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AN INTERNATIONAL DELPHI SURVEY FOR THE DEFINITION OF NEW CLASSIFICATION CRITERIA FOR FAMILIAR MEDITERRANEAN FEVER, MEVALONATE KINASE DEFICIENCY, TNF-RECEPTOR ASSOCIATED PERIODIC FEVER SYNDROMES AND CRYOPYRINOPATHIES

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Abstract

Objectives: Provisional evidence-based classification criteria for inherited periodic fever (HPF) have been recently developed. However, no consensus on how to combine clinical criteria, laboratory test and results of molecular analysis has been reached. Objective of the study is to understand which variables physicians consider as important for the classification of patients with HPF.

Methods: Two following Delphi surveys were sent to health professionals working in the field of autoinflammation. In the first open survey 124 researchers could list all the variables they consider as useful for the diagnosis of each monogenic periodic fever. The variables could be of any type and each researcher could complete the survey for one or more disease. In the second survey 162 researcher were asked to select, from a list of items coming from the first survey, the 10 top variables and to rank them by assigning a score from 10 to 1.

Results: The overall rate of response to the Delphi surveys, was of 85% for both sessions. The variables selected for each disease (corresponding to the 3rd quartile considering the total score obtained by the variables after the second Delphi survey) were respectively: 21 for MKD, 22 for CAPS, 18 for FMF, and 20 for TRAPS. A positive genetic test reached the top rank in all the HPF.

Conclusion: Our process led to the identification of those features considered to be the most important as candidate variable to be included in a new set of evidence based classification criteria for HPF.

Introduction

The hereditary periodic fever (HPF) syndromes are a group of monogenic disorders manifesting with recurrent episodes of fever lasting from few to several days accompanied by systemic inflammation and organ-specific manifestations. Several diseases are encrypted under this term such as the Familiar Mediterranean Fever syndrome (FMF), the Mevalonate Kinase Deficiency (MKD), the TNF-receptor associated periodic fever syndrome (TRAPS) and

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the Cryopyrinopathies (CAPS) ranging from the mildest Familial Cold Autoinflammatory Syndrome (FCAS), through the intermediate Muckle–Wells syndrome (MWS) to the Chronic Infantile Neurological Cutaneous and Articular syndrome (CINCA) or Neonatal-Onset Multisystem Inflammatory Disease (NOMID) that represent the most severe form of the spectrum. Familiar Mediterranean fever is the most common monogenic autoinflammatory syndrome due to gain of function mutation on the MEFV gene. FMF attacks usually last from 12 to 72 hours and are characterized by serosal inflammation causing chest and abdominal pain, arthralgia/arthritis and erysipeloid erythematous rash. TNF receptor associated periodic fever is inherited as an autosomal dominant disease due to mutations in the TNFRSF1A gene. The episodes are longer lasting from 1-4 weeks or more and are characterized by a variable skin manifestations (maculo-papular, urticarial or erythematous migratory rash) myalgia, fasciitis, abdominal pain, periorbital edema or conjunctivitis. Amyloidosis, although less common than in untreated FMF, may lead to renal failure. Mevalonate kinase deficiency (MKD) is caused by mutations in the MVK gene, which encodes mevalonate kinase. Attacks last 3 to 7 days and are often precipitated by triggering factor like immunizations, surgery, trauma or mild infections. Gastrointestinal manifestations with abdominal pain, nausea/vomiting and diarrhea often dominate the clinical picture associated with possible maculopapular rash , cervical lymphadenopathy and splenomegaly. The Cryopyrinopathies (or CAPS, cryopyrin associated periodic syndrome) include a wide spectrum (from the milder familial cold autoinflammatory syndrome, FCAS, to the most severe Chronic Infantile neurological cutaneous articular syndrome, CINCA) of clinical manifestations caused by dominantly inherited missense mutations in the NLRP3 gene.
A number of diagnostic and classification clinical criteria for HPF are available in the literature and used in clinical practice but all of them present some limitations mainly related to the methodology used, patient's sample characteristics, the absence of the result of genetic analysis. Additionally there is not a clear distinction between diagnostic which usually rely on pathognomic findings (eg genetic analysis, glicemia for diabetes etc) and classification criteria which are aimed to identify a set of clinical/laboratory/genetic findings with high sensitivity and specificity[1,2] .

The overall aim of this project was to obtain a large consensus on the development of novel, more sensitive and specific classification criteria for FMF, MKD, TRAPS and CAPS through consensus formation technique and data validation in the large dataset of EUROFEVER Registry[3,4] . In this manuscript we report the results of the first step of the process aimed to

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identify, by an international Delphi consensus, the candidates measures for the proper classification of each of these condition.

Materials and Methods

For the development of the HPF classification criteria we used a multistep approach. The first step (Delphi) relates to the identification of the most important variables that could be used to classify each of the diseases. In the second step (Classification and analysis) we asked a selected panel of clinicians/researchers to classify individual patients from Eurofever as per each HPF (reference standard) and then analyze the Eurofever database to derive a series of classification criteria for each HPF. In the third and final step we selected the final classification criteria in a consensus conference. This manuscript report the first of these steps.

Step 1: Delphi Questionnaire Surveys. The Delphi Technique utilizes a series of well defined mail questionnaires, with the first open in order to avoid any biases, and the subsequents based on the results of the prior ones.

The surveys have been conducted via a secure web based system thanks to the technical help of the Pediatric Rheumatology INternational Trials Organization (PRINTO at www.printo.it)[5]. Participants were pediatric/adult rheumatologists involved in their daily clinical practice in treating patients with autoinflammatory diseases.

The first Delphi questionnaire was sent by e-mail to centers belonging to the PRINTO network actively enrolling patients in the Eurofever registry[6].
Independent ethical approval for entering patients in the Eurofever registry and consent for participation was obtained in the participating countries, in accordance with local requirements. Approval at the Coordinating Center (Istituto G. Gaslini) was obtained (Protocol number 1-17/03/2015). Consent was obtained asking the permission to use clinical data for research purpose.

Clinicians and researchers working in the field of autoinflammatory diseases were asked to indicate by free text the variables thought most likely to be helpful and relevant in their clinical and research practice for the diagnosis/classification of FMF, TRAPS, MKD and CAPS. The questionnaire was anonymous and in the letter of invitation all the experts were asked to

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give their permission to analyze and publish data coming from the survey. Variables to be included could be of any type and each responder could fill the survey for one or more disease on the basis of his/her expertise. Two reminder were sent every 6 weeks to all investigators who had not replied.

From the first survey a list of clinical and laboratory variables were obtained with redundancies deleted. All remaining variables were grouped into mutually exclusive categories and, within each category, listed in alphabetical order (no rank provided). Additional missing variables derived from the already published classification/diagnostic criteria for any disease were eventually included in the list derived from the first Delphi open survey.

The second Delphi questionnaire, was sent to all the people invited to participate in the previous survey except to those who declined further involvement. In this phase 43 American clinicians dealing with auto-inflammatory diseases, not participating to the Eurofever registry, but members of Pediatric Rheumatology Collaborative Study Group (PRCSG) and Childhood Arthritis and Rheumatology research Alliance (CARRA), were also additionally involved. Participants were firstly asked to choose, among the variables listed coming from the first Delphi survey, the top 10 they consider as the most important for the classification of each periodic fever syndrome. In a second step, they were asked to rank the previously selected items by assigning a score from one to ten, where 1 was the least important and ten the most important. Each rank could be used only once even though some features were thought to be equally important. At the end of the questionnaire, the participants could add any missing feature from the list that they considered as relevant.

After the second Delphi survey a list of variables including any chosen at least once by the participants was obtained for each disease. The sum of ranks, frequency of ranking and median score with 1st and 3rd quartile was calculated for each variable. Those variables falling in the higher 3rd quartile considering the total score obtained were selected and will be used in the second steps of the study as previously described.

Results

The first survey was sent to 124 participants coming from 63 countries.

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A total of 106/124 (85%) responded to the initial invitation and 84/106 (79%) completed and confirmed it (figure 1)

A total of 73/84 clinicians completed the survey for FMF, 55 for TRAPS, 65 for CAPS and 55 for MKD.

The number of variables obtained for each disease at the end of the first Delphi survey, were 104 for FMF, 98 for TRAPS, 108 for CAPS and 116 for MKD (supplementary table S1).

The candidate variables cited for all the diseases, cleaned for redundancies, were classified in 5 mutually exclusive categories: history, characteristic of fever episodes, sign and symptoms, laboratory test and other investigation (supplementary table S1). All the variable present in the published criteria were cited by at least one participant to the survey

The second survey was sent to a total of 162 people, 118 from the PRINTO network and 44 from CARRA/PRCSG. The overall rate of response was 141/162 researchers and among these 120 completed the survey. In particular 109 participants completed the survey for FMF, 93 for TRAPS, 102 for CAPS and 94 for MKD (Figure 2).

At the end of the second Delphi survey the variables chosen at least once by any participants were respectively 70/104 for FMF, 76/98 for TRAPS, 81/108 for CAPS and 81/116 for MKD. The remaining variables have not been ranked by any of the participants. Moreover, none of the participants added any variables to the list proposed, suggesting that participants agreed that the items coming from the first survey were exhaustive.

For the subsequent statistical analysis we selected those variables falling in the 3rd quartile considering the total score obtained thus including 18 variables for FMF (Table1), 20 for TRAPS (Table 2), 21 for MKD (Table 3) and 22 for CAPS (Table 4). The ranking including frequencies of selection and medium score for each disease in shown in Tables 1 to 4.

For all HPF the presence of a "positive genetic test" for the causative gene was the variable with the highest rank (Table 1-4).

Among the clinical manifestations abdominal pain, South-east Mediterranean ethnicity, duration of fever episodes between 1 to 3 days, serositis and erysipeloid rash have been the most cited variables for FMF (Table 1). The presence of recurrent long lasting fever episodes associated with positive family history, periorbital edema, abdominal pain, myalgia, cutaneous rash, monocytic fasciitis and conjunctivitis classified in the highest rank for TRAPS (Table 2). For MKD the early age of onset, the presence of triggering factors, cervical lymphadenopathy (often painful) and gastrointestinal manifestation (abdominal pain, diarrhea, vomiting) received the highest ranks (Table 3). For CAPS the urticarial rash reached

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the 2nd position followed by hearing loss, early age of onset and chronic meningitides (Table 4).

The increase of acute phase reactants during fever episodes (and in some cases their persistence between episodes) also received a high rank in all the diseases (Table 1-4).

The determination of mevalonic acid in the urine and the reduction of enzymatic activity reached respectively the 2nd and 17th positions (Table 2) for MKD, whereas the response to colchicine and IL-1 blockers reached the 2nd and 3rd position respectively for FMF and CAPS. For TRAPS and MKD, none of the variable indicating a response to a specific therapy , reached a total score sufficient to be ranked in the 3rd quartile. In these diseases the response to steroids reached respectively the 22th and 34th position while a response to anti-TNF agent reached the 24th rank for TRAPS (Supplementary Table2).

A number of variables falling in the 3rd quartile indicated by the Delphi survey were not included in the diagnostic/classification criteria available so far (Tables 1-4). As already shown, a positive genetic test reached the first rank in all diseases.

The elevation of acute phase reactants were considered as a criterion in the recently proposed CAPS criteria, only (Table 4). Moreover, MVK enzymatic activity, urinary secretion of mevalonic acid and high IgD serum levels were considered important for the classification of MKD (Table 3).

Finally, the Delphi was able to identify a number of clinical manifestations not included in previous criteria were pointed out by the experts, especially for TRAPS (abdominal pain, arthralgia, monocytic fasciitis) (Table 2) and MKD (early onset, presence of triggering factors, abdomianl pain and skin rash) (Table 3). A positive response to anti-IL-1 treatment was included as possible diagnostic/classification criteria for CAPS (Table 4).

We than analyzed the possible differences in the rank given to the each variable falling in the top quartile between European and American clinicians. Both groups indicated the same variables in the higher positions, even in a slightly different order. Notably, in all disease, the positive genetic test reached the top position in both groups (supplementary Material 2).

Discussion

This is the first Delphi survey for the identification of candidate variables for a new set of classification criteria for monogenic periodic fever syndromes. The good rate of response to the Delphi underline the interest of clinicians in this field.

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To date a number of diagnostic/classification criteria for some HPF are already available in the literature. Nonetheless most of them have been created based on the judgment of a limited group of experts, mainly in countries with a dominant prevalence of a single disease. such as FMF in south-eastern Mediterranean countries. .

For example, the two historical criteria for FMF, Tel-Hashomer[7] and Livneh's criteria[8], were created in the Israeli population before the identification of the gene responsible for the disease. Similarly the more recent pediatric FMF criteria[9] were developed in theTurkish population. The main limitation of the current FMF criteria is related to their low accuracy when tested in populations in which the other monogenic diseases display a similar prevalence [10]. This is mainly due to the evident overlap among the different conditions that share a number of clinical manifestations.

To overcome these limitations, preliminary evidence-based criteria for monogenic HPF were developed from the Eurofever registry[11]. These criteria have been built on the basis of a statistical analysis conducted on a large a cohort of real adult and pediatric patients affected by different HPF enrolled in the Registry. These criteria were expressed as a score with a cut-off based on the best performance in a validation set of patients. The high accuracy of these criteria was mainly related to the presence of either "positive" and "negative" criteria for each condition. This means that, in the these latter criteria, are included symptoms whose presence is indicative for the disease and symptoms whose absence increase the risk for being affected[11].

Recently, Kummerle-Deschner and co-workers have developed a new set of clinical diagnostic criteria for CAPS that were validated in the context of a number of confounding diseases[12].

In the present study we took advantage of the Delphi technique process to involve a large number of clinicians dealing with the management of patients with systemic autoinflammatory diseases worldwide.

We obtained a list of variables ranked in order of importance considered to be useful for the classification of these patients. Interestingly, in all diseases the higher rank was obtained by the presence of a positive genetic test, even for those diseases, like FMF, in which the diagnosis is frequently based on clinical ground, especially in the Mediterranean countries displaying a high incidence of this condition.

A number of laboratory examinations were also considered. Elevation of acute phase reactants resulted to be in the first 6 positions in all HPF. So far, the only diagnostic criteria including laboratory examinations are those recently proposed for CAPS, in which the

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elevation of acute phase reactants in association to the clinical manifestations is considered as a mandatory criterion[12].

Despite the limitation in their availability in all centers, both the urinary secretion of mevalonic acid during fever episodes and determination of an impaired MVK enzymatic activity were considered to play a relevant role in the diagnosis/classification of MKD. The same was suggested for the high serum IgD levels, even if previous studies already showed their low sensitivity and specificity[13].

Overall, the results obtained by the Delphi survey reflect the current clinical practice for the diagnosis of HPF. a Although in some countries the diagnosis of periodic fever is still based only on clinical features, the current overall approach is certainly that of a combination of clinical, genetic and laboratory data.

The strong indication coming from the clinicians involved in the field support the need to overcome the era diagnostic/classification criteria based uniquely on clinical variables, including genetic and laboratory variables.

This indications seems particularly true in the next-generation sequencing (NGS) era, in which the increasing availability of genetic test will increase the need to integrate data coming from the genetic analysis with the clinical manifestations. Of course, not all variants associated to a given gene can be consider as pathognomonic. In fact, hypomorphic variants (polymorphisms, low penetrance mutations), variants of uncertain pathogenic significance and incomplete genotypes (i.e. heterozygous status in autosomal recessive diseases) represent a possible in the next future

To avoid possible mis-interpretations of data coming from molecular testing we will need: i) a precise characterization of the actual pathogenicity of each variant associated to HPF genes, ii) novel evidence-based criteria based on the combination of clinical manifestations and data coming from molecular analysis. These two aims will represent the actual goal of the future steps for the identification of novel evidence-based classification criteria. .

In conclusion, this study report the results from an international Delphi survey involving a large number of experts dealing with HPF from …. countries. The process allowed the identification of those features that are considered by the experts the most important as candidate variables to be included in a new set of evidence-based classification criteria for HPF. The next steps of this project will include the analysis of the performance of the variables chosen by the present Delphi in real patients in accordance with the judgment of experienced clinicians and geneticists. A final consensus on the best combination of clinical,

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laboratory and genetic variables will allow for the final identification of the best evidence-based classification criteria to be used in the clinical setting.

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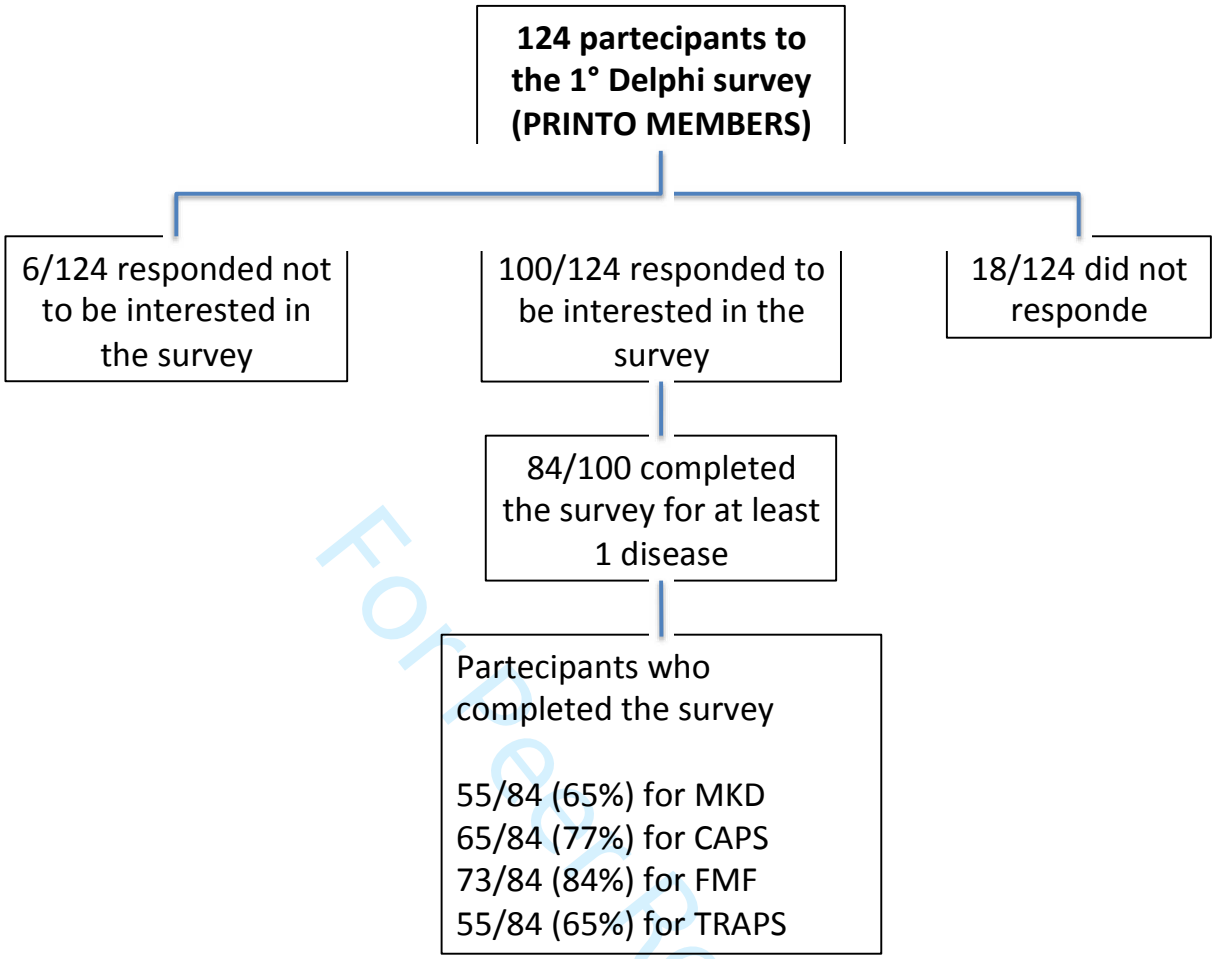

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Figure 1. Response to the first open Delphi survey

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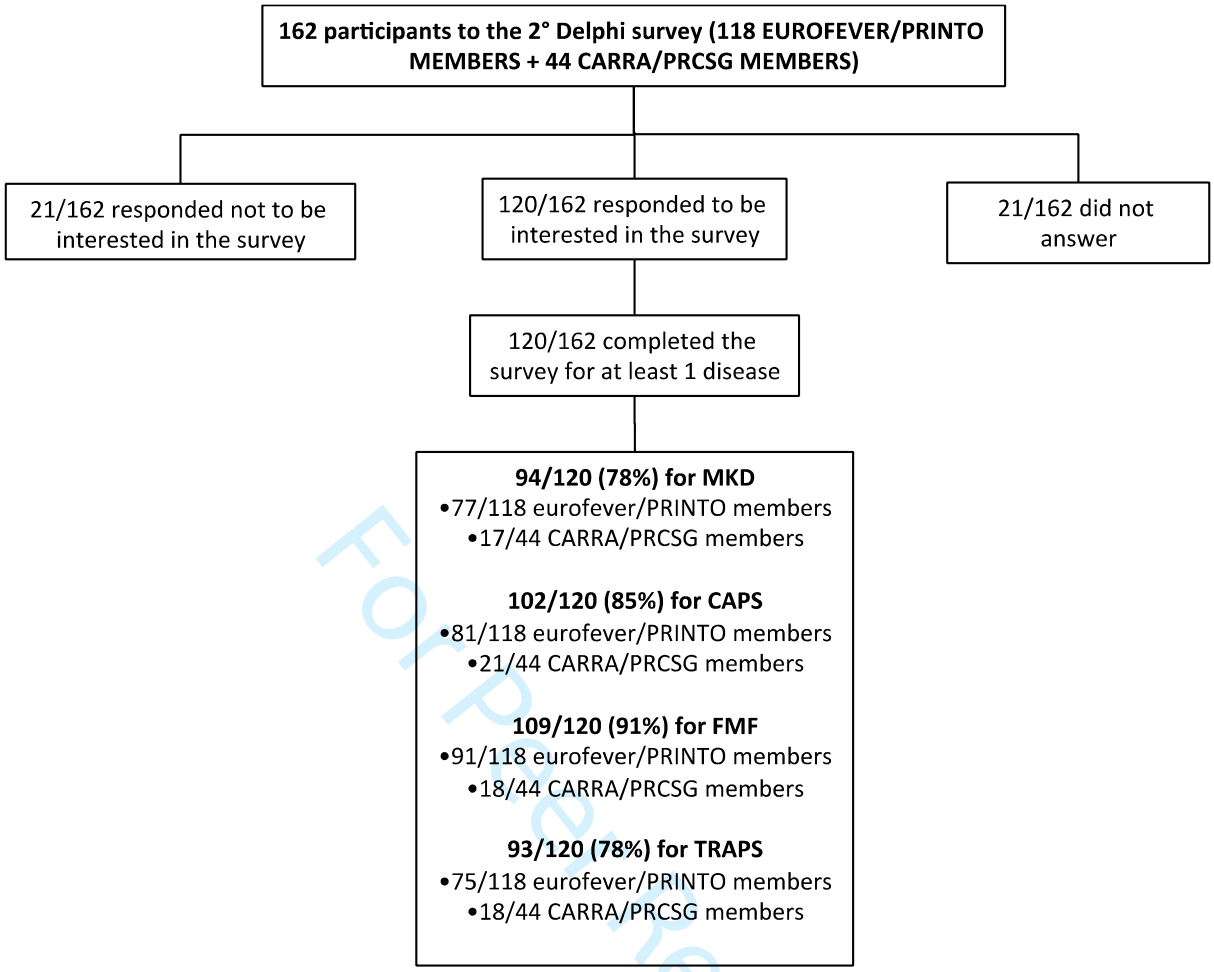

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Figure 2. Response to the second open Delphi survey

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Table 1: variables falling in the 3rd quartile considering the total score obtained for Familial Mediterranean Fever (FMF).

FMF				
Rank	**Variable**	**Score**	**Frequence of citation**	**Medium score**
1	Positive genetic analysis for *MEFV* gene	**626**	84	7.5
2	Response to colchicine^*	**568**	87	6.5
3	Increase of acute phase reactants and serum amyloid A during fever episodes* °	**471**	77	6.1
4	Abdominal pain * ° §	**466**	84	5.5
5	Ethnic (turkish, arabs, armenian, kurdis jeweish) * §	**426**	66	6.5
6	Classic recurrent fever pattern ^ * °	**378**	46	8.2
7	Duration of attacks 1-3 days * °	**313**	42	7.5
8	Positive family history ^ * °	**253**	51	5.0
9	Serositis ^ *	**220**	36	6.1
10	Erysipeloid rash^	**198**	47	4.2
11	Self-limiting episodes*	**181**	35	5.2
12	Duration of attacks few hours to 3-4 days * °	**166**	22	7.5
13	Chest pain*° §	**152**	35	4.3
14	Arthritis* °	**127**	32	4.0
15	Well-being between episodes*	**124**	32	3.9
16	Amyloidosis^	**104**	20	5.2
17	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	**100**	17	5.9
18	Arthralgia	**80**	24	3.3

Variable already present in Livneh criteria*; Tel Hashomer criteria^, Pediatric FMF criteria°; preliminary Eurofever criteria§

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Table 2. Variables falling in the 3rd quartile considering the total score obtained for TNF receptor associated autoinflammatory syndrome (TRAPS).

TRAPS				
Rank	**Variable**	**Score**	**Frequence of citation**	**Medium score**
1	Positive genetic analysis for *TNFRSF1A* gene	**637**	74	8.6
2	Increase of acute phase reactants and serum amyloid A during fever episodes	**323**	50	6.5
3	Recurrent prolonged episodes of fever	**301**	35	8.6
4	Periorbital edema§	**286**	55	5.2
5	Positive family history§	**282**	48	5.9
6	Irregular long lasting fever episodes	**254**	31	8.2
7	Abdominal pain	**251**	57	4.4
8	Myalgia §	**176**	39	4.5
9	Fever lasting more than 7 days§	**169**	23	7.3
10	Localized intense myalgia§	**135**	23	5.9
11	Skin rash§	**129**	32	4.0
12	Migratory rash§	**128**	27	4.7
13	Duration of attacks 1-3 weeks	**121**	15	8.1
14	Arthralgia	**119**	32	3.7
15	Monocytic fasciitis	**114**	17	6.7
16	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	**114**	17	6.7
17	Fever lasting more than 5 days§	**86**	10	8.6
18	Conjunctivitis	**86**	20	4.3
19	Recurrent episodes of fever	**82**	10	8.2
20	Painful maculopapular rash	**82**	12	6.8

Variable already present in preliminary Eurofever criteria§

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Table 3: variables falling in the 3rd quartile considering the total score obtained for mevalonate kinase deficiency (MKD).

MKD				
Rank	**Variable**	**Score**	**Frequence of citation**	**Medium score**
1	Positive genetic test for *MVK* gene	**637**	73	8.7
2	Increased urinary mevalonic acid during episodes	**352**	54	6.5
3	Duration of attacks 3-7 days	**328**	49	6.7
4	Fever§	**327**	42	7.8
5	Disease onset < 1 year§	**317**	39	8.1
6	Increase of acute phase reactants and serum amyloid A during fever episodes	**276**	48	5.8
7	Increased IgD levels	**252**	45	5.6
8	Presence of triggering factors (immunization, infection, minor trauma, surgery)	**218**	35	6.2
9	Abdominal pain	**184**	45	4.1
10	Lymphadenopathy (often painful) §	**150**	31	4.8
11	Early disease onset§	**139**	25	5.6
12	Cervical lymphadenopathy§	**137**	31	4.4
13	Gastrointestinal manifestation§	**113**	21	5.4
14	Diarrhea§	**106**	26	4.1
15	Maculopapular rash	**85**	19	4.5
16	Skin Rash	**83**	21	4.0
17	Mevalonate kinase activity	**80**	12	6.7
18	Aphtosis§	**80**	21	3.8
19	Disease onset <2 years§	**73**	12	6.1
20	Irregular periodicity	**73**	19	3.8
21	Self limiting episodes	**72**	15	4.8

Variable already present in the preliminary Eurofever criteria§

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Table 4: variables falling in the 3rd quartile considering the total score obtained for Cryopyrin associated periodic syndrome (CAPS).

CAPS				
Rank	**Variable**	**Score**	**Frequence of citation**	**Medium score**
1	Positive genetic analysis for *NLRP3* gene	**554**	71	7.8
2	Urticarial rash[§ #]	**479**	66	7.3
3	Response to IL-1Beta blockade	**469**	69	6.8
4	Recurrent fever[§]	**434**	55	7.9
5	Increase of acute phase reactants and serum amyloid A during fever episodes [#]	**331**	52	6.4
6	Hearing loss[§ #]	**314**	57	5.5
7	Episodes triggered by cold exposure[#]	**291**	50	5.8
8	Age at onset <1 year	**185**	28	6.6
9	Chronic urticaria[§]	**177**	29	6.1
10	Chronic meningitis[#]	**171**	39	4.4
11	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	**166**	28	5.9
12	Chronic disease course	**165**	29	5.7
13	Fever	**157**	22	7.1
14	Positive family history	**151**	34	4.4
15	Eye involvement[§]	**104**	19	5.5
16	Neurologic involvement[#]	**102**	18	5.7
17	Positive *NLRP12* genetic test	**94**	14	6.7
18	Conjunctivitis[§]	**85**	20	4.3
19	Osteo-arthropathy[#]	**74**	14	5.3
20	Arthralgia[#]	**70**	24	2.9
21	Cartilage overgrowth[#]	**66**	14	4.7

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22	Age at onset <1 month	**66**	11	6.0

Variable already present in the Eurofever criteria[§]; Variable already present in the CAPS criteria[#]

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Supplementary Material 1: variables obtained for each disease at the end of the first Delphi survey

MKD	
Duration of attacks 5-7 days	Characteristic of fever episodes
Duration of attacks 3-6 days	
Duration of attacks 3-7 days	
Duration of attacks 4-6 days	
Fever	
Irregular periodicity	
Recurrence every 2- 8 weeks	
Recurrence every 2-6 weeks	
Recurrence every 4 weeks	
Self-limiting episodes	
Consanguinity	History
Disease onset < 1 year	
Disease onset <2 years	
Disease onset <3 years	
Disease onset <5 years	
Early disease onset	
Exclusion of infection	
Incomplete/no response to steroids	
Positive family history	
Presence of autoimmunity	
Presence of triggering factors (immunization, infection, minor trauma, surgery)	
Response to steroids	
Response to treatment	
Abdominal pain	Signs and Symptoms
Amyloidosis	
Aphtosis	
Arthralgia	
Arthritis	
Aseptic furuncles	
Ataxia	
Bad general condition during episodes	
Bipolar aphtosis	
Cerebellar syndrome	
Cervical lymphadenopathy	
Chest pain	
CNS abnormality/epilepsy	
Colitis	
Complete well-being between episodes	
Conjunctivitis	

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Diarrhea	
Early onset Inflammatory bowel disease/ colitis	
Encephalopathy	
Episcleritis	
Erythema marginatum like rash	
Erythema nodosum	
Eye involvement	
Fatigue	
Fever chills	
Gastrointestinal manifestation	
Genital ulcers	
Growth retardation	
Headache	
Hemocolitis	
Hepatomegaly	
Joint manifestation	
Lymphadenopathy (often painful)	
Machrophagic activation syndrome	
Maculopapular rash	
Muscle weakness	
Musculoskeletal pain	
Myalgia	
Nausea	
Odynophagia	
Oral sores	
Pericarditis	
Peritonitis	
Pharingotonsillitis	
Polymorphous rash	
Psoriatic like rash	
Psychomotor delay	
Purpuric lesions/petechiae	
Renal involvement	
Renal involvement	
Renal tubular acidosis	
Sensorineural hearing loss	
Serositis	
Skin manifestation	
Skin Rash	
Splenomegaly	
Strong local reaction to vaccination and perfusion	
Urticarial rash	
Uveitis	
Vertigo	

Vomiting	
Anemia	Laboratory tests
Coagulation tests	
Complete Cells Blood count	
Evaluation of IgG subclasses	
Evaluation of liver function	
Evaluation renal function	
Genetic exclusion of others Autoinflammatory diseases	
Increase of acute phase reactants and serum amyloid A during fever episodes	
Increase of acute phase reactants and serum amyloid A during fever episodes and well being	
increased IgA level	
Increased IgD levels	
Increased urinary mevalonic acid during episodes	
Level of autoantibodies	
Level of cholesterol	
Level of Immunoglobulines	
Level of procalcitonin	
Level of proteinuria	
Lumbar puncture	
Mevalonate kinase activity	
Normalization of inflammatory markers during well being	
Positive genetic test for *MVK* gene	
Throat swab	
Thrombocytopenia	
Urine analysis	
Urine culture	
Abdominal ultrasound	Other investigation
Cardiac ultrasound	
Chest ultrasound	
CT/MR scan	
Joint ultrasound	
Physical growth assessment	
X ray	

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FMF	
Classic recurrent fever pattern	Characteristic of fever episodes
Duration of attacks 1-2 days	
Duration of attacks 1-3 days	
Duration of attacks 1-5 days	
Duration of attacks few hours to 3-4 days	
Fever duration less than 3 days	
Fever duration less than 4 days	
Presence of prodromal symptoms	
Recurrence every 2-4 weeks	
Regular periodicity	
Self-limiting episodes	
Age at onset	History
At least 3 attacks (x year)	
Consanguinity	
Early age at onset	
Ethnicity (turkish, arabs, armenian, kurdis jeweish)	
Exclusion of infection	
Positive family history	
Presence of triggering factors	
Response to colchicine	
Unproductive laparotomy	
Well-being between episodes	
Abdominal pain	Signs and Symptoms
Absence of adenopathy	
Absence of diarrhea	
Absence of recurrent aphtosis	
Absence of vomiting	
Acute scrotum	
Amyloidosis	
Aphtosis	
Arthralgia	
Arthritis	
Bone pain	
Chest pain	
Conjunctivitis	
Constipation	
Diarrhea	
Epididymitis	
Erysipeloid rash	
Fatigue	

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Fever chills	
Flank pain	
Headache	
Hepatomegaly	
Lymphadenitis	
Myalgia	
Nausea	
Non amyloid nephropathy	
Normal growth/development	
Pain under the feet during exercise	
Pericarditis	
Periorbital edema	
Peritonitis	
Pharingotonsillitis	
Pleuritis	
Post exertional myalgia	
Retrosternal pain	
Satisfaction of Livneh criteria	
Serositis	
Skin rash	
Splenomegaly	
Testicular pain	
Testicular swelling	
Uveitis	
Vomiting	
Coagulation tests	Laboratory tests
Complete cells blood count	
Dosage of calprotectine	
Evaluation of hematuria	
Evaluation of liver function	
Evaluation of microalbuminuria	
Evaluation of neutrophilia	
Evaluation of proteinuria	
Evaluation of renal function	
Evaluation of serum lipid profile	
Evauation of ionogramme	
Hemoculture	
Increase of acute phase reactants and serum amyloid A during fever episodes	
Increase of acute phase reactants and serum amyloid A during fever episodes and well being	
Level of alkaline phosphatase	
Level of autoantibodies	
Level of carbamide	

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Level of complement factors	
Level of fibrinogen	
Level of haptoglobine	
Level of IgD and/or IgA during fever	
Level of lupus anticoagulant	
Level of procalcitonine	
Level of S100 protein	
Level of serum immunoglobulin	
Level of serum proteins	
Level of tiroid hormons	
Negative genetic test for other monogenic Autoinflammatory diseases	
Positive genetic analysis for *MEFV* gene	
Urinary albumin/creatinine ratio	
Urine analysis	
Abdominal ultrasound	Other investigation
Cardiac ultrasound	
Chest X ray	
Fundoscopy	
Musculoskeletal ultrasound	
Physical growth assessment	
Renal, subcutaneous fat or rectal biopsy	
Slit lamp examination	

For Review

TRAPS	
Duration of attacks 1-3 weeks	Characteristic of fever episodes
Duration of attacks 2-3 weeks	
fever	
Fever lasting more than 10 days	
Fever lasting more than 5 days	
Fever lasting more than 7 days	
Fever of any duration in young children	
Irregular long lasting fever episodes	
Recurrent episodes of fever	
Recurrent prolonged episodes of fever	
Consanguinity	History
Early age at onset	
Onset after 1st decade of life	
Onset after 2nd decade of life	
Positive family history	
Presence of triggering factors	
Responce to therapy	
Response to anti-TNF therapy	
Response to steroids	
School attendance, social and extra-curricular activities	
Spontaneaous remission of episodes	
Well being between flares	
Abdominal pain	Signs and Symptoms
Absence of abdominal pain	
Absence of aphtosis	
Amyloidosis	
Aphtosis	
Arthralgias	
Arthritis	
Aseptic meningitis	
Auricular swelling	
Cervical lymphadenitis	
Chest pain	
Conjunctivitis	
Constipation	
Diarrhea	
Eye inflammation	
Eye involvement	
Eye involvment	
Fever chills	
Flank pain	

For Peer Review

Headache	
Hepatomegaly	
Localized intense myalgia	
Lymphadenitis	
Macular rash	
Migratory rash	
Monocytic fasciitis	
Mucosal inflammation	
Muscular involvement	
Musculoskeletal pain	
Myalgia	
Myositis	
Nausea	
Painful maculopapular rash	
Pathergy	
Periorbital edema	
Periorbital pain	
Periorbital rash	
Peritonitis	
Pharingitis	
Pharingotonsillitis	
Pleuritis	
Pseudo-cellulitis	
Recurrent pericarditis	
Retrosternal pain	
Serositis	
Skin involvment	
Skin rash	
Splenomegaly	
Testicular pain	
Urticarial like rash	
Uveitis	
Vomiting	
Complete blood cells count	Laboratory tests
Evaluation of liver function	
Evaluation of microalbuminuria	
Evaluation of proteinuria	
Evaluation of renal function	
Increase of acute phase reactants and serum amyloid A during fever episodes	
Increase of acute phase reactants and serum amyloid A during fever episodes and well being	
Level of autoantibodies	
Level of complement	

Level of IgG	
Level of procalcitonine	
Level of soluble TNF receptor	
Patient not affected if carrier of R92Q e P46L unless typical clinical picture	
Positive genetic analysis for *TNFRSF1A* gene	
Throat swab	
Urine analysis	
Urinary albumine/creatinine ratio	
Urine cultures	
Abdominal ultrasound	Other investigation
Joint assessment	
Ophthalmologic evaluation	
Physical growth assessement	
Renal, subcutanous fat or rectal biopsy	
X ray	

For Peer Review

CAPS	
Fever	Characteristic of fever episodes
Fever duration > 3 days	
Irregular intercritic periods	
Recurrent fever	
Absence of autoimmunity	History
Age at onset <1 month	
Age at onset <1 year	
Caucasian ethnicity	
Chronic disease course	
Consaguinity	
Episodes triggered by cold exposure	
Positive family history	
Presence of triggering factors	
Response to anti histaminic therapy	
Response to IL-1Beta blockade	
Response to steroids	
Abdominal pain	Signs and Symptoms
Absence of oral apthosis	
Amyloidosis	
Arthralgia	
Arthritis	
Band erythema over the knuckles	
Cartilage overgrowth	
Chest pain	
Chronic meningitis	
Chronic urticaria	
Conjunctivitis	
Diarrhea	
Edema of the extremities	
Episcleritis	
Erysipeloid rashof the ankle	
Eye involvement	
Fatigue	
Fever chills	
Frontal bossing	
Fundus oculi abnormalities	
Growth retardation	
Headache	
Hearing loss	
Hepatomegaly	

For Pe

Intracranial hypertension	
Iritis	
Irritability during attack	
Joint contractures	
Limb pain	
Lymphadenopathy	
Malaise	
Myalgia	
Nail clubbing	
Nanism	
Nausea	
Neurocognitive impairment	
Neurologic involvement	
Optic disc changes	
Optical nerve athrophy	
Oral ulcers	
Osteitis	
Osteo-arthropathy	
Papilledema	
Papillitis	
Peculiar facies/dysmorphism	
Peculiar musculoskeletal features	
Pericarditis	
Peritonitis	
Pharingitis	
Renal involvement	
Seizures	
Solitary pretibial lesion similar to erythema nodosum	
Splenomegaly	
Urticarial rash	
Uveitis	
Visual loss	
Vomiting	
Anemia	
Coagulation tests	Laboratory tests
Complete cells blood count	
Dosage of calprotectine	
Elevated liver enzymes	
Evaluation of liver function	
Evaluation of microalbuminuria	
Evaluation of proteinuria	
Evaluation of renal function	
Exclusion of M protein (in adults)	

Gene sequencing for other monogenic Autoinflammatory diseases	
Increase of acute phase reactants and serum amyloid A during fever episodes	
Increase of acute phase reactants and serum amyloid A during fever episodes and well being	
Leucocytosis	
Level of complement factors	
Level of procalcitonine	
Level of serum Immunoglobulines	
Levels of autoantibodies	
Not necessary genetic confirmation	
Positive lumbar punction	
Positive *NLRP12* genetic test	
Positive *NLRP3* genetic test	
Urinanalysis	
Urinary albumine/creatinine ratio	
Abdominal ultrasound	Other investigation
Acoustic evoked potentials	
Bone x-ray	
Joint ultrasound	
Ophthalmologic evaluation	
Physical growth assessment	
Positive central nervouse system MRI	
Positive inner ear MRI	
Skin biopsy	
Subcutaneous fat biopsy	
Visual evoked potentials	

For Review

Supplementary table S2: variables obtained after the second Delphi survey divided into 5 categories in alphabetical order

Variables obtained from the second Delphi survey	
Classic recurrent fever pattern	Characteristic of fever episode
Duration of attacks 5-7 days	
Duration of attacks 1-2 days	
Duration of attacks 1-3 days	
Duration of attacks 1-3 weeks	
Duration of attacks 1-5 days	
Duration of attacks 2-3 weeks	
Duration of attacks 3-6 days	
Duration of attacks 3-7 days	
Duration of attacks 4-6 days	
Duration of attacks few hours to 3-4 days	
Fever	
Fever duration > 3 days	
Fever duration less than 3 days	
Fever duration less than 4 days	
Fever lasting more than 10 days	
Fever lasting more than 5 days	
Fever lasting more than 7 days	
Fever of any duration in young children	
Irregular intercritic periods	
Irregular long lasting fever episodes	
Irregular periodicity	
Presence of prodromal symptoms	
Recurrence every 2- 8 weeks	
Recurrence every 2-4 weeks	
Recurrence every 2-6 weeks	
Recurrence every 4 weeks	
Recurrent episodes of fever	
Recurrent prolonged episodes of fever	
Regular periodicity	
Self-limiting episodes	
Well-being between flares	History
Unproductive laparotomy	
Spontaneous remission of episodes	
School attendance, social and extra-curricular activities	
Response to steroids	
Response to IL-1Beta blockade	
Response to colchicine	

Response to anti-TNF therapy	
Response to anti histaminic therapy	
Response to treatment	
Response to therapy	
Presence of triggering factors (immunization, infection, minor trauma, surgery)	
Presence of autoimmunity	
Positive family history	
Onset after 2nd decade of life	
Onset after 1st decade of life	
Incomplete/no response to steroids	
Exclusion of infection	
Ethnicity (turkish, arabs, armenian, kurdis jeweish)	
Episodes triggered by cold exposure	
Early disease onset	
Disease onset <5 years	
Disease onset <3 years	
Disease onset <2 years	
Disease onset < 1 year	
Consanguinity	
Chronic disease course	
Caucasian ethnicity	
At least 3 attacks (x year)	
Age at onset <1 year	
Age at onset <1 month	
Age at onset	
Absence of autoimmunity	
Abdominal pain	Signs and Symptoms
Absence of abdominal pain	
Absence of adenopathy	
Absence of diarrhea	
Absence of recurrent aphtosis	
Absence of vomiting	
Acute scrotum	
Amyloidosis	
Anemia	
Aphtosis	
Arthralgia	
Arthritis	
Aseptic furuncles	
Aseptic meningitis	
Ataxia	
Auricular swelling	
Bad general condition during episodes	

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Band erythema over the knuckles	
Bipolar aphtosis	
Bone pain	
Cartilage overgrowth	
Cerebellar syndrome	
Cervical lymphadenitis	
Cervical lymphadenopathy	
Chest pain	
Chronic meningitis	
Chronic urticaria	
CNS abnormality/epilepsy	
Colitis	
Complete well-being between episodes	
Conjunctivitis	
Constipation	
Diarrhea	
Early onset Inflammatory bowel disease/ colitis	
Edema of the extremities	
Encephalopathy	
Epididymitis	
Episcleritis	
Erysipeloid rash	
Erysipeloid rash of the ankle	
Erythema marginatum like rash	
Erythema nodosum	
Eye inflammation	
Eye involvement	
Fatigue	
Fever chills	
Flank pain	
Frontal bossing	
Fundus oculi abnormalities	
Gastrointestinal manifestation	
Genital ulcers	
Growth retardation	
Headache	
Hearing loss	
Hemocolitis	
Hepatomegaly	
Intracranial hypertension	
Iritis	
Irritability during attack	
Joint contractures	
Joint manifestation	

Limb pain	
Localized intense myalgia	
Lymphadenopathy	
Lymphadenopathy (often painful)	
Machrophagic activation syndrome	
Macular rash	
Maculopapular rash	
Malaise	
Migratory rash	
Monocytic fasciitis	
Mucosal inflammation	
Muscle weakness	
Muscular involvement	
Musculoskeletal pain	
Myalgia	
Myositis	
Nail clubbing	
Nanism	
Nausea	
Neurocognitive impairment	
Neurologic involvement	
Non amyloid nephropathy	
Normal growth/development	
Odynophagia	
Optic disc changes	
Optical nerve atrophy	
Oral sores	
Oral ulcers	
Osteitis	
Osteo arthropathy	
Pain under the feet during exercise	
Painful maculopapular rash	
Papilledema	
Papillitis	
Pathergy	
Peculiar facies/dysmorphism	
Peculiar musculoskeletal features	
Pericarditis	
Periorbital edema	
Periorbital pain	
Periorbital rash	
Peritonitis	
Pharingitis	

Pharingotonsillitis	
Pleuritis	
Polymorphous rash	
Post exertional myalgia	
Pseudo-cellulitis	
Psoriatic like rash	
Psychomotor delay	
Purpuric lesions/petechiae	
Recurrent pericarditis	
Renal involvement	
Renal tubular acidosis	
Retrosternal pain	
Satisfaction of Livneh criteria	
Seizures	
Sensorineural hearing loss	
Serositis	
Skin manifestation	
Skin rash	
Solitary pretibial lesion similar to erythema nodosum	
Splenomegaly	
Strong local reaction to vaccination and perfusion	
Testicular pain	
Testicular swelling	
Urticarial rash	
Uveitis	
Vertigo	
Visual loss	
Vomiting	
Anemia	Laboratory tests
Coagulation tests	
Complete cells blood count	
Dosage of calprotectine	
Elevated liver enzymes	
Evaluation of hematuria	
Evaluation of IgG subclasses	
Evaluation of liver function	
Evaluation of microalbuminuria	
Evaluation of neutrophilia	
Evaluation of proteinuria	
Evaluation of renal function	
Evaluation of serum lipid profile	
Evauation of ionogramme	
Exclusion of M protein (in adults)	

Gene sequencing for other monogenic Autoinflammatory diseases	
Genetic exclusion of others Autoinflammatory diseases	
Hemoculture	
Increase of acute phase reactants and serum amyloid A during fever episodes	
Increase of acute phase reactants and serum amyloid A during fever episodes and well being	
increased IgA level	
Increased IgD levels	
Increased urinary mevalonic acid during episodes	
Leukocytosis	
Level of alkaline phosphatase	
Level of autoantibodies	
Level of carbamide	
Level of cholesterol	
Level of complement factors	
Level of fibrinogen	
Level of haptoglobine	
Level of IgD and/or IgA during fever	
Level of IgG	
Level of lupus anticoagulant	
Level of procalcitonine	
Level of proteinuria	
Level of S100 protein	
Level of serum immunoglobulin	
Level of serum proteins	
Level of soluble TNF receptor	
Level of tiroid hormons	
Lumbar puncture	
Mevalonate kinase activity	
Negative genetic test for other monogenic Autoinflammatory diseases	
Normalization of inflammatory markers during well being	
Not necessary genetic confirmation	
Patient not affected if carrier of R92Q e P46L unless typical clinical picture	
Positive genetic analysis for *MEFV* gene	
Positive genetic analysis for *TNFRSF1A* gene	
Positive genetic test for *MVK* gene	
Positive lumbar punction	
Positive *NLRP12* genetic test	
Positive *NLRP3* genetic test	
Throat swab	

For Peer Review

Thrombocytopenia	
Urinary albumin/creatinine ratio	
Urine analysis	
Urine cultures	
Abdominal ultrasound	Other tests
Acoustic evoked potentials	
Bone x-ray	
Cardiac ultrasound	
Chest ultrasound	
Chest X ray	
CT/MR scan	
Fundoscopy	
Joint assessment	
Joint ultrasound	
Muscoloskeletal ultrasound	
Ophthalmologic evaluation	
Physical growth assessment	
Positive central nervouse system MRI	
Positive inner ear MRI	
Renal, subcutaneous fat or rectal biopsy	
Skin biopsy	
Slit lamp examination	
Subcutaneous fat biopsy	
Visual evoked potentials	
X ray	

view

Supplementary table S3: Variable included in the top quartile considering the total score obtained at the end of the second Delphi survey in the two groups of clinicians (European vs American)

FMF							
EUROFEVER/PRINTO				CARRA/ PRCSG			
		Rank	Medium rank			Rank	Medium rank
1	Positive genetic analysis for *MEFV* gene	515	7.4	**1**	Positive genetic analysis for *MEFV* gene	111	7.9
2	Response to colchicine	502	6.8	**2**	Duration of attacks 1-3 days	71	7.9
3	Increase of acute phase reactants and serum amyloid A during fever episodes	400	6.2	**3**	Increase of acute phase reactants and serum amyloid A during fever episodes	71	5.9
4	Abdominal pain	398	5.7	**4**	Classic recurrent fever pattern	69	9.9
5	Ethnia (turkish, arabs, armenian, kurdis jeweish)	360	6.5	**5**	Abdominal pain	68	4.9
6	Classic recurrent fever pattern	309	7.9	**6**	Positive family history	67	5.2
7	Duration of attacks 1-3 days	242	7.3	**7**	Ethnia (turkish, arabs, armenian, kurdis jeweish)	66	6
8	Positive family history	186	4.9	**8**	Response to colchicine	66	5.1
9	Serositis	175	6.0	**9**	Serositis	45	6.4
10	Erysipeloid rash	173	4.3	**10**	Self limiting episodes	29	7
11	Self limiting episodes	152	5.1	**11**	Duration of attacks few hours to 3-4 days	26	8.7
12	Chest pain	144	4.5	**12**	Erysipeloid rash	25	3.6
13	Duration of attacks few hours to 3-4 days	140	7.4	**13**	Arthritis	22	3.7
14	Well being between episodes	108	3.7	**14**	Arthralgias	19	3.2
15	Arthritis	105	4.0	**15**	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	17	5.6
16	Amyloidosis	89	5.6	**16**	Well being between episodes	16	5.3
17	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	83	5.9	**17**	Amyloidosis	15	3.75
18	Arthralgias	61	3.4	**18**	Chest pain	8	2.7

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MKD							
EUROFEVER/PRINTO				CARRA/ PRCSG			
		Rank	Medium rank			Rank	Medium rank
1	Positive genetic test for *MVK* gene	528	8.7	**1**	Positive genetic test for *MVK* gene	109	9.1
2	Increased urinary mevalonic acid during episodes	279	6.6	**2**	Increased urinary mevalonic acid during episodes	73	6.1
3	Disease onset < 1 year	279	8.2	**3**	Fever	65	8.1
4	Duration of attacks 3-7 days	265	6.6	**4**	Duration of attacks 3-7 days	63	7
5	Fever	262	7.7	**5**	Increase of acute phase reactants and serum amyloid A during fever episodes	55	5.5
6	Increase of acute phase reactants and serum amyloid A during fever episodes	221	5.8	**6**	Increased IgD levels	52	6.5
7	Increased IgD levels	200	5.4	**7**	Presence of triggering factors (immunization, infection, minor trauma, surgery)	46	5.8
8	Presence of triggering factors (immunization, infection, minor trauma, surgery)	172	6.4	**8**	Disease onset < 1 year	38	7.6
9	Abdominal pain	151	4.1	**9**	Abdominal pain	33	4.1
10	Lymphadenopathy (often painful)	124	5	**10**	Lymphadenopathy (often painful)	26	4.3
11	Cervical lymphadenopathy	120	4.3	**11**	Early disease onset	24	4.8
12	Early disease onset	115	5.8	**12**	Irregular periodicity	23	5.8
13	Gastrointestinal manifestation	104	5.5	**13**	Mevalonate kinase activity	22	7.3
14	Diarrhea	91	4.3	**14**	Skin Rash	20	5.0
15	Maculopapular rash	76	4.5	**15**	Cervical lymphadenopathy	17	5.7
16	Aphtosis	71	3.7	**16**	Disease onset <2 years	15	7.5
17	Skin Rash	63	3.7	**17**	Diarrhea	15	3
18	Self limiting episodes	62	5.2	**18**	Self limiting episodes	10	3.3
19	Mevalonate kinase activity	58	6.4	**19**	Gastrointestinal manifestation	9	4.5
20	Disease onset <2 years	58	5.8	**20**	Maculopapular rash	9	4.5
21	Irregular periodicity	50	3.3	**21**	Aphtosis	9	4.5

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TRAPS							
EUROFEVER/PRINTO				**CARRA/ PRCSG**			
		Rank	**Medium rank**			**Rank**	**Medium rank**
1	Positive genetic analysis for *TNFRSF1A* gene	513	8.4	**1**	Positive genetic analysis for *TNFRSF1A* gene	124	9.5
2	Increase of acute phase reactants and serum amyloid A during fever episodes	265	6.6	**2**	Periorbital edema	61	5.1
3	Recurrent prolonged episodes of fever	254	8.5	**3**	Irregular long lasting fever episodes	61	7.6
4	Periorbital edema	225	5.2	**4**	Positive family history	60	5,0
5	Positive family history	222	6.2	**5**	Abdominal pain	60	5,0
6	Irregular long lasting fever episodes	193	8.4	**6**	Increase of acute phase reactants and serum amyloid A during fever episodes	58	5.8
7	Abdominal pain	191	4.2	**7**	Recurrent prolonged episodes of fever	47	9.4
8	Fever lasting more than 7 days	150	7.5	**8**	Fever lasting more than 5 days	43	8.6
9	Myalgia	146	4.7	**9**	Migratory rash	34	4.9
10	Monocytic fasciitis	112	7	**10**	Skin rash	33	3.7
11	Localized intense myalgia	105	5.8	**11**	Myalgia	30	3.8
12	Duration of attacks 1-3 weeks	104	8.7	**12**	Localized intense myalgia	30	6,0
13	Arthralgias	98	3.9	**13**	Recurrent episodes of fever	27	9,0
14	Skin rash	96	4.2	**14**	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	23	7.7
15	Migratory rash	94	4.7	**15**	Arthralgias	21	3,0
16	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	91	6.5	**16**	Conjunctivitis	21	4.2
17	Painful maculopapular rash	82	6.8	**17**	Fever lasting more than 7 days	19	6.3
18	Conjunctivitis	65	4.3	**18**	Duration of attacks 1-3 weeks	17	5.7
19	Recurrent episodes of fever	55	7.9	**19**	Monocytic fasciitis	2	2,0
20	Fever lasting more than 5 days	43	8.6	**20**	Painful maculopapular rash	/	/

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CAPS							
EUROFEVER/PRINTO				CARRA/ PRCSG			
		Rank	Medium rank			Rank	Medium rank
1	Positive NLRP3 genetic test	430	7.7	**1**	Positive NLRP3 genetic test	124	8.3
2	Urticarial rash	377	7.3	**2**	Urticarial rash	102	7.3
3	Response to IL-1Beta blockade	377	6.7	**3**	Recurrent fever	102	7.3
4	Recurrent fever	332	8.1	**4**	Response to IL-1Beta blockade	92	7.1
5	Increase of acute phase reactants and serum amyloid A during fever episodes	279	6.5	**5**	Episodes triggered by cold exposure	83	5.9
6	Hearing loss	260	5.4	**6**	Positive family history	71	6.5
7	Episodes triggered by cold exposure	208	5.8	**7**	Hearing loss	54	6.0
8	Chronic urticaria	145	6.0	**8**	Increase of acute phase reactants and serum amyloid A during fever episodes	52	5.8
9	Fever	143	7.5	**9**	Age at onset <1 year	50	5.6
10	Age at onset <1 year	135	7.1	**10**	Chronic disease course	43	5.4
11	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	134	5.6	**11**	Chronic meningitis	42	4.2
12	Chronic meningitis	129	4.4	**12**	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	32	8.0
13	Chronic disease course	122	5.8	**13**	Chronic urticaria	32	6.4
14	Eye involvement	99	5.5	**14**	Positive NLRP12 genetic test	32	6.4
15	Neurologic involvement	81	5.4	**15**	Neurologic involvement	21	7.0
16	Positive family history	80	3.5	**16**	Fever	14	4.7
17	Conjunctivitis	72	4.0	**17**	Conjunctivitis	13	6.5
18	Osteo-arthropathy	69	5.3	**18**	Age at onset <1 month	10	
19	Cartilage overgrowth	63	4.8	**19**	Arthralgia	7	1.8
20	Arthralgia	63	3.2	**20**	Eye involvement	5	5.0
21	Positive NLRP12 genetic test	62	6.9	**21**	Osteo-arthropathy	5	5.0
22	Age at onset <1 month	56	5.6	**22**	Cartilage overgrowth	3	3.0

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Supplementary material 2

S2.a Differences in the ranks between Eurofever/PRINTO and American experts for FMF

		Eurofever/PRINTO				CARRA			
		Rank	Medium rank		%	Rank	Medium rank		%
1	Positive genetic analysis for MEFV gene	515	7.4	910	56,6	111	7.9	180	61,7
2	Response to colchicine	502	6.8	910	55,2	66	5.1	180	36,7
3	Increase of acute phase reactants and serum amyloid A during fever episodes	400	6.2	910	44,0	71	5.9	180	39,4
4	Abdominal pain	398	5.7	910	43,7	68	4.9	180	37,8
5	Ethnicity (turkish, arabs, armenian, kurdis jeweish)	360	6.5	910	39,6	66	6	180	36,7
6	Classic recurrent fever pattern	309	7.9	910	34,0	69	9.9	180	38,3
7	Duration of attacks 1-3 days	242	7.3	910	26,6	71	7.9	180	39,4
8	Positive family history	186	4.9	910	20,4	67	5.2	180	37,2
9	Serositis	175	6.0	910	19,2	45	6.4	180	25,0
10	Erysipeloid rash	173	4.3	910	19,0	25	3.6	180	13,9
11	Self limiting episodes	152	5.1	910	16,7	29	7	180	16,1
12	Duration of attacks few hours to 3-4 days	140	7.4	910	15,4	26	8.7	180	14,4
13	Chest pain	144	4.5	910	15,8	8	2.7	180	4,4
14	Arthritis	105	4.0	910	11,5	22	3.7	180	12,2
15	Well being between episodes	108	3.7	910	11,9	16	5.3	180	8,9
16	Amyloidosis	89	5.6	910	9,8	15	3.75	180	8,3
17	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	83	5.9	910	9,1	17	5.6	180	9,4
18	Arthralgias	61	3.4	910	6,7	19	3.2	180	10,6

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S2b. Differences in the ranks between Eurofever/PRINTO and American experts for MKD

		PRINTO				CARRA			
		Rank	Medium rank		%	Rank	Medium rank		%
1	Positive genetic test for MVK gene	528	8.7	770	68,6	109	9.1	170	64,1
2	Increased urinary mevalonic acid during episodes	279	6.6	770	36,2	73	6.1	170	42,9
3	Duration of attacks 3-7 days	265	6.6	770	34,4	63	7	170	37,1
4	Fever	262	7.7	770	34,0	65	8.1	170	38,2
5	Disease onset < 1 year	279	8.2	770	36,2	38	7.6	170	22,4
6	Increase of acute phase reactants and serum amyloid A during fever episodes	221	5.8	770	28,7	55	5.5	170	32,4
7	Increased IgD levels	200	5.4	770	26,0	52	6.5	170	30,6
8	Presence of triggering factors (immunization, infection, minor trauma, surgery)	172	6.4	770	22,3	46	5.8	170	27,1
9	Abdominal pain	151	4.1	770	19,6	33	4.1	170	19,4
10	Lymphadenopathy (often painful)	124	5	770	16,1	26	4.3	170	15,3
11	Early disease onset	115	5.8	770	14,9	24	4.8	170	14,1
12	Cervical lymphadenopathy	120	4.3	770	15,6	17	5.7	170	10,0
13	Gastrointestinal manifestation	104	5.5	770	13,5	9	4.5	170	5,3
14	Diarrhea	91	4.3	770	11,8	15	3	170	8,8
15	Maculopapular rash	76	4.5	770	9,9	9	4.5	170	5,3
16	Skin Rash	63	3.7	770	8,2	20	5.0	170	11,8
17	Mevalonate kinase activity	58	6.4	770	7,5	22	7.3	170	12,9
18	Aphtosis	71	3.7	770	9,2	9	4.5	170	5,3
19	Disease onset <2 years	58	5.8	770	7,5	15	7.5	170	8,8
20	Irregular periodicity	50	3.3	770	6,5	23	5.8	170	13,5
21	Self limiting episodes	62	5.2	770	8,1	10	3.3	170	5,9

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S2c. Differences in the ranks between Eurofever/PRINTO and American experts for TRAPS

		PRINTO					CARRA		
		Rank	Medium rank		%	Rank	Medium rank		%
1	Positive genetic analysis for TNFRSF1A gene	513	8.4	750	68,4	124	9.5	180	68,9
2	Increase of acute phase reactants and serum amyloid A during fever episodes	265	6.6	750	35,3	58	5.8	180	32,2
3	Recurrent prolonged episodes of fever	254	8.5	750	33,9	47	9.4	180	26,1
4	Periorbital edema	225	5.2	750	30,0	61	5.1	180	33,9
5	Positive family history	222	6.2	750	29,6	60	5,0	180	33,3
6	Irregular long lasting fever episodes	193	8.4	750	25,7	61	7.6	180	33,9
7	Abdominal pain	191	4.2	750	25,5	60	5,0	180	33,3
8	Myalgia	146	4.7	750	19,5	30	3.8	180	16,7
9	Fever lasting more than 7 days	150	7.5	750	20,0	19	6.3	180	10,6
10	Localized intense myalgia	105	5.8	750	14,0	30	6,0	180	16,7
11	Skin rash	96	4.2	750	12,8	33	3.7	180	18,3
12	Migratory rash	94	4.7	750	12,5	34	4.9	180	18,9
13	Duration of attacks 1-3 weeks	104	8.7	750	13,9	17	5.7	180	9,4
14	Arthralgias	98	3.9	750	13,1	21	3,0	180	11,7
15	Monocytic fasciitis	112	7	750	14,9	2	2,0	180	1,1

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16	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	91	6.5	750	12,1	23	7.7	180	12,8
17	Fever lasting more than 5 days	43	8.6	750	5,7	43	8.6	180	23,9
18	Conjunctivitis	65	4.3	750	8,7	21	4.2	180	11,7
19	Recurrent episodes of fever	55	7.9	750	7,3	27	9,0	180	15,0
20	Painful maculopapular rash	82	6.8	750	10,9	/	/	180	/

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S2d. Differences in the ranks between Eurofever/PRINTO and American experts for CAPS

		PRINTO				**CARRA**			
		Rank	Medium rank		%	Rank	Medium rank		%
1	Positive NLRP3 genetic test	430	7.7	810	53,1	124	8.3	210	59,0
2	Urticarial rash	377	7.3	810	46,5	102	7.3	210	48,6
3	Response to IL-1Beta blockade	377	6.7	810	46,5	92	7.1	210	43,8
4	Recurrent fever	332	8.1	810	41,0	102	7.3	210	48,6
5	Increase of acute phase reactants and serum amyloid A during fever episodes	279	6.5	810	34,4	52	5.8	210	24,8
6	Hearing loss	260	5.4	810	32,1	54	6.0	210	25,7
7	Episodes triggered by cold exposure	208	5.8	810	25,7	83	5.9	210	39,5
8	Age at onset <1 year	135	7.1	810	16,7	50	5.6	210	23,8
9	Chronic urticaria	145	6.0	810	17,9	32	6.4	210	15,2
10	Chronic meningitis	129	4.4	810	15,9	42	4.2	210	20,0
11	Increase of acute phase reactants and serum amyloid A during fever episodes and well being	134	5.6	810	16,5	32	8.0	210	15,2
12	Chronic disease course	122	5.8	810	15,1	43	5.4	210	20,5
13	Fever	143	7.5	810	17,7	14	4.7	210	6,7
14	Positive family history	80	3.5	810	9,9	71	6.5	210	33,8
15	Eye involvement	99	5.5	810	12,2	5	5.0	210	2,4
16	Neurologic involvement	81	5.4	810	10,0	21	7.0	210	10,0
17	Positive NLRP12 genetic test	62	6.9	810	7,7	32	6.4	210	15,2
18	Conjunctivitis	72	4.0	810	8,9	13	6.5	210	6,2
19	Osteo-arthropathy	69	5.3	810	8,5	5	5.0	210	2,4
20	Arthralgia	63	3.2	810	7,8	7	1.8	210	3,3

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21	Cartilage overgrowth	63	4.8	810	7,8	3	3.0	210	1,4
22	Age at onset <1 month	56	5.6	810	6,9	10		210	4,8

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