00001$) and for the V726A mutation (122 of 824 FMF alleles versus 141 of 4018 control alleles; $p = 0.00001$).

Overrepresentation in patients compared to controls is considered one of the cornerstones in differentiating a mutation from a benign polymorphism. This study is the largest to date comparing the frequency of E148Q in patients and controls; yet it could not provide evidence supporting the notion that E148Q is a mutation and not just a polymorphism. In contrast to the data presented above, glutamic acid is conserved throughout evolution at position 148, favoring a mutation over a polymorphism. In addition, E148Q has been found to appear on the same allele with the V726A mutation (E148Q-V726A complex allele). Patients who are homozygous for the complex allele (E148Q-V726A/ E148Q-V726A), or compound heterozygotes (E148Q-V726A/ V726A), have a more severe disease compared to patients homozygous for V726A. Thus E148Q may be considered a polymorphism with an effect on the phenotype when it appears in combination with V726A.

Table 1. The frequency of E148Q in controls and in FMF patients.

Study	No. of Chromosomes in the Study	No. of Chromosomes with E148Q	Frequency, %
Control Gershoni-Baruch[5]	960	65	6.7
Control Stoffman[7]	800	53	6.6
Control Kogan[6]	1042	45	4.3
Control, total	2802	163	5.8
Patients Zaks[8]	824	58	7.0

Can a mutation appear in a similar frequency in patients and controls? D1152H is a well established mild cystic fibrosis (CF) mutation that in the homozygote state usually appears as congenital bilateral absence of the vas deferens (CBAVD) with mild, late-onset pulmonary disease. In the heterozygote state with another severe mutation (compound heterozygote) it usually presents as an intermediate phenotype. The deleterious effect of this mutation has been proven by functional studies. Interestingly, this mutation was found in 6.27% of referrals for CF carrier screening among Hispanics, but no cases of clinical disease were detected in this population group. In a study from Israel the D1152H allele was found in 12 (8%) of 148 CF alleles among patients compared to a prevalence of 5.3% in a control population of Israeli Jews, a difference that did not reach statistical significance[10]. In contrast to CF, there are no functional studies available to assess the role of sequence variations in *MEFV* and therefore until such tests are available, discriminating between benign polymorphisms and disease-causing mutations would have to rely on epidemiological data and circumstantial evidence. Despite the large size of our sample we could not provide evidence that would support the notion that E148Q is a mutation and not a polymorphism.

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