Is the country of living important in the phenotypic expression of E148Q mutation? The Armenian experience

Sirs,

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterised by recurrent attacks of fever and serositis (1). Over 20 years ago the gene associated with the disease (*MEFV*) was isolated (2, 3). At the beginning only 4 mutations were identified: M694V, M680I, A726V on exon 10 and E148Q on exon 2. Now, more than 300 sequence variants have been documented and recorded in the INFEVERS database (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Some of them are pathogenic and clearly cause FMF whereas many others have a very low penetrance and are not associated with any clinical feature. Over the years, many studies showed that mutations on exon 10 such as M694V and M680I and A726V are almost always associated with clinical expression of FMF (4). However, the role of mutation E148Q in causing FMF remained controversial. A study conducted in Israel raised a serious question regarding the pathogenic role of E148Q mutation (5, 6). This doubt was based upon the following observations: a. Many individuals carrying two E148Q mutations (homozygotes) are asymptomatic. b. The prevalence of this sequence alteration in Israel was similar among FMF patients and healthy controls (about 7%). c. The mutation E148Q is relatively common among Israeli Ashkenazi Jews and yet FMF is relatively rare in this community (7). A study from France by Tchernitchko *et al*. supported the above view claiming that E148Q is a polymorphism rather than sequence alteration causing FMF (8). Furthermore, in a study from Saudi Arabia, increased frequency of E148Q mutation was found within Arab tribes. However, further analysis disclosed that it was the most common mutation among healthy adults but not in affected people (9). Additional studies reported that the carrier rate of E148Q mutation among the healthy population in China is about 15% and in Korea even higher (10, 11). Yet, FMF is hardly seen among Chinese and Koreans. These are the reasons why in a recent study by Shinar *et al*. E148Q was defined as a sequence variant of unknown significance (VOUS) (12). On the other hand, a few other studies mainly from Turkey, reported that E148Q does cause FMF (13, 14).

Thus, based upon the above publications, the debate regarding the real penetrance of E148Q remained unsolved. Nevertheless, individuals carrying E148Q mutation in combination with an additional exon 10 mutation almost always present with FMF (15).

Table I. Comparison of clinical features between carriers of different combinations of *E148Q* (heterozygotes, homozygotes and combined heterozygotes).

FMF- patients	Fever	Abdomen	Thorax	Arthralgia	Arthritis	Skin	Myalgia
Total n=1440	1030	1068	586	681	223	211	333
(%)	71.5	74.1	40.6	47.2	15.5	14.6	23.1
E148Q/M694V n=907	659	668	360	393	135	127	192
(%)	72.6	73.6	39.7	43.3	14.9	14	21.1
E148Q/V726A n=233	131	148	65	105	26	28	46
(%)	56.2	63.5	27.8	45	11.1	12	19.7
E148/M680I n=213	153	165	80	96	26	27	40
(%)	71.8	77.4	37.6	45	12.2	12.6	18.8
E148Q/E148Q n=16	**16**	**16**	**10**	**16**	**6**	**3**	**6**
(%)	**100**	**100**	**65.5**	**100**	**37.5**	**18.8**	**37.5**
E148Q/N n=71	**71**	**71**	**71**	**71**	**30**	**26**	**49**
(%)	**100**	**100**	**100**	**100**	**42.2**	**36.6**	**69**
Non-FMF individuals (carriers)							
E148Q/N n=1519	720	860	242	576	108	138	174
(%)	47.3	56.6	15.9	37.9	7.1	9	11.4

Recently, we have summarised our data on FMF patients and healthy individuals, who were screened in our National Centre of Medical Genetics and Primary Care in Yerevan, Armenia. We have analysed the clinical features of individuals carrying either E148Q mutation alone (heterozygote) or in homozygous state or in combination with other mutations (combined heterozygotes). Table I depicts our results concerning 1440 FMF patients. Seventy-one were heterozygotes for E148Q, 16 were homozygotes and the rest were combined heterozygotes with mutations M694V, A726V and M680I. When we compared the clinical features between the different groups, we clearly found that in Armenia patients with a single E148Q mutation or in homozygous state display FMF features almost the same as those carrying combined heterozygotes with mutations known to cause severe FMF (M694V, M680I). Moreover, when we interviewed 1519 apparently healthy individuals who carried a single mutation E148Q (heterozygotes), almost half of them displayed either fever or abdominal pain. Yet, none of them fulfilled the diagnostic criteria for FMF.

These observations contradict the impression reported in Israel and France and are in accord with publications from Turkey (13, 14). This suggests that the country of origin may play a major role in expressing the potential pathogenic role of E148Q sequence alteration. It is tempting to hypothesise that there is a common environmental or epigenetic factor(s) which may affect the phenotypic expression of E148Q in Armenian and Turkish patients. The above mentioned opposite observations from Israel, France and China where E148Q heterozygotes are not associated with FMF, further support this notion. A study by Touitou *et al*. found that the country of origin was the most important factor leading to amyloidosis in FMF patients (16). Similar explanation can be proposed for the observation regarding the different expression of E148Q in various countries. Still the question is what stands behind the term "country of origin"? Is it related to environmental factors, diet, health services, access to medical treatments etc.? The exact factors underlying this term remained to be explored in the future.

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