

Supplementary Table S1. Demographics and disease characteristics of pR92Q variant patients comparing patients labelled as having TRAPS and non-TRAPS.

	pR92Q variant patients labelled as having TRAPS N=67	pR92Q variant patients labelled as having non-TRAPS N=10	<i>p</i> -value
Male, n (%)	34 (50.7)	5 (50.0)	NS
Ethnicity±, n			NS
Caucasian	66	10	
Arab	1	0	
Asian	0	0	
West-African	0	0	
Hispanic	1	0	
Diagnosis, n (%)			NA
TRAPS	67 (100)	0 (0)	
PFAPA	0 (0)	1 (10.0)	
SURF	0 (0)	5 (50.0)	
CAPS	0 (0)	2 (20.0)	
FMF	0 (0)	1 (10.0)	
CRMO	0 (0)	1 (10.0)	
Age at disease onset in years, median (IQR)	8.1 (3.0-25.1)	4.9 (0.5-29.3)	NS
Age at diagnosis in years, median (IQR)	15.3 (6.1-39.7)	16.0 (4.4-35.6)	NS
Diagnostic delay in years, median (IQR)	2.8 (0.9-9.8)	2.9 (1.0-7.2)	NS
Number of episodes per year, median (IQR)	6.0 (3.0-12.0)	10.0 (3.5-21.0)	NS
Flare duration in days, median (IQR)	7.0 (4.0-13.0)	6.0 (3.0-12.8)	NS
Disease course, n (%)			NS
Recurrent	62 (92.5)	9 (90.0)	
Continuous	5 (7.5)	1 (10.0)	
Continuous with flares	0 (0)	0 (0)	
Regular pattern of frequency, n (%)	11 (20.0)	4 (44.4)	NS
Trigger, n (%)	10 (14.9)	2 (20.0)	NS
Relatives affected, n (%)	10 (14.9)	4 (40.0)	NS

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

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.

Supplementary Table S2. Genetic characteristics in pR92Q variant, classical TRAPS, PFAPA and SURF patients.

	pR92Q variant patients, classification (n) N=77	Classical TRAPS patients, classification (n) N=72	PFAPA patients, classification (n) N=152	SURF patients, classification (n) N=60
<i>TNFRSF1A</i>	R92Q, US (77)	c.269C>A, LP (2) C29F, P (1) C29Y, P (1) C30R, P (3) C30Y, P (1) C33Y, P (11) C43R, P (3) C43S, P (1) C43Y, P (1) C52Y, P (5) C55Y, P (3) C73R, LP (1) C73W, LP (1) C88Y, P (1) C96Y, P (1) D42Del, P (3) F60L, P (2) H22Q, LP (2) H22R, LP (3) H69fs, LP (1) L167_G175del, LP (1) N65I, P (2) R92P, LP (1) S59P, LP (1) T37I, LP (2) T50K, LP (2) T50M, P (13) V95M, LP (2) Y38S, LP (1)	-	D12E, US (1)
<i>MEFV</i>	E148Q, US (1)	E148Q, US (1)	c.36 A>G, US (1) c.625+10A/G, US (1) K695R, LP (1) M694I, P (1) M694V, P (1) R202Q, B (3) V726A, P (1)	A744S, US (2) E148Q, US (1) R202Q, B (5)
<i>MVK</i>	-	-	-	S52N, B (1) T356M, US (1) R488K, US (1) Q703K, US (1)
<i>NLRP3</i>	D646Y, US (1) V198M, US (2)	V198M, US (1)	-	F402L, NC (1) G39V, NC (3) P268S/SNP5, LB (4) V955I, LB (1)
<i>NLRP12</i>	-	-	-	-
<i>NOD2</i>	-	-	No mutations found or no genetic testing performed (144)	No mutations found (46)

P: pathogenic; LP: likely pathogenic; LB: likely benign; B: benign; US: uncertain significance; NC: not classified; PFAPA: periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SURF: syndrome of undefined recurrent fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

Supplementary Table S3. Combinations of mutations found in pR92Q variant, classical TRAPS, PFAPA and SURF patients.

pR92Q variant patients:

- TNFRSF1A (R92Q) + MEFV (E148Q)
- TNFRSF1A (R92Q) + NLRP3 (D646Y)
- TNFRSF1A (R92Q) + NLRP3 (V198M)
- TNFRSF1A (R92Q) + NLRP3 (V198M)

Classical TRAPS patients:

- TNFRSF1A (C33Y) + MEFV (E148Q)
- TNFRSF1A (Y38S) + NLRP3 (V198M)

PFAPA patients:

- MEFV (c.36 A>G) + MEFV (c.625+10A/G)

SURF patients:

- MEFV (R202Q) + MVK (S52N) + NOD2 (P268S/SNP5)
- MEFV (R202Q) + NLRP12 (G39V) + NOD2 (P268S/SNP5)
- NLRP12 (F402L) + NLRP12 (G39V) + NOD2 (P268S/SNP5)
- MEFV (A744S) + NLRP12 (G39V) + NOD2 (V955I)

Supplementary Table S4. Clinical phenotype in pR92Q variant patients comparing patients labelled as TRAPS and non-TRAPS.

	pR92Q variant patients labelled as having TRAPS, n (%) N=67	pR92Q variant patients labelled as having non-TRAPS, n (%) N=10	<i>p</i> -value
Muco-cutaneous			
Aphthous stomatitis	15 (22.4)	4 (40.0)	NS
Exudative pharyngitis	13 (19.4)	2 (20.0)	NS
Erythematous pharyngitis	21 (31.3)	3 (30.0)	NS
Maculo-papular rash	10 (14.9)	2 (20.0)	NS
Urticarial rash	10 (14.9)	2 (20.0)	NS
Migratory rash	2 (3.0)	1 (10.0)	NS
Musculoskeletal system			
Arthralgia	36 (53.7)	6 (60.0)	NS
Myalgia	35 (52.2)	5 (50.0)	NS
Fasciitis	1 (1.5)	0 (0)	NS
Bone pain	5 (7.5)	3 (30.0)	NS
Monoarthritis	4 (6.0)	1 (10.0)	NS
Oligoarthritis	5 (7.5)	1 (10.0)	NS
Polyarthritis	5 (7.5)	0 (0)	NS
Bone alterations	1 (1.5)	1 (10.0)	NS
Ocular manifestation			
Periorbital oedema	9 (13.4)	2 (20.0)	NS
Periorbital pain	5 (7.5)	2 (20.0)	NS
Conjunctivitis	12 (17.9)	2 (20.0)	NS
Gastrointestinal system			
Vomiting	13 (19.4)	1 (10.0)	NS
Abdominal pain	31 (46.3)	5 (50.0)	NS
Constipation	6 (9.0)	1 (10.0)	NS
Diarrhea	11 (16.4)	2 (20.0)	NS
Lymphoid organs			
Generalised enlargement	5 (7.5)	3 (30.0)	NS
Enlarged cervical lymph nodes	21 (31.3)	4 (40.0)	NS
Hepatomegaly	5 (7.5)	2 (20.0)	NS
Splenomegaly	8 (11.9)	3 (30.0)	NS
Cardio-respiratory system			
Chest pain	19 (28.4)	4 (40.0)	NS
Pericarditis	10 (14.9)	3 (30.0)	NS
Pleurisy	4 (6.0)	1 (10.0)	NS
Persistent cough	3 (4.5)	0 (0)	NS
Neurological manifestations			
Headache	18 (26.9)	3 (30.0)	NS
Constitutional symptoms			
Fatigue	36 (53.7)	8 (80.0)	NS
Malaise	28 (41.8)	7 (70.0)	NS
Sensation of fever, chills without fever	7 (10.4)	0 (0)	NS
Systemic manifestations			
AA-Amyloidosis	1 (1.5)	0 (0)	NS
Fever	55 (82.1)	9 (90.0)	NS
Low grade fever	33 (49.3)	8 (80.0)	NS

NS: not significant; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.