Genotype-Phenotype Relation and Correlation in Familial Mediterranean Fever

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Familial Mediterranean fever (also known as recurrent polyserositis and periodic fever) is an autosomal recessive disease that affects populations surrounding the Mediterranean Sea. It is characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like erythema [1,2]. One of the most significant complications of FMF is amyloidosis, usually affecting the kidneys and resulting in renal insufficiency. The presentation of the disease and its severity vary [3]: one patient may have several attacks a month, while another may experience few attacks – if any – a year. Furthermore, there may be differences in clinical manifestations between FMF patients and even within the same patient at various periods during his or her lifetime.

Many years ago it was observed that FMF patients of North African origin displayed a more severe disease compared with those of Iraqi origin [4]. This observation was later confirmed by Pras et al. [5], who showed that Israel Iraqi Jews with FMF had lower severity scores of the disease compared with North African Jews.

The cloning of the gene responsible for the disease – MEFV – and the isolation of the mutations associated with the disease raised the possibility of matching the previous observations with genotype analysis of these patients [6,7]. Indeed, in the beginning, both consortia that isolated the MEFV gene noticed that FMF patients homozygous for the M694V mutation displayed a more severe disease than those who bear the V726A mutation and were "prone" to develop amyloidosis [6]. Furthermore, the finding that FMF patients with the V726A mutation did not have amyloidosis (in these preliminary studies) raised the possibility that it may have a "protective effect" against amyloidosis [6]. The fact that the mutation M694V was commonly found among patients of North African origin whereas the V726A was more common among Iraqi Jews supports the previous observation about the different severity of FMF in these populations. Later, numerous studies from France and from Israel confirmed this impression, claiming that patients homozygous for the M694V mutation had earlier onset of the disease, more severe attacks, higher frequency of joint involvement and higher risk of developing amyloidosis [8–12]. The explanation suggested that this mutation is at the pivotal point of exon 10, a coding area of the functional portion of the protein (pyrin, marenostrin). Mutations in another part of exon 10 or even in other exons such as E148Q, which is on the second exon, may not significantly affect the function of the protein and therefore will not cause severe disease, if at all [13]. This concept was placed in doubt following several studies from Turkey showing that in their populations FMF patients bearing different combinations of mutations had severe disease and also developed amyloidosis [14,15]. Thus, the popular concept of a clear genotype-phenotype correlation became equivocal.

In the present issue of *IMAJ*, Cattan et al. [16] analyzed 106 FMF patients of whom 59 were North African Jews and 47 were Armenians. They compared the distribution of MEFV mutations among the patients of this cohort and compared the severity of the disease between the two populations and among the various mutation combinations. As expected, they found that the mutation M694V was very common among North African Jews, either in the homozygous state or as heterozygotes. They again confirmed the observation that patients homozygous for M694V had more severe disease, regardless of their origin (Armenian or North African). Another finding was that FMF patients homozygous for the M680I or compound heterozygous (M694/M680I) had a severity of disease similar to those homozygous for M694V. Since there were only two patients homozygous for the M680I, this conclusion should be taken with caution. However, the fact that compound heterozygotes bearing the M694V mutation have a severe disease can be explained by the major contribution of this mutation to the damage of the gene. This observation may support the notion that low penetrant mutations may express severe disease when they are accompanied by the M694V mutation.

Thus, the controversial results in the various studies and the observation that patients with identical genotype have different expressions of the disease, even when they are from the same

FMF = familial Mediterranean fever

family, led investigators to look for other environmental and genetic modifiers. Indeed, many years ago, Schwabe and Peters [17] noticed that Armenian FMF patients residing in the United States did not develop amyloidosis, whereas those residing in Armenia did. This observation suggests that environmental factor(s) may play a role in the development of amyloidosis. A recent study by Touitou et al. [18] found that the presence of the major histocompatibility complex class I chain-related gene A (MICA) A9 in FMF patients homozygous for M694V mutation was associated with more severe disease. On the other hand, the presence of MICA A4 dramatically reduced the frequency of FMF attacks in patients with the same genotype [18]. This was the first study identifying a genetic modifier that may partially explain the variability of FMF manifestations.

Recently, Livneh et al. [19] noted that the presence of Behcet's disease intensifies the expression of FMF even in individuals bearing a single mutation. They suggested that FMF may be precipitated in carriers of a single mutated FMF gene by the presence of concomitant inflammatory disease. This idea was prompted by the observation of Cattan et al. [20] of a higher than expected association between FMF and inflammatory bowel disease, and that the bowel disease is more severe in FMF patients.

Thus, the general idea is that a concomitant inflammatory process may aggravate the expression of FMF and vice versa. Our data do not support this notion, and at least in cases of FMF and Behcet's disease we could not find support for a mutual effect of one on the other [21].

Regarding the question of amyloidosis induced by FMF, a study by Melikoglu and coworkers [22] revealed that one of the most predictive factors for this complication is a positive family history for amyloidosis. This may suggest either an environmental or a genetic cause in this process. However, research by Cazeneuve et al. [23] disclosed that the presence of the serum amyloid A (SAA1) alfa/alfa genotype of amyloidosis was associated with a sevenfold risk increase for renal amyloidosis in FMF patients compared with other SAA genotypes. This association was extremely marked in patients homozygous for the M694V mutation. Furthermore, these investigators found that the risk of male patients developing amyloidosis was fourfold higher than that for female patients. This association was particularly prevalent in patients not homozygous for the M694V mutation and was independent of the SAA1 allelic variation. These data suggest that susceptibility for amyloidosis in FMF is influenced by at least two independent factors of genetic origin – SAA gene and gender, which are independent of each other.

In conclusion, it seems that the issue of genotype-phenotype correlation is somewhat complex. FMF expression depends upon the composition of the mutations but is influenced by many genetic and environmental factors, some of which have been mentioned and many others that are still to be discovered. The isolation of the MEFV gene has opened new possibilities for investigating the etiology, pathogenesis, clinical expression, diagnosis, prognosis and treatment of FMF. Unfortunately, only scant progress has been made so far in understanding the etiology and pathogenesis of the disease. Regarding the clinical manifestations and prognosis, the genotype-phenotype correlation has provided some clues and uncovered other mysteries yet to be unraveled. It seems that the most important contribution of gene cloning to date is in the field of diagnosing atypical cases suspected of having FMF. Nonetheless, the diagnosis of this disease is still based on clinical grounds, since in many patients none of the known mutations is detectable and a wide differential diagnosis of other periodic diseases is opened [24]. It is hoped that in the years to come we will be more fortunate and that more genetic and molecular studies will uncover the secrets of this fascinating disease.

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