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Letter to the Editor

Complexity of familial Mediterranean fever genetics

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Dear Editor,

I have read the article entitled "Exon 2: Is it the good police in familial mediterranean fever?" by Bilge et al. (1) and would like to discuss the results of this study further in light of recent findings in this field.

Although classically proposed to be a recessively inherited monogenic disease (OMIM #249100), the genetics of familial Mediterranean fever (FMF) is known to be more complex than that of a simple Mendelian disease. Notably, 10%–20% of patients with FMF do not possess any identifiable *Mediterranean Fever* (*MEFV)* mutations even after complete sequencing, and up to 30% possess heterozygous mutations (2). Moreover, it was shown that dominantly inherited FMF exists (OMIM #134610) and some even consider that FMF is actually a dominantly inherited disease with variable penetrance (3). Approximately 40% of patients had either no or monoallelic mutations in *MEFV* in the present study (1). Genetic analyses were not based on sequencing in this study, but sequencing of the exons 2 and 10 or the whole *MEFV* gene is not expected to provide much additional information after proper mutation-specific assays, which typically include 90%–95% of mutations encountered in specific populations (2, 3). Epigenetic dysregulation of *MEFV* expression and mutations/polymorphisms in the genes encoding proteins associated with or regulating the metabolism of pyrin and other related proteins were speculated but could not be shown to explain this situation, particularly in the context of the recessive inheritance theory (3). Somatic mosaicism and microchimerism, shown to be causes of disease in other autoinflammatory and rheumatic diseases, may be the possible explanations for "mutation negative FMF" if dominant inheritance is considered. They are not detectable by conventional mutation analysis or sequencing techniques designed to detect germline mutations. Mosaicism and microchimerism have not been reported to be studied in FMF to date, but a case of FMF due to an acquired somatic mutation in *MEFV* was reported (4). Models of *MEFV*-knock-out and mutant *MEFV*-knock-in mice were unable to explain the genetic complexity of FMF in humans because the mouse ortholog of pyrin lacks the B30.2/SPRY domain where most of the pathogenic human mutations cluster (3).

Another point to be discussed is the pathogenicity of *MEFV* mutations. Almost all deletions, duplications, or insertions causing frameshift and nonsense mutations that result in early termination in any exon are likely to be pathogenic (5). Missense mutations that cause significant substitutions, such as charge changes in any exon, may also be pathogenic and associated with symptomatic FMF (see R39G, S242R, R354W, R501C, and T577N). Amino acid changes, including a minor substitution (e.g., valine to alanine at the 726th position) in a critical position may be clearly pathogenic. The founder mutations, such as M680I, M694V, and V726A, are located in exon 10, which encodes C-terminal B30.2/SPRY, the major interacting domain of pyrin. However, more than half of the amino acid changing mutations in exon 10 are not clearly or likely pathogenic (5). Therefore, it is not the exon but the exact position of a mutation and the resulting substitution and conformational change affecting the interaction of pyrin with other proteins that determines its pathogenicity (6).

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