The Distribution of *MEFV* Common Mutations among Israeli Patients with Familial Mediterranean Fever

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Familial Mediterranean fever is an autosomal recessive hereditary disease characterized by recurrent episodes of fever, accompanied by peritonitis, pleuritis, arthritis or erysipelas-like erythema [1]. The disease is prevalent among Turks, Armenians, Arabs and non-Ashkenazi (East European origin) Jews. In 1997, two independent consortia isolated and cloned the *MEFV* gene associated with FMF [2,3]. The International Consortium found three mutations (M694V, V726A, M680I) while the French Consortium detected four mutations, the additional one being M694I. Later, another common sequence alteration (E148Q) was reported [4]. Since then, over 30 mutations have been detected, of which the above 5 are the most common and cover more than 85% of the mutations present in the above-mentioned populations.

The relationship between the M694V mutation and the severity of the disease was shown in the original articles on the isolation of the gene [2,3] and later in numerous studies [5–8]. The relationship with amyloidosis has also been demonstrated [9,10]. Nevertheless, it should be emphasized that in Turkey, all the mutations were shown to be equally conductive in causing severe disease and amyloidosis [11]. The reason for this observation is not clear. However, it does seem that other genetic modifiers and environmental factors may play a role in the manner of FMF expression and its complications in the various populations.

In the present issue of *IMAJ*, Zaks et al. [12] report on their analysis of the three most common mutations (M694V, V726A, E148Q) among 412 patients with FMF. Most of their results are expected and actually confirm data contained in previous publications. Since most of the patients with "pure" origin were of North African extraction it was anticipated that the mutation M694V would be most prevalent. It is most likely that the common ancestral origin for this mutation is Jewish families with FMF who accompanied the Moslems during their conquest of North Africa and Spain [1]. The Jews who remained in the Middle East with the Moslems share a wide and almost similar range of mutations, suggesting the presence of intermarriage between these two populations, or even the possibility of common origin prior to the Islamic period. Yet, several points in the paper are interesting and deserve some comment.

The role of genetic diagnosis in FMF

In their article, Zaks and colleagues report that 56% of the FMF patients had two mutations, whereas 27% were heterozygous and the rest displayed no mutation. These findings, which are in line with some of our results, suggest either that the disease has a dominant mode (since heterozygotes are also symptomatic) or that there are mutations that have not yet been detected [13]. This finding also raises a question regarding the value of genetic testing in these cases, since it cannot differentiate heterozygous FMF patients from "healthy carriers." Again we see that the clinical manifestations and the response to colchicine treatment are more important and useful than the genetic tests when diagnosing FMF.

Other points that should be addressed are related to the two opposite genetic groups: one comprises FMF patients who have no mutations, and the other comprises subjects with two mutations but without symptoms or clear disease manifestations.

FMF patients with no mutations

The presence of FMF patients in whom no mutation was found may be explained in several ways:

- These patients may have mutations that we cannot detect – as yet.
- The disease is caused by a gene other than *MEFV*, supporting the hypothesis regarding the heterogeneity of FMF [14].
- The diagnosis of FMF is mistaken, which means that we are including patients with other hereditary periodic fever syndromes in this group. This misdiagnosis is based on the assumption that the periodic fever diseases are rare and almost non-existent among the "typical" populations in whom FMF is prevalent. However, this assumption was found to be inaccurate by Dode et al. [15], who recently described several North African Jewish and Moslem patients with tumor necrosis factor-alpha receptor-associated periodic fever syndrome (TRAPS) – populations usually prone to developing FMF. Moreover, in many patients with familial cold urticaria/Muckle-Wells syndrome (FCU/MWS) the sequence alterations detected were dominant *de novo* mutations, suggesting that in any ethnic origin such mutations may suddenly arise with no previous genetic background [16]. Therefore, one should exercise caution in making a diagnosis of FMF in patients with periodic fever, but with no *MEFV* mutations.

Bi-allelic mutations in non-affected subjects

This group, which is called Phenotype III, includes subjects who bear two mutations and yet do not express any manifestation of FMF [17]. The presence of such individuals warrants several comments.

FMF = familial Mediterranean fever

- Is there any significance to the homozygous mutation present in these cases? The answer is probably yes. If both mutations are E148Q, it is very doubtful that this is a sequence alteration causing disease or a simple polymorphism. We have shown that the prevalence of this alteration is similar in FMF patients and control subjects [18]. A recent but unpublished study from France found similar results [personal communication]. Furthermore, the authors claim that even the prevalence of the combination of M694V/E148Q was similar among FMF patients and control subjects, suggesting that E148Q is a benign polymorphism rather than a genuine mutation.
- In cases where the subjects bear either V726A or M694V, one must be quite sure that the patient is really asymptomatic. In such cases, it is still possible that the subject was symptomatic at one point in his or her life, but that at the time of genetic testing the disease changed its course and became less symptomatic. Alternatively, these subjects may become symptomatic later in life. In fact, in a paper by Kogan and associates [17], it was claimed: "there was an excess of frequent febrile episodes (more than 4 per year) among carriers of any of the two mutations and among the carriers of the V726A as opposed to non-carriers." Thus, in such cases the exact definition of clinical activity of the disease may sometimes be problematic.
- Kogan et al. [17] found one asymptomatic subject homozygous for E148Q among 300 Ashkenazi Jews, and another two among 100 Iraqi Jews. They also found two asymptomatic subjects homozygous for V726A among the Iraqi Jews. None of the healthy control subjects was homozygous for M694V. In the pre-genetic testing era, it was observed that the North African Jews experienced more severe FMF symptoms than did Iraqi Jews [19]. Following the cloning of the gene, the finding that most of the North African Jews bear the M694V mutation, which was associated with more severe disease, explained this previous observation. The absence of asymptomatic subjects with bi-allelic mutations among the North African Jews raises the possibility that Iraqi and Ashkenazi Jews may have exclusively suppressive environmental factors or suppressor modifier genes, leading to the finding of asymptomatic double mutated subjects among them. This explanation is quite plausible since several enhancing modifier genes have already been described. The first is the major histocompatibility complex class I chain-related gene A (*MICA*), a modifier gene described by Touitou and co-workers [20], which may cause mild FMF attacks (*MICA* 4) or severe disease (*MICA* 9). The presence of a specific allele in the *SAA1* gene was associated with a higher risk for amyloidosis in FMF patients [21]. The presence of a concomitant inflammatory disease was reported as an additional potential aggravating factor for FMF. Thus, the presence of suppressive modifier genes in Iraqi or Ashkenazi Jews is quite feasible.
- Regarding the term Phenotype III suggested for the unaffected subjects with bi-allelic mutations, it seems that this is an oxymoron. When one uses the word phenotype, one means that the subject expresses clinical manifestations or symptoms. Therefore one cannot use this term for an *asymptomatic* group that has only positive genotype. If such a group really does exist, we suggest that it be termed Genotype X rather than Phenotype III.
- In order to further characterize the group of subjects with bi-allelic mutations but no symptoms, it would be worthwhile to look for these individuals in FMF families and to compare them with subjects in non-FMF families who bear two mutations with no symptoms. Such a comparison may lead to a better understanding as to why different subjects with similar genotype express the disease differently.
- Lastly, since a large proportion of FMF patients in Israel are Palestinian Arabs who bear two more frequent mutations, M680V and M694I, we suggest that they be included in the primary screening of FMF suspects in our Middle Eastern area.

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