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Familial Mediterranean fever is no longer a rare disease in Italy

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder, characterised by short, recurrent attacks of fever with abdominal, chest or joint pain and erysipelas-like erythema. It is an ethnically restricted genetic disease, found commonly among Mediterranean populations, as well as Armenians, Turks, Arabs and Jews. Traditionally, Italians have been considered little affected by FMF, despite the geographical position of Italy (northern Mediterranean basin) and the migratory changes in its population. The objective was to characterise the demographic, clinical and genetic features of FMF in Italy. Patients of Italian origin were recruited from those referred to Italian-French medical centres for FUO (Fever of Unknown Origin) or 'surgical' emergencies; clinical history, genealogy and physical examination were recorded; all other possible infectious, neoplastic, auto-immune and metabolic diseases were excluded. Mutational analysis of the gene responsible for FMF (MEFV on 16p13.3) was performed, after which geno-phenotypical correlations were established. Italian FMF patients, 40 women and 31 men, aged from 3 to 75 years, have shown all the clinical manifestations indicative of FMF described in the literature, but with a lower incidence of amyloidosis. The genetic tests have been contributive in 42% of cases. The frequency of each different mutation has been similar to that found in a series of 'endemic' countries. The geno-phenotypical correlations have suggested the existence of genetic and/or environmental modifier-factors. Among Italians FMF seems to be more frequent than was believed in the past. The data presented are consistent with their geographical location and their history. *European Journal of Human Genetics* (2003) 11, 50–56. doi:10.1038/sj.ejhg.5200916

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Background and objectives

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterised by short, recurrent bouts of fever, accompanied by pain in the abdomen, chest or joints, and an erysipelas-like erythema.¹ It is an ethnically restricted genetic disease commonly found among Jews originating in North African countries, Armenians, Turks, and Arabs.² The predisposing gene has been localised on

chromosome 16p13.3. Using the 'positional cloning' approach, a French and an international consortium, in parallel and independently, isolated the MEFV (Mediterranean fever gene^{3,4}) in the summer of 1997; the encoded protein was named Marenostin/Pyren. Although mutations in MEFV recently have been found to cause FMF, the exact pathogenesis of the disease remains unclear; indeed several authors have suggested that other modulating genes or environmental trigger factors, possibly specific for every population, should be studied.

Generally the evaluated estimation of disease in Mediterranean populations ranges from 1:256 among North African Jews to 1:500 among Armenians and Israelis;² therefore the

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clinical diagnosis of FMF among these populations is enhanced by a known prevalence of the disease. Instead, in Italy, it was long considered a very rare disease, in spite of its Mediterranean location; until now very few papers reported Italian cases of FMF;^{5–9} therefore a long delay is commonly observed before diagnosis of FMF in Italian patients.¹⁰

To estimate the prevalence of this disease among Italians, a consortium of Italian and French centres selected from subjects with fever of unknown origin (FUO), a number of patients who remained undiagnosed after accurate exclusion of infectious, metabolic, autoimmune and neoplastic diseases. They were predominantly affected by relapsing fever and their blood samples were sent to the referral Centre (Laboratoire de Génétique Moléculaire et Chromosomique, Hôpital A. de Villeneuve, Montpellier, France) to be tested for MEFV mutations.

Closely following the pattern of autosomal recessive inheritance, FMF is recognised by two phenotypically independent manifestations: (1) acute, short-lasting painful, febrile attacks of peritonitis, pleuritis, or arthritis, and (2) nephropathic amyloidosis, which can lead to terminal renal failure even at a young age. Although clinical manifestations appear early in life (in half of the patients before age 10), they can be confused with a variety of diseases.

Diagnosis requires an awareness of FMF prevalence in the population; this explains the frequent diagnostic delay. The identification of FMF is based on clinical findings, family history, physical examination and laboratory results obtained from patients experiencing attacks. The genetic characterisation, confirming the diagnosis in 60–80% of FMF patients, is very important because it allows epidemiological surveys. Moreover, in atypical cases genetic analysis may prove to be very useful;¹¹ particularly amyloidosis can affect undiagnosed and untreated FMF patients. Its early stage is recognised by the appearance of proteinuria. Colchicine treatment, introduced in 1972,¹² in a dose of 1–2 mg/day on a continuous basis, has been found to prevent attacks in most patients and amyloidosis in all patients.¹³ However, amyloidosis is still encountered in uncompliant patients and in those with diagnostic delay.¹⁴

The present study will prove to be useful in avoiding diagnostic delay and preventing a number of complications such as undue surgery and dialysis for renal failure. Moreover, although the prevalence can only be calculated from a general population screening, this investigation can provide an indirect estimation of FMF among Italians.

Design, setting, patients and measurements

Patients with FUO were referred to our Centres from 1999 for further evaluation; history and physical examination were recorded and all infectious, autoimmune, neoplastic, metabolic causes of recurrent fever and abdominal/articular/thoracic pain were excluded by clinical, laboratory and instrumental examinations. The patients have been chosen among people referred for fever of unknown origin (FUO)

or (in a few cases) for surgical emergency. The diagnosis of FUO has been made according to Petersdorf and Beeson¹⁵ criteria modified by Durack and Street.¹⁶ Among criteria proposed for FMF diagnosis, we have chosen those of Tel-Hashomer¹³ (rather than criteria of Arthritis and Rheumatism¹⁷ or Sohar¹⁸ *et al.* and Eliakim *et al.* criteria),¹⁹ because they include the phenotype II, attacks with only fever, secondary manifestations like orchitis and erysipelas and the presence of FMF disease in a first degree relative. Data on fever, abdominal pain, other serosal involvements, renal function and skin lesion, in personal and familial history, were recorded; for every patient a genealogy was established.

On the basis of Tel-Hashomer criteria, selected patients are divided into three groups: S (sure): certain clinical diagnosis in the presence of two major criteria or one major and two minor criteria; P (probable): clinical diagnosis was considered probable in the presence of one major and one minor criterium or two minor criteria; I (improbable): clinical diagnosis was considered improbable in the presence of only one minor or one major criterium.

It is important to stress that some patients do not yet take Colchicine, so the major criterium 'Response to Colchicine' is not applicable. Some of these patients have been defined 'probable' but it is very likely that they are 'sure'. However, they are 'sure' according to Arthritis and Rheumatism criteria.

Moreover, it is extremely difficult to evaluate the response to therapy for a disease, such as familial Mediterranean fever with clinical swinging in her own natural course and widely unknown trigger factors. Finally, genealogic information is not available for all patients; but 'FMF in a first-degree relative' is a minor criterium, so its influence is mild.

All patients underwent genetic analysis of the FMF locus on 16p13.3. A routine genetic test was applied as previously described.²⁰ Briefly, DNA samples were amplified for exon 10 and 2. Mutations in exon 10 were screened by denaturing gradient gel electrophoresis and confirmed by either amplification refractory mutation system or after digestion with appropriate restriction enzyme. E148Q (exon 2) was specifically searched by digestion with *Ava*I.

According to genetic test results, we again classified the patients in 7 groups (Table 1): S++ (certain genetic and clinical

Table 1 Patients subdivided according to Tel-Hashomer criteria and genetic analysis results

S++	P++	S+	P+	S	P	I
16	3	6	2	15	16	5

(S++ certain genetic and clinical diagnosis; S+ probable genetic diagnosis and certain clinical diagnosis; P++ certain genetic and probable clinical diagnosis P+ probable genetic and probable clinical diagnosis; S genetic non contributive and certain clinical diagnosis; P genetic non contributive and probable clinical diagnosis; I genetic non contributive and improbable clinical diagnosis).

diagnosis): group S with two mutations; S+ (*probable genetic diagnosis and certain clinical diagnosis*): group S with one mutation; P++ (*certain genetic and probable clinical diagnosis*): group P with two mutations; P+ (*probable genetic and probable clinical diagnosis*): group P with one mutation; S (*genetic non contributive and certain clinical diagnosis*): group S with no mutation found with our routine genetic test; P (*genetic non contributive and probable clinical diagnosis*): group P with no mutation found with our routine genetic test; I (*genetic non contributive and improbable clinical diagnosis*): group I with no mutation found with our routine genetic test; this type of patient was considered not affected by FMF. Further, we classified our patients according to the Tel-Hashomer Severity Score.¹³ And retrospectively analysed this group to correlate genotype to phenotype.

Finally, we followed these patients by serial, clinical, physical and laboratory examinations to assess the natural history of their disease, to diagnose complications, and to evaluate response to therapy.

We divided the patients according to response to therapy as follows: *best response* disappearance of attacks for long periods (>1 year); *good response* decrease of frequency, duration and intensity of attacks >75%; *partial response* decrease in frequency, duration and intensity of attacks from 75–25% or lack of some previous symptoms (i.e. fever but not abdominal pain or joint pain but no fever, and so on); *minimal response* very mild change in clinical features; <25%; *non responders* Colchicine ineffective.

Results

We collected 71 subjects, all of Italian origin; 32 were referred to the ‘A. Gemelli’ Polyclinic; all of them (or their parents) came from southern or central Italy; while the remaining 39 were referred to other Italian or French medical centres; all excluded non Italian ancestry. The subjects are 40 women and 31 men, from 3 to 75 years old; age distribution is shown in Table 2.

The towns of provenance are known for 38 patients and their location is marked on a map of Italy (Figure 1).

The age at onset of disease is widely variable; most patients began having symptoms when they were under 30 years of age (61/71; 90%) with three peaks of frequency; a few of them when they were from 5 to 10 years old (6 patients; 8.4%) and a few when they were over 30 years old (four patients; 5.6%). Data for onset age are not available for six patients (details in Figure 2).

In our group the more affected sex is female (40 *versus* 31).

In most cases our patients started to have symptoms early in their life: 64% under 20 years of age. An early onset, also in our group, increases the risk of a severe disease. These subjects have shown attacks of fever up to 40°C, more once than *per mensem*, lasting about 4 days (with some exceptions). Also skin lesions have been very common in this group (seven patients with cutaneous

Table 2 Age distribution in our series

Age	No patients (%)
0–20 years	18 (25)
21–30 years	8 (11)
31–50 years	15 (21)
> 50 years	11 (15)
Unknown	19 (28)

Figure 1 Distribution within the peninsula of the Italian patients affected by FMF (regions of provenance); note the high density in central-southern Italy.

involvement had an early onset of disease), as well as oral aphthosis (six patients with oral manifestations had an early onset of disease).

Regarding the Severity Score, not all subjects proved valuable for this endpoint, sometimes because of shortage of available data (eight patients), or because they had not yet started Colchicine, one of the score-keys (29 patients). Most (20/33, 66%) were affected by a moderate form of disease; 8/33 (24%) by a mild form; and only five patients by severe disease (score >10); however, nobody exceeded a score of 14. This score was obtained in a 40 year-old woman with onset at two years of age with frequent attacks (two or three per week), mainly peritoneal attacks, but also with early renal involvement and itching without skin lesions, chronic hip arthritis and pericardial thickening. Genetically, she is the patient with the first non-sense, probably dominant MEFV mutation.²¹

In our group, the attacks have been widely varied: not always presenting the same characteristics in terms of symptoms, frequency and duration even in the same

patient. The symptoms during the, so called, 'free intervals' often have proved as important as the attacks themselves. In particular, it is necessary to stress the spontaneous or exercise-induced myalgias seriously influence the quality of life of nine subjects, between one attack and another.

Our series shows the complete range of FMF manifestations described in the literature¹³ (Table 3).

We have found an impressive association in seven women (in the group of women referred to the 'A. Gemelli' Polyclinic) between attacks and menses and between menarche and the need for Colchicine. Colchicine need increases significantly in the pre-menstrual period of many women; e.g. a 14 year-old girl, who has been taking Colchicine (0.5 mg/d) since she was 4 years old with good response, after the menarche (from one month to another), has required a fourfold dose increase (from 0.5 to 2 mg/day). This correlation of attacks to menses could suggest an estrogen modulation on the physiopathology of the attacks.

Nine patients have another relative with almost analogous symptoms in their family (six in a first-degree relative). Consanguinity in the family is known in two cases and it goes back three generations. Fever has been the main symptom in 65/71 patients (92%, relative heterogeneity 0.2772); only 6/71 (8.5%) patients have had attacks without fever.

The second symptom, in order of frequency, has been abdominal pain (63/71; 91%). Two patients with pain in

Figure 2 Age at onset in our series.

Table 3 Clinical manifestations of familial Mediterranean fever: comparison between Italian (our series) and Israeli patients

Clinical manifestations	Italians	Jews
Fever	92	90
Abdominal pain	91	90
Articular pain	65	75
Thoracic pain	52	45
Skin lesions	25	25
Myalgias	12	18
Renal lesions	7	90
Orchitis	3	4

Data about Israeli patients from Pras M, What is familial Mediterranean fever? Familial Mediterranean fever II International Conference, 3–7 May 2000, Antalya – Turkey).

the right hypocondrium have had also hyperbilirubinemia (diagnosis of Gilbert's jaundice) during attacks and one other hyperchromic urine (hyperbilirubinemia with bilirubinuria, without cholelithiasis). In the longest clinical histories the patients have been submitted to emergency surgery during attacks, due to missing diagnosis. One young girl underwent surgery 13 times because of suspected pathology of appendix, gall bladder or ovary, pelvis bone or iatrogenic complications of surgery (fistula, abscess). A specific index of clinical suspicion for FMF may be an early appendectomy without the disappearance of attacks of 'acute abdomen', (8/32 patients referred to the 'A. Gemelli' Polyclinic).

Joints have been involved in 45 patients (63.5%).

Thoracic pain, pleural or pericardial, has been complained by 37 patients (52%).

In over 60% cases, abdominal and thoracic or articular pain have been associated in the same attack.

We have observed two brothers, 13 and 17 years old, suffering from orchitis (not parotitis virus related), as further serosal involvement.

Generally, the renal function has not been compromised in our group; only five patients (four women and one man) have reported an early renal damage (microproteinuria); they have a disease lasting 20, 13, 21, 40 and 25 years, respectively.

Among other 'minor' manifestations, we observed urticarial or erysipelas-like lesions, even outside the time of acute attacks (16 patients), myalgia (seven patients), splenomegaly (six patients). Moreover, we have observed that these patients, generally, show frequent hypersensitivity manifestations to drugs, foods and inhalants.

Among associated diseases or manifestations we recorded Purpura of Henoch-Schoenlein (1) Kawasaki disease (1), asthma (3), oral aphthosis (9), headache (6) and persistent anaemia (3).

None of the fertile women has reported misconception, abortion, premature birth or chromosomic diseases in the new born.

Forty of these patients (56.3%) regularly take Colchicine p.o. (0.5–3 mg/d). The longest treatment has lasted 22 years.

We have estimated the response to Colchicine in terms of persistence/disappearance or frequency, duration and intensity of attacks. 75% responded to Colchicine (best response five patients, 7%; good response 12 patients, 59%; partial response seven patients, 9%). Only a majority (16%) reached a minimal response (8%) or did not receive any benefit at all (8%); these latter are taking the drug to prevent amyloidosis. Data on 26 patients are not available.

The genetic test pointed out 29/71 (41%) patients with at least one MEFV mutation. FMF was genetically ascertained in 16/71 (23% of them). The genotype distribution of our 71 patients with FUO is shown in Table 4. We cannot

exclude that some of our patients had still unknown mutations or rare mutations in other exons. The five most frequent FMF-associated mutations (i.e. M694V, V726A, M680I, M694I, and E148Q) were found in our Italian group. We calculated the prevalence of MEFV mutations in patients of the P+ group (two patients have R761H and E148Q, respectively).

M694V was the most frequent mutation (16%), as in all Mediterranean populations, followed by E148Q (14%) and the common M680I G>C mutation (14%). The prevalence of M694I, a mutation frequently encountered in Maghrebins, and of the rare form of M680I (M680I G>A) was relatively high in Italians (10 and 8% respectively). Other rare exon 10 mutations were also found: A744S, R761H and a stop codon mutation Y688X.²³ No complex allele was detected.

The following results, drawn from geno-phenotypical correlations, are similar to those of other authors: (a) M694V and M680I homozygotes and any type of compound heterozygotes at these two codons confirmed their association with a severe phenotype^{22–24} (7/9 patients showed a high severity score, from moderate to severe >6; the patient with FMF-associated Henoch-Schoenlein purpura belongs to these, as well as two patients with microproteinuria); (b) among the compound heterozygotes: M694V and M680I confirmed a probable up-modulator effect on the other mutation (the patient with M694V/M680I had the most severe phenotype), while V726A and E148Q¹¹ a suspected down-modulator effect; (c) the patients with only one known mutation, whatever it is, are not a phenotypically homogeneous group, with a clinical picture ranging from short and few attacks (6–7 in 10 years) in an Italo-British girl (E148Q) to one long-lasting attack every second month with protracted febrile myalgia in a 'pure' Italian patient (E148Q); (d) the clinical picture of M694V 'true' heterozygotes includes early onset (<5 years), severe and frequent attack with fever and every kind of serositis, high responsivity to colchicine but no amyloidosis or renal dysfunction; (e) we are able to compare two girls of the same age, onset and genotype (V726A, M694V), but of different ancestry, Armenian and Italian; after 12 years of disease the Armenian (not included in this present series) has already developed amyloidosis; the Italian has not. So we may attribute these phenotypical differences to their different genetic background and/or environmental factors; (f) finally, the R761H heterozygote is interesting from an epidemiological point of view: she is the grand-daughter of another of our FMF patients, but they have not the same mutation (grandfather: V726A/M680I). As we can exclude a non-paternity, this data, along with the low registered consanguinity in our group (only in two families) may suggest that the prevalence of altered MEFV carriers is high enough in Italy (genealogy tree in Figure 3).

Conclusions

In 1970, Reich CB and Franklin EC gave an account⁵ of a family of Italian origin, affected by FMF (three consecutive

Figure 3 Genealogy tree of an Italian family affected by FMF. Grandfather (1) and grand-daughter (3) were genetically assessed (compound heterozygous, M680I/V726A and single heterozygous, R761H, respectively). The father of (3), son of (1) is symptomatic, but he refused the genetic analysis. Surprisingly, the grandfather and the grand-daughter don't have the same mutations.

generations); at that time only four cases of FMF in Italians were known (Brick and Cajigas, 1951; Calligaris, 1953; Dormer and Hale, 1962). They suggested that 'a survey conducted among people of Italian ancestry could find many more pedigrees with FMF'. Indeed in Italy there were no systematic epidemiological surveys of FMF prevalence, even if in the literature there were a few communications about sporadic FMF cases.

Our group of Italian patients with FMF have several particular epidemiological, clinical and genetic characteristics: (a) the more affected sex, for example, is female, not male as in other countries; (b) there is a prevalence-gradient from South to North with a major concentration of cases in the Southern regions (the cases found in North of Italy are mainly due to South-North emigration during the centuries); (c) the clinical pattern is typical enough, so the long diagnostic delay (mean 18 years $\pm$ 9) can be attributed mainly to a non-popular knowledge of the disease; (d) the evaluation of severity in comparison with genotype shows a trend of decreasing severity from M694V homozygous, through heterozygous compounds, down to E148Q heterozygous; (e) if one looks at the frequency of the different Severity Scores shown in Figure 4, it is clear enough that Italian FMF-cases are not too severe (mild-moderate forms represented 74% of the assessable patients – complete –; moreover, among the not-wholly assessable ones – incomplete – most are mild and, if the lacking data had the maximum score, they would not exceed the moderate range); (f) amyloidosis would seem a rare complication in Italian patients, in spite of the fact that M694V mutation is as frequent as in other people. Phenotype II, similarly, is uncommon (nobody in our group, until now), but it could be the result of misdiagnosis. Probably, an accurate survey in dialysis-units could count enough cases of FMF-

related amyloidosis among patients with chronic renal failure not otherwise explained. Guidelines to the biopsy in patients with possible renal involvement should be implemented taking into account renal dysfunction signs such as microalbuminuria, in patients with FUO or abdominal pain; (g) geno-phenotypically, the correlations between clinics and the 4 more frequent MEFV mutations (M680I, M694V, E148Q, V726A) were confirmed, but genetically Italians have the highest percentage of unknown mutations (32% versus 20% among Jews), at the moment.¹¹

Are there some specific 'Italian' mutations? Or are they the sum of the single amounts of unknown mutations of the different ancient Mediterranean peoples from whom they derive? In fact, there are at least five historical reasons

Figure 4 Severity Score in our series according to *Tel-Hashomer* key to FMF severity score (Pras M, What is Familial Mediterranean fever? FMF II International Conference, 3–7 May, 2000).

to account the presence of the FMF gene in the Central-Southern regions of Italy (Figure 5).

1. Greek²⁵ colonization of Sicily (VIII century B.D.) and Southern Italy (VIII–VI centuries B.D.)
2. the Jewish diaspora after the destruction of Jerusalem's Temple (70 A.D.)
3. arrival of the early Christians in Rome under the Roman Empire (they were people of various ancestry: Greek, Jewish, North-African, etc) (I–II century A.D.)
4. Turkish colonization of little areas of eastern-southern Italy (in X century A.D.)
5. the Arab conquest of Sicily in IX century A.D.
6. moreover, the ancient Etruscan inhabitants of Tuscania, according to Herodotus, are considered descendants of Phoenicians coming from the Eastern Mediterranean basin, before Greek colonization.

Our results confirm the conclusions of A. Piazza,²⁶ which stated that, before Roman domination, 1/10–15 inhabitants of Italy had Greek ancestry. Italians, according to Piazza, from a genetic point of view, should be considered a mosaic of four ethnic groups: Greek, Etruscan, Ligurian and Eastern-Italic. Indeed, most of our patients come from the regions of ancient *Magna Graecia* (Calabria, Lucania, Sicily, Apulia, Campania). On the basis of these observations, it would be useful to compare the frequency of each different MEFV mutation among Greeks and Italians.

A subset of our patients come from Latium, the region which includes Rome. Probably, our Latium's cases have a different ancestry, however, Jewish in addition to Greek. Recently, Oddoux C and Guillen-Navarro E²⁷ have demon-

Figure 5 The way familial Mediterranean fever arrived in Italy during the centuries.

strated by a genetic study which has compared Ashkenazi Jews and the Roman Jewish community, that MEFV mutations, as well as mutations of Gaucher disease and Connexine 26, are over 2000 years old. The Roman Jewish community has been historically continuous in Rome since pre-Christian times and may have been the progenitor of the Ashkenazi Jewish community.

In conclusion, we demonstrated and genetically confirmed that FMF does exist in Italy and is frequently undiagnosed or a long delay precedes the diagnosis. Indeed the history of these patients and their families involves much suffering before finding the right diagnosis and treatment.

A universally accepted definition of rare disease does not exist, but the European Committee on rare diseases defines a disease as rare when the prevalence is less than five per 10,000 inhabitants. To calculate the real prevalence in Europe of Episodic Febrile diseases such as Hibernian fever, FMF, PFAPA etc, health authorities should establish national and European registries of such diseases.

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References

- 1 Nir-Paz R, Ben-Chetrit E, Pikarsky E, Hassin D, Hasin Y, Chajek-shaul T: Unusual presentation of familial Mediterranean fever: role of genetic diagnosis. *Ann Rheum Dis* 2000; **59**: 836–838.
- 2 Ben-Chetrit E, Levy M: Familial Mediterranean fever. *Lancet* 1998; **351**: 659–664.
- 3 The French FMF Consortium: A candidate gene for familial Mediterranean fever. *Nat Genet* 1997; **17**: 25–31.
- 4 The International FMF Consortium: Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; **90**: 797–807.
- 5 Reich CB, Franklin EC: Familial Mediterranean fever in an Italian family. *Arch Intern Med* 1970; **125**: 337–340.
- 6 Marinone C, Bisbocci D, Pellacani A, Chiandussi L: Familial Mediterranean fever: a report of 2 cases of Italian origin. *Ann Ital Med Int* 1992; **7**: 114–117.
- 7 Gentilone N, Gabbriellini N, Caradonna P *et al*: Familial Mediterranean fever and electroencephalographic changes. A clinical case. *Minerva Med* 1992; **83**: 307–310.

- 8 Gentilone N, Febbraro S, Barone C *et al*: Peritoneal mesothelioma in recurrent familial peritonitis. *J Clin Gastroenterol* 1997; **24**: 276–279.
- 9 Breda L, Magri M, Morgese G, Chiarelli F: Familial Mediterranean fever in two Italian brothers. *Panminerva Med* 1998; **40**: 157–160.
- 10 Manna R, La Regina M, Vulpiani P *et al*: Clinical features of familial mediterranean fever in Italy. *Clin Exp Rheumatol* 2000; **18**: 288.
- 11 Toutou I: The spectrum of Familial Mediterranean Fever (FMF) mutations. *Eur J Hum Genet* 2001; **9**: 473–483.
- 12 Goldfinger SE: Colchicine for familial Mediterranean fever. *N Engl J Med* 1972; **287**: 1302.
- 13 Pras M: What is familial Mediterranean fever. *Familial Mediterranean Fever; II International Conference, 3–7 May, 2000 Antalya, Turkey*.
- 14 Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J: Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986; **314**: 1001–1005.
- 15 Petersdorf RG, Beeson PB: Fever of unexplained origin: report on 100 cases. *Medicine* 1961; **40**: 1.
- 16 Durack DT, Street AC: Fever of unknown origin – reexamined and redefined. *Curr Clin Top Infect Dis* 1991; **11**: 35–51.
- 17 Livneh A, Langevitz P, Zemer D *et al*: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; **40**: 1884–1890.
- 18 Sohar E, Gafni J, Pras M, Heller H: Familial Mediterranean Fever. A Survey of 470 cases and review of the literature. *Am J Med* 1967; **43**: 227–253.
- 19 Eliakim M, Levy M, Ehrenfeld M: *Recurrent polyserositis (Familial Mediterranean fever, periodic disease)*. Amsterdam: Elsevier/North-Holland Biomedical Press, 1981; 16–17 pp.
- 20 Bernot *et al*: A transcriptional Map of the FMF region. *Genomics* 1998; **50**(2): 147–160.
- 21 Notarnicola C, Manna R, Rey JM, Toutou I: Y688X, the first nonsense mutation in familial Mediterranean fever (FMF). *Hum Mutat* 2001; **17**: 79.
- 22 Cazeneuve C *et al*: MEFV genet analysis in Armenians patients with FMF: diagnostic value, unfavorable renal prognosis of the M694V homozygous genotype, genetic and therapeutic implications. *Am J Hum Genet*; **65**: 88–97.
- 23 Dewalle M, Domingo C, Rozembaum M, Ben-Chetrit E, Cattani D, Bernot A, Dros C: Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). *Eur J Hum Genet* 1998; **6**: 95–97.
- 24 Shohat M, Magal N, Shohat T *et al*: Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. *Eur J Hum Genet* 1999; **7**: 287–292.
- 25 Costantinou Deltas C, Mean C, Rossou R *et al*: Familial Mediterranean fever (FMF) is a frequent disease in the Greek-Cypriot Population of Cyprus. *Genetic Testing* 2002; **6**: 15–21.
- 26 Piazza A: A genetic history of Italy. *Ann Hum Genet* 1998; **52**: 203–213.
- 27 Oddoux C, Guillen Navarro E *et al*: Mendelian Disease among Roman Jews: implications for the origins of disease alleles. *J Clin End Met* 1999; **12**: 4405–4409.