IN THE NAME OF GOD

The distribution of MEFV mutations in Iranian FMF patients: (multicenter study)

Author:Dr.Enayatollah Nemat Khorasani-MD.Pediatric Gastroentrologist.Faculty of TUMS.pediatric Departement of Baharloo hospital.Tehran.Iran

Corresponding author:Dr.E.N.Khorasani-MD.Gastroentrologist.Faculty of TUMS.Pediatric Departement of Baharloo hospital.Tehran.Iran.E.mail:Khorasani@dr.com

Mobile:0989120879727.

### Abstract: Background/aim

The distribution of Mediterranean fever (MEFV) gene mutations in Iranian familial Mediterranean fever (FMF) patients varies according to geographic area of Iranian. There is a need for highly representative data for Iranian FMF patients. The aim of my study was to investigate the distribution of the common MEFV mutations in Iranian FMF patients in a nationwide, multicenter study.(Tehran,Mashhad,Kermanshah,Tabriz)that were visited by me for 20 years.

Materials and methods

Data of the 324 FMF patients, from 4 pediatric clinics located in different parts of the country, were evaluated retrospectively. The following mutations have been tested in all patients: M694V, M680I, M694I, V726A, and E148Q.

Results

There were 324 FMF patients with available genetic testing. According to the genotyping, hetrozygous E148Q, present in 254 patients (78%), was the most common mutation .25 of patients had no detectable mutations. Allele frequencies of common mutations were:E148Q (n = 254, 78%), M694V (n = 23, 7%), V726A (n = 13, 4%), M694I (n =7 ,2%), and M680I (n = 2, <1%).298 of them were Males&26 Females.The ages of them between 1.5 year to 48 year.The common symptoms were(Abdominal pain,,Recurrent vomiting,Artheralgia, Headche,Skin rash,Chest pain.Diarreha .).and the common sign was periodic fever.

Conclusion

In this large-scale multicenter study, we provided information about the frequencies of common MEFV gene mutations obtained from children to adults Iranian FMF patients. The maximal of the patients were carrying at least one E148Q mutations in their alleles.

**Keywords:**Familial Mediterranean fever, Mediterranean fever gene mutations,E148Q,Iranian.

 Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease with self-limiting attacks characterized by serositis and fever (1). The disease primarily occurs in individuals of Mediterranean ancestry, and particularly among certain ethnic groups such as Jews, Turks, Armenians, and Arabs (2). Turks are considered to have the highest prevalence with an estimated rate of 1:150 to 1:1000 (1,3). FMF is caused by the mutations in the MEFV (Mediterranean fever) gene and inherited in an autosomal recessive manner. However, nearly 30% of documented FMF patients exhibit non-Mendelian genetic transmission, carrying only one mutation, and up to 20% of patients do not have detectable mutations as per current technology (4). So far, more than 300 sequence variations have been identified in the MEFV gene, mostly due to single nucleotide substitutions (5). Five founder mutations, located on exon 10 (M694V, V726A, M694I, and M680I) and exon 2 (E148Q), account for nearly 80% of patients with typical cases from these ethnic groups (1). A previous study of 1090 Turkish FMF patients reported in 2005 showed that M694V was the most frequently observed mutation, followed by M680I and V726A (3,7,8).

Materials and methods

In this study, according to the researched on the syptoms&sigins of my refer patients by myself in 4 pediatric clinics  located in different regions of Iran(at Tehran.Mashhad.Kermanshah.Tabriz),I investigated them by DNA Extraction,PCR-RFLP(FMF strip assey)Direct Sequencing method for detection of five founder mutation and enforceable in our genetic laboratories(M694V, V726A, M694I, M680I andE148Q).

Statistical analysis

Continuous variables were presented as mean ± SD, and categorical variables were presented as frequency (n) and percent. The chi-square statistic was used for testing relationships between categorical variables. IBM SPSS Statistics 21 was used for descriptive statistics.

Results

There were 324 FMF patients with available genetic testing. According to the genotyping, hetrozygous E148Q, present in 254 patients (78%), was the most common mutation .25 of patients had no detectable mutations. Allele frequencies of common mutations were:E148Q (n = 254, 78%), M694V (n = 23, 7%), V726A (n = 13, 4%), M694I (n =7 ,2%), and M680I (n = 2, <1%).298 of them were Males&26 Females.The ages of them between 1.5 year to 48 year.The common symptoms were(Abdominal pain,,Recurrent vomiting,Artheralgia, Headche,Skin rash,Chest pain.Diarreha .).and the common sign was periodic fever.

Discussion

FMF is the most common autoinflammatory disease and Iran has one of the highest incidence and prevalence ratios in the world. The frequency of FMF is reported to be nearly 1% in some geographic regions, the overall prevalence is around 0.1% (10). Unfortunately estimated number of patients in Iran is unknown . The disease is clinically characterized by self-limiting inflammatory attacks. It may also be related to severe complications such as amyloidosis. Nearly 10% of the group had amyloidosis. Homozygosity of M694V was the most important genotype associated with this condition (6). In the current study, we investigated the frequency of MEFV mutations in 324 FMF patients. To our knowledge, this sample size is larger than any studies previously conducted and is meant to reflect all of Iran. According to the genotype, heterozygous E148Q (n=254,78% ) was the most common mutation.followed, M694V (n = 23, 7%), V726A (n = 13, 4%), M694I (n =7 ,2%), and M680I (n = 2, <1%) .

According to the previously studies in theother regions of the world M694V allele in FMF is reported in a range of 20%–65% in different ethnic populations (11,28).But  Studies that included screening for R202Q polymorphism found a higher frequency of this variant than the M694V pathogenic variant; however, it is now accepted that the common R202Q variant is not associated with FMF morbidity (23,25,27). There are also differences in the freuqency of other common genotypes between the regions.  E148Q was the most common mutation in a study from the southeastern region by Ece et al. (26), whereas E148Q was the second most common mutation in the eastern region (16,17,20), northeastern region (19), and central Anatolia of Turkey (12,18).But,According to the my study,It’s the common mutation (espscially heterozygous type)in Iran.

Although FMF is typically transmitted via autosomal recessive inheritance, a considerable number of patients may have 1 (up to 30%) or no identifiable mutations (up to 20%) in their MEFV genes (4, 13, 28, 29). In my study, 17% of patients did not show the typical autosomal recessive pattern. Seven percent had no detectable mutation, and 53% had mutation in only one allele. This may be explained by the fact that: 1 - most of the genetic testing was designed to screen for commonly observed mutations, so rare mutations may not be among those screened for and thus not be present in the results or 2 - current diagnostic methods may be insufficient for the detection of all possible mutations.

Differences between geographic regions may be caused by the wide genetic diversity in our country due to ongoing interactions between different ethnic and cultural groups through history. The frequency of MEFV in Iranian FMF patients is similar to populations in Mediterranean and Middle Eastern countries.

The increased frequency of genetic diseases like FMF, and similar genetic mutations in populations living in the same geographic area for thousands of years, suggests the possibility of genetic interactions.

In conclusion, in this large FMF patient cohort, we must determine the prevalence and clinical significance of common MEFV variants. Additionally, I found opposed the previous studies that probability M694V as the most common pathogenic mutation in mediterranean popultions FMF patients and Iranian,E148Q mutation is common variant.But,we have need to any other investigations.

References

1. Sari I Birlik M Kasifoglu T. Familial Mediterranean fever: an updated review. *Eur J Rheumatol.*2014;1:21. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5042258/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/27708867)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Eur+J+Rheumatol&title=Mediterranean+fever:+an+updated+review&volume=1&publication_year=2014&pages=21&pmid=27708867&)]
2. Yilmaz E Ozen S Balci B Duzova A Topaloglu R Besbas N Saatci U Bakkaloglu A Ozguc M. Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. *Eur J Hum Genet.*2001;9:553. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/11464248)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Eur+J+Hum+Genet&title=Mutation+frequency+of+familial+Mediterranean+fever+and+evidence+for+a+high+carrier+rate+in+the+Turkish+population&volume=9&publication_year=2001&pages=553&pmid=11464248&)]
3. Tunca M Akar S Onen F Ozdogan H Kasapcopur O Yalcinkaya F Tutar E Ozen S Topaloglu R Yilmaz E Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore)*2005;84:1. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/15643295)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Medicine+(Baltimore)&title=Familial+Mediterranean+fever+(FMF)+in+Turkey:+results+of+a+nationwide+multicenter+study&volume=84&publication_year=2005&pages=1&pmid=15643295&)]
4. Ben-Zvi I Herskovizh C Kukuy O Kassel Y Grossman C Livneh A. Familial Mediterranean fever without MEFV mutations: a case-control study. *Orphanet Journal of Rare Diseases.*2015;10:34–34. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4377009/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/25887307)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Orphanet+Journal+of+Rare+Diseases&title=Livneh+A.+Familial+Mediterranean+fever+without+MEFV+mutations:+a+case-control+study&volume=10&publication_year=2015&pages=34-34&pmid=25887307&)]
5. Kasifoglu T Bilge SY Sari I Solmaz D Senel S Emmungil H Kilic L Oner SY Yildiz F Yilmaz S Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. *Rheumatology (Oxford)*2014;53:741. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/24369413)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Rheumatology+(Oxford)&title=Amyloidosis+and+its+related+factors+in+Turkish+patients+with+familial+Mediterranean+fever:+a+multicentre+study&volume=53&publication_year=2014&pages=741&pmid=24369413&)]
6. Livneh A Langevitz P Zemer D Zaks N Kees S Lidar T Migdal A Padeh S Pras M Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum.*1997;40:1879. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/9336425)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Arthritis+Rheum&title=Criteria+for+the+diagnosis+of+familial+Mediterranean+fever&volume=40&publication_year=1997&pages=1879&pmid=9336425&)]
7. Pras M. Familial Mediterranean fever: from the clinical syndrome to the cloning of the pyrin gene. *Scand J Rheumatol.*1998;27:92. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/9572633)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Scand+J+Rheumatol&title=Mediterranean+fever:+from+the+clinical+syndrome+to+the+cloning+of+the+pyrin+gene&volume=27&publication_year=1998&pages=92&pmid=9572633&)]
8. Rabinovich E Livneh A  Langevitz P Brezniak N Shinar E Pras M Severe disease in patients with rheumatoid arthritis carrying a mutation in the Mediterranean fever gene. *Ann Rheum Dis.*2005;64:1009. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1755576/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/15958759)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Ann+Rheum+Dis&title=Severe+disease+in+patients+with+rheumatoid+arthritis+carrying+a+mutation+in+the+Mediterranean+fever+gene&volume=64&publication_year=2005&pages=1009&pmid=15958759&)]
9. Kisacik B Yildirim B Tasliyurt T Ozyurt H Ozyurt B Yuce S Kaya S Ertenli I Kiraz S. Increased frequency of familial Mediterranean fever in northern Turkey: a population-based study. *Rheumatol Int.*2009;29:1307. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/19152093)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Rheumatol+Int&title=Kiraz+S.+Increased+frequency+of+familial+Mediterranean+fever+in+northern+Turkey:+a+population-based+study&volume=29&publication_year=2009&pages=1307&pmid=19152093&)]
10. Touitou I. The spectrum of Familial Mediterranean fever (FMF) mutations. *Eur J Hum Genet.*2001;9:473. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/11464238)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Eur+J+Hum+Genet&title=The+spectrum+of+Familial+Mediterranean+fever+(FMF)+mutations&volume=9&publication_year=2001&pages=473&pmid=11464238&)]
11. Dundar M Emirogullari EF Kiraz A Taheri S Baskol M. Common familial Mediterranean fever gene mutations in a Turkish cohort. *Mol Biol Rep.*2011;38:5065. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/21153919)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Mol+Biol+Rep&title=Common+familial+Mediterranean+fever+gene+mutations+in+a+Turkish+cohort&volume=38&publication_year=2011&pages=5065&pmid=21153919&)]
12. Akar N Misiroglu M Yalcinkaya F Akar E Cakar N Tümer N Akcakus M Tastan H Matzner Y. MEFV mutations in Turkish patients suffering from Familial Mediterranean Fever Hum Mutat. 2000;15:118. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/10612841)] [[Google Scholar](https://scholar.google.com/scholar?q=+Akar+++N+++Misiroglu+++M+++Yalcinkaya+++F+++Akar+++E+++Cakar+++N+++T%C3%BCmer+++N+++Akcakus+++M+++Tastan+++H+++Matzner+++Y.++2000+MEFV+mutations+in+Turkish+patients+suffering+from+Familial+Mediterranean+Fever+Hum+Mutat+15+118+)]
13. Ceylan GG Ceylan C Frequency of alterations in the MEFV gene and clinical signs in familial Mediterranean fever in Central Anatolia, Turkey. *Genet Mol Res.*2012;11:1185. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/22614345)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Genet+Mol+Res&title=Frequency+of+alterations+in+the+MEFV+gene+and+clinical+signs+in+familial+Mediterranean+fever+in+Central+Anatolia,+Turkey&volume=11&publication_year=2012&pages=1185&pmid=22614345&)]
14. Demirkaya Tunca Y Gok F Ozen S Gul D. A very frequent mutation and remarkable association of R761H with M694V mutations in Turkish familial Mediterranean fever patients. *Clin Rheumatol.*2008;27:729. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/18000697)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Clin+Rheumatol&title=A+very+frequent+mutation+and+remarkable+association+of+R761H+with+M694V+mutations+in+Turkish+familial+Mediterranean+fever+patients&volume=27&publication_year=2008&pages=729&pmid=18000697&)]
15. Oztuzcu S Ulaşlı M Ergun S Iğci YZ Iğci M Bayraktar R Nacarkahya G Tamer A Cevik MO Cakmak EA Screening of common and novel familial Mediterranean fever mutations in south-east part of Turkey. *Mol Biol Rep.*2014;41:2601. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/24469716)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Mol+Biol+Rep&title=Screening+of+common+and+novel+familial+Mediterranean+fever+mutations+in+south-east+part+of+Turkey&volume=41&publication_year=2014&pages=2601&pmid=24469716&)]
16. Akin H Onay H Turker E Cogulu O Ozkinay F. MEFV mutations in patients with familial Mediterranean fever from the Aegean region of Turkey. *Mol Biol Rep.*2010;37:93. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/19449169)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Mol+Biol+Rep&title=MEFV+mutations+in+patients+with+familial+Mediterranean+fever+from+the+Aegean+region+of+Turkey&volume=37&publication_year=2010&pages=93&pmid=19449169&)]
17. Coşkun S  Keskin E  Sönmez F Frequency of mutations in Mediterranean fever gene, with gender and genotype-phenotype correlations in a Turkish population. *J Genet.*2015;94:629. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/26690517)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=J+Genet&title=Frequency%C2%A0of%C2%A0mutations%C2%A0in%C2%A0Mediterranean%C2%A0fever%C2%A0gene,+with%C2%A0gender%C2%A0and%C2%A0genotype-phenotype%C2%A0correlations%C2%A0in+a+Turkish%C2%A0population&volume=94&publication_year=2015&pages=629&pmid=26690517&)]
18. Dogan H Faruk Bayrak O Emet M Keles M Gulluoglu S Gul Z Pirim I Familial Mediterranean fever gene mutations in north-eastern part of Anatolia with special respect to rare mutations. *Gene.*2015;568:170. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/26003477)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Gene&title=Familial+Mediterranean+fever+gene+mutations+in+north-eastern+part+of+Anatolia+with+special+respect+to+rare+mutations&volume=568&publication_year=2015&pages=170&pmid=26003477&)]
19. Coşkun S Ustyol L Bayram Y Selçuk Bektaş M Gulsen S Çim A Uluca U Savaş D. The spectrum of MEFV gene mutations and genotypes in Van province, the eastern region of Turkey, and report of a novel mutation (R361T) 2015;562:128. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/25703702)] [[Google Scholar](https://scholar.google.com/scholar?q=+Co%C5%9Fkun+++S+++Ustyol+++L+++Bayram+++Y+++Sel%C3%A7uk+Bekta%C5%9F+++M+++Gulsen+++S+++%C3%87im+++A+++Uluca+++U+++Sava%C5%9F+++D.++2015+The+spectrum+of+MEFV+gene+mutations+and+genotypes%C2%A0in%C2%A0Van%C2%A0province,+the%C2%A0eastern%C2%A0region%C2%A0of%C2%A0Turkey,+and+report%C2%A0of+a%C2%A0novel%C2%A0mutation%C2%A0(R361T)+562+128+)]
20. Etem EO Deveci SD Erol D Yuce H Elyas H. Familial Mediterranean Fever: a retrospective clinical and molecular study in the East of Anatolia region of Turkey. *Open Rheumatol J.*2010;4:1. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2825617/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/20177433)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Open+Rheumatol+J&title=Fever:+a+retrospective+clinical+and+molecular+study+in+the+East+of+Anatolia+region+of+Turkey&volume=4&publication_year=2010&pages=1&pmid=20177433&)]
21. Barut K Sahin S Adrovic A Sinoplu AB Yucel G Pamuk G Aydın AK Dasdemir S Turanlı ET Buyru N et al. *Rheumatol Int*2018;38:67. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/28828621)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Rheumatol+Int%C2%A0&title=Buyru+N+et+al&volume=38&publication_year=2018&pages=67&)]
22. Kilinc M Ganiyusufoglu E Sager H Celik A Olgar S Cetin GY Davutoglu M Altunoren O. The report of sequence analysis on familial Mediterranean fever gene (MEFV) in South-eastern Mediterranean region (Kahramanmaraş) of Turkey. 2016;36:25. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/26215181)] [[Google Scholar](https://scholar.google.com/scholar?q=+Kilinc+++M+++Ganiyusufoglu+++E+++Sager+++H+++Celik+++A+++Olgar+++S+++Cetin+++GY+++Davutoglu+++M+++Altunoren+++O.++2016+The+report+of+sequence+analysis+on+familial+Mediterranean%C2%A0fever%C2%A0gene+(MEFV)+in%C2%A0South-eastern%C2%A0Mediterranean+region%C2%A0(Kahramanmara%C5%9F)+of%C2%A0Turkey+36+25+)]
23. Sayın Kocakap DB Günel-Özcan A Çabuk F Ensari C. The frequency of familial Mediterranean fever gene mutations and genotypes at Kirikkale and comparison with the mean of regional MEFV mutation frequency of Turkey. *Mol Biol Rep.*2014;41:1419. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/24381109)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Mol+Biol+Rep&title=The+frequency+of+familial+Mediterranean+fever+gene+mutations+and+genotypes+at+Kirikkale+and+comparison+with+the+mean+of+regional+MEFV+mutation+frequency+of+Turkey&volume=41&publication_year=2014&pages=1419&pmid=24381109&)]
24. Gunesacar R Celik MM Arica V Elmacioglu S Ozturk OH Frequency of MEFV gene mutations in Hatay province, Mediterranean region of Turkey and report of a novel missense mutation (I247V) *Gene.*2014;10:546–546. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/24929125)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Gene&title=Frequency+of+MEFV+gene+mutations+in+Hatay+province,+Mediterranean+region+of+Turkey+and+report+of+a+novel+missense+mutation+(I247V)&volume=10&publication_year=2014&pages=546-546&)]
25. Ece A  Çakmak E Uluca Ü Kelekçi S Yolbaş İ  Güneş A  Yel S Tan İ Şen V. The MEFV mutations and their clinical correlations in children with familial Mediterranean fever in southeast Turkey. 2014;34:207. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/24071932)] [[Google Scholar](https://scholar.google.com/scholar?q=+Ece+++A+++%C2%A0%C3%87akmak+++E+++Uluca+++%C3%9C+++Kelek%C3%A7i+++S+++Yolba%C5%9F+++%C4%B0+++%C2%A0G%C3%BCne%C5%9F+++A+++%C2%A0Yel+++S+++Tan+++%C4%B0++2014+%C5%9Een+V.+The%C2%A0MEFV%C2%A0mutations%C2%A0and+their%C2%A0clinical%C2%A0correlations%C2%A0in%C2%A0children%C2%A0with%C2%A0familial+Mediterranean%C2%A0fever%C2%A0in%C2%A0southeast+Turkey+34+207+)]
26. Lidar Tokov I Chetrit A Zaks N Langevitz P Livneh A Diagnosis delay in familial Mediterranean fever (FMF): social and gender gaps disclosed. *Clin Exp Rheumatol.*2005;23:357. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/15971424)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=Clin+Exp+Rheumatol&title=Diagnosis%C2%A0delay%C2%A0in+familial+Mediterranean+fever+(FMF):+social+and+gender+gaps+disclosed&volume=23&publication_year=2005&pages=357&pmid=15971424&)]
27. Clinical disease among patients heterozygous for familial Mediterranean fever. 2009. p. 1862. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/19479871)]
28. Aksentijevich I. Familial Mediterranean fever with a single MEFV mutation: where is the second hit? Arthritis Rheum  2009. p. 1851. [[PMC free article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2753538/)] [[PubMed](https://pubmed.ncbi.nlm.nih.gov/19479870)]