EXTENDED REPORT

Clinical impact of *MEFV* mutations in children with periodic fever in a prevalent western European Caucasian population

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ABSTRACT

Objective To evaluate the actual impact of *MEFV* mutations on clinical manifestations associated with fever attacks in Caucasian children with periodic fever.

Methods 113 children carrying *MEFV* mutations (44 with mutations in two alleles, 69 heterozygous) and 205 children negative for mutations in genes associated with periodic fevers were analysed. The following groups of patients were considered: patients carrying two high penetrance mutations (M694V, M694I, M680I); one high, one low penetrance mutation; two low penetrance mutations; one high penetrance mutation; one low penetrance mutation; genetically negative patients.

Results Patients with two *MEFV* mutations displayed a shorter duration of fever attacks and higher prevalence of a positive family history than patients carrying one *MEFV* mutation and genetically negative patients. Severe abdominal pain, chest pain and pleurisy were also more frequent in patients with two *MEFV* mutations compared with children with one *MEFV* mutation and genetically negative patients. Conversely, a higher frequency of exudative and erythematous pharyngitis, enlargement of cervical lymph nodes, aphthous stomatitis and non-specific skin rash was observed in genetically negative patients and, to a lesser extent, in patients with one *MEFV* mutation. The frequency of 'familial Mediterranean fever (FMF)-like symptoms' decreases from patients carrying two high penetrance mutations towards patients with a single low penetrance mutation with an opposite trend for 'periodic fever, aphthous stomatitis, pharyngitis, adenitis-like symptoms'.

Conclusions This clinical observation supports recent findings contrasting the notion of FMF being a pure autosomal recessive disorder associated with recurrence of mutations leading to loss of protein function. A dosage effect could be invoked, giving rise to symptom onset even in the presence of one wild-type allele.

First described as an autonomous clinical entity in 1945,[1] familial Mediterranean fever (FMF) is characterised by recurrent, self-limited attacks of fever, serosal inflammation, arthritis and cutaneous involvement. Linkage analysis[2] and positional cloning based on an autosomal recessive model of inheritance allowed two independent consortia to identify mutations in a single gene responsible for the disease.[3 4] The gene, denoted *MEFV* for mediterranean fever, encodes a protein product alternatively termed pyrin or marenostin. Mutations of the *MEFV* gene are present at a very high frequency in non-Ashkenazi Jews, Arabs, Turks, Armenian and in North-African populations.[5] FMF is also present, but with a lower prevalence, in other populations living around the Mediterranean basin[6 7] and along the silk road.[8] Five main mutations of *MEFV* (M680I, M694V, M694I and V726A on exon 10 and E148Q on exon 2) are responsible for more than 85% of FMF patients.[9] Further sequencing of *MEFV* in patients and families beyond those studied in the initial linkage analysis, showed that the relation between genotype and phenotype was more complex. Although most FMF patients inherit two pyrin mutations recessively, one third of patients with compatible clinical phenotype and optimal therapeutic response to colchicine display only a single *MEFV* mutation. In particular, some *MEFV* variants (such as M694V, M694I and M680I), usually associated with a more severe disease course, may determine a disease phenotype even when present in a heterozygous state.[10] On the other hand, a high proportion of asymptomatic carriers is also observed in different populations. To complicate this picture further, some common *MEFV* variants (eg, V726A and E148Q) are either characterised as low penetrance genes or as polymorphic variants depending on the populations.[11 12] This study analyses the impact of different *MEFV* genotypes on the clinical picture in children with periodic fever, using genetically negative periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) patients as disease controls. Our data show that the number and penetrance of *MEFV* mutations are able to influence the clinical picture towards a typical FMF-like phenotype in line with the hypothesis of a gain of function of pyrin mutations.[13]

PATIENTS AND METHODS

Starting from 2002, a nationwide laboratory facility for the genetic diagnosis of autoinflammatory disorders in children was established at the Gaslini Institute in collaboration with the Ospedale Galliera in Genoa, Italy, providing the possibility to perform the molecular analysis of the three genes (*MEFV*, *MVK* and *TNFRS1A*) responsible for the inherited periodic fever in patients with suspected

autoinflammatory syndrome.[14] The extracellular region of the p55 tumour necrosis factor receptor (from exon 1 to exon 6) of the *TNFRSF1A* gene, the 10 coding exons (from 2 to 11) of the *MVK* gene and exons 2, 3, 5 and 10 of the *MEFV* gene were analysed by means of denaturing high-performance liquid chromatography and DNA sequencing of amplimers displaying anomalous chromatographic patterns, as previously described.[14–16] Whenever possible, analysis of both parents was undertaken for children displaying a compound heterozygous state for *MEFV* in order to verify the transmission of one mutated allele from each parent. Similarly, the search for rare *MEFV* mutations in other exons was performed in heterozygous patients. For each patient detailed clinical information about family and personal history, prevalence and frequency of the clinical manifestations associated with fever episodes had been collected by means of a standardised questionnaire.[14] The presence of abdominal pain is commonly observed in children with periodic fever.[14] However, the frequency and severity of this clinical manifestation is extremely variable. The presence of a clear peritonism, which is a distinctive manifestation of FMF, is rather unusual in the early paediatric age range that was the target population of the present study.[17] However, long-lasting episodes of abdominal pain recurring in the large majority of fever attacks are strongly characteristics of FMF.[14 17] Conversely, abdominal pain of short duration and low severity can be sporadically observed in patients with periodic fever not carrying mutations of the three genes and in PFAPA patients.[14 18] For this reason we classified the abdominal pain as severe (long-lasting and frequent) or mild (of short duration and observed in some fever attacks only). The study was approved by the ethical board of G Gaslini Institute.

Complete clinical information regarding 386 consecutive children with periodic fever screened for all three genes was available. In 181 patients at least one mutation for one of the genes analysed was found. One hundred and thirteen patients were positive for mutations of the *MEFV* gene. Two hundred and five children with a clinical picture consistent with periodic fever, but negative for mutations in the three genes studied were considered as 'genetically negative' periodic fevers. One hundred and thirty-one of them (64%) were positive for PFAPA criteria.[19] Sixty-eight children displayed mutations for the other two genes (38 for *MVK*, 30 for *TNFRSF1*, respectively) and were excluded from the study. Paediatric criteria for FMF were recently developed[17] and validated.[20] These criteria include a set of five clinical variables: fever episodes, abdominal pain, chest pain and oligoarthritis (of 6–72 h duration) and a positive family history for FMF. Patients were considered positive if satisfying two or more of the five proposed criteria.[17] The vast majority of patients (97.1%) were western European (Italian origin). Three were Arab or North-African, two mixed Caucasian/North African, one Brazilian, one Sephardic Jewish.

Statistical analysis

Group comparisons were carried out using a non-parametric Mann–Whitney U test for continuous variables and a Fisher's exact test for dichotomous variables. The prevalence of symptoms was compared between negative, positive for one and two mutations using a χ^2 test for trend.

RESULTS

Clinical phenotype of *MEFV* mutated and PFAPA patients

Among the 113 patients positive for mutations of the *MEFV* gene, 44 were homozygous or compound heterozygous, whereas 69 displayed one single mutation or two mutations in *cis* (table 1). E148Q was the most common mutation found (26%), followed by M680I (18%), M694V (18%) and V726A (12%).

Table 1 *MEFV* mutations found in 113 consecutive children with periodic fever

Homozygous (n=18)	Compound heterozygous (n=26)	Heterozygous (n=69)
	M694V V726A (6)	E148Q (27)
	E148Q M694V (4)	M694V (14)
	M680I V726A (4)	K695R (7)
M680I M680I (9)	M694I M694V (2)	M680I (5)
M694V M694V (4)	M680I R761H (2)	P369S R408Q* (4)
L110P L110P (1)	E148Q R761H (2)	A744S (4)
E148Q E148Q (1)	(4)	V726A (3)
V726A V726A (1)	M680I M694V (1)	Y232X (1)
R761H R761H (1)	E148Q S339F (1)	L372P (1)
P369S/P369S + R408Q/R408Q (1)	E148Q V726A (1)	V487M (1)
	E148Q A744S (1)	R717L (1)
	E225G M680I (1)	R761H (1)
	S108R V726A (1)	

*Mutations in *cis*.

Forty out of 46 (87%) patients carrying two *MEFV* mutations were positive for paediatric FMF diagnostic criteria that were also positive in 31/67 (46%) of patients carrying one *MEFV* mutation and in 34/205 (16.5%) genetically negative patients. As the aim of the study was to verify the impact of the *MEFV* genotype on clinical manifestations independently from the classification resulting by the application of FMF clinical criteria, patients were grouped according to genetic analysis. The main clinical features and symptoms associated with fever attacks for each subgroup of patients are reported in table 2. We first analysed the difference in the clinical presentation among patients carrying two *MEFV* mutations, patients with a single mutation and control PFAPA patients. A significant heterogeneity among the three subgroups was found for a number of clinical variables (table 2).

Patients with two *MEFV* mutations displayed a later disease onset with higher prevalence of a positive family history compared with patients carrying one *MEFV* mutation and PFAPA patients (table 2). Post-hoc analysis showed that patients with two *MEFV* mutations displayed a shorter duration of fever attacks, a higher frequency of severe abdominal pain, chest pain and pleurisy (figure 1) compared with the other two subgroups. Conversely, a higher frequency of exudative pharyngitis, enlargement of cervical lymph nodes, non-specific skin rash (figure 1), aphthous stomatitis erythematous pharyngitis and mild abdominal pain (not shown) was observed in PFAPA patients and, to a lesser extent, in patients with one *MEFV* mutation.

Influence of number and penetrance of *MEFV* mutations on the clinical phenotype

As stated in the introduction, even though FMF is classically considered an autosomal recessive disease, the presence of a single mutation is often associated with a classic FMF phenotype, including the response to colchicine. This is particularly true for high penetrance mutations, such as M694V, M680I and M694I.[10] Based on these considerations we further analysed possible differences in patients' phenotype according to six different genotypes: patients carrying two high penetrance mutations

Table 2 Clinical features of the 318 paediatric patients with periodic fever according to different genotypes

	MEVF			
	Two mutations	One mutation	Negative	p Value*
No of patients	44	69	205	
Age at onset (months; mean±SD)	48±41	30±36	41±50	0.05
Disease duration at screening (years; mean±SD)	9±6.8	5.1±6.2	3.6±3.4	NS
Duration of fever episodes (days; mean±SD)	3±1.6	5.0±6.9	6.0±7.1	0.02
Positive family history (%)	33	25	12	0.01
Severe abdominal pain (%)	82	33	32	<0.001
Mild abdominal pain (%)	5	35	20	<0.001
Chest pain (%)	41	7	6	<0.001
Pleurisy (%)	20	3	2	<0.001
Arthritis (%)	13	9	12	NS
Arthralgia (%)	43	43	47	NS
Myalgia (%)	28	19	39	0.009
Rash† (%)	7	26	26	<0.001
Conjunctivitis (%)	7	15	19	NS
Exudative pharyngitis (%)	26	51	52	0.005
Erythematous pharyngitis (%)	30	60	69	<0.001
Enlarged cervical lymph nodes (%)	22	51	71	<0.001
Painful cervical lymph nodes (%)	15	28	35	0.002
Oral aphthosis (%)	18	25	43,9	<0.001
Headache (%)	52	37	45	NS
Splenomegaly (%)	9	12	14	NS
Diarrhoea (%)	37	48	27	0.005
Vomiting (%)	33	40	31	NS
Erysipeloid rash (%)	0	6	2.4	NS
Periorbital oedema (%)	0	9	9	NS

*p Values were assessed by a χ^2 test for heterogeneity.
†Non-specific rash (urticarial, erythematous, maculopapular), in at least one occasion.
NS, not significant.

(M694V, M694I or M680I); patients carrying one high and one low penetrance (other than M694V, M694I and M680I) mutation; patients carrying two low penetrance mutations; patients carrying one high penetrance mutation; patient carrying one low penetrance mutation; genetically negative patients. The distribution of the clinical manifestations associated with fever episodes in the different subgroups is shown in supplementary table SI (available online only). As shown in figure 2, we found a significant heterogeneity among the six subgroups, with a clear trend for the frequency of 'FMF-like symptoms' to decrease from patients carrying two high penetrance mutations towards patients with a single low penetrance mutation and genetically negative patients with a converse increase of 'PFAPA-like symptoms' and non-specific skin rash. This behaviour was even more evident for 'PFAPA-like symptoms' when the 131 genetically negative patients and positive for PFAPA criteria were analysed (see supplementary figure S1, available online only). These findings were consistent with the different rate of patients carrying *MEFV* mutations positive for PFAPA criteria, which ranged from 0 (in patients carrying two high penetrance mutations) to 56% of patients with one low penetrance mutation (see supplementary figure S2, available online only).

DISCUSSION

In the present study we analysed the actual relevance of the different *MEFV* genotypes in children with periodic fever sharing a highly prevalent Italian Caucasian background.

Data from our study shed some new light on the actual contribution of *MEFV* mutations to the definition of the 'FMF phenotype' in the paediatric age range, in which PFAPA and other causes of idiopathic periodic fevers are most frequently observed. Indeed, the presence of at least one high penetrance mutation in patients carrying two *MEFV* variants identifies a subgroup of patients that displays a clearly defined clinical phenotype characterised by a significantly higher incidence of severe abdominal pain, chest pain, pleurisy and short fever attacks and by a lower incidence of other less specific manifestations

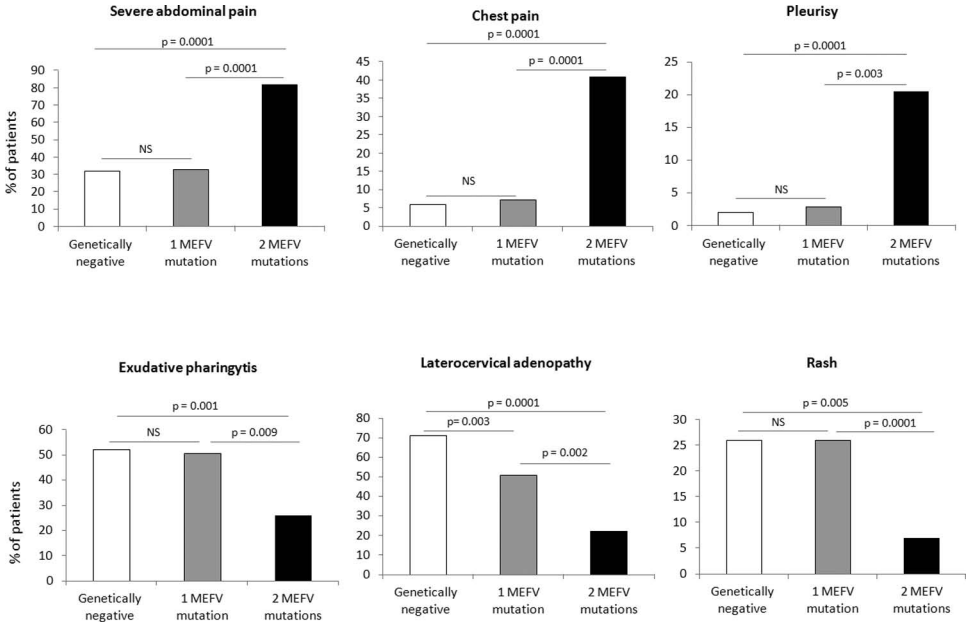

Figure 1 Prevalence of the clinical manifestations associated with periodic fever among patients carrying two MEFV mutations, patients heterozygous for *MEFV* and patients negative for genes associated with periodic fever. p Values were assessed by Pearson $\chi 2$.

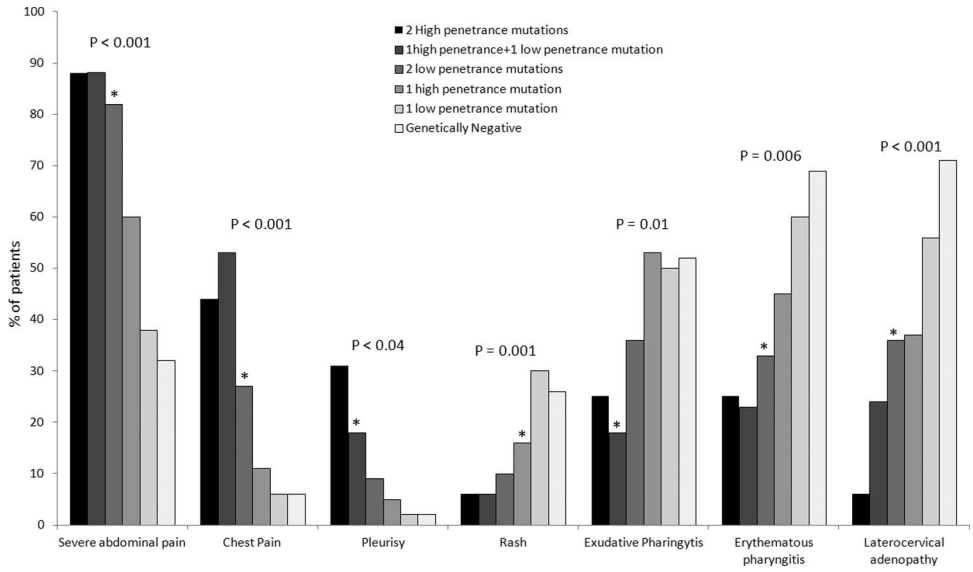

Figure 2 Prevalence of the clinical manifestations associated with fever attacks in patients with different *MEFV* genotypes (see text) and in children with periodic fever negative for mutations of *MEFV*, *MVK* and *TNFSRF1A* genes. p Values were assessed by a χ^2 test for trend. For each clinical manifestation, asterisks identified the subgroup of *MEFV*-positive patients presenting a significant difference with genetically negative patients (Pearson χ^2).

such as those related to PFAPA (pharyngitis, enlargement of cervical lymph nodes, aphthous stomatitis) and non-specific skin rash, which is rather unusual in FMF. In contrast, children with periodic fever heterozygous for *MEFV* display an intermediate phenotype with a lesser prevalence of typical 'FMF-like' clinical manifestations and a higher degree of overlap with the PFAPA-like phenotype, as recently observed in a study from Israel.[21] Notably, in their study, Berkun *et al*[21] showed a high prevalence of the high penetrance mutation (M694V) in patients presenting a typical PFAPA-phenotype, most of them not responding to a colchicine trial.[21] Interestingly, the clinical PFAPA phenotype in *MEFV* mutations carriers was characterised by shorter fever episodes and less oral aphthosis than in PFAPA patients without *MEFV* mutations.[21] In our study more that 50% of patients carrying one *MEFV* mutation did not fulfil the paediatric criteria for FMF, while an equivalent percentage was positive for PFAPA criteria. It is therefore conceivable that a relevant proportion of carriers of *MEFV* mutations, especially those with only one allele involved, should be considered to be affected by PFAPA, rather than FMF. The study on the long-term follow-up of these patients (including the response to different treatments) is ongoing. These observations confirm the challenges in interpreting genetic results in children with periodic fever, and raises the issue of the actual pathogenic relevance of a single *MEFV* mutation.[10 22] The early studies investigating the functional role of pyrin suggested its possible regulatory role on the NLRP3 inflammasome, a cytoplasmatic multiprotein complex that plays a crucial role in the production and secretion of pro-inflammatory cytokines, such as interleukin 1β.[23–25] Based on the above-mentioned observations it was postulated that mutations of pyrin could induce a loss of function of the protein, in line with the autosomal recessive pattern of inheritance of the disease. However, the use of different experimental approaches in subsequent studies have showed that pyrin interacts with other cytoplasmatic proteins (such as ASC and PSTPIP1) in a tri-molecular complex that is able directly to recruit and activate caspase 1, which is responsible for the secretion of the active form of interleukin 1β.[26] A recent study on a FMF knock-in mouse model has provided further evidence of the hypothesis that mutations of the *MEFV* gene could lead to a gain of function of the pro-inflammatory pyrin protein, independently of the activation of the NLRP3 inflammasome.[13]

In the present study the prevalence of 'FMF-associated clinical manifestations' displayed a clear 'dose effect' with *MEFV* genotypes, increasing from genetically negative patients to those carrying two high penetrance *MEFV* mutations, and showing that the actual contribution of *MEFV* mutations to a disease phenotype is proportional to the severity of the genotype.[22] The phenotype–genotype correlation thus drawn also prompts us to reason about the FMF mutation effects and mode of inheritance of FMF disease. According to present observations and data already reported,[10] the actual picture is no longer consistent with the notion of FMF being a pure autosomal recessive disorder associated with recurrence of mutations leading to loss of protein function. Indeed, a dosage effect could be invoked, giving rise to symptom onset even in the presence of one wild-type allele. In heterozygote patients the clinical severity would then be dependent either on the kind of mutation (low vs high penetrance), on possible dominant negative or gain of function effects exerted by specific severe mutations or, finally, on variants of still unidentified modifier genes.[27##]

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