Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever

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Giancane G(1), Ter Haar NM(2), Wulffraat N(1), Vastert SJ(1), Barron K(3), Hentgen V(4), Kallinich T(5), Ozdogan H(6), Anton J(7), Brogan P(8), Cantarini L(9), Frenkel J(10), Galeotti C(11), Gattorno M(12), Grateau G(13), Hofer M(14), Kone-Paut I(15), Kuemmerle-Deschner J(16), Lachmann HJ(17), Simon A(18), Demirkaya E(19), Feldman B(20), Uziel Y(21), Ozen S(22).

Familial Mediterranean fever (FMF) is a disease of early onset which can lead to significant morbidity. In 2012, Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched with the aim of optimising and disseminating diagnostic and management regimens for children and young adults with rheumatic diseases. The objective was to establish recommendations for FMF focusing on provision of diagnostic tools for inexperienced clinicians particularly regarding interpretation of MEFV mutations. Evidence-based recommendations were developed using the European League against Rheumatism standard operating procedure. An expert committee of paediatric rheumatologists defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey and statements with less than 80% agreement were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique and were accepted if more than 80% agreement was reached. The literature search yielded 3386 articles, of which 25 were considered relevant and scored for validity and level of evidence. In total, 17 articles were scored valid and used to formulate the recommendations. Eight recommendations were accepted with 100% agreement after the consensus meeting. Topics covered were clinical versus genetic diagnosis of FMF, genotype-phenotype correlation, genotype-age at onset correlation, silent carriers and risk of amyloid A (AA) amyloidosis, and role of the specialist in FMF diagnosis. The SHARE initiative provides recommendations for diagnosing FMF aimed at facilitating improved and uniform care throughout Europe.

Recommendation

Table 3 Recommendations for familial Mediterranean fever (FMF) genetic diagnosis

	Strength of evidence
1. FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing	B
2. Consider patients homozygous for M694V at risk of developing, with very high probability, a severe phenotype	B
3. FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations at position 680 to 694 on exon 10, must be considered at risk of having a more severe disease	B
4. The E148Q variant is common, of unknown pathogenic significance and, as the only *MEFV* variant, does not support the diagnosis of FMF	B
5. Patients homozygous for M694V mutation are at risk of early onset disease	C
6. Individuals homozygous for M694V who are not reporting symptoms should be evaluated and followed closely in order to consider therapy	A
7. For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for AA amyloidosis (such as the country, family history and persistently elevated inflammatory markers, particularly serum amyloid A protein), close follow-up should be started and treatment considered	B
8. Consultation with an autoinflammatory disease specialist may be helpful in order to aid in the indication and interpretation of the genetic testing and diagnosis	C

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