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Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes

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***Objective*. Hereditary autoinflammatory syndromes are characterized by recurrent episodes of fever and inflammation. Seven subtypes have been described, caused by mutations in four different genes. Apart from a common phenotype of lifelong recurrent inflammatory attacks, all subtypes have distinct features and specific therapeutic options, which emphasizes the need for a specific diagnosis in each case. Our aim was to examine whether genetic screening would allow classification of previously unclassified patients, and whether individual patients suffering from an autoinflammatory syndrome carry additional mutations in one of the other autoinflammatory genes.**

***Methods*. We included 60 patients with an unclassified autoinflammatory syndrome, 87 patients diagnosed with either hyper-IgD syndrome, familial Mediterranean fever (FMF) or tumour necrosis factor (TNF)-receptor-associated periodic syndrome and 50 healthy controls. Deoxyribonucleic acid samples were screened for the most prevalent mutations in the *MEFV*, *TNFRSF1A*, *MVK* and *CIAS1* genes.**

***Results*. We found only one possible diagnosis of FMF in the 60 previously unclassified patients. Two low-penetrance mutations were found in equal numbers in the groups of patients and controls.**

***Conclusions*. Screening of highly prevalent mutations in known genes involved in these disorders does not yield additional relevant information. Differential diagnosis of hereditary autoinflammatory syndromes can be made by thorough clinical examination followed by targeted genetic analysis of the one or two most likely syndromes. High-prevalence low-penetrant mutations from autoinflammatory genes do not occur more frequently in patients with hereditary autoinflammatory syndromes compared with the general population.**

KEY WORDS: Hereditary autoinflammatory syndromes, Periodic fever, FMF, HIDS, TRAPS, CAPS, Mevalonate kinase, Pyrin, Cryopyrin, *TNFRSF1A*.

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Periodic fever syndromes are characterized by recurrent episodes of fever and inflammation [1]. Currently they are designated by the term (hereditary) autoinflammatory syndromes, because fever may be absent, while periodic inflammation (triggered by an often unknown stimulus and without signs of autoimmunity) is a key feature. Seven distinct hereditary autoinflammatory syndromes have been genetically characterized (Table 1). Apart from lifelong recurrent inflammatory attacks, these syndromes have distinctive features, such as age of onset, duration of attacks, accompanying symptoms, prognosis and ethnic origin of patient [2]. The differential diagnosis remains a challenge. A correct diagnosis enables specific therapeutic interventions, and options have expanded considerably [3–5].

The advent of genetic testing for the autoinflammatory syndromes has had a number of consequences: (i) the clinical phenotypes and ethnic distribution of each of these syndromes has turned out to be much more variable than anticipated; (ii) a number of patients with clear periodic fever symptoms cannot be classified by genetic testing; (iii) patients with a combination of mutations in two autoinflammatory genes have been reported [6–9], which raises the question of whether this might be more common than expected.

In this study we asked whether more rigorous and non-restricted genetic screening would allow the classification of patients with undiagnosed periodic fever. Further, we aimed to examine whether the combination of gene mutations for various autoinflammatory syndromes in a single patient occurs more often than expected.

Patients and methods

Patients

For this study we included all patients with suspected autoinflammatory syndrome referred to our clinic (as a tertiary referral centre in The Netherlands) and through the International HIDS [hyper-immunoglobulin D (IgD) syndrome] Registry (http://hids.net/) between January 1992 and December 2003. Control deoxyribonucleic acid (DNA) samples from 50 healthy Dutch people were donated by the Department of DNA Diagnostics, UMC Nijmegen. We discerned two groups of patients: those without a classifying diagnosis (unclassified) and those with a confirmed diagnosis (diagnosed). This study was approved by the institutional ethics committee and all patients gave informed consent.

Unclassified patients

Clinical work-up in these patients had failed to establish a specific diagnosis. Inclusion criteria were: (i) recurring episodes with fever and documented acute phase response for more than 2 yr; (ii) no genetic diagnosis, despite one or two specific genetic tests for the most likely syndrome; (iii) available DNA sample or nucleated cells. We were able to collect 60 patients. Clinical information was collected with a standardized questionnaire (24 patients) or by our clinical observation (36 patients). A positive family history was present in nine patients. Fifty-five patients were of northwest European Caucasian origin, including 36 Dutch patients, others came from Italy (two), Greece (one), Slovakia (one) and Japan (one). The clinical phenotype in this group was variable. The average age of onset in this group was 103 months (range 0–636 months). The average length of an inflammatory episode was 4–6 days and the episodes recurred on average every 6–9 weeks. The following symptoms occurred in more than 70% of this group: cold chills, headache, arthralgia or arthritis, abdominal pain and lymphadenopathy. Twenty-nine of these patients were previously designated as variant type HIDS [10], as a clinical phenotype compatible with HIDS, elevated serum IgD and no mevalonate kinase gene mutations.

Diagnosed patients

This group encompassed 87 patients, whom we previously diagnosed using clinical work-up (history taking, physical examination) and specific genetic analysis. It included 64 classical type HIDS patients from 49 families in the International HIDS Registry, 15 Dutch patients with tumour necrosis factor (TNF)-receptor associated periodic syndrome (TRAPS) from seven families, and eight unrelated patients with familial Mediterranean fever (FMF).

DNA analysis (Supplementary data available at Rheumatology Online)

Deoxyribonucleic acid was isolated from blood lymphocytes by standard procedures. Polymerase chain reaction (PCR) amplification of specific segments of the *MVK*, *MEFV*, and *TNFRSF1A* genes was performed for restriction fragment length polymorphism (RFLP) analysis. We amplified exons 2, 3 and 4 of *TNFRSF1A* and exon 3 of *CIAS1* for DNA sequencing. Primers were either designed by us or adapted from the available literature with minor modifications [11–14]. For the RFLP analysis, PCR products were digested by restriction enzymes at appropriate temperatures and incubation times. Digested samples were run on a 2–3% agarose gel (Biozym) and stained with ethidium bromide. Using purified PCR products, sequencing was performed according to standard procedures on both DNA strands using the same forward and reverse primers as those in the PCR step.

Statistical analysis was done by χ^2 contingency test, using Graphpad Prism version 4.0 for Windows (GraphPad Software, San Diego, CA, USA; http://www.graphpad.com/).

Results

Unclassified patients

In 60 unclassified patients, we identified three patients who carried one mutation for one of the genes mentioned in Table 1. We found no patients with a V377I *MVK* gene mutation and no mutations in exon 3 of *CIAS1* or exons 2, 3 and 4 of *TNFRSF1A* (Table 2).

A 13-yr-old Slovakian girl was heterozygous for the M694V *MEFV* gene mutation. This patient had her first fever episode at the age of 5 yr; these episodes lasted about 3 days and were accompanied by abdominal pain and lymphadenopathy. In the last few years she has been free of symptoms. Her maximal IgD concentration was 134 U/ml (normal reference value <100 U/ml). Her family has no Jewish or Mediterranean ancestry, and colchicine had not been tried. As the phenotype resembled HIDS, she was analysed for HIDS, but comprehensive sequencing of *MVK* was negative. She did not carry any of the other FMF mutations tested.

Secondly, we detected a R92Q *TNFRSF1A* gene mutation in a 10-yr-old Swedish boy presenting with fever episodes, lasting about 7 days, since the age of 4 months. He also had headache, diarrhoea, abdominal pain and lymphadenopathy. Laboratory examination showed a high concentration of C-reactive protein during fever, and a continuously high IgD (680 U/ml). Previous analysis of the entire *MVK* gene showed no mutations. His older sister and his father have similar symptoms and laboratory values, but did not carry this mutation. Elaborate sequencing of *TNFRSF1A* yielded no other abnormalities.

Lastly, we detected a E148Q mutation in the *MEFV* gene in a 12-yr-old Japanese boy whose case history has already been published [15]. This boy has recurrent episodes of fever, cervical lymphadenopathy, headache and occasional abdominal pain, with a continuously raised serum IgD (maximal 371 U/ml).

Table 1. Hereditary autoinflammatory syndromes

Syndrome (MIM no)	Inheritance pattern	Gene (GenBank no)	Protein	Mutations studied
Familial Mediterranean fever (FMF) (249100)	Autosomal recessive	*MEFV* (NM_000243)	Pyrin (marenostrin)	c.2080A > G (p.M694V), c.2177T > C (p.V726A), c.2082G > A (p.M694I), c.2040G > A/C (p.M680I), c.442G > C (p.E148Q)[b]
Mevalonate kinase deficiency (MKD)[a] (260920; 251170)	Autosomal recessive	*MVK* (M88468)	Mevalonate kinase	c.1129G > A (p.V377I)
TNF-receptor associated periodic syndrome (TRAPS) (142680; 191190)	Autosomal dominant	*TNFRSF1A* (NM_001065)	TNF-receptor type I (p55)	c.362G > A (p.R92Q)[b], c.224C > T (p.P46L)[b]; various mutations in exon 2–4
Cryopyrin-associated periodic syndrome (CAPS)[c] (606416)	Autosomal dominant	*CIAS1* (AF410477)	Cryopyrin	Various mutations in exon 3

Not included in this table or study: Blau syndrome, caused by mutations in *NOD2/CARD15,* and pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, caused by mutations in *CD2BP1*. See the INFEVERS database at http://fmf.igh.cnrs.fr/infevers.
[a]This includes hyper-IgD and periodic fever syndrome (HIDS) and classic mevalonic aciduria.
[b]These mutations are alternatively described as low-penetrance mutations, disease-modifying factors or even polymorphisms instead of disease-causing mutations.
[c]This includes Muckle–Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and chronic infantile neurological cutaneous and articular syndrome [CINCA; also known as neonatal onset multisystemic inflammatory disease (NOMID)].

Table 2. Results

Gene	Variant[a]	Autoinflammatory phenotype ($n = 60$)	Healthy controls ($n = 50$)	Classical type HIDS ($n = 64$)	TRAPS ($n = 15$)	FMF ($n = 8$)
MVK	V377I	0	0	NA (52)[b]	0	0
MEFV	M694V	1	0	0	0	NA[c]
	V726A	0	0	1	0	NA
	M694I	0	0	0	0	NA
	M680I	0	0	0	0	NA
	E148Q	1	2	2	1	NA
TNFRSF1A	P46L	0	0	0	NA	0
	R92Q	1	1	1	NA	0
	Sequencing exons 2,3,4	0[d]	ND	ND	NA[e]	ND
CIAS1	Sequencing exon 3	0	ND	ND	ND	ND

Autoinflammatory phenotype = patient with autoinflammatory syndrome not otherwise specified; NA = not applicable; ND = not determined.
[a]Sequence variant at the protein level.
[b]The V377I mutation was previously found in 52 of the 64 classical-type HIDS patients.
[c]FMF patients included five with at least one M694V allele, one with a V726A allele, two with an M680I allele and one with M694I homozygosity.
[d]Except for the R92Q mutation as detected by restriction enzyme analysis.
[e]TRAPS patients included all had cysteine mutations (C29F, C70Y, Y38C and C43Y), except for one patient with a D93E mutation.

Comprehensive DNA analysis of the *MVK* gene failed to detect mutations.

Diagnosed patients

In the group in whom we had previously made a clinical and genetic diagnosis of HIDS, TRAPS or FMF, we detected five patients with mutations in other autoinflammatory genes.

An Armenian refugee girl, aged 7 yr, living in The Netherlands, had been diagnosed as classical HIDS because of monthly episodes of fever, arthralgia, abdominal pain, oral ulcers and erythematous rash, which last 4–6 days and had started in her first year of life. She did not respond to colchicine. Her IgD serum concentration was 700 U/ml and *MVK* gene analysis demonstrated homozygosity for the V377I mutation, confirmed by sequencing of her parents. Now, she was found to be a carrier of a V726A mutation in the *MEFV* gene. No other *MEFV* mutations were found.

An E148Q mutation in the *MEFV* gene was detected in DNA samples from two brothers of Dutch Caucasian origin, with classical HIDS (*MVK* genotype P167L/I268T). A man of Dutch origin, previously diagnosed with TRAPS (D93E mutation in *TNFRSF1A*), was identified as carrier of the E148Q mutation in *MEFV*. None of the latter three are of Mediterranean or Jewish descent. A Dutch woman with classical HIDS (*MVK* genotype V377I/I268T) was found to be a carrier of a R92Q mutation in *TNFRSF1A*.

Control DNA samples

We detected one R92Q *TNFRSF1A* gene mutation and two E148Q *MEFV* gene mutations in 50 control DNA samples (Table 2). This is similar to the prevalence in the group of unclassified patients and diagnosed patients ($P > 0.05$).

Discussion

Systematic genetic screening for the most prevalent known autoinflammatory gene mutations in patients with unclassified periodic fever, who had previously undergone one or two specific genetic tests, yielded no mutations in 57/60 patients. Our screen netted only one possible diagnosis of FMF. Before this study,

we had considered HIDS in this patient, but in hindsight FMF was more likely given her clinical phenotype.

Another patient carried an E148Q mutation in the *MEFV* gene, and one a R92Q mutation in the *TNFRSF1A* gene. The latter are regarded as low-penetrance mutations, disease-modifying factors or even polymorphisms instead of disease-causing mutations, because of the high prevalence in control populations (frequency 1.2–6.4%) [16–19]. We confirm this in our study, as 4 and 2%, respectively, of our relatively small group of 50 healthy Dutch controls carries these mutations. It is therefore questionable whether these patients should be diagnosed with either FMF or TRAPS.

These results demonstrate that clinical examination combined with directed genetic testing for one or two of the most likely syndromes forms the basis for diagnosis of the autoinflammatory syndromes included in this study. While it is true that clinical phenotype of the autoinflammatory syndromes may overlap and that therefore clinical diagnostic criteria, such as those of Tel-Hashomer for FMF [20], are not useful for differential diagnosis within this group of disorders, in the large majority of patients clinical examination will point towards one or two specific syndromes [1, 2]. Analysis of DNA can be focused on syndromes with the highest clinical suspicion. As we have shown, screening of all known genes involved in these disorders is unlikely to yield additional relevant information.

This notion is confirmed by the clinical work-up of the 87 previously diagnosed patients. We made a positive diagnosis in 84/87 using a single genetic test, while in only three cases was an additional genetic test necessary to establish a positive diagnosis.

This study also re-emphasizes that a substantial proportion of patients with a definite autoinflammatory syndrome do not fall into any known genetic category. Most are sporadic cases, although there are patients with affected family members. The cause of disease in these patients remains elusive.

The second part of this study focused on the prevalence of combinations of mutations in more than one autoinflammatory gene. Although we found the low-penetrance sequence variants R92Q in *TNFRSF1A* and E148Q in *MEFV* in patients with a different autoinflammatory disorder, their prevalence was not different from that in controls. Thus, the combination of disease-causing mutations in the mevalonate kinase gene with a mutation in another autoinflammatory gene in a single patient only reflects the high prevalence of these latter low-penetrance mutations (or polymorphisms) in the general population [6–9]. The same holds true for the V726A *MEFV* mutation found in the Armenian girl with HIDS: carrier frequency in healthy Armenians for exon 10 mutations in this gene is 16%, of which about one-fifth is the V726A mutation [21]. Identical results were found in a smaller group of patients with TRAPS and FMF which were included in this study.

With the inclusion of 147 patients with periodic fever symptoms, this is one of the largest studies published on this subject lately. One limitation of this study is the fact that the study population is mostly of northwest European descent. A second limitation is related to the first, namely, the large proportion of HIDS patients in our study group with only a small number of FMF patients. It still needs to be determined whether our results hold true for populations with a large prevalence of FMF, for example, and thus this study cannot be extrapolated to every region without further data.

In conclusion, for diagnosis of an autoinflammatory syndrome we recommend a thorough clinical examination, including a detailed medical history, use of medication, family history, ethnic origin and physical examination during an attack. An acute phase response (raised CRP or leucocytosis) should be present during the inflammatory episode. With current clinical knowledge of autoinflammatory syndromes, this information will yield a working diagnosis of one or two possible syndromes [1]. Subsequently, confirmation of this working diagnosis can be sought by directed genetic tests. Screening for prevalent mutations in all possible genes is not recommended, because this is not likely to yield extra information. Development of a set of validated discerning clinical criteria for help in the first phase of this suggested sequential diagnosis protocol is more likely to be helpful. This study also confirms that a substantial proportion of patients with documented recurrent periodic fever attacks still remains without a definite (genetic) diagnosis.

Rheumatology	Key messages
	• Differential diagnosis of hereditary auto-inflammatory syndromes starts with good clinical examination. • Mutations from (other) autoinflammatory genes occur as often in periodic fever patients as in the general population.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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