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Original article

# Comorbidities in familial Mediterranean fever: analysis of 2000 genetically confirmed patients

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## Abstract

**Objectives.** FMF is the most common periodic fever syndrome, characterized by recurrent episodes of fever and serosal inflammation accompanied with high acute phase reactants. The analysis of possible comorbidities is important to understand the impact of these conditions on clinical care and whether they share a common aetiological pathway. In this study, we aimed to evaluate the comorbidities associated with FMF patients in a large genetically diagnosed cohort.

**Methods.** We retrospectively evaluated the medical and genetic records of FMF patients who were followed up by rheumatologists in Hacettepe University for 15 years. The FMF patients who had homozygous or compound heterozygous mutations were included in the study. Comorbidities associated with FMF were divided into three groups: (i) comorbidities directly related to FMF, (ii) comorbidities due to increased innate inflammation, and (iii) comorbidities that were regarded as being incidental.

**Results.** A total of 2000 patients with a diagnosis of FMF were enrolled in the study. Among them 636 were children (31.8%) and M694V was the most common mutation in patients with associated inflammatory conditions. The frequency of AS, Iga Vasculitis (Henoch–Schönlein purpura), juvenile idiopathic arthritis, polyarteritis nodosa, multiple sclerosis and Behçet's disease were increased in patients with FMF when compared with those in the literature.

**Conclusion.** This study represents the largest genetically confirmed cohort and compares the frequencies with existing national and international figures for each disease. The increased innate immune system inflammation seen in FMF may be considered as a susceptibility factor since it predisposes to certain inflammatory conditions.

**Key words:** familial Mediterranean fever, comorbidity, inflammation

CLINICAL SCIENCE

**Rheumatology key messages**

- Identifying possible comorbidities is important to understand the impact of these conditions on clinical care.
- FMF is associated with some inflammatory/rheumatic diseases.

## Introduction

FMF is a periodic fever syndrome, characterized by recurrent episodes of fever and painful serosal inflammation, along with high acute phase reactants. The disease occurs in all ages and tends to be common in people of Mediterranean descent, predominantly in Armenians, Arabs, Jews and Turks. However, FMF-related cases have been reported all around the world. The gene *MEFV* (*MEditerranean FeVer*), located on chromosome 16p13.3, accounts for FMF and consists of 10 exons encoding the protein pyrin. Five founder mutations, M694V, M680I, V726A, M694I and E148Q, are responsible for over 85% of Mediterranean origin-based FMF cases. M694V is known to reflect the most severe clinical phenotype [1, 2]. The pyrin protein, expressed predominantly in the cell lineage of myeloid origin, is considered as an immunoregulatory molecule (up- or down-regulating) playing a key role in inflammation; FMF phenotypes occur due to abnormal activation of IL-1β and nuclear factor-κB by mutations on *MEFV*. Hence, prolonged or enhanced inflammation in patients and FMF carriers is associated with mutant pyrin [3, 4]. The acute inflammation attacks are generally short-term [5]. Colchicine effectively reduces recurrent attacks of the disease. The use of colchicine is known to have a dramatic effect on the course of the

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disease and prevents the increase in the number of patients suffering renal amyloidosis [6]. Although colchicine is an effective treatment for FMF, associated comorbidities or complications arising from ongoing disease activity may cause significant morbidity and even mortality.

Comorbidity can be simply defined as the presence of one or more additional condition(s) to the existing disease in a patient. Comorbidity is a crucial prognostic factor for various diseases such as cancer, diabetes and cardiovascular disorders [7–9]. The analysis of possible comorbidities in an individual is important to understand the impact of these conditions on clinical care and whether they share a common aetiological pathway. However, the concept of comorbidity has been understood poorly and not completely integrated into the research area and medical care of FMF. The association with certain diseases and the effect of these associations should be considered very carefully by clinicians involved in autoinflammatory diseases. Comorbidities may have negative impacts on the quality of life of the patient and may be associated with mortality. Health care, especially in the countries where FMF is common, needs to address the management of patients with coexisting diseases. To date, the impact of comorbidity on FMF has not been systematically addressed.

In this study, we aimed to investigate the comorbidities associated with FMF patients in a large genetically diagnosed cohort. We analysed a 15-year genetic database and clinical records of 2000 patients, homozygous or compound heterozygous for pathogenic *MEFV* mutations. The comorbidities were classified in three groups as (i) those directly related to FMF, (ii) those associated with FMF due to increased innate inflammation, and (iii) those regarded as incidental. It is hoped that the results of our study will shed light on the epidemiology of inflammatory diseases and improve clinical care in FMF.

## Methods

### Study cohort

The 15-year-genetic database of Hacettepe University, Department of Medical Biology and clinical records of Hacettepe University Hospitals were analysed. The study population consisted of patients with FMF diagnosed by the rheumatologists in our university hospital and confirmed genetically. Accordingly, 2000 of 5638 patients with a diagnosis of FMF were enrolled in the study; 3638 patients were excluded from this study since their disease course was not monitored by rheumatologists in our hospital. The patients were followed up for 1–352 months. The cohort study included homozygous and compound heterozygous patients for predominantly M694V, V726A, M680I and E148Q mutations (E148Q homozygotes were also excluded). National ethics committee approval (18 March 2015, no. GO 15/214-26) was obtained according to the relevant guidelines by the ethics committee. The study was conducted in accordance with the Declaration of Helsinki.

### Statistical analysis

All patients were categorized according to age and gender distributions, dates of entry and exit from hospital, symptom onset and period of colchicine treatment. Subsequently, we calculated frequency and proportions of patients with FMF according to variable comorbidities. Comorbid conditions were classified and identified with the following modified criteria.

Conditions were concordant to FMF: (i) comorbidities directly related to FMF, (ii) comorbidities associated with FMF due to increased innate inflammation, and (iii) comorbidities that may be incidental.

SPSS Statistics 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Comorbidities and age/gender distribution were assessed via a categorical score system as follow: yes (1), no (2). Means with standard deviations and medians were calculated for all patients in the study. Results were evaluated with an appropriate *t*-test and $P < 0.05$ was considered statistically significant.

## Results

Among the 2000 patients included in this, 636 were children (31.8%), 1029 of the patients were males (51.5%), with a mean (S.D.) age of 31.60 (16.01) years. The mean follow-up time was 4.50 (3.99) years [median (range): 3.84 (0.21–29.4) years]. Of the FMF patients, 880 of 2000 (44.0%) had homozygous *MEFV* gene mutations, the most common one being M694V homozygosity. The remaining were compound heterozygous. Of the patients, 656 (32.8%) had one or more than one comorbidity associated with FMF.

### Comorbidities directly related to FMF

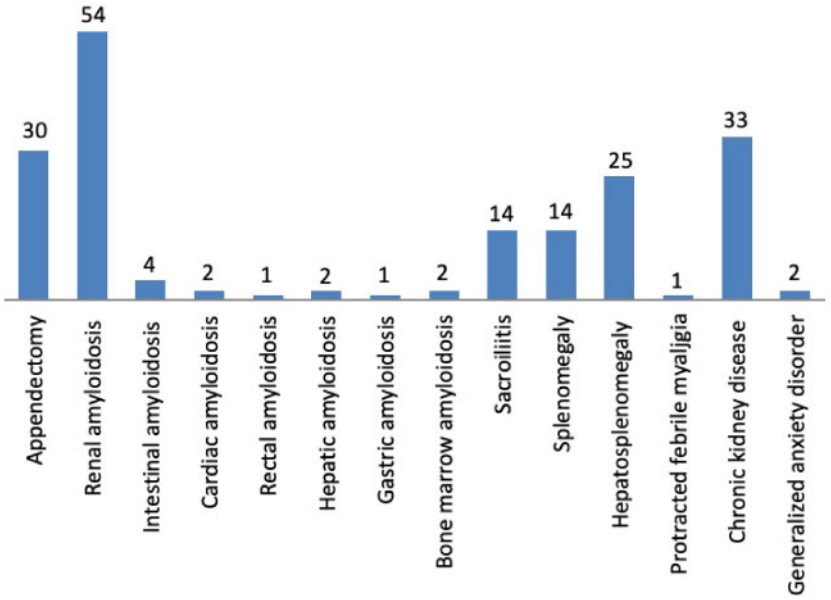
Of the comorbidities directly related to FMF, renal amyloidosis was in the first place with 2.7%, which is in agreement with previous data. The rate of amyloidosis in total rose to 3.3% when amyloidosis in other tissues was also included. Other related comorbidities were chronic kidney disease, appendectomy, hepato-splenomegaly and sacroiliitis (Fig. 1).

Mutation distribution and allele frequencies for mutations in the *MEFV* gene in comorbidities directly related to FMF are given in Table 1. M694V allele frequency was the highest in a range of 50–100% for all comorbidities directly related to FMF. This was followed by M680I, V726A, E148Q, R761H and F479L mutations.

### Comorbidities associated with FMF due to increased innate inflammation

When comorbidities associated with FMF due to increased inflammation were examined, AS ranked the highest with 7.75%. JIA (1.55%), IgA vasculitis [IgAV (HScP); 1.25%], IBD (0.85%), ARF (0.8%) and RA (0.5%) were the other frequently associated inflammatory diseases in our FMF patients. The occurrences of atherosclerotic heart disease (ASHD), PAN, uveitis, Behçet's disease (BD), lymphadenopathy, vasculitic aorta, psoriatic

Fig. 1 Comorbidities directly related to FMF




Number of patients: 2000.

arthritis, leucocytoclastic vasculitis and multiple sclerosis (MS) were <0.5% (Fig. 2).

### Comparison of comorbid diseases with high frequency in FMF patients with the literature

We compared comorbidities associated with FMF due to increased innate inflammation with the literature. In Fig. 3 we have included the diseases in which prevalences in the Turkish population were available. This comparison showed that JIA, AS, ARF, BD and ASHD were increased among our patients as compared with the healthy Turkish population. We observed that the risk of JIA, AS, ARF, BD and ASHD was increased by 24.21-, 7.38-, 1.42-, 1.26- and 1.28-fold, respectively, in FMF patients compared with the data available for Turkey [10–19].

If we did not have national figures we compared the frequencies of the diseases in our cohort with the international figures (Fig. 4). We observed significant increases for IgAV (HScP), PAN, and MS disease among our FMF patients. In our study, the risk of IgAV (HScP), PAN, IBD and MS was increased by 62.5-, 112.9-, 1.02- and 2.68-fold, respectively, in FMF patients [20–25].

### Comorbidities that may be incidental

Comorbidities that were interpreted as being incidental are shown in Table 2. Among these diseases osteoporosis ($n = 77$), hepatosteatosis ($n = 53$) and cholecystectomy ($n = 20$) were the most common in this group (all adults). Other comorbidities were observed in one patient each (Table 2).

## Discussion

FMF is a prototype of an autoinflammatory disease with a dysregulated innate immune system response. The disease is classified as an inflammasomopathy where intense inflammation is associated with excess IL-1 production [3, 26]. Comorbidities may be seen in FMF patients associated with this inflammation. The analysis of possible comorbidities in an individual is important to understand the impact of these conditions on clinical care and whether they share a common aetiological pathway. In this study we have classified the comorbidities into three categories: (i) those directly related to FMF, (ii) those associated with FMF due to increased innate inflammation, and (iii) those that may be incidental.

Among the first category, amyloidosis was the most common complication of FMF and can result in renal failure or death [27]. Deposition of serum amyloid A in various organs is the consequence of ongoing chronic inflammation. In our study, 54 patients (2.7%) had renal amyloidosis. In their web-based MetaFMF project consisting of 35 centres, Touitou *et al*. [28] found that 260 of 2482 (10.5%) cases developed renal amyloidosis. Development of amyloidosis can be prevented by effective control of inflammation. Besides renal involvement, amyloidosis can be observed in other organs such as the heart, liver and intestine.

Hepatomegaly and splenomegaly are again associated with ongoing inflammation. Good control of disease activity and the judicious use of biologics when necessary are expected to prevent the comorbidities directly related to FMF. We have included appendectomy here, since severe

TABLE 1 Mutations in *MEFV* gene in comorbidities directly related to FMF

| Mutation | Allele frequency | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Appendectomy | Renal amyloidosis | Intestinal amyloidosis | Cardiac amyloidosis | Rectal amyloidosis | Hepatic amyloidosis | Gastric amyloidosis | Bone marrow amyloidosis | Sacroiliitis | Splenomegaly | Hepatosplenomegaly | Chronic kidney disease | Protracted febrile myalgia | Generalized anxiety disorder |
| M694V | 38 (63.3) | 87 (80.5) | 10 (83.3) | 4 (100) | 2 (100) | 4 (100) | 2 (100) | 2 (50) | 22 (78.5) | 16 (57.1) | 29 (58) | 50 (75.7) | 2 (100) | 4 (100) |
| V726A | 7 (11.6) | 7 (6.4) | 1 (8.3) | – | – | – | – | – | – | 3 (10.7) | 6 (12) | 7 (10.6) | – | – |
| M680I | 10 (16.6) | 8 (7.4) | 1 (8.3) | – | – | – | – | 1 (25) | 2 (7.1) | 5 (17.8) | 8 (16) | 7 (10.6) | – | – |
| E148Q | 4 (6.6) | 4 (3.7) | – | – | – | – | – | – | 3 (10.7) | 2 (7.1) | 6 (12) | 2 (3) | – | – |
| R761H | 1 (1.6) | 2 (1.9) | – | – | – | – | – | 1 (25) | 1 (3.6) | 1 (3.6) | 1 (2) | – | – | – |
| F479L | – | – | – | – | – | – | – | – | – | 1 (3.6) | – | – | – | – |
| Total number of patients | 30 | 54 | 6 | 2 | 1 | 2 | 1 | 2 | 14 | 14 | 25 | 33 | 1 | 2 |

Data are n (%).

abdominal pain is known to be often mistaken for appendicitis in FMF patients. Appendectomy rate was 1.5% in our study. In a multicentre study, 19% of 2838 FMF patients had a history of appendectomy [29]. Many of the abdominal surgeries are performed before the diagnosis of FMF [30].

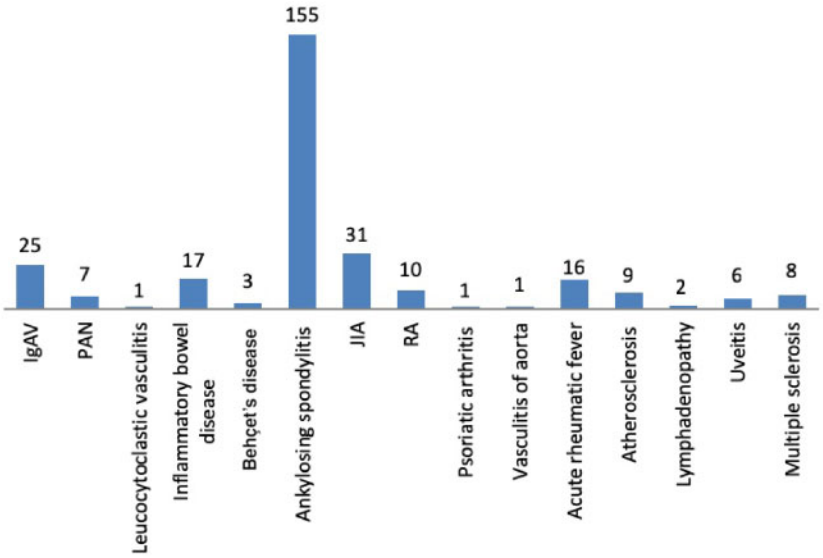
Sacroiliitis deserves a special discussion since the jury is out on whether it is a feature of FMF *per se* or a feature of associated AS or enthesitis-related arthritis (ERA). We and others have highlighted the high frequency of *MEFV* mutations in these patients [31, 32]. We have also shown that patients with FMF and sacroiliitis have distinguishing features when compared with patients with ERA [33]. Coexisting FMF and AS have been reported in several studies [32]. In our study, we found that the prevalence of spondylarthropathies was higher than the prevalence in our country and the relevant literature [12, 13]. Increased frequency of *MEFV* variants has also been reported in AS patients [34].

Comorbidities associated with FMF due to increased innate inflammation are all inflammatory or rheumatic conditions and require additional medication. We have shown that many inflammatory or rheumatic diseases such as JIA, IgAV (HScP), AS, PAN, BD, IBD and MS were increased among our patients as compared with the healthy population. As of today we do not have definite explanations on why certain patients have these associations. The associations with these inflammatory rheumatic diseases may simply be because of the increased inflammatory milieu, as we have previously suggested [35, 36]. Indeed it has been shown that not only patients but also carriers for the *MEFV* mutations have increased CRP levels [37, 38]. Most of these associations have been previously reported. However this cohort represents the largest genetically confirmed cohort and compares the figures with existing national, if not international, figures for each disease.

In our study, 31 patients (1.5%) had JIA and 155 patients (7.75%) had AS. While the prevalence of JIA in our country is 64 per 100 000, the prevalence of JIA in other countries ranges from 3.8 to 400 per 100 000 in children [10, 11]. We observed that the risk of JIA was increased by 24.23-fold in FMF patients compared with data obtained in Turkey. The pathogenesis of JIA involves both autoimmune and various genetic factors [39]. *MEFV* mutations may be one of the genetic determinants associated with JIA. The effect may be more pronounced in systemic-onset JIA, where IL-1 is one of the major cytokines [39]. Our group has showed that *MEFV* mutations were significantly higher in the patients with systemic JIA [40]. However, in our study we did not distinguish the JIA subtypes.

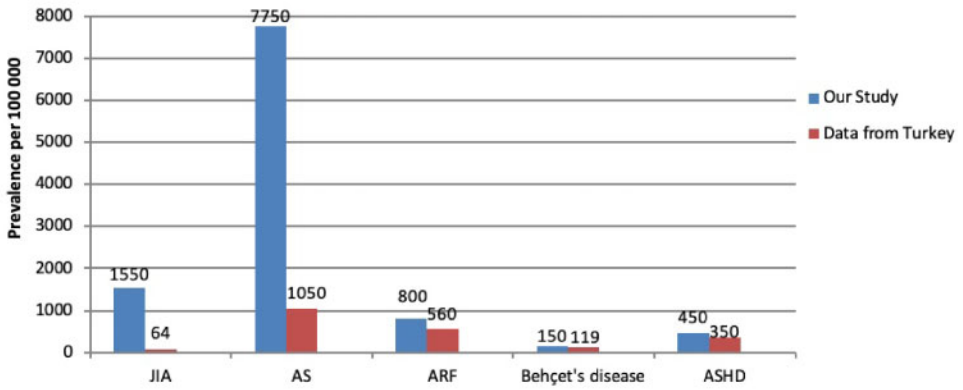
Chronic inflammation has been suggested to predispose to cardiovascular risk in FMF patients [41]. In our study, we did not find a prominent increase in the prevalence of ASHD compared with the literature [18, 19]. While Grimaldi *et al.* claimed that carrying the M694V mutation may increase the risk of acute myocardial infarction, Langevitz *et al.* showed that colchicine-treated FMF

Fig. 2 Comorbidities associated with FMF due to increased innate inflammation




Number of patients: 2000.

Fig. 3 Comorbidities associated with FMF due to increased innate inflammation



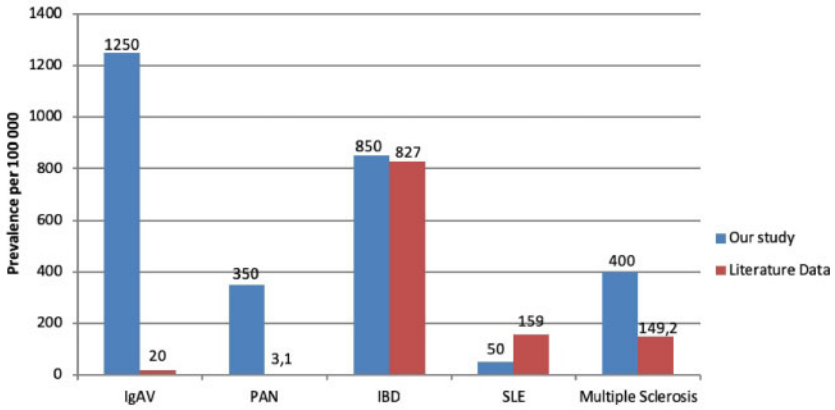

Only diseases where we have national figures were included in this figure. ASHD: atherosclerotic heart disease; ARF: acute rheumatic fever.

patients are not more predisposed to ischaemic heart disease than the normal population [42, 43]. Similarly to ASHD comorbidity, the prevalence of acute rheumatic fever did not significantly increase in our study [14, 15]. Differentiation of these two diseases can be difficult and may explain the previously suggested association. Patients with FMF who had arthritis, elevated acute phase reactants and evidence of a recent streptococcal infection may be misdiagnosed with ARF.

Several studies show that IgAV (HScP) and PAN are more common in FMF patients [44, 45]. IgAV (HScP) is the most common vasculitis in childhood, the prevalence is estimated to be 10–20 per 100 000 in children [20–22]. In our study, the risk of IgAV (HScP) was increased by 62.5-fold in FMF patients. Tunca *et al.* showed the prevalence of vasculitides for HScP was 2.7% in FMF patients [29].

Several studies emphasized that alterations in the *MEFV* gene are important susceptibility factors for PAN [44, 46–48]. The prevalence per 1 000 000 adults was estimated to be 30.7 for PAN [49]. In our study there were seven patients with diagnosed PAN, which was an increased prevalence. In a study consisting of 2838 FMF patients, the prevalence was 0.9% for polyarteritis nodosa [29]. Another study also

FIG. 4 Comorbidities associated with FMF due to increased innate inflammation




Figures were compared with international ones since national prevalences are not present. IgAV: immunoglobulin A vasculitis.

showed that 15 of 207 FMF patients (1%) had PAN. Both FMF and PAN are characterized by fever and abdominal pain. Diagnosis of PAN in patients with FMF may be difficult and paediatricians should be aware of this association. The association of PAN—and other inflammatory comorbidities—may well be associated with insufficient control of the inflammation in FMF [46]. We have not been able to analyse this in detail due to the set-up of this study; however, all but one PAN patient indeed had elevated CRP before the diagnosis of PAN.

*MEFV* mutations may be one of the susceptibility factors for BD as well. Prevalence of BD is 2.4 per 100 000 in those of European ancestry, 34.6 per 100 000 in those of North African ancestry, and 17.5 per 100 000 in those of Asian ancestry [16]. The prevalence of BD in Turkey was 119.8 per 100 000 [17]. BD is undoubtedly more common in Turkey and other parts of the Middle East [50]. In our study we found that 3 of 2000 patients had BD which is not higher compared with the prevalence in Turkey. Schwartz *et al*. found 39 individuals who also suffered from BD in a cohort of about 4000 FMF patients. [47]. The reason for a lack of increased BD prevalence in our cohort may be because of the fact that one-third of the patients were children and the prevalence of BD is lower among them. On the other hand BD is known to be associated with higher incidence of *MEFV* mutations [48].

MS is an inflammatory disease of the CNS with multiple attacks. Many studies suggest an increased rate of MS among FMF patients. Kalyoncu *et al.* showed that the rate of MS in FMF patients was two times higher than the expected MS prevalence in Turkey [49]. Akman-Demir *et al.* found that the rate of FMF among MS patients is almost four times the expected prevalence in Turkey [51]. The MS prevelance was 149.2 per 100 000 individuals in the USA's commercially insured population in 2012 [25]. We observed in our study that the risk of MS was increased by 2.68-fold in FMF patients. Contrary to this study, a Turkish FMF study group claimed that demyelinating lesions were not detected in their nationwide multicentre study [29].

Interestingly, as we had pointed out previously, FMF patients are not expected to have an increase in autoimmune diseases such as SLE, which was confirmed in our cohort [52].

FMF and IBD are both characterized by chronic inflammatory attacks. We found that IBD accompanied 17 (0.85%) of the patients who had a diagnosis of FMF. The highest reported prevalence values for IBD were in Europe (827 per 100 000 persons) and North America (568 per 100 000 persons) [24]. According to these figures there was a small increase in the prevalence of IBD. Similarly, in a registry of 5000 FMF patients, Crohn's disease appeared to be more prevalent in FMF [53].

Comorbidities that were regarded as being incidental were not thought to be associated with inflammation or the mutations. Since FMF is so frequent among the Turkish population, we believe that these diseases have occurred incidentally.

Several studies in the literature showed that M694V is the most common *MEFV* mutation. Patients with M694V mutations should be considered at risk of early onset disease and developing a severe phenotype [54]. As expected, M694V was the most common mutation in patients with associated inflammatory conditions in our study.

The limitations of our study include a retrospective design and having a retrospective analysis of the patients. Another limitation was that the healthy Turkish population figures include heterozygotes since the carrier rate is so high.

In conclusion the mutations leading to FMF may have offered a certain advantage to the carriers in ancient times. However the increased innate immune system inflammation may be regarded as a pay-back since they render them predisposed to certain inflammatory conditions.

**Table 2** Comorbidities that may be incidental

| Comorbidity (number of patients) (total number of patients = 2000) | | | |
|---|---|---|---|
| Acute disseminated encephalomyelitis (2) | Diabetes mellitus (7) | Hypothyroidism (10) | Rectal polyp (2) |
| Asthma (4) | Duodenit (2) | Infertility (4) | Renal hypoplasia (2) |
| Autoimmune hepatitis (2) | Endometriosis (2) | Lumbar hernia (2) | Renal transplant (8) |
| Avascular necrosis of the femoral head (2) | Enuresis nocturna (2) | Major depression (3) | Rhythm disorders (2) |
| Bronchiectasis (4) | Epilepsy (6) | Membranoproliferative glomerulonephritis (2) | Selective IgA deficiency (8) |
| Celiac disease(5) | Eyelid chalazia (2) | Nephrolithiasis (6) | Sensorineural hearing loss (2) |
| Cerebrovascular disease (5) | Fibromyalgia (3) | Neurogenic bladder (2) | Septic arthritis (4) |
| Cholecystectomy (20) | Focal segmental glomerulosclerosis (3) | Obesity (2) | Sjögren's syndrome (3) |
| Cholelithiasis (6) | Gastritis (5) | Osteoarthritis (3) | SLE (1) |
| Chronic hepatitis B (2) | Goitre (4) | Osteoporosis (77) | Testis hydrocele (3) |
| Chronic obstructive pulmonary disease (2) | Growth hormone deficiency (2) | Ovarian cyst (4) | Thalassemia trait (5) |
| Congenital heart disease (3) | Haemolytic anaemia (2) | Ovarian cystectomy (3) | Tonsillectomy (2) |
| Deep vein thrombosis (2) | Hepatic haemangioma (2) | Polycystic ovary syndrome (4) | Tuberculosis (2) |
| Dermoid cyst (2) | Hepatosteatosis (53) | Precocious puberty (2) | Vesicoureteral reflux (4) |
| | Hypertension (9) | Pulmonary nodule (2) | Vitamin $B_{12}$ deficiency (4) |
| | Hyperthyroidism (3) | Raynaud's syndrome (3) | |
| Comorbidity for which number of patients is 1 | | | |
| Actinic keratosis | Essential thrombocythaemia | Macular degeneration | Portal vein thrombosis |
| Adenoid vegetation | Ganglioneuroma | Malabsorption of glucose-galactose | Post-cerebellar tumour |
| Adrenal adenoma | Gaucher's disease | Marginal zone lymphoma | Pott's disease |
| ALCAPA syndrome | Gilbert's syndrome | Menier's disease | Primary ciliary dyskinesia |
| Allergic rhinitis | Gliosis | Meningoencephalitis | Psoriasis |
| Alopecia | Granuloma anulare | Migraine | Rectovaginal fistula |
| Anaphylactic shock | Hidradenitis | Mixed connective tissue disease | Renal agenesis |
| Aplastic anaemia | Hirschsprung disease | Muscular dystrophy | Renal angiomyolipoma |
| Acute post-streptococcal glomerulonephritis | Hodgkin's disease | Myoma uteri | Renal artery stenosis |
| | Hydatid cyst | Myopathy | Restless legs syndrome |
| Ataxia telangiectasia | Hydronephrosis | Ovarian cancer | Sialolithiasis |
| Attention-Deficit/Hyperactivity Disorder | Hypoglycaemia | Pancreatic steatosis | Spastic column |
| Bikuspit aorta | Hypogonadotrophic hypogonadism | Pectus excavatum | Splenectomy |
| Bronchiolitis obliterans | Hypotonic infant | Pelvic congestion syndrome | Strabismus |
| C4, C5 protrusion | Infective endocarditis | Peripheral neuropathy | Suicide attempt with colchicine |
| Carpal tunnel syndrome | Inguinal hernia | Pesplanus/plantal fascitis | Thalamic infarct |
| Cerebral infarction | Internal haemorrhoid | Phenylketonuria | Thrombophilia |
| Cerebral palsy | Irregular period | Pilonidal sinus | Thrombophlebitis |
| Cleft palate anomaly | Ischaemic central nervous system disorders | Pituitary adenoma | Thyroid nodule |
| Congenital hip dislocation | Klippel–Feil anomaly | Pityriasis lichenoides chronica | Thyroidectomy |
| Congenital neutropenia | Left brachial artery narrowing | Platelet dysfunction | Tracheomalacia |
| Cortical atrophy | Left kidney double collector system | Polycystic kidney disease | Uterine dysplasia |
| Cranial thrombosis | Lentigo maligna | Polymyositis | Vertigo |
| Endometrium cancer | Lichen planus | Polyneuropathy | Voiding dysfunction |
| Erythema nodosum | | | |

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