SIR, We read with interest the letter by Standing et al. [1] on a case of FMF complicated by PAN and Budd-Chiari syndrome (BCS). This case deserves special interest as the authors claim a pathophysiological association of FMF not only with PAN but also with BCS. The FMF–PAN association has already been described in the literature [2]. However, in this letter, Standing et al. [1] claim association of BCS with both the two other entities, namely FMF and PAN. We note that, in this case, the first well-documented medical problem of the patient is BCS. Thrombotic tendency predisposed by the methylenetetrahydrofolate reductase mutation documented might suffice for a BCS occurring; however, the case was only heterozygote and homocystein status is not reported. Furthermore, the case also developed pain of the abdomen, myalgias, anorexia and night sweats. According to Standing et al. [1], these symptoms indicated FMF; a favourable response to colchicine was considered as pointing to FMF diagnosis. They claim that this diagnosis is further supported by E148Q homozygosity of the Mediterranean Fever gene.

We note that, given the anti-inflammatory action of colchicine, a favourable non-specific clinical response must be expected on practically every inflammatory condition and not only in auto-inflammatory entities as FMF. Therefore, if other criteria are not met, the favourable response of colchicine per se is not a strongly supported argument. Furthermore, if the MEFV gene is involved in modifying other diseases [3] then a favourable effect of colchicine on them sounds reasonable. As for the role of E148Q homozygocity in causing FMF phenotype, this still remains rather controversial and the results are inconclusive [4]. First, one should take into account that homozygotes for FMF mutations are not all symptomatic and this refers not only to E148Q mutations [5]. Racial parameters and the putative interaction with other genetic elements must be considered before any association. Documentation of the E148Q mutation and distinction from E148V mutation depends on the restriction enzyme applied in testing and the relevant banding pattern that must be taken into account [6].

To the best of our knowledge, coagulation tendency is not an established complication of FMF, although several single cases are reported in the literature [7]. The role of the auto-inflammatory process in coagulation may sound reasonable, but it merits further investigation. Before well-designed clinical studies are conducted, one must be cautious in considering such a coincidence as pointing to underlying association. The main reason for reluctance is that molecular testing for these putative markers is expensive and not always available. Before accepting the rationality of an association of MEFV mutations with other entities such as inflammatory diseases and/or thrombotic tendency, we need further data on relevant populations. It is worth noting that, recently, wide genome association studies (WGAS) conducted on diseases that have been associated with MEFV mutations, such as Behçet’s [8], Crohn’s disease [9] and ulcerative colitis [10], have not included MEFV-associated markers among the genome areas tested. In this context, WGAS studies encompassing MEFV within the areas under investigation must be encouraged.

Disclosure statement: The authors have declared no conflicts of interest.

Kostas Konstantopoulos1 and Alexandra Kanta1
1First Department of Medicine, Athens University Medical School, Athens, Greece.
Accepted 18 March 2011
Correspondence to: Kostas Konstantopoulos, First Department of Medicine, Athens University Medical School, 75 M Asias Street 11527 Athens, Greece.
E-mail: kkonstan@med.uoa.gr

References


Rheumatology 2011;50:1349–1350
doi:10.1093/rheumatology/ker170
Advance Access publication 17 May 2011

Comment on: Familial Mediterranean fever caused by homozygous E148Q mutation complicated by Budd–Chiari syndrome and polyarteritis nodosa: reply

Sr., We thank Konstantopoulos and Kanta [1] for comments on our case report [2]. We agree that E148Q homozygosity does not necessarily generate a FMF phenotype in all cases, and racial influence may be an important consideration in this respect. E148Q mutations may have a greater pathogenicity in non-Mediterranean Caucasians where this variant is rare, and in our case the compelling clinical features, E148Q homozygosity and dramatic response to colchicine led us to the diagnosis of FMF. In our experience, colchicine has little or no therapeutic efficacy for systemic vasculitides such as classical PAN (when not associated with FMF), which usually require CSs and cytotoxic immunosuppression [3].

We are increasingly interested in the association between inflammation and thrombosis, particularly the increasingly described thrombotic complications associated with systemic vasculitis [4–6]. FMF may be one of many potential genetic factors predisposing to vascular inflammation [7]. Vasculitis in this context could increase thrombotic risk via several mechanisms including endothelial injury and tissue factor exposure on endothelial cells and monocytes [8], platelet activation [9], inhibition of thrombolytic pathways [10]; structural arterial injury including aneurysm formation and/or stenoses resulting in altered shear stress forces and flow dynamics [11]; or other as yet undefined mechanisms. We are aware of two cases of co-occurrence of Budd–Chiari syndrome and FMF [12]; and other thrombotic complications in patients with FMF, including E148Q homozygotes [13–18]. We agree that the mechanism(s) of this increased prothrombotic tendency deserve further exploration, an area of ongoing research in our group.

We were also interested in the findings of the first Whole Genome Association Studies (WGAS) in Behçet’s disease and IBD, which so far do not indicate an association with MEFV [19–21]. Since in each of these studies no association with the region of MEFV (C16p13.3) was detected, this was not selected for fine-mapping in any of the follow-up cohorts. These WGAS studies at face value could suggest that the previously reported cases of MEFV mutations in Behçet’s disease or IBD occurred by chance. However, it is likely that these WGAS are under-powered to detect association of these disease states with infrequently occurring mutations, and that the ethnicity of the populations being examined is of considerable relevance in this context: we note that the WGAS of Behçet’s disease was in Japanese and Korean patients [19]; ulcerative colitis in northern and southern Europeans (including Jewish) patients [20]; and Crohn’s disease in US, Canadian (including Jewish), Belgian, French and British patients [21]. Another WGAS of Behçet’s disease in Turkish patients again did not demonstrate any association with MEFV, although it only included 152 patients and 170 controls [22]. We suggest, therefore, that these studies do not yet definitively exclude MEFV as a genetic predisposing factor for these diseases in some individuals.

Disclosure statement: The authors have declared no conflicts of interest.

Ariane S. I. Standing1, Despina Eleftheriou1, Helen J. Lachmann2 and Paul A. Brogan1

1Department of Rheumatology, Institute of Child Health and 2National Amyloidosis Centre, Royal Free Hospital, London, UK.

Accepted 24 March 2011
Correspondence to: Ariane S. I. Standing, Department of Rheumatology, Institute of Child Health, 30 Guildford Street, London WC1N 1EH, UK. E-mail: a.standing@ich.ucl.ac.uk

References


