

# **TNFRSF1A-pR92Q variant identifies a subset of patients more similar to systemic undifferentiated recurrent fever than TNF receptor-associated periodic syndrome**

A.M. Gerritsma<sup>1</sup>, D. Sutera<sup>2,3</sup>, L. Cantarini<sup>4</sup>, M. Cattalini<sup>5</sup>, H.J. Lachmann<sup>6</sup>, K. Minden<sup>7</sup>, A.F. Jansson<sup>8</sup>, I. Touitou<sup>9</sup>, M. Bustaffa<sup>2</sup>, J. Antón<sup>10</sup>, A. Insalaco<sup>11</sup>, E. Moreno<sup>12</sup>, J. Sanchez-Manubens<sup>13</sup>, N. Ruperto<sup>14</sup>, J. Frenkel<sup>1</sup>, M. Gattorno<sup>2</sup> for Eurofever/Eurotraps projects and Paediatric Rheumatology International Trials Organisation (PRINTO)

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<sup>1</sup>Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands; <sup>2</sup>IRCCS Istituto Giannina Gaslini, UOC Reumatologia e Malattie Autoinfiammatorie, Genova, Italy; <sup>3</sup>Paediatric Unit, University "Magna Graecia" of Catanzaro, Italy; <sup>4</sup>Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy; <sup>5</sup>Paediatric Clinic, University of Brescia and Spedali Civili of Brescia, Italy; <sup>6</sup>National Amyloidosis Centre, Royal Free Hospital, London, UK; <sup>7</sup>Department of Paediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt - Universität zu Berlin; German Rheumatism Research Centre, Berlin, Germany; <sup>8</sup>Department of Paediatric Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig Maximilian University, Munich, Germany; <sup>9</sup>Stem Cells, Cellular Plasticity, Regenerative Medicine and Immunotherapies, INSERM, University of Montpellier, Department of Medical Genetics, Rare Diseases and Personalized Medicine, National Referral Centre of Auto-Inflammatory Diseases and Inflammatory Amyloidosis, CEREMAIA CHU Montpellier, France; <sup>10</sup>Division of Paediatric Rheumatology, Hospital Sant Joan de Déu, Universitat de Barcelona, Esplugues de Llobregat, Barcelona, Spain; <sup>11</sup>Department of Paediatric Medicine, Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; <sup>12</sup>Paediatric Rheumatology Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain; <sup>13</sup>Department of Paediatric Rheumatology, Hospital Universitari Parc Taulí, Autonomous University of Barcelona, Sabadell, Barcelona, Spain; <sup>14</sup>IRCCS Istituto Giannina Gaslini, UOC Servizio di Sperimentazioni Cliniche Pediatriche, PRINTO, Genova, Italy.

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## **Abstract**

### **Objective**

To describe the clinical phenotype and response to treatment of autoinflammatory disease (AID) patients with the TNFRSF1A-pR92Q variant compared to patients with tumour necrosis factor receptor-associated periodic syndrome (TRAPS) due to pathogenic mutations in the same gene and patients diagnosed with other recurrent fever syndromes including periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) and syndrome of undefined recurrent fever (SURF).

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### **Methods**

Clinical data from pR92Q variant associated AID, classical TRAPS, PFAPA and SURF patients were obtained from the Eurofever registry, an international, multicentre registry enabling retrospective collection of data on AID patients.

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### **Results**

In this study, 361 patients were enrolled, including 77 pR92Q variant, 72 classical TRAPS, 152 PFAPA and 60 SURF patients. pR92Q carriers had an older age of disease onset than classical TRAPS and PFAPA patients. Compared to pR92Q variant patients, classical TRAPS patients had more relatives affected and were more likely to have migratory rash and AA-amyloidosis. Despite several differences in disease characteristics and symptoms between pR92Q variant and PFAPA patients, part of the pR92Q variant patients experienced PFAPA-like symptoms. pR92Q variant and SURF patients showed a comparable clinical phenotype. No major differences were observed in response to treatment between the four patient groups. Steroids were most often prescribed and effective in the majority of patients.

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### **Conclusion**

Patients with AID carrying the TNFRSF1A-pR92Q variant behave more like SURF patients and differ from patients diagnosed with classical TRAPS and PFAPA in clinical phenotype. Hence, they should no longer be diagnosed as having TRAPS and management should differ accordingly.

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### **Key words**

autoinflammatory diseases, tumour necrosis factor receptor-associated periodic syndrome (TRAPS), pR92Q, periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA), syndrome of undefined recurrent fever (SURF)

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Anna M. Gerritsma, MD  
 Diana Sutura, MD  
 Luca Cantarini, MD, PhD  
 Marco Cattalini, MD  
 Helen J. Lachmann, MD  
 Kirsten Minden, MD  
 Annette F. Jansson, MD  
 Isabelle Touitou MD, PhD  
 Marta Bustaffa, MD  
 Jordi Antón, MD, PhD  
 Antonella Insalaco, MD  
 Estefania Moreno, MD  
 Judith Sanchez-Manubens, MD, PhD  
 Nicolino Ruperto, MD  
 Joost Frenkel, MD, PhD\*  
 Marco Gattorno, MD\*

\*These authors contributed equally.

Please address correspondence to:

Joost Frenkel

University Medical Center Utrecht,  
 Wilhelmina Children's Hospital,  
 Department of General Paediatrics,  
 Lundlaan 6,

3584 EA Utrecht, the Netherlands.

E-mail: j.frenkel@umcutrecht.nl

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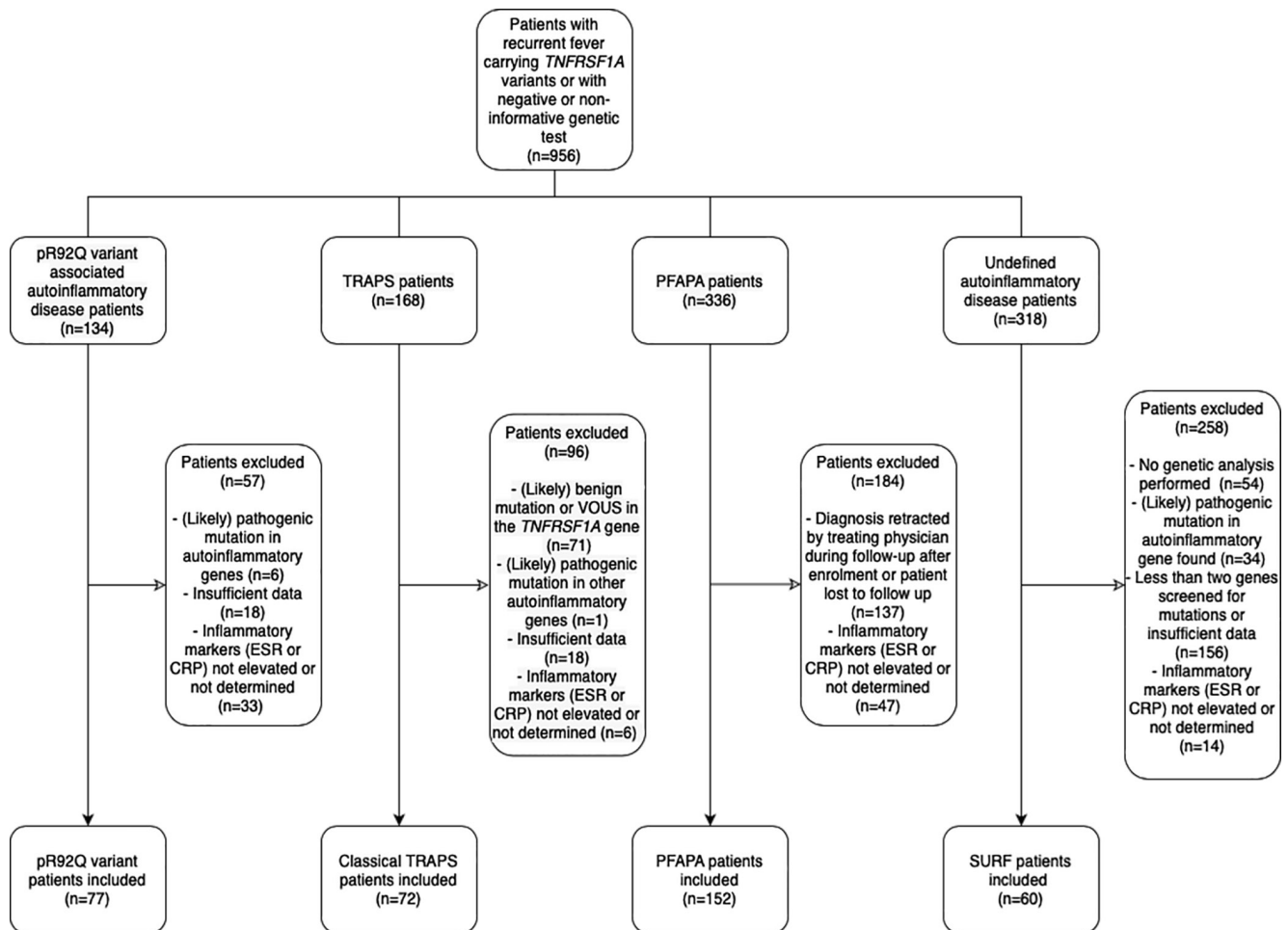
## Introduction

Recurrent fever syndromes (RFS) are autoinflammatory diseases (AID) characterised by recurrent episodes of fever accompanied by a spectrum of systemic symptoms and high inflammatory markers resulting from dysregulation of the innate immune system (1). Tumour necrosis factor receptor-associated periodic syndrome (TRAPS), an autosomal dominant inherited AID, results from mutations in the *TNFRSF1A* gene, encoding tumour necrosis factor receptor 1 (TNFR1), the 55-kD receptor for tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), a key regulator of inflammation (1-4). Currently, of the 181 known variants in the *TNFRSF1A* gene, 104 may cause TRAPS (5). The pR92Q variant was originally listed as a TRAPS-causing mutation and was reported in a large proportion (12-83%) of TRAPS patients (6-9). However, this variant can also be found in 1-3% of the general population (4, 10-14). Previous studies and clinical experience suggest that the pathogenesis, symptomatology, and response to treatment of pR92Q variant patients differ from classical TRAPS patients (4, 15). In contrast to the mutant protein of classical TRAPS patients, the pR92Q-TNFR1 functions very similarly to the wild-type protein (4, 10, 16-24). The classic phenotype of TRAPS includes seemingly unprovoked recurrent, often prolonged (>1 week) episodes of fever, that can be accompanied by severe abdominal pain, sterile peritonitis, arthritis, myalgia, migratory skin rash and/or periorbital oedema (4, 25). Patients also risk developing systemic AA-amyloidosis, which occurs in 14% of the TRAPS patients (26). In classical TRAPS, treatment with the anti-interleukin-1 (IL-1) agent canakinumab resulted in a 100% response rate, compared to only 25% in pR92Q patients (27). Therefore, evidence-based therapy for TRAPS patients does not necessarily apply to those carrying pR92Q. This warrants further research into the response to treatment of patients with pR92Q-associated disease. Additionally, several studies reported a role for pR92Q in the susceptibility to periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA)(15) and to other multifactorial inflammatory conditions (4, 13, 26, 28-31), such as multiple sclerosis (11, 12, 14). PFAPA, a non-monogenic fever syndrome, is characterised by frequent short episodes with aphthous stomatitis, pharyngitis, and cervical lymphadenopathy generally responding well to steroids (32). Diagnosis of RFS is based on the clinical phenotype and genetic findings. Although classification criteria for RFS have been developed, not all patients presenting with periodic fever can be unambiguously classified. Patients presenting with periodic fever exhibiting the incomplete phenotype of a known disease, showing overlapping signs of more than one RFS or having non-diagnostic genetic tests, are diagnosed with syndrome of undefined recurrent fever (SURF) (33-35). Previous studies suggested that SURF is caused by a combination of genetic, epigenetic and environmental factors (36). The pR92Q variant has also been described in patients diagnosed with SURF (37). In this article, clinical characteristics and response to treatment of the largest cohort of pR92Q variant, classical TRAPS, PFAPA and SURF patients are described in order to investigate to what extent the pR92Q-associated AID phenotype is comparable to classical TRAPS, PFAPA and SURF patients and to find out whether the pR92Q-associated AID is a distinct entity.

**Materials and methods**

*Study design and participants*

Data of AID patients harbouring the pR92Q variant and patients without this variant diagnosed with classical TRAPS, PFAPA and SURF were extracted from the Eurofever registry, which has been enrolling patients with AIDs since November 2009 (38). This international, multicentre registry retrospectively collects information on clinical presentation, outcome and response to treatment. This registry provided a sufficiently large sample of both pR92Q variant patients and classical TRAPS, PFAPA and SURF patients for a meaningful comparison. All patients with AIDs harbouring the pR92Q variant were included as pR92Q variant patients, regardless of initial diagnosis provided by the enrolling physician.



**Fig. 1.** Flowchart of patient inclusion.

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PFAPA: periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SURF: syndrome of undefined recurrent fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; VOUS: variant of uncertain significance.

pR92Q variant patients also harbouring a (likely) pathogenic mutation in an AID associated gene, leading to the diagnosis of an AID, were excluded. Classical TRAPS patients are defined as patients diagnosed with TRAPS harbouring a (likely) pathogenic variant in the *TNFRSF1A* gene (39). Patients with variants of uncertain significance (VOUS) or with (likely) benign variants were excluded. Patients harbouring a (likely) pathogenic mutation in an AID associated gene other than *TNFRSF1A*, were excluded. Variants in the *TNFRSF1A* gene were identified in patients upon solely screening of the *TNFRSF1A* gene or as component of an autoinflammatory gene panel. PFAPA patients were defined according to the original diagnostic criteria (40). Enrolling centres were retrospectively contacted before analysis to check whether the diagnosis of PFAPA was still applicable.

If the diagnosis could not be confirmed by the centre or patients had been lost to follow-up, patients were excluded. Patients diagnosed with undefined AID, in whom genetic analysis of at least two genes had yielded no (likely) pathogenic variants were selected as SURF patients. Patients were excluded if inflammatory markers (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)) had not been elevated during fever episodes, regardless of clinical diagnosis. Ethical approval for entering patients in the registry and informed consent by patients and/or guardians were obtained in all participating centres, in agreement with local requirements.

#### Data collection

Data on demographic information, laboratory findings, clinical manifestations and response to treatment were retrieved from the registry, as was information

about molecular genetic analysis including the sequence variants found. Genetic variants were classified as pathogenic, likely pathogenic, likely benign, benign, VOUS or not classified (NC) (39).

The presence of symptoms during episodes in patients had been registered by the entering physician as never, sometimes/often or always. We graded symptoms to be present when a symptom was reported as sometimes/often or always. Response to treatment was registered by the entering physician as worsening, failure, partial response or complete response either as ineffective or leading to remission. We classified response to treatment as beneficial when it was reported as partial or complete response or leading to remission.

#### Statistical analysis

Descriptive categorical variables were presented as frequencies and percent-

**Table I.** Demographics and disease characteristics.

	pR92Q variant patients n=77	Classical TRAPS patients n=72	p-value <sup>a</sup>	PFAPA patients n=152	p-value <sup>b</sup>	SURF patients n=60	p-value <sup>c</sup>
Male, n (%)	39 (50.6)	36 (50.0)	NS	84 (55.3)	NS	29 (48.3)	NS
Ethnicity ±, n			NS		NS		NS
Caucasian	76	68		141		60	
Arab	1	1		3		0	
Asian	0	2		1		1	
West-African	0	2		0		0	
Hispanic	1	0		0		0	
Unknown	0	1		7		0	
Diagnosis, n (%)			NA		NA		NA
TRAPS	67 (87.0)	72 (100)		0 (0)		0 (0)	
PFAPA	1 (1.3)	0 (0)		152 (100)		0 (0)	
SURF	5 (6.5)	0 (0)		0 (0)		60 (100)	
CAPS	2 (2.6) <sup>†</sup>	0 (0)		0 (0)		0 (0)	
FMF	1 (1.3) <sup>‡</sup>	0 (0)		0 (0)		0 (0)	
CRMO	1 (1.3)	0 (0)		0 (0)		0 (0)	
Age at disease onset in years, median (IQR)	6.3 (2.5-25.9)	2.8 (0.6-8.0)	<0.001	1.6 (0.9-3.4)	<0.001	3.5 (1.1-9.5)	NS
Age at diagnosis in years, median (IQR)	15.3 (5.3-39.0)	28.9 (10.1-44.0)	NS	4.0 (2.9-6.3)	<0.001	7.9 (4.3-15.3)	NS
Diagnostic delay in years, median (IQR)	2.8 (0.9-9.7)	20.6 (7.8-34.2)	<0.001	1.8 (1.1-3.2)	NS	2.8 (1.4-6.9)	NS
Number of episodes per year, median (IQR)	7.5 (3-12.3)	5.0 (3.0-12.0)	NS	12.0 (10.0-16.0)	<0.001	12.0 (7.5-15.0)	NS
Flare duration in days, median (IQR)	7.0 (4.0-13.0)	10.0 (6.0-13.0)	NS	4.0 (3.0-5.0)	<0.001	6.5 (3.3-8.0)	NS
Disease course, n (%)			NS		NS		<0.001
Recurrent	71 (92.2)	60 (83.3)		151 (99.3)		50 (83.3)	
Continuous	6 (7.8)	4 (5.6)		0 (0)		1 (1.7)	
Continuous with flares	0 (0)*	8 (11.1)		1 (0.7)		9 (15.0)*	
Regular pattern of frequency, n (%)	15 (23.4)	7 (13.7)	NS	101 (66.4)	<0.001	29 (49.2)	NS
Trigger, n (%)	12 (15.6)	22 (30.6)	NS	16 (10.5)	NS	8 (14.0)	NS
Relatives affected, n (%)	14 (18.2)	56 (77.8)	<0.001	5 (3.3)	<0.001	9 (15.0)	NS

<sup>a</sup>Classical TRAPS vs. pR92Q variant patients; <sup>b</sup>PFAPA vs. pR92Q variant patients; <sup>c</sup>SURF vs. pR92Q variant patients.

± The total number of patients in the column exceeds the total number of patients included in the study since people can have multiple ethnicities.

<sup>†</sup>One patient harbouring the V198M mutation in the NLRP3 gene and one patient without known additional mutations in AID associated genes.

<sup>‡</sup>One patient without known additional mutations in AID associated genes.

CAPS: cryopyrin-associated periodic syndrome; CRMO: chronic recurrent multifocal osteomyelitis; FMF: familial Mediterranean fever; IQR: interquartile range; NA: not applicable; NS: not significant; PFAPA: periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SURF: syndrome of undefined recurrent fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

\*Statistically significantly different.

ages. Descriptive numeric variables non-normally distributed were reported as the median and interquartile range (IQR). Dichotomous variables were compared using the Fisher's exact test. Associations between dichotomous variables and nominal variables were assessed using the Chi-squared test or Fisher-Freeman-Halton Test when >20% of the cells had an expected count <5. The Chi-squared for trend test was used to compare dichotomous variables with ordinal variables. To compare dichotomous variables with non-normally distributed interval variables, the Mann-Whitney U-test was used. *p*-values of 0.05 and less were considered significant. Since multiple variables were tested for significance, *p*-values were adjusted with Bonferroni correction. This means that the calcu-

lated *p*-values were multiplied by 208. *p*-values after Bonferroni correction are described in this paper. SPSS 28 was used for statistical analysis.

## Results

The data of 134 AID patients carrying the pR92Q variant, 168 classical TRAPS patients, 336 PFAPA patients (41) and 318 SURF patients were retrieved from the Eurofever registry. At the end, 77 pR92Q variant, 72 classical TRAPS, 152 PFAPA and 60 SURF patients were included for analysis. See Figure 1 for the flowchart of patient inclusion.

### Demographic data

A total of 361 patients (188 male) were enrolled in the analysis. Most patients were Caucasian (n=345), other report-

ed ethnicities were Arab (n=5), Asian (n=4), West-African (n=2) and Hispanic (n=1). pR92Q variant patients had been entered into the registry under a variety of clinical diagnoses as determined by their attending physicians, including TRAPS in most patients (n=67, 87.0%). Other diagnoses included SURF (n=5, 6.5%), cryopyrin-associated periodic syndrome (CAPS) (n=2, 2.6%), PFAPA (n=1, 1.3%), familial Mediterranean fever (FMF) (n=1, 1.3%) and chronic recurrent multifocal osteomyelitis (CRMO) (n=1, 1.3%) (Table I).

### Disease characteristics

Classical TRAPS patients had a lower median age of disease onset compared to pR92Q variant patients (2.8 vs. 6.3 years, *p*<0.001). A family history with an affected relative was more often



**Table II.** Clinical phenotype in pR92Q variant, classical TRAPS, PFAPA and SURF patients.

	pR92Q variant patients, n (%) n=77	Classical TRAPS patients, n (%) n=72	p-value <sup>a</sup>	PFAPA patients, n (%) n=152	p-value <sup>b</sup>	SURF patients, n (%) n=60	p-value <sup>c</sup>
<b>Muco-cutaneous</b>							
Aphthous stomatitis	19 (24.7)	4 (5.6)	NS	111 (73.0)	<0.001	21 (35.0)	NS
Exudative pharyngitis	15 (19.5)	1 (1.4)	<0.001	111 (73.0)	<0.001	15 (25.0)	NS
Erythematous pharyngitis	24 (31.2)	8 (11.1)	NS	117 (77.0)	<0.001	24 (40.0)	NS
Maculo-papular rash	12 (15.6)	22 (30.6)	NS	9 (5.9)	NS	18 (30.0)	NS
Urticarial rash	12 (15.6)	21 (29.2)	NS	4 (2.6)	<0.001	11 (18.3)	NS
Migratory rash	3 (3.9)	21 (29.2)	<0.001	0 (0)	NS	1 (1.7)	NS
<b>Musculoskeletal system</b>							
Arthralgia	42 (54.5)	47 (65.3)	NS	43 (28.3)	<0.001	41 (68.3)	NS
Myalgia	40 (51.9)	56 (77.8)	NS	18 (11.8)	<0.001	35 (58.3)	NS
Fasciitis	1 (1.3)	5 (6.9)	NS	0 (0)	NS	0 (0)	NS
Bone pain	8 (10.4)	2 (2.8)	NS	1 (0.7)	<0.001	3 (5.0)	NS
Monoarthritis	5 (6.5)	3 (4.2)	NS	0 (0)	NS	0 (0)	NS
Oligoarthritis	6 (7.8)	6 (8.3)	NS	1 (0.7)	NS	4 (6.7)	NS
Polyarthritis	5 (6.5)	0 (0)	NS	1 (0.7)	NS	1 (1.7)	NS
Bone alterations	2 (2.6)	1 (1.4)	NS	0 (0)	NS	2 (3.3)	NS
<b>Ocular manifestation</b>							
Periorbital oedema	11 (14.3)	17 (23.6)	NS	1 (0.7)	<0.001	3 (5.0)	NS
Periorbital pain	7 (9.1)	13 (18.1)	NS	0 (0)	<0.001	1 (1.7)	NS
Conjunctivitis	14 (18.2)	30 (41.7)	NS	7 (4.6)	NS	7 (11.7)	NS
<b>Gastrointestinal system</b>							
Vomiting	14 (18.2)	9 (12.5)	NS	25 (16.4)	NS	14 (23.3)	NS
Abdominal pain	36 (46.8)	54 (75.0)	<0.001	62 (40.8)	NS	35 (58.3)	NS
Constipation	7 (9.1)	14 (19.4)	NS	6 (3.9)	NS	7 (11.7)	NS
Diarrhoea	13 (16.9)	13 (18.1)	NS	15 (9.9)	NS	11 (18.3)	NS
Aseptic peritonitis	0 (0)	4 (5.6)	NS	0 (0)	NS	1 (1.7)	NS
<b>Lymphoid organs</b>							
Generalised enlargement	8 (10.4)	7 (9.7)	NS	7 (4.6)	NS	10 (16.7)	NS
Enlarged cervical lymph nodes	25 (32.5)	20 (27.8)	NS	125 (82.2)	<0.001	30 (50.0)	NS
Hepatomegaly	7 (9.1)	5 (6.9)	NS	2 (1.3)	NS	10 (16.7)	NS
Splenomegaly	11 (14.3)	6 (8.3)	NS	3 (2.0)	<0.001	10 (16.7)	NS
<b>Cardio-respiratory system</b>							
Chest pain	23 (29.9)	20 (27.8)	NS	1 (0.7)	<0.001	8 (13.3)	NS
Pericarditis	13 (16.9)	2 (2.8)	NS	0 (0)	<0.001	3 (5.0)	NS
Pleurisy	5 (6.5)	9 (12.5)	NS	0 (0)	NS	5 (8.3)	NS
Persistent cough	3 (3.9)	3 (4.2)	NS	2 (1.3)	NS	4 (6.7)	NS
<b>Neurological manifestations</b>							
Headache	21 (27.3)	8 (11.1)	NS	28 (18.4)	NS	24 (40.0)	NS
<b>Constitutional symptoms</b>							
Fatigue	44 (57.1)	44 (61.1)	NS	33 (21.7)	<0.001	42 (70.0)	NS
Malaise	35 (45.5)	37 (51.4)	NS	40 (26.3)	NS	41 (68.3)	NS
Sensation of fever, chills without fever	7 (9.1)	11 (15.3)	NS	4 (2.6)	NS	1 (1.7)	NS
<b>Systemic manifestations</b>							
AA-Amyloidosis	1 (1.3)	14 (19.4)	<0.001	0 (0)	NS	0 (0)	NS
Fever	64 (83.1)	59 (81.9)	NS	152 (100)	<0.001	57 (95.0)	NS
Low grade fever	41 (53.2)	27 (37.5)	NS	24 (15.8)	<0.001	27 (45.0)	NS

<sup>a</sup>Classical TRAPS vs. pR92Q variant patients; <sup>b</sup>PFAPA vs. pR92Q variant patients; <sup>c</sup>SURF vs. pR92Q variant patients.

NS: not significant; PFAPA: periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SURF: syndrome of undefined recurrent fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

reported by classical TRAPS patients (77.8% vs. 18.2%,  $p<0.001$ ). Number of episodes per year, flare duration and presence of triggers were comparable between classical TRAPS and pR92Q variant patients. Disease onset was earlier in PFAPA patients compared to pR92Q variant patients (1.6 vs. 6.3 years,  $p<0.001$ ). The pattern of recur-

rence was more often regular in PFAPA patients (66.4% vs. 23.4%,  $p<0.001$ ) and PFAPA patients reported more episodes per year (12.0 vs. 7.5 episodes,  $p<0.001$ ) although the episodes lasted shorter compared to pR92Q variant patients (4.0 vs. 7.0 days,  $p<0.001$ ). While a continuous disease course with flares was described in 15.0% of the SURF

patients, it was not reported by any pR92Q variant patient ( $p<0.001$ ). Age at disease onset, number of episodes per year, flare duration and pattern of frequency were comparable between SURF and pR92Q variant patients (Table I). Subgroup analysis comparing pR92Q variant patients diagnosed with TRAPS disease versus pR92Q variant

patients diagnosed with other AID revealed that disease characteristics were comparable in both groups (Supplementary Table S1).

#### Genetic characteristics

Genetic analysis differed between participating centres. At least the *TNFRSF1A* gene had been analysed in all classical TRAPS and pR92Q variant patients. In several patients additional AID associated genes had been screened, including the *MEFV*, *MVK*, *NLRP3*, *NLRP12* and *NOD2* gene. Genetic screening had been done either by screening of the complete gene, most relevant exons or most relevant point mutations. Genetic screening of at least two genes without the finding of a (likely) pathogenic mutation was by definition needed to be diagnosed with SURF. Classical TRAPS patients by definition harboured a (likely) pathogenic variant in the *TNFRSF1A* gene, with T50M (n=13), C33Y (n=11) and C52Y (n=5) as the three most frequent variants. In two (11.8%) of the seventeen classical TRAPS patients and four (8.7%) of the 46 pR92Q variant patients in whom additional autoinflammatory genes had been tested, a VOUS was identified in an additional genetic locus. No correlation was found between the number of additional variants and classical TRAPS patients or pR92Q variant patients. It should be noted that additional screening was more often conducted in pR92Q variant patients than in classical TRAPS patients. A variant of (likely) pathogenic, (likely) benign or uncertain significance was found in eight (5.3%) PFAPA patients and fourteen (23.3%) SURF patients. It is unknown whether the remaining 144 PFAPA patients did not undergo genetic testing or if there were no mutations found. Therefore, the percentage of PFAPA patients harbouring the pR92Q variant is unclear (Suppl. Tables S2 and S3).

#### Clinical characteristics

The three most reported symptoms (in addition to fever) in pR92Q variant patients were fatigue (57.1%), arthralgia (54.5%), and myalgia (51.9%). Migratory rash (29.2% vs. 3.9%,  $p<0.001$ ) and abdominal pain (75.0% vs. 46.8%,

$p<0.001$ ) were more often reported by classical TRAPS compared to pR92Q variant patients, while exudative pharyngitis was more often seen in pR92Q variant patients (1.4% vs. 19.5%,  $p<0.001$ ). AA-amyloidosis was reported in only one (1.3%) pR92Q variant patient, while this feared complication occurred in fourteen (19.4%) classical TRAPS patients ( $p<0.001$ ). PFAPA patients more often reported aphthous stomatitis (73.0% vs. 24.7%,  $p<0.001$ ), exudative (73.0% vs. 19.5%,  $p<0.001$ ) and erythematous pharyngitis (77.0% vs. 31.2%,  $p<0.001$ ) and enlarged cervical lymph nodes (82.2% vs. 32.5%,  $p<0.001$ ) compared to pR92Q variant patients. Several other symptoms including myalgia (11.8% vs. 51.9%,  $p<0.001$ ), periorbital oedema (0.7% vs. 14.3%,  $p<0.001$ ), chest pain (0.7% vs. 29.9%,  $p<0.001$ ) and pericarditis (0% vs. 16.9%,  $p<0.001$ ) were less often seen in PFAPA patients compared to pR92Q variant patients. There were no major differences observed in any symptoms experienced by SURF and pR92Q variant patients (Table II). Subgroup analysis showed that pR92Q variant patients initially diagnosed with TRAPS experienced comparable symptoms to pR92Q variant patients diagnosed with other AID (Suppl. Table S4).

#### Treatment

Although different therapeutic strategies were noted, no major differences in response to treatment between pR92Q variant and classical TRAPS, PFAPA and SURF patients were reported (Table III). The majority of patients were treated with steroids, which led to comparable beneficial outcomes in most patients. Other drugs often used included nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. Only one out of five (20.0%) SURF patients benefited from NSAIDs, compared to 73.5% (n=25) of the pR92Q variant patients. pR92Q variant patients tended to benefit more from colchicine than classical TRAPS patients and showed a pattern of response to colchicine similar to that of SURF patients. Anakinra led to a beneficial response in most pR92Q variant and classical TRAPS patients (81.8% and 100%, respectively), but

only 33.3% of the SURF patients benefited from anakinra. (Adeno)tonsillectomy was favourable in all PFAPA patients who underwent surgery, while this intervention was beneficial in 50.0% (n=2) of the pR92Q variant patients.

#### Discussion

This retrospective, cross-sectional, multi-centre cohort study presents phenotypic characteristics and response to treatment in the largest cohort of pR92Q variant autoinflammatory patients described so far and compares these to patients diagnosed with classical TRAPS, PFAPA and SURF.

The diagnosis of TRAPS is based on the presence of periodic episodes of fever accompanied by typical symptoms and supported by the finding of a pathogenic mutation in the *TNFRSF1A* gene (42). The meaning of the presence of the pR92Q variant in the *TNFRSF1A* gene has been unclear. Although this variant can also be found in the general population, the prevalence is higher in TRAPS patients (6-9). Therefore, it has been suggested that this variant does play a role in the pathogenesis of AIDs (4, 6-8). However, this prevalence may be unintentionally enriched in this group because the definition of TRAPS requires a *TNFRSF1A* mutation. Hence similar patients without this variant would not have ended up in the TRAPS group. Indeed, previous research and clinical experience suggest that the pathogenesis, symptomatology, and response to treatment of pR92Q variant patients differ from classical TRAPS patients (4). Studies on the pathogenesis of TRAPS reported conformational and functional abnormalities of the TNFR1 caused by structural mutations in the *TNFRSF1A* gene. Among other, conformational changes of the extracellular domain (17-19), reduced surface expression of the TNFR1 (17-21), decreased shedding of soluble TNFR1, which is the natural antagonist of TNF- $\alpha$  (4, 10, 18, 23), impaired TNF- $\alpha$  binding (17-20), enhanced TNF- $\alpha$  independent signalling (19, 24), and reduced TNF- $\alpha$  dependent signalling have been described (10, 18-20). In contrast to structural mutations, the 3D structure of the TNFR1-pR92Q

**Table III.** Response to treatment in pR92Q variant, classical TRAPS, PFAPA and SURF patients.

Medication	pR92Q variant patients n=64		Classical TRAPS patients n=71		<i>p</i> -value <sup>a</sup>	PFAPA patients n=129		<i>p</i> -value <sup>b</sup>	SURF patients n=43		<i>p</i> -value <sup>c</sup>
	n*	Beneficial, n (%)	n*	Beneficial, n (%)		n*	Beneficial, n (%)		n*	Beneficial, n (%)	
Steroids	53	51 (96.2)	54	52 (96.3)	NS	119	118 (99.2)	NS	18	13 (72.2)	NS
NSAIDs	34	25 (73.5)	33	24 (72.7)	NS	-	-	NA	5	1 (20.0)	NS
Colchicine	25	18 (72.0)	18	8 (44.4)	NS	10	8 (80.0)	NS	24	15 (62.5)	NS
Anakinra	11	9 (81.8)	29	29 (100)	NS	1	0 (0)	NS	6	2 (33.3)	NS
Etanercept	15	14 (93.3)	21	20 (95.2)	NS	-	-	NA	-	-	NA
Canakinumab	1	1 (100)	3	3 (100)	NS	1	1 (100)	NA	1	0 (0)	NS
(Adeno)tonsillectomy	4	2 (50.0)	4	1 (25.0)	NS	30	30 (100)	NS	-	-	NA

<sup>a</sup>Classical TRAPS vs. pR92Q variant patients; <sup>b</sup>PFAPA vs. pR92Q variant patients; <sup>c</sup>SURF vs. pR92Q variant patients.

\*Number of patients that was treated with the specified medication.

NSAIDs: non-steroidal anti-inflammatory drugs; NS: not significant; NA: not applicable; PFAPA: periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SURF: syndrome of undefined recurrent fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

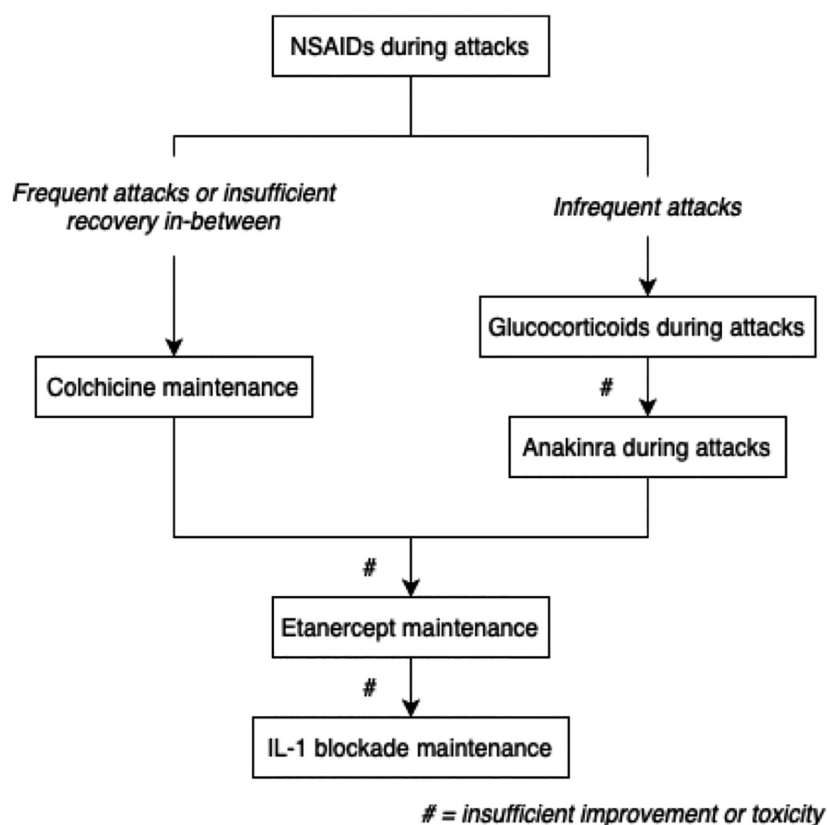
variant is only minimally affected and the TNFR1 functions mostly similar to the wild type (4, 10, 16-24). Nonetheless, many patients with periodic episodes of fever harbouring the pR92Q variant have been listed as TRAPS patients. This study revealed that there are essential differences between pR92Q variant and classical TRAPS patients.

In accordance with previous research, pR92Q variant patients were older at disease onset compared to classical TRAPS patients (6, 8-10, 15). These studies also showed that pR92Q variant patients experienced shorter disease episodes, while this study only revealed a trend towards shorter disease episodes in pR92Q variant patients. A positive family history, which is one of the variables in the Eurofever/PRINTO clinical classification criteria for TRAPS disease, was more often reported in classical TRAPS compared to pR92Q variant patients (42). Migratory rash, one out of three TRAPS core symptoms, was more often experienced by classical TRAPS patients compared to pR92Q variant patients. Periorbital oedema and myalgia, the second and third TRAPS core symptoms, tended to be more common in classical TRAPS patients than in pR92Q variant patients, but these differences were not statistically significant. Pharyngitis, which is typically absent in TRAPS patients, was, like in previous research, more often experienced by pR92Q variant patients compared to classical TRAPS patients (10, 15). Additionally, in accordance with previous research, the incidence of AA-amyloidosis was far higher in classical

TRAPS patients compared to pR92Q variant patients (4, 6, 26, 43). Although one out of 77 pR92Q variant patients (1.3%) was reported to have developed AA-amyloidosis, this is still a very rare occurrence and insufficient proof that pR92Q is an independent risk factor for the development of AA-amyloidosis. The possibility that an additional unknown gene mutation could have played a role for the development of this severe complication in this patient is not excluded. Yet, as with any RFS patient, monitoring inflammation markers and proteinuria is recommended. In the CLUSTER trial, the efficacy of canakinumab in RFS was studied (27). All fourteen (100%) classical TRAPS patients compared to only one out of four (25%) pR92Q variant patients responded well to canakinumab. This is in line with the study of Papa *et al.* (44), where treatment efficacy was compared between three groups based on the variant in their *TNFRSF1A* gene: (likely) pathogenic variants, VOUS or NC variant and (likely) benign variants. The group harbouring a VOUS or NC variant (78 patients) included 47 pR92Q variant patients. Treatment with anti-IL-1 led to more beneficial outcomes in patients with a (likely) pathogenic mutation, compared to patients harbouring a VOUS or NC variant. Treatment with colchicine, NSAIDs or steroids was frequently effective in patients carrying a VOUS or NC variant. In our study, pR92Q variant patients also showed a slightly more beneficial response to colchicine compared to classical TRAPS patients, while both patient groups

reacted equally well to steroids and NSAIDs. Anakinra tended to give less beneficial results in pR92Q variant patients. Etanercept, a TNF- $\alpha$  antagonist, on the other hand, was equally effective in both patient groups. Given the results of the CLUSTER trial (27) and the study of Papa *et al.* (44), the efficacy of anti-IL-1 in pR92Q variant patients is uncertain at best. Although there is evidence-based therapy for TRAPS patients, there is insufficient evidence for any treatment in pR92Q variant RFS patients. Where IL-1 blockade is the main therapy used in classical TRAPS patients, it is not primarily indicated in pR92Q variant patients, as it is an expensive treatment without evidence for effectiveness in this group. Hence, we suggest therapy with NSAIDs, steroids or colchicine to be tried before TNF-blockade or IL-1 blockade are prescribed. In the absence of evidence, we suggest a stepwise pragmatic approach as summarised in Figure 2.

In comparison to PFAPA patients, pR92Q variant patients were older at disease onset and reported less frequent but longer episodes. Notably, the percentage of affected relatives in PFAPA patients was lower than has been reported in literature (45). Whether this was due to underreporting or a different cause could not be ascertained. Aphthous stomatitis, exudative and erythematous pharyngitis and enlarged cervical lymph nodes, symptoms characteristic for PFAPA disease, were all more common in PFAPA patients compared to pR92Q variant patients. Pelagatti *et al.* (15) concluded that pR92Q vari-



**Fig. 2.** Empirical treatment of *TNFRSF1A* pR92Q associated AID in the absence of evidence-based therapy as suggested by the authors. During attacks, symptomatic treatment with NSAIDs and simple analgesics is warranted. Patients may require intensification of both intermittent and maintenance therapy. The choice to try etanercept before maintenance IL-1 blockade is arbitrary and entirely based on consideration of costs and convenience.

IL-1: interleukin-1; NSAIDs: non-steroidal anti-inflammatory drugs.

ant patients showed more similarities with PFAPA patients than with classical TRAPS patients. Although several differences in clinical phenotype are observed between PFAPA and pR92Q variant patients, in our cohort, eleven pR92Q variant patients (14%), of which only one had received the clinical diagnosis PFAPA, experienced all three PFAPA core symptoms, whereas this was the case for none of the classical TRAPS patients ( $p < 0.001$ ). Of these eleven patients, nine were treated with steroids, being effective in all patients. Given this high number of patients with PFAPA-like symptoms, it is conceivable that the pR92Q variant can contribute to the pathogenesis of PFAPA. The absence of major differences in disease characteristics and clinical symptoms experienced by pR92Q variant and SURF patients is remarkable. Additionally, steroids and colchicine led to comparable responses in both patient groups. However, SURF pa-

tients may benefit less from NSAIDs and anakinra compared to pR92Q variant patients. Phenotypic characteristics and response to therapy have not yet been compared between pR92Q variant patients and SURF patients in previous research.

The incidence of pericarditis was higher in pR92Q variant patients (16.9%) compared to classical TRAPS, PFAPA and SURF patients (2.8%, 0.0% and 5.0%, respectively). Cantarini *et al.* (31) described thirty patients with idiopathic recurrent pericarditis refractory to colchicine treatment. Of four patients with a variant in the *TNFRSF1A* gene, three carried the pR92Q variant. Given the higher incidence of pericarditis in pR92Q variant patients compared to classical TRAPS patients and the high prevalence of the pR92Q variant in patients with idiopathic recurrent pericarditis, it is conceivable that the pR92Q variant can contribute to the pathogenesis of this disease.

Our study has a number of limitations, the first being its retrospective observational design. Thereby, part of the clinical variables concerning symptoms was reported by the clinician as “not known” since the variable was not described in the clinical chart, which suggests that the feature was not prominent in the disease presentation. Since observations are more often not written down when negative, symptoms were presumed negative when reported as “not known” to prevent selection bias (46). Second, in our cohort the pR92Q variant was identified in autoinflammatory patients upon screening of the *TNFRSF1A* gene, alone or as component of an autoinflammatory gene panel. This inevitably skews the patient selection towards an autoinflammatory phenotype. Therefore, we cannot describe the full phenotype of individuals carrying the pR92Q variant. Third, there was no clear definition of complete and partial response to treatment and clinicians had to interpret the response. Besides, it is unknown whether patients were treated with multiple drugs sequentially or simultaneously. This makes it hard to assign a reported effect to an individual drug. Additionally, most data were collected when IL-1 blockade therapy was not yet registered for RFS. Therefore, IL-1 blockade was not used by many patients in this study.

In conclusion, the pR92Q variant occurs both in healthy individuals and in patients with evident AID, suggesting that the clinical phenotype is determined by additional (epi)genetic or environmental factors that have not yet been identified. This study shows that pR92Q variant autoinflammatory patients behave more like SURF patients and have distinct clinical phenotypes compared to classical TRAPS and PFAPA. We conclude that the finding of the pR92Q variant in autoinflammatory patients does not justify a diagnosis of TRAPS and that management should differ accordingly.

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