Clinical characteristics and genetic analyses of 202 patients with undifferentiated recurrent fever

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Abstract
Objectives: To describe the clinical characteristics, treatment response and genetic findings in the largest cohort of patients with syndrome of undifferentiated recurrent fever (SURF).
Methods: Clinical and genetic data from patients with SURF were extracted from the Eurofever registry, an international web-based registry that retrospectively collects clinical information on patients with autoinflammatory diseases.
Results: In this study 202 patients were included. Seven patients had a chronic disease course, 195 patients had a recurrent disease course. The median age at disease onset was 4.6 years. Patients had a median of 12 episodes per year, with a median duration of 4 days. In 25 patients relatives were affected as well. Most commonly reported symptoms were arthralgia (n=125), myalgia (n=95), abdominal pain (n=98), fatigue (n=120), malaise (n=112), and mucocutaneous manifestations (n=139). In 17 patients genetic variants were found in autoinflammatory genes. These patients more often had affected relatives compared to patients without genetic variants (p=0.002). Most patients responded well to NSAIDs, corticosteroids, colchicine and anakinra. Complete remission was rarely achieved with NSAIDs alone.
Notable patterns were found in patients with distinctive symptoms. Patients with pericarditis (n=12) were older at disease onset (32.3 years), and had fewer episodes per year (3.0/year) compared to other patients. Patients with an intellectual impairment (n=8) were younger at disease onset (2.2 years) and often had relatives affected (28.6%).
Conclusion**:** This study describes the clinical characteristics in the largest cohort of SURF patients. Patients with genetic variants found more often had relatives affected.

Keywords: Autoinflammatory diseases, Recurrent fever, Inflammation, Eurofever

Key messages:
What is already known about this topic?
- Individuals with undifferentiated recurrent fever represent the majority of patients approaching the services devoted to the diagnosis and management of autoinflammatory diseases.

What does this study add?
- This study provides a detailed description of the clinical characteristics of largest cohort of patients with undifferentiated recurrent fever, along with known genetic data and response to treatment.

How might this impact on clinical practice or future developments?
- The detailed description of patients with specific symptoms can be used to identify similar patients in other centers and will aid future research regarding the identification of new autoinflammatory diseases

Introduction
Systemic Autoinflammatory diseases (SAIDs) are disorders characterized by periodic or persistent activation of the innate immune system in the absence of infection or autoimmunity. In monogenic SAIDs this is caused by mutations in a single gene.[1] The best-characterized monogenic SAIDs are familial Mediterranean fever (FMF), cryopyrin associated periodic syndromes (CAPS), tumor necrosis factor-receptor associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD).[2,3] Other SAIDs, such as periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome or Behçet's disease are multifactorial; multiple genes may be involved, but there is no single genetic cause. Clinical diagnostic criteria are available for these diseases.[4,5] However, approximately 50% of patients with recurrent inflammation do not fit the clinical picture of any well-defined SAID and do not have pathogenic mutations causing a known hereditary SAID.[6,7] This group of patients is said to have 'undefined SAIDs'. Undefined autoinflammatory syndromes characterized by recurrent febrile episodes were named 'syndrome of undifferentiated recurrent fever' (SURF).[8] Despite the ambiguous classification of this condition, individuals with SURF represent the majority of patients approaching the services devoted to the diagnosis and management of SAIDs.

Characteristics of patients with SURF had not been extensively described in current literature. This might be due to the rarity of SAIDs, hampering sufficient patient numbers for research. To overcome this problem an international network for the study of SAIDs was established, the Eurofever Project.[9,10] Beside the well-defined SAIDs, the Eurofever Project also collects clinical information on patients with undefined SAIDs, including SURF, providing a sufficient cohort for our study.
This paper describes the clinical characteristics of the largest cohort of patients with SURF, along with known genetic data and response to treatment.

Methods

Eurofever registry

Data of patients with SURF were collected from the Eurofever undefined SAID cohort. To enrol patients as undefined SAID in the registry, other confounding conditions (well-defined SAIDs including PFAPA, infectious, autoimmune, neoplastic) should have been reasonably excluded.
Data entered before the 2th of November 2016 from the Eurofever registry (Executive Agency for Health and Consumers project no. 2007332), which has been collecting retrospective patient data since November 2009, were extracted.[10] Ethical committee approval and informed consent was obtained in all participating centers. Detailed epidemiological, demographic and clinical data were collected anonymously.

Inclusion and exclusion criteria

Patients of which clinical information was available were included in this study. Patients were excluded from analysis if there was no evidence of increased acute phase reactants during episodes, or if there was no fever reported.
Additional data were collected from patients with a clinical picture consistent of a defined SAID according to the Federici criteria, but without genetic analysis performed on the associated gene.[11] Centers of these patients were asked if further genetic analysis was performed since registration. Patients were excluded from analysis if genetic analysis revealed a defined SAID or if they received another diagnosis explaining their symptoms.

Clinical and genetic information

The clinical characteristics included the disease pattern (defined by either recurrent acute episodes, chronic disease or chronic with acute exacerbations), disease manifestations and response to treatment. Clinical manifestations were reported by the entering physician as being present never, sometimes/often or always during episodes. Treatment response was graded as complete (absence of clinical manifestations with normalization of inflammatory markers), partial (general amelioration of the clinical picture but not complete normalization of the clinical manifestations and/or systemic inflammation), or failure (lack of response). Information on molecular genetic analyses regarding the main SAIDs was collected. Genetic variants were classified as being pathogenic, likely pathogenic, of uncertain significance, likely benign or benign.[12,13] Only pathogenic or likely pathogenic variants and variants of uncertain significance were noted in this study and were regarded as genetic variants in further analyses.[14] Patients with (likely) pathogenic variants were included in this study as SURF if these were present on only one allele of a gene involved in autosomal recessive disease.

Statistical analysis

Categorical variables were described as frequencies and percentages. Numeric variables were reported as the median and interquartile range (IQR). To compare dichotomous variables with interval or ordinal variables the Mann-Whitney U test was performed. Correlations between two dichotomous variables, or a dichotomous variable and a nominal variable were assessed using the Chi-squared or Fisher's exact test. The Spearman's rank correlation was performed to assess differences between two interval variables or between interval and ordinal variables.
The threshold for statistical significance was $p<0.05$. Statistical analysis was performed with IBM Statistical Package for the Social Sciences (SPSS) version 24.

Results

Patient inclusion

In total, 337 patients were collected from the Eurofever registry. Patients came from 30 different centers. Clinical information was available for 235 patients. Patients were excluded when inflammatory markers were not elevated during fever episodes (n=26), or no fever was reported (n=3). Twenty-nine patients, coming from 10 centers, had a clinical picture consistent with a monogenetic SAID according to the Federici criteria, without genetic analysis performed on the associated gene.[11] For this reason, a specific query was raised to the enrolling centers, allowing additional information for 24 patients. Thirteen patients had genetic analysis performed on the associated genes. One patient, who clinically classified as MKD, had pathogenic mutations in the *MVK* gene. Furthermore, 3 patients were diagnosed with diseases other than their clinical classification: systemic juvenile idiopathic arthritis (n=2) and ARPC1B-combined immunodeficiency (n=1). These 4 patients were excluded from further analysis (Figure 1).

Baseline characteristics

Patients came from 17 different countries. Most patients came from Italy (n=110) and the United Kingdom (n=21). A complete list of the countries of residence is shown in supplementary table 1. Almost half of the patients were female (48%). The median age at disease onset was 4.6 years (IQR 1.3-13.0)(Figure 2A). Thirty-eight patients had a disease onset in adulthood.

Episode characteristics

Seven patients had a chronic disease course, 18 patients had a chronic disease course with recurrent acute exacerbations, 177 patients had a disease course with recurrent episodes. Patients with recurrent episodes had a median of 12.0 episodes per year (IQR 4.0-15.0), with a median duration of 4.0 days (IQR 3.0-7.0)(Figure 2B,2C). An irregular disease pattern was more frequently seen than a regular disease pattern (55.0% vs. 39.1%). A minority of patients (14.4%) reported specific triggers for disease episodes, including emotional stress and infection (Figure 2D). Clinical manifestations for patients with chronic and recurrent disease course are summarized in Table 1. Most commonly reported symptoms were arthralgia, myalgia, abdominal pain, fatigue, malaise and mucocutaneous manifestations.

Treatment response

NSAIDs and steroids were frequently used during attacks. NSAIDs were beneficial in 89/119 patients, but were rarely completely effective. Steroids were beneficial in 95/114 patients (45 complete, 50 partial response). With colchicine therapy 9/52 patients had a complete response, and 23 had a partial response. Thirteen patients got treated with anakinra, 5 had a complete response, 3 had a partial response. Methotrexate was given in 11 patients, with a complete response in 2 and a partial response in 5 patients. Adenoidectomy and/or tonsillectomy had limited effect; 8/9 adenotonsillectomies, 2/2 tonsillectomies and 1/2 adenoidectomies were ineffective. Figure 2E summarizes the responses to treatment.

Comparing treatment response to other clinical information, we found that patients with a good response to NSAIDs or colchicine had a shorter episode duration (p=0.022 and p=0.024, respectively) compared to poor responders. In addition, a regular pattern of febrile episodes was more often described in patients with a good response to steroids or colchicine (p=0.041 and p=0.001, respectively). Patients with a good response to anakinra had a lower episode frequency (p=0.037), were older at disease onset (p=0.018) and more often had an irregular disease pattern (p=0.018) compared to patients with a moderate or bad response to anakinra.

Family history

Twenty-five patients had affected relatives. In 13 patients first degree relatives were affected. Three patients had multiple relatives affected. Within our cohort 2 patients were related to each other: 2

sisters from Italy with a disease onset at 1 year and 12-13 attacks/year with a duration of 3 days. Common features of these sisters were a recurrent disease course, exudative pharyngitis, bilateral enlarged cervical lymph nodes, fatigue and malaise.
Patients with relatives affected were significantly younger at disease onset and more often had a regular disease pattern (65.2% vs 33.1%, p=0.005) compared to patients without relatives affected (2.0 vs 5.9 years, p=0.006). Furthermore, genetic variants were more often found in patients with relatives affected (30.4% vs. 5.8%, p=0.002).

Genetic characteristics

Analysis of one or more SAID-related genes was performed in 168 patients (83,2%), either by complete gene screening, screening of most relevant exons or screening of most relevant point mutations. In total, 17 patients carried pathogenic variants, likely pathogenic variants or variants of uncertain significance. Two patients had a genetic variant in the *NLRP3* gene, 8 in the *MEFV* gene, 2 in the *MVK* gene, 5 in the *TNFRSF1A* gene and lastly, 1 patient had a variant in the *NOD2* gene (Table 2). No variants were reported in the *PSTPIP1, NLRP12*, *CECR1*, or *IL1RN* gene. One patient had variants found in two genes, the p.R92Q variant in the *TNFRSF1A* gene and the p.V198M variant in the *NLRP3* gene.

Clinical classification criteria

When applying the Federici criteria, the majority of the patients (n=133, 66%) did not classify clinically for any of the major periodic fever syndromes.[11] Sixty-four patients classified as clinically compatible with one hereditary periodic fever: 24 TRAPS, 12 CAPS, 14 FMF and 14 MKD. In addition, 5 patients scored positive for multiple diagnoses: TRAPS and CAPS, TRAPS and MKD, CAPS and FMF, TRAPS and CAPS and MKD. Most patients had genetic analysis performed, in total 5 variants were found in the associated genes. Notably, in 13 patients genetic analysis of the associated gene was not performed (Figure 3).

Distinctive manifestations

More distinctive manifestations were reported in 51 patients (Table 3); most frequently reported were seizures (n=13), pericarditis (n=12), intellectual impairment (n=8) and bone alteration/deformity (n=5). A detailed description for these more severely affected patients can be found in supplementary table 2.
Two groups of patients stood out. First, patients with pericarditis (n=12) were older at disease onset (32.3 vs. 4.0 years, p<0.001) and had a lower episode frequency (3.0 vs. 12.0/year, p=0.001), which was more often reported as irregular (10/12 vs. 94/171, p=0.005). Patients with pericarditis often reported arthralgia (6/12), myalgia (6/12), and abdominal pain (3/12). In 3 of 10 tested patients genetic variants were found; twice the p.R92Q variant in the *TNFRSF1A* gene and once the p.A744S variant in the *MEFV* gene.
Secondly, patients with an intellectual impairment (n=8) were younger at disease onset (2.2 vs. 4.9 years, p=0.030). Their median episode duration was 4.5 (3.0-6.3) days, they had a median of 12.0 (5.5-15.8) episodes per year and in 28.6% relatives were affected, this did not differ from other patients. The following symptoms were more frequently reported in patients with an intellectual impairment: abdominal pain (100% vs. 47.8%, p=0.048), headache (87.5% vs. 35.3%, p<0.001) and generalized lymph node enlargement (57.2% vs. 9.9%, p<0.001). Seven of these patients had genetic analyses performed, all without genetic variants found.

Discussion

We describe the largest cohort of patients with SURF reported so far, enabling us to provide a broad description of the clinical characteristics, the genetic characteristics and the treatment response.

An advantage of our study is the standardized and elaborate list of symptoms, which yields a comprehensive clinical picture of the patients. In addition to fever, most commonly reported symptoms were rather non-specific: arthralgia, myalgia, abdominal pain, mucocutaneous manifestations, fatigue and malaise. Arthralgia, myalgia and mucocutaneous manifestations were frequently reported in other smaller cohorts of patients with undefined periodic inflammation as well.[15,16,17,18,19] Abdominal pain was frequently seen in another study with patients with a paediatric age at onset, but was not frequently reported in studies where patients had an adult age at onset.[16] Fatigue and malaise were reported by more than half of our patients, but were only mentioned in one other study.[19] As fatigue and malaise are generally often encountered by patients with rheumatic diseases, an underreporting of these symptoms in other cohorts seems to be the most likely explanation of this discrepancy.[19,20]

Most of our patients had a disease onset before the age of 5 years. However, even though a relevant number of patients with an adult-onset have been included, a selection bias could have decreased the average age of onset, due to an overrepresentation of paediatric centers in the Eurofever project. In other studies the age of disease onset varied from 4-43 years. [15,16,17,18,19]

As in most of the defined SAIDs, the vast majority of patients in our cohort had a favourable response to NSAIDs, steroids, colchicine, and anakinra, but patients rarely achieved complete response with NSAIDs alone.[21,22,23,24] Contrary to the good effect observed in PFAPA syndrome, tonsillectomy and/or adenoidectomy were rarely effective in patients with SURF.[22,23] Nonetheless, we cannot exclude a reporting bias, as physicians tend to enrol patients with a long-standing or difficult-to-treat disease course and thus leave out patients with a complete response to NSAIDs, tonsillectomy and/or adenoidectomy.

We have found a correlation between the presence of genetic variants and a positive family history of (undefined) SAIDs. Whether this represents a causal relation is uncertain. One might reason that these genetic variants, although not by themselves pathogenic, could contribute to autoinflammation in combination with environmental triggers or other (epi)genetic factors. However, there may be mere confounding by indication as patients with a positive family history might have been more likely to undergo genetic testing. Furthermore, the method of genetic screening varied among patients and this registry was not designed for in-depth analyses of family history nor disease aetiology. Laboratory experiments and population-based genetic studies are necessary to define a causal relation between genetic variants and autoinflammation. Moreover, genetic screening was often limited, both in the number of genes tested and the proportion of the individual genes that was sequenced. Hence, genetic diagnoses might have been missed, because the relevant genes or the relevant regions of the affected gene were not tested. Similarly, somatic mosaicism for autosomal dominant mutations would not have been detected.

Many patients in our cohort classified positive with the Federici clinical score.[11] However, over 75% of these patients had negative genetic results on the associated gene. This shows that patients with SURF resemble defined SAID patients, confirming the difficulty in differentiating between SURF and defined SAID on clinical grounds alone. Therefore, patients with recurrent inflammation should undergo thorough genetic screening.
Unfortunately, 19% of the patients with a positive clinical score did not have genetic analysis performed on the associated gene. It should be noted that some patients were registered before the Federici criteria became available, therefore possibly less genetic tests were ordered. We reached out to the centers for additional data. This resulted in the exclusion of 4 patients for having received a different diagnosis, one patient had the SAID compatible with the clinical score. We cannot exclude with certainty that some patients within our cohort did have defined SAIDs or other diagnoses explaining their symptoms, especially for those who had not underwent thorough genetic screening. Therefore, we want to stress the importance of thorough diagnostics. The age of sequential single

gene analysis is over. Patients with SURF deserve whole exome sequencing, where and when available and affordable.

Looking at patients with distinctive manifestations, we found that patients with pericarditis, in line with published data concerning idiopathic recurrent pericarditis, had a disease onset in adulthood and a low episode frequency.[25] However, patients with pericarditis in our cohort seem to form a specific cluster, since they also often suffered from musculoskeletal symptoms and abdominal pain, usually not reported in typical recurrent pericarditis.[26] This could mean that these patients either display an extension of the spectrum of idiopathic recurrent pericarditis, or they form a distinct entity. Secondly, patients with an intellectual impairment often had relatives affected and were young at disease onset. Possibly these patients form a distinct entity on their own as well. Supplementary table 2 can be used to identify similar patients in other centers with distinctive symptoms.

A limitation of our study is its retrospective design. As mentioned previously, we cannot exclude a bias in the selection of patients entered in the registry, favouring patients with more severe disease. An additional selection bias was introduced by the design of this analysis, excluding patients with normal acute phase proteins. Furthermore, for some patients parts of the clinical variables were missing as they were not retraceable from their clinical charts and, as mentioned previously, not all patients had thorough genetic analysis performed. More importantly, the lack of prospective follow-up data hampers conclusions regarding outcome and long-term therapy response in these patients. As mentioned in previous Eurofever reports, the treatment response is also difficult to interpret due to the possibility that the natural disease course or simultaneous use of other drugs influenced the response to therapy.[22]

In conclusion, we provide the first detailed description of the clinical characteristics of the largest international cohort of patients with SURF. This protean group of patients represents one of the most frequent subset observed in the daily practice of autoinflammatory disease clinics.[6, 7]Despite the large variability of this heterogeneous group of patients, the availability of a relevant number of affected individuals allowed to identify some interesting clues. A relevant proportion of the patients had other affected family members, A whole exome sequencing approach would be appropriate in such families in order to identify possible new genes. Moreover, some distinctive manifestations (like pericarditis or intellectual impairment) could allow the identification of novel SAID clinical clusters, possibly related to specific genes.
In this study we described the characteristics of patients with SURF as a single group. However, different underlying causes for autoinflammation are undoubtedly present in this cohort. Future research, combining extensive genetic data with functional and phenotypic data, is likely to provide insight in genotype-phenotype relation, leading to the eventual identification of new SAIDs within this group.[27]

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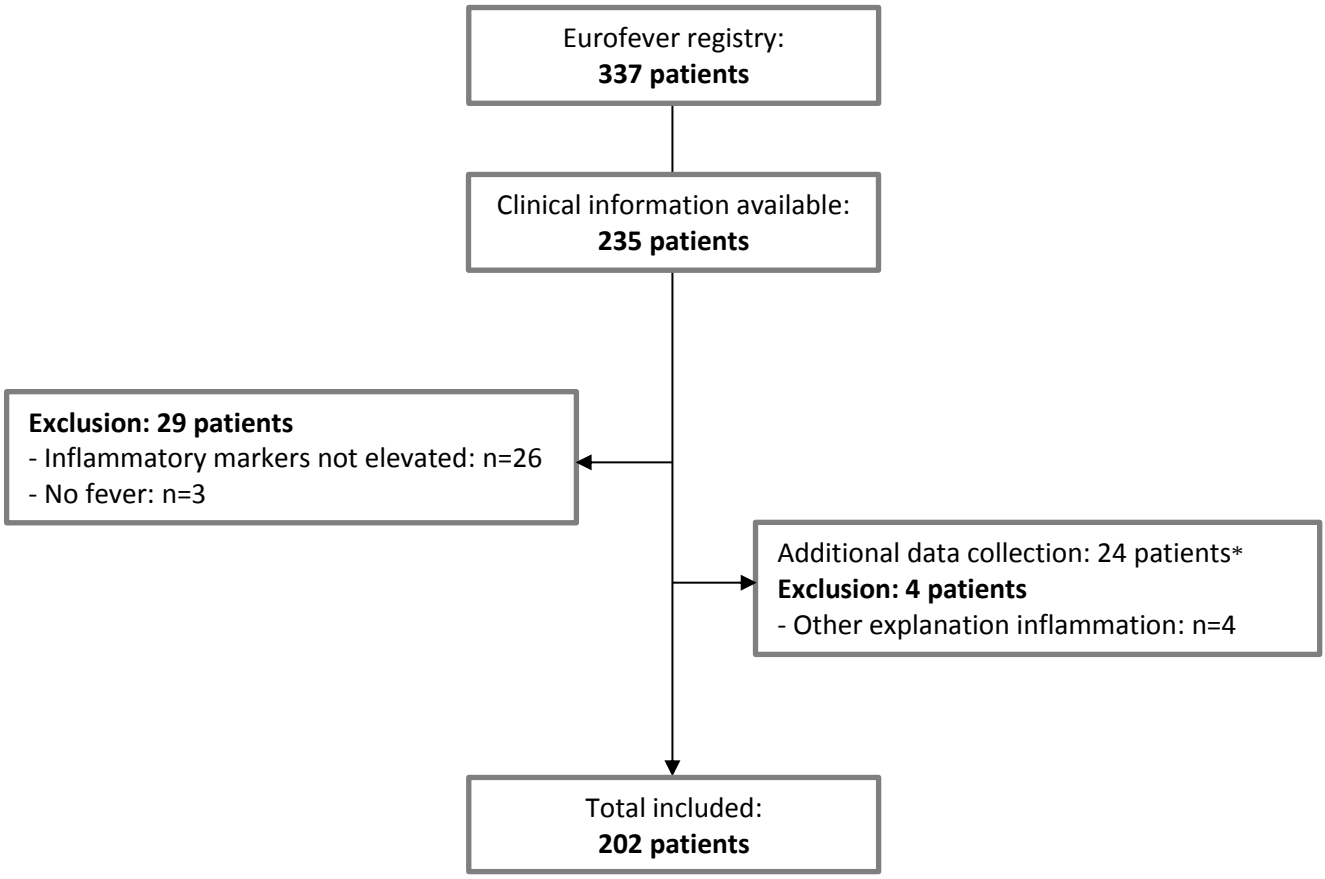
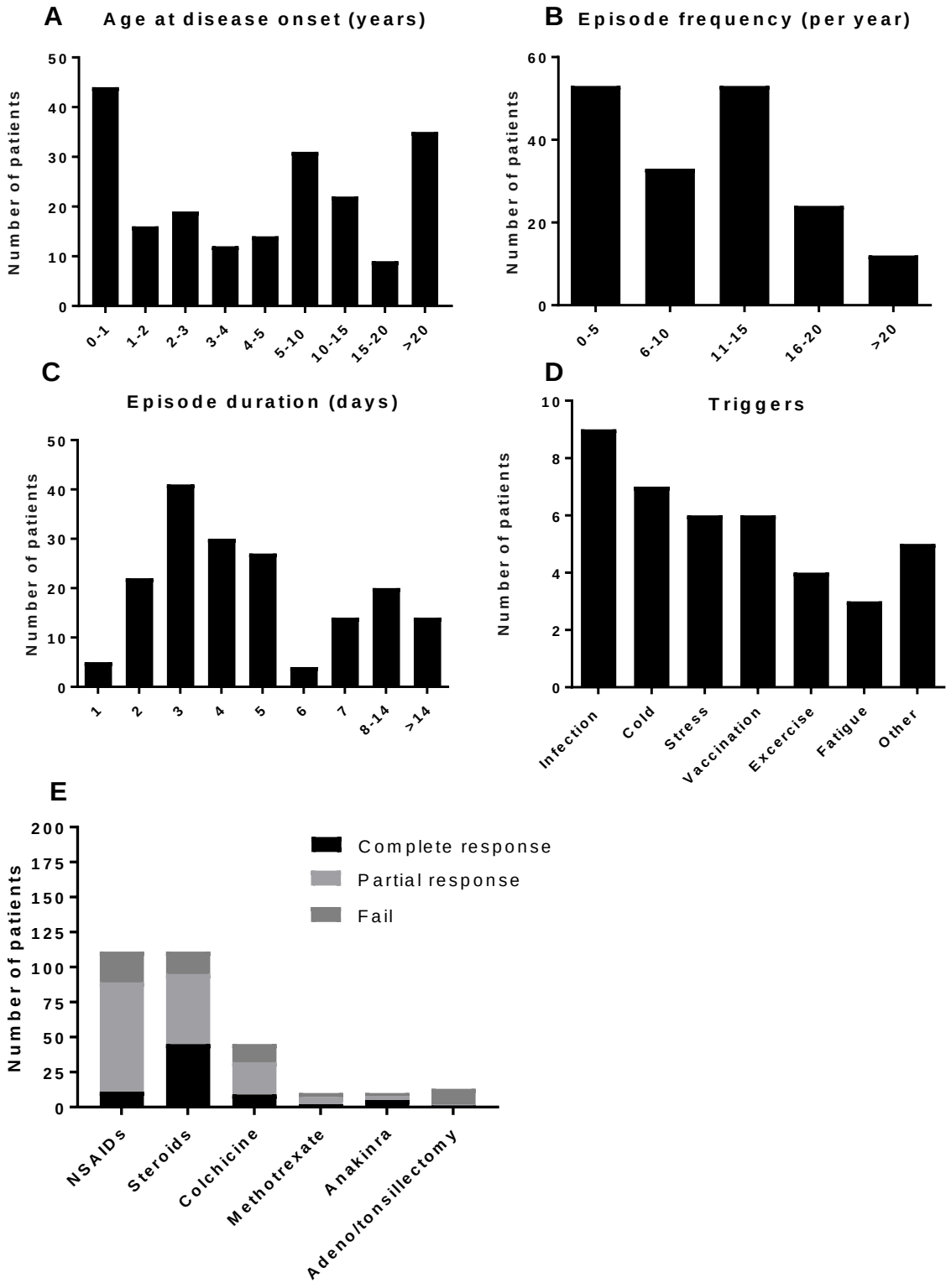
Figure 1. Flowchart of included patients



* Additional data were collected from 24/29 patients with a clinical picture consistent with a monogenetic SAID according to the Federici criteria[11], without genetic analysis performed in the associated gene

Figure 2. Disease characteristics, medication response



Other triggers were travel (1), teething (1), surgery (1), constipation (1), heath (1).

Table 1. Clinical manifestations during episodes

	Chronic disease course (7)	Recurrent disease course patients (195)[#]	
	n (%)^	n (%)^ Always	Sometimes/often
Mucocutaneous	5 (71%)	134 (69%)	
Apthous stomatitis	1 (14%)	10 (5%)*	47 (25%)**
Erythematous pharyngitis	1 (14%)	6 (3%)*	47 (25%)**
Exudative pharyngitis	0	6 (3%)*	30 (15%)**
Maculopapular rash	4 (57%)	10 (5%)*	29 (15%)**
Gastro-intestinal	2 (29%)	113 (58%)	
Abdominal pain	2 (29%)	25 (13%)*	71 (36%)**
Vomiting	0	8 (4%)*	40 (21%)**
Diarrhea	1 (14%)	2 (1%)*	35 (18%)**
Musculoskeletal	7 (100%)	130 (67%)	
Arthralgia	6 (86%)	31 (16%)*	88 (45%)**
Myalgia	6 (86%)	19 (10%)*	70 (36%)**
Oligoarthritis	1 (14%)	3 (2%)*	11 (6%)**
Ocular	1 (14%)	32 (16%)	
Conjunctivitis	1 (14%)	0	19 (10%)**
Periorbital edema	0	1 (1%)*	10 (5%)**
Lymphoid	5 (71%)	96 (49%)	
Enlarged cervical lnn	1 (14%)	22 (11%)*	59 (30%)**
Hepatomegaly	1 (14%)	8 (4%)*	19 (10%)**
Splenomegaly	1 (14%)	6 (3%)*	19 (10%)**
Cardio-respiratory	2 (29%)	34 (17%)	
Chest pain	1 (14%)	3 (2%)*	23 (12%)**
Pericarditis	1 (14%)	1 (1%)*	10 (5%)**
Neurological	2 (29%)	82 (42%)	
Headache	2 (29%)	23 (12%)*	51 (26%)**
Morning headache	0	3 (2%)*	23 (12%)**
Genito-urinary	0	14 (7%)	
Urethritis/cystitis	0	0	7 (4%)**
Gonadal pain	0	1 (1%)*	2 (1%)**
Constitutional	7 (100%)	194 (>99%)	
Fatigue	5 (71%)	35 (18%)*	80 (41%)**
Malaise	5 (71%)	35 (18%)*	72 (37%)**

Clinical manifestations of all patients, separated for patients with a chronic disease course and recurrent disease course. In grey: number of patients that reported at least one symptom of that organ system. In white: most commonly reported symptoms of that organ system. For patients with a recurrent disease course the separate symptoms are split into in always (left column) or sometimes/often present during episodes (right column).

[#] Patients with recurrent disease course and chronic disease course with recurrent acute exacerbations.

^ percentage of total with chronic or recurrent disease course (7 or 195 patients)

*Always present during episodes, ** sometimes/often present during episodes

lnn=lymph nodes, n=number of patients.

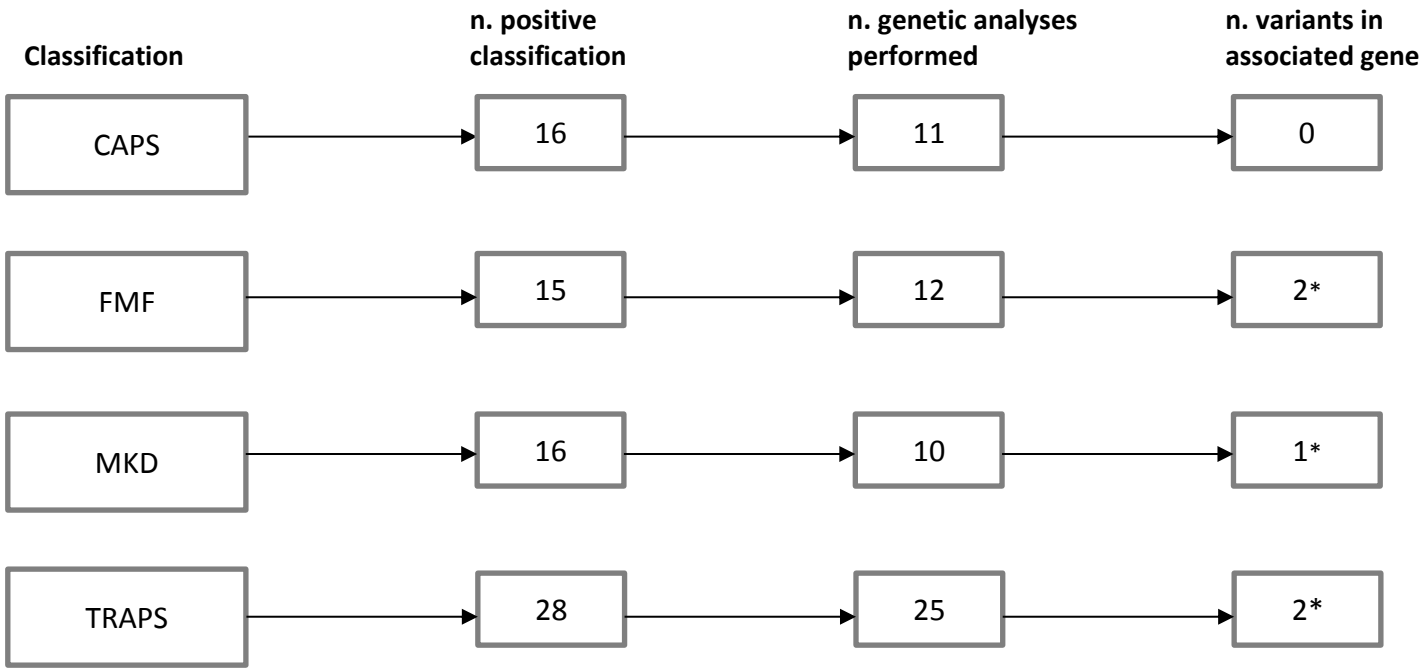
Table 2. Genetic characteristics

		Molecular analyses						
	N. tested	Complete gene screening	Most relevant exons	Most relevant point mutations	Unknown	N. variants found	Variants	Genetic class*
MEFV	118	34	70	4	10	8	p.A744S	3
							p.E148Q	3
							p.K25R	4
							p.R761H	4
							p.S339F	3
							p.V726A	5
NLRP3	40	18	15		7	2	p.R488K	3
							p.V198M	3
TNFRS1A	125	28	89		8	5	p.R92Q	3
MVK	80	41	28	1	10	2	p.T356M	3
NOD2	9	7	2			1	p.R702W/SNP8	3
NLRP12	6	3	1		2	0		
PSTPIP1	3	1	2			0		
CECR1	1	1				0		
IL1RN	1	1				0		

N.= number of patients. class= classification

* genetic classification: 3= uncertain significance, 4= likely pathogenic, 5= pathogenic. Patients with pathogenic mutations only had one mutation in the *MEFV* gene.

Figure 3. Clinical classification criteria and genetic outcome



This figure shows the patients who fulfilled the clinical classification criteria for a hereditary periodic fever syndrome.[11] The third column (nr. genetic analyses) displays the number of patients with genetic analyses performed of the associated gene.

* Variants found in the associated genes: FMF p.A744S and p.V726A; MKD p.T356M; TRAPS p.R92Q

Table 3. Distinctive manifestations in 51 patients

	N.		N.
Musculoskeletal	8	**Gastro-intestinal**	8
Bone alteration/deformity	5	Aseptic peritonitis	4
Flexion contractures	4	Gastro-intestinal ulcers	4
Osteitis	2	Gastro-intestinal bleeding	1
Osteolytic lesions	2	Intestinal occlusion	2
Muscular atrophy	3	Peritoneal adhesions	1
Hyperostotic lesions	1	Gut perforation	1
Neurological	25	**Cardio-respiratory**	16
Seizures	13	Pericarditis	12
Intellectual impairment	8	Venous thrombosis	1
Aseptic meningitis	2	Cardiomyopathy	0
Cranial neuropathy	3	Arterial thrombosis	1
Peripheral neuropathy	3	Pulmonary fibrosis	3
Hydrocephalus	2	(mild;severe)	(2;1)
Cerebellar syndrome	1		
Mucocutaneous	4	**Ocular**	1
Genital ulcers	2	Retinal vasculitis	1
Pyoderma gangrenosum	1	**Other**	2
Necrotic lesions extremities	1	Macrophage activation syndrome	1
		Death	1

N. =number of patients

Supplementary table 1.Countries of residence

Argentina	(n=3)
Croatia	(n=3)
Czech Republic	(n=4)
France	(n=18)
Germany	(n=1)
Iceland	(n=1)
Italy	(n=110)
Latvia	(n=2)
Lebanon	(n=1)
Norway	(n=1)
Romania	(n=6)
Russia	(n=3)
Serbia and Montenegro	(n=2)
Slovenia	(n=1)
Spain	(n=4)
The Netherlands	(n=21)
United Kingdom	(n=21)

Supplementary table 2. 51 patients with distinctive manifestations

Pt	Age onset in years	Attacks /year	Attack duration (days)	Distinctive manifestations
1	0.07	6	1	Death due to cardiovascular insufficiency, seizures, peripheral neuropathy
2	0.3	14	4	Bone alteration, flexion contractures, gastro-intestinal bleeding, seizures, mental retardation
3	1.3	8	7	Bone alteration, osteolytic lesions, osteitis, hyperostosis
4	8.4			Bone alteration, osteolytic lesions, osteitis, muscular atrophy
5	9.6	12	3	Bone alteration, muscular atrophy
6	6.6			Flexion contractures, muscular atrophy, necrotic lesions at extremities
7	0.9	24	7	Flexion contractures, seizures, gastrointestinal ulcers, aseptic peritonitis, occlusion
8	2.7	25	2	Hydrocephalus, seizures, sensorineural hearing loss, cerebellar syndrome, cranial neuropathy, arterial thrombosis, mild pulmonary fibrosis
9	3.6			Mild mental retardation, aseptic meningitis, seizures
10	0.7			Mild mental retardation, aseptic peritonitis, pyoderma gangrenosum, gastro-intestinal ulcers,
11	0.8	10	7	Mild mental retardation, aseptic peritonitis,
12	34.4			Pericarditis, aseptic peritonitis
13	10.3	1		Pericarditis, peripheral neuropathy
14	3.5	9		Gut perforation, peritoneal adhesions, occlusion
15	38.7	5	3	Retinal vasculitis
16	11.3			Flexion contractures
17	16.2	12	1	Hydrocephalus,
18	5.9	4		Aseptic meningitis
19	37.8	3	2	Peripheral neuropathy
20	11.3	12	10	Cranial neuropathy
21	23.6	9	13	Cranial neuropathy
22	0.3			Pulmonary fibrosis
23	0.7			Pulmonary fibrosis
24	11.2	4	8	Venous thrombosis
25	9.6	1	21	Gastro-intestinal ulcers
26	14.1	12	15	Gastro-intestinal ulcers
27	19.2	5	3	Ulcers genitalia
28	45.0	18	5	Ulcers genitalia
29	6.8	12	21	Macrophage activation syndrome
Pt	**Age onset Range (Mdn)**	**Attacks /year Range (Mdn)**	**Attack duration Range (Mdn)**	**Distinctive manifestations**
30-37	0.03 - 7.0 (1.7)	5-20 (12)	3-13 (5)	Seizures
38-41	0.0 - 8.3 (3.8)	4-18 (11)	3-6 (4)	Mental retardation
42-51	8.0 - 56.6 (32.3)	2-16 (3)	2-18 (6)	Pericarditis

Mdn=median. Pt=patient