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# Mutations/polymorphisms in a monogenetic autoinflammatory disease may be susceptibility markers for certain rheumatic diseases: lessons from the bedside for the benchside

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## ABSTRACT

*Certain vasculitides have an increased prevalence among patients with familial Mediterranean fever (FMF). Subsequently, it was noticed that patients with certain rheumatic diseases had an increased carrier rate for mutations in the MEFV gene including seronegative spondyloarthritis, Henoch Schönlein purpura, polyarteritis nodosa and some forms of juvenile idiopathic arthritis. Furthermore in populations where the disease is rare, certain polymorphisms have been associated with a severe inflammatory complication in arthritis. The effect of these polymorphisms are probably through the up-regulation of the innate immune system which serves as the initial response to the environmental trigger. It may be suggested for the aforementioned clinical associations that mutations/polymorphisms in the MEFV gene may well be susceptibility factors for the disease or a more severe course of the disease for a number of rheumatic diseases*

Diseases that do not demonstrate Mendelian inheritance but that are presumably dependent on interactions of multiple genes for disease occurrence have been defined to have a “complex mode of inheritance”. Many of the common diseases including a majority of rheumatic diseases are complex genetic trait diseases. Many gene associations have been described in diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and vasculitis however familial cases are rare (1-3). In the recent years advances in technology has enabled us to do elegant studies to identify genetic susceptibility factors in rheumatic diseases, especially rheumatoid arthritis. Genome wide association studies have identified a number of risk loci for RA including the HLA region, protein tyrosine phosphatase non-receptor type 22

(PTPN22), STA4 and the TRAF1/C5 loci (4, 5). Among these, PTPN22 has been associated with many autoimmune diseases including diabetes mellitus, JIA and systemic lupus erythematosus (SLE) (6). The association of PTPN22 was significant in many western populations that it was studied. On the other hand, a Japanese study showed that this polymorphism was not a significant risk factor in their RA patients thus highlighting the importance of ethnic differences in the genetic interactions underlying the rheumatic diseases (7).

Vasculitides are rarer than RA and genome wide association studies have not been yet performed in this group of patients. However, they have also been associated with a number of genetic polymorphisms. On the other hand, a certain (“MRL”) mouse model has provided some insights into occurrence of vasculitis. In an elegant review, Nose has suggested that (8) in studies of susceptibility loci to vasculitis in MRL mouse models, development of systemic vasculitis is a cumulative effect of multiple gene loci, each of which by itself did not have a significant effect to induce the related phenotype, thus indicating a polygenic system. Some of the susceptibility loci seemed to be common to those in other collagen diseases as well.

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in the Mediterranean Fever (MEFV) gene (9, 10). The identification of the genes and proteins involved in the autoinflammatory diseases have shed light to our understanding of the inflammatory pathway in general. The mutations of the MEFV gene are associated with increased IL-1beta production and an enhanced innate immune system response (11). In the last decade we and others have been involved in research regarding the clinical implications of the inflammation

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associated with mutations in the MEFV gene. FMF is an autosomal recessive disease and the patients have high acute phase inflammatory markers and attacks of manifest clinical inflammation (9, 10). One of the breakthrough findings was the increased inflammation in the carriers of MEFV mutation (12, 13). In fact the mean ESR and CRP levels were higher than normal in these carriers (12, 13). Furthermore we started to note that inflammatory diseases were increased among the carriers for MEFV mutations (14).

Certain rheumatic diseases have an increased prevalence among patients with FMF. We initially noted in small series that certain vasculitides were increased among these patients (13, 15). In both pediatric and adult series of Behçet's disease showed an increased frequency of MEFV mutations (in a single allele) suggesting that the mutated MEFV allele was acting as a susceptibility factor (16, 17). Finally in a multicenter study in Turkey in almost 3000 patients (with a significant percentage of children) we showed that indeed polyarteritis nodosa (24 patients, 0.9%) and Henoch-Schönlein purpura (HSP) (75 patients, 2.7%), Behçet's disease (14 patients, 0.5%), seronegative spondyloarthritis (64 patients, 2.3%) and chronic inflammatory arthritis (37 patients, 1.3%) had a higher frequency as expected in the normal population (18). In a collaborative study with Israel we also suggested that patients with FMF and PAN had some specific features (15).

Subsequently we started to realize that patients with certain rheumatic diseases had an increased carrier rate for mutations in the MEFV gene. In a pediatric cohort we showed that the mutated MEFV allele frequency among patients with rheumatic diseases was significantly higher than those in controls ( $p < 0.05$ ) (13). Studies from Israel showed an increased rate of MEFV mutations among seronegative spondyloarthritis and a more severe RA among carriers for these mutations (19, 20). Brik *et al.* (21) showed increased MEFV mutations among children with HSP. Subsequently we showed a high carrier rate of MEFV mutations among childhood PAN patients in Turkey (22).

All these values reached statistical significance and were from two countries with a very high carrier rate for MEFV mutations. However, there were studies from other ethnic groups as well.

E148Q is a mutation in the MEFV gene associated with a low penetrance. In fact some consider it to be a polymorphism since it has such a high frequency in our populations reaching 17/100 in the Turkish population (23). On the other hand in a recent study from Japan E148Q was the most frequent mutation associated with the FMF phenotype among their 14 patients (24). We have also described an E148Q homozygote patient with severe phenotype who responded to colchicines (25). An interesting report came from the group of Dr Hawkins where they showed that three of their patients who developed amyloidosis secondary to inflammatory arthritis were carriers for E148Q although none of the 76 healthy British controls had E148Q (26). Furthermore among the 5 Indian patients who developed amyloidosis secondary to inflammatory arthritis 3 were homozygous and one was heterozygous for E148Q. The authors suggested that general upregulation of the inflammatory response in individuals with pyrin Q148 was the most likely explanation for their increased susceptibility to AA amyloidosis (26) or more intense inflammation.

On the other hand, in a recent study Ustek *et al.* (27) have observed a genetic association between 3'-UTR SNPs and the FMF patients with no coding region mutations and have suggested a role for 3'-UTR sequences in the regulation of MEFV expression. Subsequently, in a large group of JIA patients in the UK, Day *et al.* (28) showed significant associations with two autoinflammatory genes in the subgroup of patients with psoriatic JIA (MEFV SNP rs224204 and NLRP3 SNP rs3806265). The authors concluded that the findings supported the use of monogenic loci as candidates for investigating the genetic component of complex disease and provide preliminary evidence of association between SNPs in autoinflammatory genes and psoriatic JIA and that their findings raised the interesting possibility of a shared disease mechanism between the

hereditary periodic fever syndromes and psoriatic JIA (28). Finally in a recent study we showed that MEFV mutations were increased among patients with systemic JIA (29). Systemic JIA is now regarded as a polygenic autoinflammatory disease (30). We thus suggested that mutations in the gene causing a monogenic autoinflammatory disease, was a susceptibility factor for a polygenic autoinflammatory disease, at least in a Turkish cohort (29).

Ethnic factors are involved in rheumatic diseases and there may be differences in the SNP associations in different populations. We suggest that the aforementioned clinical associations all of which reach substantial significance suggest that mutations/ polymorphisms in the MEFV gene are susceptibility factors for the disease or a more severe course of the disease for a number of rheumatic diseases – at least in the eastern Mediterranean population. These mutations are not specific to one disease similar to the nonspecific effect of PTPN22 in a number of autoimmune diseases. The effect of these polymorphisms is probably through the upregulation of the innate immune system which serve as the initial response to the environmental trigger. Further studies need to elucidate if there are shared environmental triggers for the diseases that are increased. It is again noteworthy that MEFV mutations have never been associated with autoimmune diseases. We have suggested that the increased CRP and SAP in these individuals offers an increase clearance of autoantibodies and hence SLE or other strictly autoimmune diseases have not been associated with MEFV mutations (25). McDermott (31) has recently suggested that diseases should be categorized ranging from autoimmune to autoinflammatory ones, where FMF is a classic example of an autoinflammatory disease with no autoimmunity. The mutations in the MEFV gene may well act as susceptibility factors the group of diseases with autoinflammatory component, at least through the state of a more intense inflammatory response. Whether polymorphisms in the autoinflammatory disease genes will serve as susceptibility factors in other populations awaits more studies.

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