Editorial

The *MEFV* E148Q allele: A deleterious mutation or harmless variation?

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Familial Mediterranean fever (FMF) is an inflammatory disease characterized by recurrent attacks of fever and peritonitis, pleuritis or arthritis (1). A typical attack lasts between 24 and 96 hours and its frequency varies between patients and even in the same patient. It is the most frequent form of the inherited periodic fever syndromes. The mode of inheritance is autosomal recessive and it affects mostly Arab, Armenian, Jewish and Turkish populations. The most devastating complication of FMF is amyloidosis caused by the deposition of AA amyloid fibers mainly in the kidneys and additional organs. Early diagnosis is crucial since it allows for the administration of colchicine, which is a highly effective medication for the prevention of the febrile attacks and the amyloidosis.

Clinical judgment has always been regarded as the sound basis for FMF diagnosis mostly due to the lack of specific laboratory tests. In fact, an unambiguous clinical history and subsequent response to medical treatment are sufficient. However, this is not always the case, and the identification of the *MEFV* gene in 1997 has provided exclusive objective support for FMF diagnosis in patients with atypical manifestations. *MEFV*, the gene responsible for FMF, comprises 10 exons and encodes the pyrin/marenostrin protein, which is expressed mainly in white blood cells. Although the current concept is that the protein is involved in suppression of the inflammatory process, its exact role has yet to be defined.

The two conditions which enable the use of gene analysis as a tool for diagnosis and for genetic counseling are detection of sequence variations and the proof that these changes are harmful. Due to limited knowledge regarding the biology of the pyrin/marenostrin protein, there is no available functional assay and it is still not possible to examine the effects of changes within the gene in a direct manner. Therefore, only epidemiologic studies and analysis of informative pedigrees can promote the understanding of the clinical significance of these sequence variants. Several authors divide DNA variations into (benign) "polymorphisms" which do not have a phenotypic effect and (deleterious) "mutations" which are pathogenic.

In our view, these definitions do not cover the entire genotypic spectrum and we suggest that sequence variations may be graded according to their penetrance rather than classify them as simple mutations or polymorphism.

More than 50 missense variations have been found thus far in the *MEFV* gene, the majority of which are located in exon 10. This exon encodes for the B30.2 domain at the C-terminal region of the protein. It harbors the four most frequent mutations - M694V, V726A, M680I and M694I - whose pathogenic significance is well established and widely accepted. M694V, for example, is the most common mutation among North African Jews. It is associated with severe disease in most FMF populations, whereas V726A is prevalent in Arabs, Armenians, Ashkenazi Jews and Iraqi Jews and causes milder disease.

In recent years, E148Q has also attracted the attention of several investigators. This is due to the fact that it is one of the most common variants in populations affected by FMF, with an allele frequency of approximately 10% (2). Unlike the mutations mentioned above, E148Q is situated in exon 2, not within a recognizable domain or motif of the protein (3). This change results in the substitution of glutamine for glutamic acid and its clinical implication is a matter of controversy. Early reports suggested that this is a disease-causing

mutation with low penetrance (3). Nevertheless, the observation that individuals homozygous for this mutation were asymptomatic raised questions as to its exact role in FMF. In a study by Topaloglu *et al.* analysis of 26 Turkish individuals homozygous for E148Q disclosed that only 22 had FMF attacks (4). In another study of 30 cases with a definite diagnosis of FMF, 21 patients carried E148Q, one of whom was homozygous (E148Q/E148Q), and the other 20 had E148Q in combination with other mutations (compound heterozygotes) (5). In this study, the authors found that in the Greek population the E148Q allele was dramatically more frequent in patients than in the control population (18.3% vs. 1.8%, respectively). These two studies support the view that E148Q is a disease - causing mutation. Nevertheless, two main concerns were raised with regard to the observations made by Topaloglu *et al.* First, four homozygotes were reported to be absolutely asymptomatic. Second, the E148Q variant was found in 12% of the healthy subjects within the Turkish population and only in 3.5% of the FMF patients.

Ben-Chetrit *et al*. reported several additional observations which support the conclusion that E148Q is not significantly pathogenic (6). First, 4 individuals aged 45 years and older, were found to be homozygous for E148Q and clearly asymptomatic. They were identified through screening of their children who were symptomatic due to the fact that they carried the M694V and V726A mutations in addition to E148Q. Second, in two separate families one of the parents was found to be a carrier of E148Q, whereas the FMF-affected children were carriers of V726A or M694V, but not E148Q. In these families the E148Q allele was not segregated with the disease and the other allele probably bears an unidentified mutation causing the disease in the children. If the E148Q was indeed pathogenic, it was expected that its combination with the other allele, which evidently caused FMF in their children, would also bring about disease manifestations in the parents. Third, in several FMF patients E148Q was accompanied by another true mutation on the same allele, such as V726A or M692del' suggesting that the disease was caused by the other mutations. Fourth, the relative frequency of the E148Q mutation in the control group and in the patient group was almost identical. These findings gained further support from a large study which analyzed 233 patients of Sephardic Jewish origin in France and 213 healthy relatives. The results of this investigation demonstrated a similar frequency of the E148Q allele in the two groups (7). Based on this study, the authors strongly support the hypothesis that E148Q is merely a benign polymorphism and not a disease-causing mutation. A recent segregation study of 14 cases showed that heterozygous healthy parents transmitted the non-E148Q allele to their affected children, in line with the previous observations of Ben-Chetrit *et al*. (8).

A survey of ethnic groups in which FMF is not common led to a somewhat different interpretation of the E148Q variant (2). Apparently, its frequency is increased in British Caucasian as well as in Punjabi Indian patients with (non-FMF) arthritis complicated by AA amyloidosis. A comparable finding was reported in British individuals with uncharacterized recurrent fever syndromes. Interestingly, a large number of Indian and Chinese homozygous for E148Q variant, did not exhibit any overt pathology. On the basis of these observations the idea has been put forward that pyrin E148Q is not deleterious by itself but may augment inflammation non-specifically.

The question of whether E148Q plays a functional role in the pathogenesis of FMF is not hypothetical but has practical implications. Symptomatic individuals who are homozygous for E148Q should obviously be treated with colchicine as should any FMF patient, even in the absence of a detectable mutation. However, the question remains whether one should treat asymptomatic individuals homozygous for E148Q. We suggest that treatment is not indicated in such individuals. In contrast, asymptomatic individuals who are homozygous or compound heterozygous for M694V or V726A mutations - in our view - should be treated. The main reason is the potential complication of amyloidosis which does not correlate with FMF attacks on one hand and the lack of reports on amyloidosis appearing in asymptomatic individuals homozygous for E148Q – on the other hand.

In summary, we do not believe that the E148Q variant has been unequivocally proven to be unrelated to the pathogenesis of FMF. However, at this point it seems that most of the data indicate that its impact on FMF manifestations is quite low. Functional studies with the pyrin protein are needed in order to solve the question regarding the true significance of the E148Q sequence variant in FMF.

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