Other autoinflammatory disease genes in an FMF-prevalent population: a homozygous *MVK* mutation and a heterozygous *TNFRSF1A* mutation in two different Turkish families with clinical FMF

İ. Karacan[1], S. Uğurlu[2], A. Tolun[3], E. Tahir Turanlı[1,4], H. Ozdogan[2]

[1]*Molecular Biology-Genetics and Biotechnology Department, Dr Orhan Öcalgiray Molecular Biology-Biotechnology and Genetics Research Centre, Graduate School of Science, Engineering and Technology, Istanbul Technical University;*
[2]*Division of Rheumatology, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, Istanbul University;*
[3]*Department of Molecular Biology and Genetics, Boğaziçi University, Istanbul;*
[4]*Department of Molecular Biology and Genetics, Istanbul Technical University, Istanbul, Turkey.*

İlker Karacan, MSc
Serdal Uğurlu, MD
Aslıhan Tolun, PhD
Eda Tahir Turanlı, PhD
Huri Ozdogan, MD

Please address correspondence to:
Prof. Huri Ozdogan,
Department of Internal Medicine,
Division of Rheumatology,
Cerrahpaşa Faculty of Medicine,
Istanbul University,
34098 Istanbul, Turkey.
E-mail: huriozdogan@yahoo.com

Received on April 6, 2017; accepted in revised form on August 2, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 108): S75-S81.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2017.

Key words: autoinflammation, familial Mediterranean fever, hyper IgD syndrome, tumour necrosis factor receptor-associated periodic syndrome, MEFV, MVK, TNFRSF1A

Funding: This work was supported by TÜBİTAK (grant no. 114Z829).

Competing interests: none declared.

ABSTRACT

Objective. *No MEFV mutations are detected in approximately 10% of the patients with clinical FMF in populations where the disease is highly prevalent. Causative mutations were searched in other genes in two such families with "MEFV negative clinical FMF".*

Methods. *Father and daughter of family A had attacks of fever, abdominal pain and AA amyloidosis. The two sibs of family B complained of febrile episodes with abdominal pain and arthritis. The patients were clinically investigated. Exome analysis in the daughter in family A and linkage analysis and candidate gene sequencing for the members of family B were performed. All patients were re-evaluated in the light of the genetic findings.*

Results. *In the daughter in family A, filtering of the exome file for variants in 25 autoimmune/inflammatory disease-related genes revealed two heterozygous missense variants in TNFRSF1A, novel p.Cys72Phe and frequent p.Arg121Gln. In family B, novel, homozygous missense p.Cys161Arg in MVK was identified. A clinical re-evaluation of the patients revealed a phenotype consistent with FMF rather than TRAPS in family A and an overlap of FMF with HIDS in family B.*

Conclusion. *In high risk populations of FMF a proportion of patients without MEFV mutations may carry causative mutations in other genes, and the clinical findings may not be fully consistent with the phenotype expected of the mutation identified but rather resemble FMF or an overlap syndrome.*

Introduction

Hereditary autoinflammatory diseases (AIDs) are caused by defects in the innate immune system and characterised by unprovoked inflammatory attacks in the absence of autoantibodies, auto-reactive T-cells and pathogens (1). Familial Mediterranean fever (FMF; MIM 249100), tumour necrosis factor receptor-associated periodic syndrome (TRAPS; MIM 142680) and hyper-immunoglobulinaemia D syndrome (HIDS; MIM 260920) which is also known as mevalonate kinase deficiency (MKD) are among the well-defined hereditary AIDs. FMF is the most common of all with an overall prevalence of 1–2 in 1000 in high-risk populations such as Armenians, Sephardic Jews, Turks and Arabs (2). Although each syndrome has a unique combination of features and a different genetic aetiology, several of those may overlap. To prevent the recurrence of inflammatory attacks and the long-term complications, differential diagnosis among AIDs is crucial (3). The vast majority of the patients with FMF, which is an autosomal recessive disease, carry mutations in the Mediterranean fever (*MEFV*) gene, encoding pyrin (4, 5). The *MEFV* mutations activate pyrin inflammasome and increase IL-1β production (6). However, approximately one third of the patients with clinically diagnosed FMF carry either no or a single *MEFV* mutation (7), therefore, FMF is considered as a clinical diagnosis.

The *MVK* gene encodes mevalonate kinase, a peroxisomal enzyme involved in the biosynthesis of cholesterol and isoprenoid (8). Although the exact mechanism of how dysregulation of isoprenoid pathway can lead to fever attacks is still unknown (9), it has been shown that a group of syndromes including HIDS and mevalonic aciduria can be caused by mutations in *MVK* (10).

Tumour necrosis factor receptor superfamily member 1A (*TNFRSF1A*) gene

encodes a receptor for the tumour necrosis factor-alpha, which can activate NF-kappaB pathway, functioning as a regulator of inflammation. The protein product is TNFR p55, expressed in various cell types and specifically bound by the proinflammatory cytokine TNF. Heterozygous mutations in *TNFRSF1A* can cause TRAPS, characterised by unexplained episodes of fever and systemic inflammation (1).

Herein, we present patients with an initial diagnosis of FMF but were negative for *MEFV* mutation. We searched for causative mutations and re-evaluated the patients.

Patients

Four patients from two unrelated Turkish families (Fig. 1) followed in the Rheumatology Division of Cerrahpaşa Medical Faculty with the diagnosis of FMF were tested negative for *MEFV* mutations twice by using FMF Strip Assays (Vienna Lab Diagnostics, Austria) and Sanger sequencing of all exons. Non-affected family members were invited to the clinic for a thorough history taking, physical examination and genetic studies. This study was approved by the Institutional Review Board of Istanbul Technical University.

Methods

A DNA sample of patient A2 in family A was subjected to whole exome sequencing. Sequencing library was prepared using NimbleGen SeqCap EZ MedExome Enrichment Kit (Roche, Switzerland), and reads were produced with Illumina Hiseq instrument. Raw sequencing data were analysed according to GATK Best Practices recommendations (11). Briefly, reads were aligned using BWA (12) to human reference genome hg19 (http://genome.ucsc.edu) later base quality score recalibration, in/del realignment and duplicate removal were performed. Then SNPs and in/dels were called by GATK (13). Detected variants were annotated with ANNOVAR (14). Variants in immune system related genes were prioritised.

In family B, SNP genotyping was performed using Illumina OmniExpress-24 BeadChip that target >700.000 SNP markers. Illumina GenomeStudio Genotyping Module (v2011.1) was used to determine genotypes. Multipoint linkage analysis was performed under the software package EasyLinkage (15). Logarithm of odds (LOD) scores were calculated assuming recessive inheritance, full penetrance and a disease allele frequency of 0.001, using GeneHunter (16). For regions that yielded relatively high LOD scores, we evaluated genotypes in order to confirm shared homozygosity only between the affected sibs.

Homozygous regions >1 Mb shared by only the affected sibs with a maximal LOD score >1.8 were considered. We evaluated the genes in those regions for any possible relation to autoinflammatory disorders, as reported in databases PubMed and InFevers. InFevers is a repository that includes a list of variants in 25 genes related to autoinflammatory disorders (17-19). *MVK* variant seemed a very strong candidate, but to exclude other variants in the most common autoinflammatory disease-related genes, *IL1RN, LPIN2*, *MEFV*, *NLRP12, NLRP3, TNFRSF1A, PSTPIP1,* we screened all exons and intronic boundaries in both patients by long PCR based amplicon sequencing using next generation sequencing (NGS) technology.

The identified mutations were validated and tested for all family members by Sanger sequencing. Population frequencies were investigated in the 1,182 exome files in the Advanced Genomics and Bioinformatics Research Centre (IGBAM), the Scientific and Technological Research Council of Turkey (TÜBİTAK). We also used computational algorithms SIFT (20), PolyPhen-2 (21) and MutationTaster2 (22) to predict possible impacts of the identified mutations.

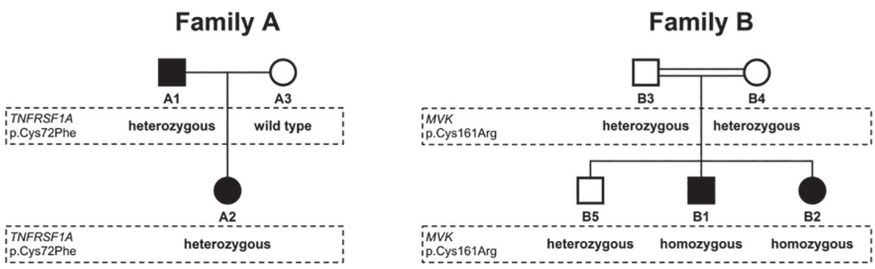

Fig.1. Pedigrees with mutation status of patients.

Results

Clinical findings

The clinical findings of the four patients are compared to the manifestations of FMF, TRAPS and HIDS in Table I.

Family A

Patient A1: The 55-year old man was referred to our Rheumatology Outpatient Clinic (OPC) from the Nephrology unit at the age of 34 years for investigation of his chronic renal failure secondary to biopsy proven amyloid A (AA) amyloidosis. His disease history revealed recurrent abdominal pain and fever attacks lasting 1-2 days per month since the age of 10 years, which decreased spontaneously during the course of the disease. There was no family history of FMF or AA amyloidosis then. He did not carry any *MEFV* mutation. At the age of 37 he underwent renal transplantation. Four years later, while receiving tacrolimus (2 mg/d), colchicine (2 mg/d), azathioprine (150 mg/d) and prednisolone (5 mg/d), AA amyloidosis recurred in the transplanted kidney. He was lost to follow-up for 7 years, until his daughter was admitted to our unit for recurrent febrile attacks. At present he is on anakinra (100 mg/d), with a significant decrease in acute phase response and proteinuria.

Patient A2: The daughter (24 years old) was admitted to our OPC at the age of 12 with monthly attacks of fever and abdominal pain that lasted 2-3 days. She also was negative for *MEFV* mutation. Initially her attacks responded to colchicine (1.5 mg/d), but her compliance was poor. At the age of 21 she developed proteinuria and her renal biopsy revealed AA amyloidosis. The high acute phase proteins and 24-hour proteinuria responded dramatically to treatment

Table I. Comparison of the findings in patients to known clinical features in three diseases.

Features and findings	A1	A2	B1	B2	FMF	TRAPS	HIDS
Ethnic origin	MED	MED	MED	MED	MED	NEU	NEU
Mode of inheritance	AD	AD	AR	AR	AR*	AD	AR
Duration of attacks							
≤1 week	+	+	+	+	+	-	+
>1week	-	-	-	-	-	+	-
Attacks of fever and serositis	+	+	+	+	+	+	+
Red arthritis	-	-	+	+	+	-	+
Rash (macula-papular, urticarial)	-	-	-	-	-	+	+
Myalgia (myositis/fasciitis)	-	-	-	-	+	+	?
Periorbital edema	-	-	-	-	-	+	-
Conjunctivitis	-	-	-	-	-	+	-
Diarrhoea/vomiting							
during attacks	-	-	-	+	-	-	+
post-attack	-	-	-	+	+	-	-
Brit ileus	-	-	-	+	+	-	+
PRES-like CNS involvement	-	-	+	-	+	-	-
Delay in growth	-	-	+	+	-	-	+[¥]
Acute phase response	+	+	+	+	+	+	+
High serum IgD	-	-	+[§]	-	-	-	+
Mevalonic aciduria	-	-	-	-	-	-	+
Response to colchicine	±	±	±	±	+	-	-
Response to anti-IL-1 treatment	+	NA	+	+	+	+	+
AA amyloidosis	+	+	-	-	+	+	+
Mutated gene	*TNFRSF1A*	*TNFRSF1A*	*MVK*	*MVK*	*MEFV*	*TNFRSF1A*	*MVK*

FMF: familial Mediterranean fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; HIDS: hyper-immunoglobulinaemia D syndrome; MED: Mediterranean; NEU: northern European; NA: not available.
*Pseudodominant and rare autosomal dominant transmission may be seen in FMF. [¥]Delay in growth is more pronounced in mevalonic aciduria. [§]Level of IgD was 50.4 IU/ml which was higher than our lab normal (>13.2 IU/ml) but lower than the diagnostic threshold of 100 IU/ml. ± Partial response.

with anti-IL-6 agent tociluzimab (400 mg/month) in addition to colchicine.

Short-lived febrile attacks and AA amyloidosis were compatible with the diagnosis of FMF. Contrary to the majority of the patients with FMF amyloidosis who carry biallelic exon 10 mutations, our cases were negative for any *MEFV* mutation. Thus, a genetic study was launched to search the putative causative mutation in other genes. After the detection of heterozygous missense variants in *TNFRSF1A*, novel p.Cys72Phe and frequent p.Arg121Gln, they were reassessed for symptoms or signs suggestive of TRAPS. The autosomal dominant transmission was compatible with TRAPS, but the characteristics of the attacks and the absence of typical features of this syndrome were not indicative of TRAPS.

Family B

Patient B1: The eldest male sib (17 years old) of consanguineous parents from Sivas, a mid-Anatolian town with very high prevalence of FMF (23), was referred to our OPC at the age of 5 years with a possible diagnosis of FMF. He had recurrent episodes of abdominal pain and fever lasting 2–4 days besides occasional erythematous swelling of a knee or an ankle since the age of 4. He had been initially diagnosed elsewhere with acute rheumatic fever, and a relevant treatment had not been successful. He was small for his age (3rd percentile). Acute phase response was over the normal levels in-between attacks. He was negative for *MEFV* mutation and HLA B27. A partial response to colchicine treatment was observed. At the age of 14 he had developed sudden bilateral vision loss following an upper respiratory tract infection. Posterior reversible encephalopathy syndrome (PRES) was considered in differential diagnosis. Vision and the cranial MRI findings improved within 3 months on prednisolone and cyclophosphamide treatment. Due to an increase in the frequency of febrile attacks and acute phase proteins, canakinumab, an IL-1 antagonist, was introduced (150 mg/month). A dramatic response was obtained; attacks disappeared and the level of the acute phase proteins returned to normal. A significant growth spurt was observed during the course of canakinumab treatment, which has been continuing for the last 52 months.

Patient B2: The sister of patient B1 (7 years old) was admitted to our OPC when she was one-year old, with bouts of severe abdominal pain, nausea, vomiting and fever lasting 4–5 days, once or twice a month. Occasional erythematous swellings of wrists or ankles were observed. She was diagnosed as FMF and put on colchicine (1 mg/d) treatment with a partial response. Laparostomy had to be performed thrice with the diagnosis of acute abdomen and ileus due to peritoneal adhesions when she was only 17, 35 and 50 months old. No vasculitis was detected in the histopathological examinations of the biopsy materials. The acute phase reactants were over normal limits between the attacks. Canakinumab (4 mg/kg/mo) was added to her treatment after the dramatic response observed in her brother. Under this regimen for the last 47 months she is attack-free, acute phase reactants are back to normal and there is a growth spurt. The two siblings had recurrent attacks of fever and serositis

compatible with FMF. However, severe abdominal attacks with very early peritoneal adhesions, limited response to colchicine administration and absence of *MEFV* mutation made this diagnosis questionable. After the possible causative *MVK* mutation was identified, the patients were re-evaluated. The mother recalled enlarged cervical lymph nodes in a few occasions in both sibs in the very early years of the disease. Detailed information on diarrhoea during attacks in patient B2 and bouts of mild abdominal pain and fever within the first year of life in patient B1 were also obtained; however, mother denied any skin eruptions or any specific association with a trigger such as vaccination, a well-known characteristics of HIDS.

Urinary mevalonic acid was not detected in any sib of family B. Serum IgD level was elevated only in patient B1 (50.4 and 6.72 IU/ml, in B1 and B2 respectively; reference range: 0.77-13.2 IU/ml), however, canakinumab treatment could have interfered with the results.

Genetic findings

Family A: We found 20 missense variants in the prioritised 25 immune system-related genes from exome file of the affected daughter. The best candidate to underlie the pathology in the family was *TNFRSF1A* c.215G>T (p.Cys72Phe), which was not listed in The Exome Aggregation Consortium (ExAC) or Exome Sequencing Project (ESP) databases or found in the IGBAM-TÜBİTAK databases. Mutation p.Cys72Phe resulted in the substitution of cysteine with hydrophobic phenylalanine. The variant is predicted as damaging by online tools PolyPhen-2, SIFT and MutationTaster2. The altered cysteine amino acid is very well conserved in mammals. The second variant *TNFRSF1A* c.362G>A (p.Arg121Gln; rs4149584) was predicted as possibly damaging by PolyPhen-2 and benign by both SIFT and MutationTaster2. It has the highest frequency of 0.02 in Europeans.

The father but not the mother, was heterozygous for the variants. We assessed that the former mutation underlies the disease.

Family B: Multipoint linkage analysis in a recessive model yielded a maximal LOD score of ~1.9 in seven regions >1-Mb and not including 16p13 where *MEFV* resides. In those regions homozygosity was shared only by the patients. Sequence analysis of *MVK* residing at the largest locus (12 Mb) and of seven other autoinflammation-related genes uncovered only one possibly detrimental homozygous mutation in the patients; parents and unaffected sib were heterozygous for this *MVK* variant, c.481T>C (p.Cys161Arg). The mutation was not present in ExAC, ESP, or IGBAM-TÜBİTAK databases. At the protein level, cysteine at position 161 is very well conserved in mammals. Mutation p.Cys161Arg resulted in the substitution of cysteine with positively charged, polar arginine. SIFT predicted it as tolerated, PolyPhen-2 as possibly damaging and MutationTaster2 as polymorphism. We concluded that this mutation underlies the pathology in the sibs because the mutation is novel and resides in the largest candidate region.

Discussion

FMF is the most frequent hereditary AID (24), which predominantly affects populations of Mediterranean descent (2). The overall prevalence of FMF in Turkey is 2/1000; however, it can be as high as 8/1000 in certain parts of the country (23, 25, 26). In addition, carrier rate of *MEFV* mutations in healthy population can range from 6.4 to 25.9 percent across different regions of Turkey (27). Hence, differential diagnosis of a rare hereditary AID in FMF-prevalent populations could be a challenge. Also there is also the possibility of a mutation in a novel disease gene as a consequence of high parental consanguinity and multi-ethnicity in this geography. Generally, any patient with a history of short bouts of fever, serositis and a positive family history is diagnosed as FMF and administered colchicine, without a genetic diagnosis. The majority of FMF patients carry mutations in *MEFV,* however, 20-30% of the clinically diagnosed FMF cases from high-risk populations carry either a single copy or no mutations, therefore FMF is considered as a clinical diagnosis (7, 28). Here we present four patients from two families who have been diagnosed as clinical-FMF but were negative for any *MEFV* mutation.

TRAPS is a rare autosomal dominant disease caused by mutations in *TNFRSF1A* gene at 12p13.2 and reported more frequently in Caucasians, with an estimated prevalence of about one per million (29). There is some clinical overlap between TRAPS and FMF, including attacks of fever, serositis, arthritis, myositis and erysipelas like erythema (ELE). Both may be complicated with AA amyloidosis. Aksentijevich *et al*. (2001) reported that approximately 14% of the patients with TRAPS developed AA amyloidosis (30). The main reason for further investigation in family A was the absence of *MEFV* mutation with a severe disease complicated with AA amyloidosis. It is well known that the vast majority of the cases with FMF, AA amyloidosis is associated mainly with p.Met694Val or some other variants in exon 10 (31, 32). Two *TNFRSF1A* variants were found in the daughter and father but not in the mother. Novel p.Cys72Phe variant is predicted as damaging by online tools, and the altered residue is very well conserved among mammals. The second variant p.Arg121Gln (rs4149584) has been classified as a low-penetrant mutation rather than a benign variant by Aksentijevich *et al*. (30), indicating that the two variants together could underlie the pathology in these cases. Patients who carried mutations affecting cysteine domains of the protein were reported as more prone to develop AA amyloidosis as compared to those who had non-cystein mutations (30). p.Cys72Phe is also a cysteine mutation, and present in both of our patients with AA amyloidosis.

Typical attacks in TRAPS last more than one week and symptoms may be continuous in a third of patients contrary to short-lasting episodes of FMF with symptom-free intervals. The typical features of TRAPS such as rash, periorbital oedema, conjunctivitis and headache are not common in FMF (33). The attacks were shorter than 4 days in both patients, while patient A2 recalled mild pain over the forearms during a few attacks, father denied any

sign consistent with TRAPS during clinical reassessment after mutation identification.

Colchicine has been reported as not effective for the treatment of TRAPS (34). However, the data from EUROFEVER registry revealed beneficial effect in 21, three with full response, of the 39 TRAPS patients who had received colchicine (35). Interestingly short-lived febrile attacks of patient A2 responded to colchicine therapy initially. One cannot help but speculate whether AA amyloidosis could be prevented if colchicine had been initiated early in the course of the disease with full compliance. Accumulating data suggest favourable results with anti-IL-1 agents in TRAPS (36, 37). The father received anakinra, an anti-IL-1 agent, only after the development of AA amyloidosis in the transplanted kidney with good response. The daughter was administered tocilizumab, also an anti-IL-6 agent, together with colchicine and had a significant decrease in proteinuria and acute phase response. She is the first patient reported with TRAPS associated AA amyloidosis who has been treated with tocilizumab. This observation, therefore adds to the scarce information available on the role of IL-6 blockade in the treatment of TRAPS (38-40).

The two sibs in family B were initially diagnosed as FMF because they had recurrent, self-limiting episodes of abdominal pain, fever and red arthritis as well as consanguineous parents from a region with the highest FMF prevalence in the country (23). Further genetic studies were launched because they were negative for *MEFV* mutations. Novel, homozygous missense c.481T>C (p.Cys161Arg) in *MVK* was identified in both patients.

MKD/HIDS is not so rare in Western European countries; especially Netherlands (41) whereas only a number of cases have been reported so far from Turkey (42-47). There are several clinical manifestations common to both diseases. One of the most striking differences between MKD/HIDS and FMF is the age of onset. In MKD/HIDS attacks generally start in infancy, with a median age of 6 months (48). In a cohort study by van der Hilst *et al*., 78% of MKD/HIDS patients were reported to experience their first attack before 12 months of age (41) whereas attack-onset before age one is reported in only 0.7% of FMF cases (49). Bilateral tender cervical lymphadenopathy is a common (in 89%), well described feature of MKD/HIDS (33) but not a sign of FMF. In patient B2 abdominal attacks were accompanied by very severe pain and diarrhoea. Abdominal pain episodes are commonly (in 86%) accompanied by diarrhoea in MKD/HIDS whereas in FMF it occurs in 27% as the attack subsides and thus defined as post-attack diarrhoea (33). It is well established that recurrent peritonitis may result in sub-ileus and peritoneal adhesions in both diseases. This was more common before the colchicine-era and was a late complication in untreated FMF patients (50). Van der Hilts *et al*., on the other hand, observed abdominal adhesions in 10 of the 103 MKD/HIDS patients with recurrent severe abdominal attacks (41). Over 60-80% of the patients with MKD/HIDS present a variety of skin lesions, especially maculopapular rash (41, 51). None of our patients developed a MKD/HIDS associated skin eruption; the only skin manifestation is erythema over the involved joint, which is also a very common feature of FMF (52).

Mevalonate aciduria and high serum IgD level (>100 IU/ml) are the diagnostic hallmarks of MKD/HIDS, but the level of IgD is normal in approximately one fifth of the patients (53, 54). Urinary mevalonic acid was not increased in our patients. IgD in patient B1 (50.4 IU/ml) was above the accepted laboratory range (normal range: 0.77-13.2 IU/ml), but nonetheless, it was lower than the diagnostic level of 100 IU/ml for HIDS. Of note, the tests were performed under canakinumab therapy, which may have interfered with the IgD levels.

Delayed growth is not observed in children with FMF (55) but a common manifestation of mevalonic aciduria (MEVA; MIM 610377), a more severe form of mevalonate kinase deficiency (56, 57); yet there is no sufficient data in children with HIDS. The same holds for central nervous system involvement. Patients with MEVA typically suffer from severe psychomotor retardation, progressive cerebellar ataxia, and progressive visual impairment. The PRES-like involvement observed in patient B1 is occasionally reported in FMF (58, 59) but not for patients with HIDS. The neurocognitive functions of these two sibs were within normal limits.

Several cases with HIDS-FMF overlap syndromes have been reported (45, 47, 60), and mutations in *MEFV* and/or *MVK* were found in these cases.

Colchicine, the mainstay of treatment in FMF, is not effective in patients with MKD/HIDS. Prednisolone, anti-TNF agents and anakinra have been tried with some beneficial effect (41, 61). There are few reported cases of MKD/HIDS who have been treated with canakinumab (62, 63); thus, the dramatic response obtained with canakinumab therapy in the two sibs of family B deserves attention also in this respect and underlines the importance of IL-1β in the pathogenesis of MKD/HIDS.

Conclusion

FMF is a clinical diagnosis, and the majority of the cases are caused by *MEFV* mutations. However, approximately one-third of the patients have either no mutation or a mutation in single *MEFV* allele. As observed in our patients, considering another hereditary AID in an FMF-prevalent population could be a challenge, because the phenotypes of those patients may not be fully compatible with the clinical presentation expected of the mutation detected. This may be due to some environmental and/or yet undefined genetic or epigenetic factors. We propose that patients with a diagnosis of clinical FMF but negative for biallelic *MEFV* mutation could benefit from further genetic studies.

Acknowledgements

We thank all the family members for their cooperation and Advanced Genomics and Bioinformatics Research Centre (IGBAM), the Scientific and Technological Research Council of Turkey (TÜBİTAK) for sharing with us the Turkish exome sequence database. We also thank Prof. Eldad Ben Chetrit for his critical reviewing of the manuscript.

References

1. MCDERMOTT MF, AKSENTIJEVICH I, GALON J *et al*.: Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999; 97: 133-44.
2. BEN-CHETRIT E, TOUITOU I: Familial mediterranean Fever in the world. *Arthritis Rheum* 2009; 61: 1447-53.
3. TOUITOU I, GALEOTTI C, ROSSI-SEMERANO L *et al*.: The expanding spectrum of rare monogenic autoinflammatory diseases. *Orphanet J Rare Dis* 2013; 8: 162.
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. TOUITOU I: The spectrum of Familial Mediterranean Fever (FMF) mutations. *Eur J Hum Genet* 2001; 9: 473-83.
6. YANG J, XU H, SHAO F: Immunological function of familial Mediterranean fever disease protein Pyrin. *Sci China Life Sci* 2014; 57: 1156-61.
7. BOOTH DR, GILLMORE JD, LACHMANN HJ *et al*.: The genetic basis of autosomal dominant familial Mediterranean fever. *QJM* 2000; 93: 217-21.
8. GOLDSTEIN JL, BROWN MS: Regulation of the mevalonate pathway. *Nature* 1990; 343: 425-30.
9. VAN DER BURGH R, TER HAAR NM, BOES ML, FRENKEL J: Mevalonate kinase deficiency, a metabolic autoinflammatory disease. *Clin Immunol* 2013; 147: 197-206.
10. DRENTH JP, CUISSET L, GRATEAU G *et al*.: Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. *Nat Genet* 1999; 22: 178-81.
11. VAN DER AUWERA GA, CARNEIRO MO, HARTL C *et al*.: From FastQ data to high confidence variant calls: the Genome Analysis Toolkit best practices pipeline. *Curr Protoc Bioinformatics* 2013; 43: 11.10 1-33.
12. LI H, DURBIN R: Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* 2009; 25: 1754-60.
13. MCKENNA A, HANNA M, BANKS E *et al*.: The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res* 2010; 20: 1297-303.
14. WANG K, LI M, HAKONARSON H: ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* 2010; 38: e164.
15. HOFFMANN K, LINDNER TH: easyLINKAGE-Plus--automated linkage analyses using large-scale SNP data. *Bioinformatics* 2005; 21: 3565-7.
16. KRUGLYAK L, DALY MJ, REEVE-DALY MP, LANDER ES: Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet* 1996; 58: 1347-63.
17. SARRAUSTE DE MENTHIERE C, TERRIERE S, PUGNERE D, RUIZ M, DEMAILLE J, TOUITOU I: INFEVERS: the Registry for FMF and hereditary inflammatory disorders mutations. *Nucleic Acids Res* 2003; 31: 282-5.
18. TOUITOU I, LESAGE S, MCDERMOTT M *et al*.: Infevers: an evolving mutation database for auto-inflammatory syndromes. *Hum Mutat* 2004; 24: 194-8.
19. MILHAVET F, CUISSET L, HOFFMAN HM *et al*.: The infevers autoinflammatory mutation online registry: update with new genes and functions. *Hum Mutat* 2008; 29: 803-8.
20. KUMAR P, HENIKOFF S, NG PC: Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc* 2009; 4: 1073-81.
21. ADZHUBEI IA, SCHMIDT S, PESHKIN L *et al*.: A method and server for predicting damaging missense mutations. *Nat Methods* 2010; 7: 248-9.
22. SCHWARZ JM, COOPER DN, SCHUELKE M, SEELOW D: MutationTaster2: mutation prediction for the deep-sequencing age. *Nat Methods* 2014; 11: 361-2.
23. OZDOGAN H, UGURLU S, HATEMI G *et al*.: Is Familial Mediterranean Fever a clinical diagnosis? Results of a field survey. *Pediat Rheumatol Online J* 2015; 13: P126-P.
24. TOPLAK N, FRENKEL J, OZEN S *et al*.: An international registry on autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis* 2012; 71: 1177-82.
25. TUNCA M, AKAR S, ONEN F *et al*.: Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine* (Baltimore) 2005; 84: 1-11.
26. KISACIK B, YILDIRIM B, TASLIYURT T *et al*.: Increased frequency of familial Mediterranean fever in northern Turkey: a population-based study. *Rheumatol Int* 2009; 29: 1307-9.
27. SOYLEMEZOGLU O, KANDUR Y, GONEN S *et al*.: Familial Mediterranean fever gene mutation frequencies in a sample Turkish population. *Clin Exp Rheumatol* 2016; 34 (Suppl. 102): S97-100.
28. LIVNEH A, LANGEVITZ P, ZEMER D *et al*.: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.
29. LACHMANN HJ, PAPA R, GERHOLD K *et al*.: The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. *Ann Rheum Dis* 2014; 73: 2160-7.
30. AKSENTIJEVICH I, GALON J, SOARES M *et al*.: The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. *Am J Hum Genet* 2001; 69: 301-14.
31. 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: 287-92.
32. MUKHIN NA, KOZLOVSKAYA LV, BOGDANOVA MV, RAMEEV VV, MOISEEV SV, SIMONYAN A: Predictors of AA amyloidosis in familial Mediterranean fever. *Rheumatol Int* 2015; 35: 1257-61.
33. FEDERICI S, SORMANI MP, OZEN S *et al*.: Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. *Ann Rheum Dis* 2015; 74: 799-805.
34. MASSON C, SIMON V, HOPPE E, INSALACO P, CISSE I, AUDRAN M: Tumor necrosis factor receptor-associated periodic syndrome (TRAPS): definition, semiology, prognosis, pathogenesis, treatment, and place relative to other periodic joint diseases. *Joint Bone Spine* 2004; 71: 284-90.
35. TER HAAR N, LACHMANN H, OZEN S *et al*.: Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis* 2013; 72: 678-85.
36. GATTORNO M, PELAGATTI MA, MEINI A *et al*.: Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. *Arthritis Rheum* 2008; 58: 1516-20.
37. GATTORNO M, OBICI L, CATTALINI M *et al*.: Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. *Ann Rheum Dis* 2017; 76: 173-8.
38. HOSOYA T, MIZOGUCHI F, HASEGAWA H *et al*.: A Case Presenting with the Clinical Characteristics of Tumor Necrosis Factor (TNF) Receptor-associated Periodic Syndrome (TRAPS) without TNFRSF1A Mutations Successfully Treated with Tocilizumab. *Intern Med* 2015; 54: 2069-72.
39. LA TORRE F, MURATORE M, VITALE A, MORAMARCO F, QUARTA L, CANTARINI L: Canakinumab efficacy and long-term tocilizumab administration in tumor necrosis factor receptor-associated periodic syndrome (TRAPS). *Rheumatol Int* 2015; 35: 1943-7.
40. AKASBI N, SOYFOO MS: Successful treatment of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) with tocilizumab: A case report. *Eur J Rheumatol* 2015; 2: 35-6.
41. VAN DER HILST JC, BODAR EJ, BARRON KS *et al*.: Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. *Medicine* (Baltimore) 2008; 87: 301-10.
42. TOPALOGLU R, SAATCI U: Hyperimmunoglobulinaemia D and periodic fever mimicking familial Mediterranean fever in the Mediterranean. *Postgrad Med J* 1991; 67: 490-1.
43. COBAN E, TERZIOGLU E: A patient with hyper-IgD syndrome in Antalya, Turkey. *Clin Rheumatol* 2004; 23: 177-8.
44. DEMIRKAYA E, CAGLAR MK, WATERHAM HR, TOPALOGLU R, OZEN S: A patient with hyper-IgD syndrome responding to anti-TNF treatment. *Clin Rheumatol* 2007; 26: 1757-9.
45. TOPALOGLU R, AYAZ NA, WATERHAM HR, YUCE A, GUMRUK F, SANAL O: Hyperimmunoglobulinemia D and periodic fever syndrome; treatment with etanercept and follow-up. *Clin Rheumatol* 2008; 27: 1317-20.
46. GENCPINAR P, MAKAY BB, GATTORNO M, CAROLI F, UNSAL E: Mevalonate kinase deficiency (hyper IgD syndrome with periodic fever)--different faces with separate treatments: two cases and review of the literature. *Turk J Pediatr* 2012; 54: 641-4.
47. TAS DA, DINKCI S, ERKEN E: Different clinical presentation of the hyperimmunoglobulin D syndrome (HIDS) (four cases from Turkey). *Clin Rheumatol* 2012; 31: 889-93.
48. ALMEIDA DE JESUS A, GOLDBACH-MANSKY R: Monogenic autoinflammatory diseases:

concept and clinical manifestations. *Clin Immunol* 2013; 147: 155-74.
49. BARUT K, SINOPLU AB, YUCEL G *et al*.: Familial Mediterranean Fever in childhood: a single center experience. *Pediat Rheumatol Online J* 2015; 13: O12-O.
50. 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: 227-53.
51. BADER-MEUNIER B, FLORKIN B, SIBILIA J *et al*.: Mevalonate kinase deficiency: a survey of 50 patients. *Pediatrics* 2011; 128: e152-9.
52. TAKAHASHI T, FUJISAWA T, KIMURA M, OHNISHI H, SEISHIMA M: Familial Mediterranean fever variant with repeated atypical skin eruptions. *J Dermatol* 2015; 42: 903-5.
53. AMMOURI W, CUISSET L, ROUAGHE S *et al*.: Diagnostic value of serum immunoglobulinaemia D level in patients with a clinical suspicion of hyper IgD syndrome. *Rheumatology* (Oxford) 2007; 46: 1597-600.
54. SAULSBURY FT: Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) in a child with normal serum IgD, but increased serum IgA concentration. *J Pediatr* 2003; 143: 127-9.
55. SAVGAN-GUROL E, KASAPCOPUR O, HATEMI S *et al*.: Growth and IGF-1 levels of children with familial Mediterranean fever on colchicine treatment. *Clin Exp Rheumatol* 2001; 19 (Suppl. 24): S72-5.
56. MULDERS-MANDERS CM, SIMON A: Hyper-IgD syndrome/mevalonate kinase deficiency: what is new? *Semin Immunopathol* 2015; 37: 371-6.
57. GLASER RL, GOLDBACH-MANSKY R: The spectrum of monogenic autoinflammatory syndromes: understanding disease mechanisms and use of targeted therapies. *Curr Allergy Asthma Rep* 2008; 8: 288-98.
58. FELD O, YAHALOM G, LIVNEH A: Neurologic and other systemic manifestations in FMF: published and own experience. *Best Pract Res Clin Rheumatol* 2012; 26: 119-33.
59. KALYONCU U, EKER A, OGUZ KK *et al*.: Familial Mediterranean fever and central nervous system involvement: a case series. *Medicine* (Baltimore) 2010; 89: 75-84.
60. MOUSSA T, ALADBE B, TAHA RZ, REMMERS EF, EL-SHANTI H, FATHALLA BM: Overlap of familial Mediterranean fever and hyper-IgD syndrome in an Arabic kindred. *J Clin Immunol* 2015; 35: 249-53.
61. KOSTJUKOVITS S, KALLIOKOSKI L, ANTILA K, KORPPI M: Treatment of hyperimmunoglobulinemia D syndrome with biologics in children: review of the literature and Finnish experience. *Eur J Pediatr* 2015; 174: 707-14.
62. CURTIS CD, FOX CC: Treatment of adult hyper-IgD syndrome with canakinumab. *J Allergy Clin Immunol Pract* 2015; 3: 817-8.
63. GALEOTTI C, MEINZER U, QUARTIER P *et al*.: Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. *Rheumatology* (Oxford) 2012; 51: 1855-9.