

Saturday night fever: bizarre recurrence of fever attacks in a patient carrying a mutation in both the *MEFV* and *TNFRSF1A* genes

Sirs,

We read with interest the article by Granel *et al.* (1) who described an overlap syndrome between familial Mediterranean fever (FMF) and tumor necrosis factor (TNF)-receptor associated periodic syndrome (TRAPS) in a patient carrying a mutation in both the *MEFV* and *TNFRSF1A* genes. In his report Granel advocated the importance of a better evaluation of the role of the R92Q mutation in *TNFRSF1A* in patients with FMF and we would like to present some additional data. We report here another case of mutations in the *MEFV* and *TNFRSF1A* genes occurring together in a single patient.

FMF is an autosomal recessive autoinflammatory disease caused by mutations in the gene *MEFV* and characterized by recurrent, self-limited febrile episodes with serositis, synovitis and, occasionally, skin involvement; attacks usually last less than 3 days (2). The diagnosis of FMF is based on clinical criteria, family history, and the patient's response to colchicine; the demonstration of *MEFV* mutations is necessary to establish a definite diagnosis in suspected patients (3). Furthermore, genotyping may help to pin down the diagnosis in the case of atypical clinical signs and late onset (4).

TRAPS is an autosomal dominant autoinflammatory condition caused by mutations in the gene *TNFRSF1A* encoding the 55-kD receptor for tumor necrosis factor- α (TNF- α) and characterized by febrile episodes often lasting more than 7 days that can include abdominal pain, pleurisy, myalgia, conjunctivitis, periorbital oedema, skin rashes, and arthritis. Attacks usually last more than 7 days and fail to respond to colchicine, but are responsive to steroids (5).

A 17-year-old female came under our observation for recurrent attacks of high fever (38°–39.5°C) accompanied by diffuse abdominal pain, localized posterior thoracic wall pain, and arthritis with effusion in the right knee. She complained of weekly flare-ups over the past 3 years, usually at the weekends, and mainly but not only during cold weather periods. She did not report any skin rashes and the duration of the symptoms was 1 to 2 days.

The fever attacks were responsive to colchicine (administered for 40 days with rapid and dramatic improvement in her clinical status), but resistant to steroids and paracetamol.

Circulating levels of serum amyloid A (SAA) (118.00 mg/L; normal value <10.0), interleukin-6 (IL-6) (42.2 pg/ml; n.v. <15) and interleukin-18 (IL-18) (384.98 pg/ml;

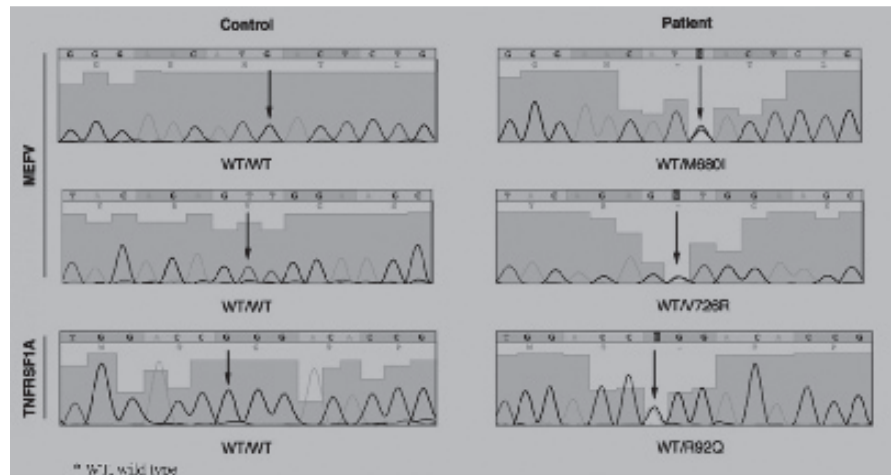


Fig. 1. DNA sequencing demonstrating the M680I, V726R and R92Q mutations in our patient; no mutation was found in healthy donors.

n.v. <180.00) were elevated, while TNF- α (1.0 pg/ml; n.v. <15) and interleukin-1 β (IL-1 β) (1.5 pg/ml; n.v. <15) were normal. On the basis of the diagnostic criteria (3) the patient was suspected of having FMF and regular colchicine treatment was started. She was analysed for mutations in the *MEFV*, *CIAS1* and *TNFRSF1A* genes. DNA analyses by PCR with specific primers, followed by sequencing on PCR products from both the patient and healthy controls identified M694I and V726R mutations in *MEFV* and a low penetrance heterozygous mutation R92Q in *TNFRSF1A* (Fig. 1).

She was diagnosed with an overlap syndrome between FMF and TRAPS and treatment with colchicine was continued at a dose of 1 mg daily, which brought about a resolution of the fever attacks and painful symptomatology (thoracic, abdominal and articular pain) after 1 month and led to marked improvement in her pro-inflammatory cytokine circulating levels: 2 months after starting treatment with colchicine, SAA levels were normal and IL-6 and IL-18 were significantly decreased.

A wide range of studies have shown that heterozygous carriers of *MEFV* mutations can be symptomatic and suffer from fever attacks and serositis (6, 7). Even asymptomatic *MEFV* heterozygotes have elevated acute phase proteins, such as CRP and SAA, compared to wild type subjects (8). Numerous studies demonstrate that the FMF phenotype is controlled by a number of factors: the *MEFV* itself, other genes, the patient's sex, and hitherto undetermined population-specific factors (6, 7).

The R92Q mutation is described as a low penetrance mutation, and TRAPS patients with the R92Q mutation present less typical manifestations (9). FMF patients with a poor response to colchicine, such as the one Granel describes, have been reported even in the absence of TRAPS mutations (2).

In our patient the duration of the fever

attacks (no more than 2 days), the high levels of SAA, which are rarely associated with R92Q mutations, the responsiveness to colchicine, the monoarthritis, and the early onset of symptoms are all features supporting the FMF diagnosis (2), while the associated R92Q did not seem to influence the clinical presentation and management of the disease. It is also possible that symptoms associated with the R92Q mutation, and the subsequent modification of the clinical picture, may develop later (5).

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Reply

Sirs,

We thank Cantarini *et al.* for their report on another instance of mutations in *MEFV* and *TNFRSF1A* occurring together in a single

patient. In their case, concerning a 17-year-old female of presumed Italian origins, the presentation was typical of familial Mediterranean fever (FMF) with recurrent attacks of fever, diffuse abdominal and thoracic pain, arthritis of the knee, onset of symptoms before the age of 20 years, and duration of flares less than 5 days. Moreover, the fever attacks were responsive to colchicines but were steroid-resistant. In their observation, no clinical signs could have evoked the diagnosis of tumor necrosis factor [TNF-receptor associated periodic syndrome (TRAPS)], contrary to our case report in which the symptoms responded poorly to colchicines but regressed with steroids (1).

In the patient described by Cantarini *et al.*, genetic analysis revealed M694I and V726R mutations in *MEFV* – both classic mutations observed in Italian patients (2) – associated with a low penetrance heterozygous R92Q mutation in *TNFRSF1A*. In fact, their observation really raises the question of the role of R92Q mutation in *TNFRSF1A*: Could it represent a modifying genetic factor for FMF, as suggested for the SAA1 loci (3)? At present it is impossible to answer this question. To better understand the role of the R92Q mutation in *TNFRSF1A* in

FMF, this mutation should be analyzed not only in FMF patients with an atypical presentation and a poor response to colchicines, or with only one *MEFV* mutation, but – as suggested by the case reported by Cantarini *et al.* – it should also be screened in typical FMF patients. Until large-scale studies are undertaken, the publication of isolated case reports is welcome.

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