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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Prototypic hereditary recurrent fever syndromes (monogenic autoinflammatory syndromes)

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1. DISEASE CHARACTERISTICS

1.1 Name of the diseases (synonyms)

Familial Mediterranean fever (FMF)	Recurrent polyserositis, familial paroxysmal polyserositis, periodic disease
Hyper-IgD syndrome (HIDS)	Hyperimmunoglobulinemia and periodic fever syndrome, periodic fever, Dutch type is a mild type of mevalonate kinase deficiency (MKD)
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	Periodic fever, familial, autosomal dominant; familial hibernian fever; TNF receptor-associated periodic syndrome
Cryopyrin-associated periodic syndromes (CAPS)	Including familial cold urticaria (FCAS), Muckle-Wells syndrome and chronic infantile neurologic cutaneous and articular syndrome (CINCA), also known as neonatal onset multisystem inflammatory disease (NOMID)
Familial cold urticaria 2 (FCAS2)	NLRP12-associated periodic syndrome (NAPS12)

1.2 OMIM# of the diseases

#249100
#260920
#142680
#607115
#611762

1.3 Name of the analyzed genes

MEFV (NG_007871.1)
MVK (NG_007702.1)
TNFRSF1A (NG_007506.1)
NLRP3 (NG_007509.2)
NLRP12 (NG_008651.1)

1.4 OMIM# of the genes

*608107
*251170
*191190
*606416
*609648

1.5 Mutational spectrum

At the moment >750 sequence variants are listed in the infevers database (http://fmf.igh.cnrs.fr/ISSAID/infevers/). There are mutations known with confirmed pathogenic effect, but many of the listed variants are either not yet confirmed or with no known pathogenic effect. Many patients with recurrent fever have shown to carry at least one mutation in one of these genes, but even in recessive disease and after extensive search no second mutation was identified.[1]

FMF	Most common of fever syndromes. It is due to mutations in the *MEFV* gene. FMF is a recessive disease and about 85% of patients from the Mediterranean origin and matching established clinical criteria[2] have a mutation in both copies of their *MEFV* gene. In about 20% of the affected FMF patients only one mutation is identified.[3] In about 80% of the cases mutations are detected in exon 10 of *MEFV* gene, some other mutations are detected in exons 2, 3, and 5, but they are rare. In very rare cases mutations are detected in exons 1, 8, and 9. Reference sequence to use is NM_000243.2 or LRG_190. Most frequent mutations that are clearly pathogenic: c.2040G>A or c.2014G>C (p.(Met680Ile)), c.2080A>G (p.(Met694Val)), c.2079G>C (p.(Met694Ile)), c.2177T>C (p.(Val726Ala)), c.2230G>T (p.(Ala744Ser)), c.2282G>A (p.(Arg761His)).[1]
Mild MKD	Autosomal recessive disease too. It is caused by mutations in the mevalonate kinase (*MVK*) gene. About 107 different mutations have been described and most patients have a change in both copies of their gene. Reference sequence to use is NM_000431.2 or LRG_156. Most frequent mutations that are clearly pathogenic: c.59A>C (p.(His20Pro)), c.803T>C (p.(Ile268Thr)), c.815C>T (p.(Ser272Phe)), c.1129G>A (p.(Val377Ile)).[1]
TRAPS	Is an autosomal dominant disease due to mutations in tumor necrosis factor receptor superfamily 1A gene (*TNFRSF1A*). As only one abnormal copy of the gene is required to cause disease, many patients have family members who also have the disease. Reference sequence to use is NM_001065.3 or LRG_193. Most frequent mutations that are clearly pathogenic: c.175T>C (p.(Cys59Arg)), c.185G>A (p.(Cys62Tyr)), c.211_213delGAC (p.(Asp71del)), c.236C>T (p.(Thr79Met)),

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	c.242G>A (p.(Cys81Tyr)), c.251G>A (p.(Cys84Tyr)), c.306C>G (p.(Cys102Trp)) (usual names C30R, C33Y, D42del, T50M, C52Y, C55Y, C73W).
CAPS	Dominant and about 75% of patients with milder disease have affected relatives. CINCA, at the most severe end of the clinical spectrum, is often due to *de novo* mutations in the *NLRP3* gene and there are usually no affected relatives. Reference sequence to use is NM_004895.4 NM_001243133.1 or LRG_197. Most frequent mutations that are clearly pathogenic: c.778C>T (p.(Arg260Trp)), c.907G>A (p.(Asp303Asn)), c.914T>C (p.(Leu305Pro)) c.931G>A (p.(Glu311Lys)), c.1043C>T (p.(Thr348Met)), c.1058T>C (p.(Leu353Pro)), c.1316T>C (p.(Ala439Val)).
FCAS2	Is dominant and mutations in *NLRP12* gene are at the origin of this disease. Reference sequence used is NM_144687.2, but still there is no LRG. First described mutations were c.850C>T (p.(Arg284*)) and c.2072+2dupT.[4] Now about 30 mutations are known (Infevers; http://fmf.igh.cnrs.fr/ISSAID/infevers).

1.6 Analytical methods

The method of choice for all genes is sequencing exons and intronic boundaries. Because the most frequent clearly pathogenic mutations cluster in specific exons (*MEFV*: exon 10; *TNFRSF1A*: exons 2–3–4; and *NLRP3*: exon 3), it is not necessary in routine procedure to analyze all exons for each gene. See EMQN guidelines.[1]

1.7 Analytical validation

External quality assessment (EQA) may be performed regularly, for example, in Europe by EMQN schemes.

1.8 Estimated frequency of the diseases (Incidence at birth ('birth prevalence') or population prevalence)

FMF	1/250 to 1/500 in Sephardic Jews and 1/1000 in the Turkish population[5]
Mild MKD	Is very rare and most common in people from North Western Europe
TRAPS	Is very rare and affects about 1 person in a million in Europe
CAPS	Is very rare and most patients are of European ancestry[6,7]
FCAS2	As rare as CAPS and less (Genetics Home Reference: http://ghr.nlm.nih.gov/condition/familial-cold-autoinflammatory-syndrome)

1.9 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☐	☒

Comment:

Depending on countries and age of individuals predictive testing and risk assessment is allowed and performed or not. Prenatal diagnosis may be discussed in some cases of CINCA (CAPS).

2. TEST CHARACTERISTICS

	Genotype or disease		A: true positives	C: false negatives
	Present	Absent	B: true positives	C: true negatives
Test				
Pos.	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Neg.	C	D	Pos. predict. value:	A/(A+B)
			Neg. predict. value:	D/(C+D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)

Depending on the quality of sequencing almost 100% for *MEFV*−, *MVK*−, *TNFRSF1A*−, *NLRP3*−, and *NLRP12*− genes

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)

Depending on quality of sequencing almost 100% for *MEFV*−, *MVK*−, *TNFRSF1A*−, *NLRP3*−, and *NLRP12*− genes

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if quantification can only be made case by case.

There are many causes for recurrent fever attacks; hence, it is difficult to define a clinical sensitivity. In cases where two mutations are identified, for example, the *MEFV* gene, it is presumed, because of high analytical sensitivity, that the patient has FMF.

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if quantification can only be made case by case.

There are many causes for recurrent fever attacks; hence, it is difficult to define a clinical specificity. In cases where no mutation is identified, for example, in the *MEFV* gene, it is presumed, because of high analytical specificity, that the patient has not FMF due to mutations in the *MEFV* gene, but it does not exclude a clinical diagnosis of FMF, and hence a corresponding treatment has not to be excluded.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive)

All these monogenic autoinflammatory syndromes (FMF, MKD, TRAPS, CAPS, and FCAS2) are children's diseases, hence adult onset is unusual. However, the FMF patients carrying the homozygous p.Met694Val genotype have obviously higher life time risk to develop amyloidosis.[8]

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

There are many causes for recurrent fever attacks; hence it is difficult to define a negative clinical predictive value. For example, in cases where no mutation is identified in the *MEFV* gene, it is presumed, because of high analytical specificity, that the patient does not have FMF at least due to mutations in the *MEFV* gene, but it does not exclude a clinical diagnosis of FMF from criteria described by Livneh *et al.*[2]

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: the tested person is clinically affected
(To be answered if in 1.9 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

	FMF	*HIDS (Mild MKD)*	*TRAPS*	*CAPS*	*FCAS2*
No (continue with 3.1.4)					
Yes	X	X	X	X	X
Clinically	X	X	X	X	X
Imaging					
Endoscopy					
Biochemistry		Mevalonic aciduria, mevalonic enzyme activity	decreased serum sTNFR <1 ng/l		
Electrophysiology					
Other (please describe)	If therapy with colchicines is positive. In Livneh *et al*[2] there are described diagnostic criteria for FMF.	2× serum IgD >100 E/ml (but not specific)			

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Delay in diagnostic resulting in life threatening complications (all diseases);

Multiple surgery unnecessary explorations (especially in FMF and maybe in TRAPS)

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Not applicable

3.1.4 Will disease management be influenced by the result of a genetic test?

	FMF	*Mild MKD*	*TRAPS*	*CAPS*	*FCAS2*
No	In any case treatment with colchicine				
Yes		X	X	X	X
Therapy		Glucocorto-costeroids, TNF receptor IgGFc fusion-protein IL-1beta-antagonistic therapies (Anakinra)	Glucocorto-costeroids, TNF antago-nist (Etaner-cept), IL-1beta-antagonistic therapies (Anakinra)	IL-1beta-antagonistic therapies (Anakinra)	IL-1beta-antagonistic therapy (Ana-kinra) is discussed[9]
Prognosis					
Management					

3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.9 'B' was marked)

It is better not to test unaffected individuals. In cases with risk of amyloidosis it may be useful to know the genotype.

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is positive (please describe)

If necessary symptoms have to be treated and kidneys have to be observed.

If the test result is negative (please describe)

Genetic testing was done because of symptoms hence despite negative test result the patient will be treated as necessary.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?
Not applicable because the patient has symptoms and in any case that will be treated as possible.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.9 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
It may sometimes resolve the genetic situation in a family.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes, genetic testing saves genetic or other testing in family members.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes, it may partly enable predictive testing in family members.

3.4 Prenatal diagnosis
(To be answered if in 1.9 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes, by knowing the mutations prenatal diagnosis will be possible, but only in some cases of CINCA (CAPS) prenatal diagnosis may be discussed.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Shinar Y, Obici L, Aksentijevich I *et al*: Guidelines for the genetic diagnosis of hereditary recurrent fevers. *Ann Rheum Dis* 2012; **71**: 1599–1605.

2 Livneh A, Langevitz P, Zemer D *et al*: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; **40**: 1879–1885.

3 Kotter I, Schedel J, Kummerle-Deschner JB: [Periodic fever syndrome/autoinflammatory syndrome]. *Z Rheumatol* 2009; **68**: 137–148, quiz 149.
4 Jeru I, Duquesnoy P, Fernandes-Alnemri T *et al*: Mutations in NALP12 cause hereditary periodic fever syndromes. *Proc Natl Acad Sci USA* 2008; **105**: 1614–1619.
5 Solak M, Yildiz H, Koken R *et al*: Analysis of familial Mediterranean fever gene mutations in 202 patients with familial Mediterranean fever. *Genet Test* 2008; **12**: 341–344.
6 Lainka E, Neudorf U, Lohse P *et al*: Analysis of cryopyrin-associated periodic syndromes (CAPS) in German children: epidemiological, clinical and genetic characteristics. *Klin Padiatr* 2010; **222**: 356–361.
7 Cuisset L, Jeru I, Dumont B *et al*: Mutations in the autoinflammatory cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France. *Ann Rheum Dis* 2011; **70**: 495–499.
8 Dusunsel R, Dursun I, Gunduz Z, Poyrazoglu MH, Gurgoze MK, Dundar M: Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. *Pediatr Int* 2008; **50**: 208–212.
9 Jeru I, Hentgen V, Normand S *et al*: Role of interleukin-1beta in NLRP12-associated autoinflammatory disorders and resistance to anti-interleukin-1 therapy. *Arthritis Rheum* 2011; **63**: 2142–2148.