EXTENDED REPORT

Clinical significance of P46L and R92Q substitutions in the tumour necrosis factor superfamily 1A gene

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Objective: Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) has been associated with several mutations in the *TNF receptor super family 1A (TNFRSF1A)*, including most cysteine substitutions. However, the nature of two substitutions, P46L and R92Q, remains a topic of discussion. The aim of this study was to assess the actual role of these two sequence variations in a series of patients with TRAPS.

Methods: The main clinical data of 89 patients with TRAPS have been prospectively registered on a standard form. 84 patients or members of families with recurrent episodes of inflammatory symptoms spanning a period of more than 6 months and harbouring a *TNFRSF1A* mutation were studied. Clinical data have been analysed according to the nature of the mutation—P46L, R92Q or others.

Results: P46L is often seen in patients from Maghreb and is associated with a mild phenotype. P46L appears as a polymorphism with a non-specific role in inflammation. R92Q is associated with a variable phenotype and presents as a low-penetrance mutation. Interpreting these results will require a comparison with clinical signs and genetic background.

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant inherited chronic and inflammatory disease, which belongs to the group of auto-inflammatory syndromes.^{1,2} This condition was initially described in a family of Irish descent as familial Hibernian fever, but similar findings were later found in families in many other populations.^{3–5} TRAPS is associated with mutations in the gene that encodes tumour necrosis factor receptor superfamily 1A (*TNFRSF1A*) on chromosome 12p13.^{6,7} Mutations occurred predominantly in exons 2, 3 and 4, encoding the extracellular cysteine-rich domain (CRD).^{2,8–11}

Characteristic features include episodes of fever accompanied by abdominal pain, arthralgia, myalgia, rash, conjunctivitis and periorbital oedema.^{8,12} The phenotype and clinical severity of TRAPS are variable.^{9,10,13} Some patients develop systemic amyloidosis, up to 15% in some series.^{14–16} To date, more than 60 mutations in the *TNFRSF1A* gene have been reported among patients with TRAPS. Two frequent mutations, R92Q and P46L, are associated with a variable phenotype and can be observed at a low level in controls. The aim of our study is to assess the actual nature of these sequence variations—mutation or polymorphism—in our series.^{12,17}

PATIENTS AND METHODS

Patients

Our study includes patients referred to the Cochin Hospital Biochemistry and Genetic Molecular Laboratory, Paris, a referral centre for the molecular diagnosis of periodic fever syndromes. Routine molecular diagnosis of TRAPS in this laboratory began in 1999. The main clinical data (age, sex, origin of both parents, consanguinity, family history, age at onset of inflammatory episodes, duration of episodes, organ involvement, frequency of episodes, amyloidosis, acute-phase response and efficacy of drugs) have been prospectively registered on a standard form for all patients with a suspicion of hereditary periodic fever syndrome.

In our study, we included all patients who presented with clinical signs compatible with the TRAPS phenotype and a

mutation in *TNFRSF1A*. We excluded five patients, four with R92Q and one with P46L substitution, who finally had another definite diagnosis. In the R92Q group, two patients had symptoms typical of Behçet's disease and were reported previously.¹³ The two others had a *CIAS1* mutation (R260W and A439V) with related phenotype (Muckle-Wells and familial cold auto-inflammatory syndromes). The patient excluded in the P46L group had presented with Crohn's disease long before complications with amyloidosis occurred. Informed consent was obtained from all the participants.

TNFRSF1A mutation detection

Detection of *TNFRSF1A* mutations was carried out as described previously.¹³ Briefly, genomic DNA was extracted from whole blood, then mutations were detected through amplification of the *TNFRSF1A* gene by polymerase chain reaction followed by denaturing high-performance liquid chromatography scanning.

TNF and soluble TNF receptor

TNF and soluble TNF receptors were measured as previously described.⁵

Statistical analysis

Unvaried statistical analyses were carried out by using χ^2 or Fisher exact tests for nominal variables and Mann-Whitney U test for quantitative variables. We compared the phenotype of P46L and R92Q mutations of patients with known mutations of TRAPS, using Stat View. The level of significance was set at $p < 0.01$.

RESULTS

In all, 84 patients were included in our series. Table 1 gives their main clinical characteristics. We classified patients who

Abbreviations: CRD, cysteine-rich domain; FMF, familial Mediterranean fever; TNF, tumour necrosis factor; TNFRSF, TNF receptor super family; TRAPS, TNF receptor-associated periodic syndrome

Table 1 Main clinical characteristics of patients

Mutation characteristics	Total	Group A (R92Q) n (%)	p Value (group A v group B)	Group B (other mutations) n (%)	Group C (P46L) n (%)	p Value (group B v group C)
Patients	84	34	—	37	13	—
Sex						
M	37	17	>0.99	16	4	>0.99
F	47	17		21	9	
Ethnicity						
56 C	28 C	27 C		1 C		
16 MA	3 MA	4 MA		9 MA		<0.001
8 ME	2 ME	5 ME	>0.99	1 ME		
2 NA	1 NA	0 NA		2 NA		
1 I	0 I	1 I		0 I		
Fever	49	16 (48)	0.128	26 (72)	7 (46)	0.30
Abdominal pain	45	12 (38.7)	0.028	24 (66)	9 (70)	<0.99
Musculoskeletal involvement*	44	15 (48)	0.33	22 (61)	7 (54)	0.745
Cutaneous involvement†	28	11 (35.5)	0.99	13 (36)	4 (35)	>0.99
Seritis‡	23	10 (32)	0.59	9 (25)	4 (35)	0.96
Neurological involvement§	22	5 (16)	0.39	10 (27.7)	7 (54)	0.172
Transit disorders¶	18	7 (22.6)	0.99	8 (22.2)	3 (35)	>0.99
Lymphadenopathy	14	6 (19)	0.13	2 (5)	6 (46)	0.003
Rhinolaryngeal involvement**	9	4 (12)	0.695	3 (8.3)	2 (15.4)	0.59
Amyloidosis	8	2 (6.4)	0.27	6 (16.6)	0 (0)	0.175
Periocular oedema	8	4 (12)	0.695	3 (8.3)	1 (7.7)	>0.99
Ocular involvement††	5	2 (6.4)	0.99	3 (8.3)	0 (0)	0.652
Mean age at the first episode (years)	15.705	18.91	0.01	9.72	22.4	0.179
Mean duration of episodes (days)	9.055	7.43	0.01	11.03	7.58	0.125
Frequency of episodes						
≤ 1 episode/month	46	13	0.017	27	6	0.418
> 1 episode/month	27	15		8	4	
Not related	11	6		2	3	
Familial case of TRAPS	36	7 (20.6)	<0.001	29 (78.4)	0 (0)	<0.001
Sporadic case of TRAPS	48	27		8	13	

C, Caucasian; I, Indian; MA, Maghrebian; ME, Mediterranean; NA, native African.

*Arthralgia and myalgia; †rash or urticaria or erythema; ‡pleurisy and pericarditis; §headache and aseptic meningitis; ¶constipation or diarrhoea; **pharyngitis; ††conjunctivitis. Comparisons are made between groups A and B, and between groups B and C.

presented R92Q, known and P46L mutations into three groups: A, B and C.

Among the 84 patients selected (47 women and 37 men), 34 (40%), 13 (15.5%) and 37 (44%) patients were genotyped, respectively, for the R92Q, P46L and other known mutations (Y20D, C43Y, T50M, Y106C, C55Y, C30S, G36E, C43R, C43S, L67P, C70Y, R92W, C96Y, Y20H and C30Y).

The main clinical features of TRAPS's disease in the cohort were as follows: fever (58.3%), abdominal pain (53.6%), musculoskeletal involvement (52.4%), skin involvement (33.3%), neurological involvement (26.2%), lymphadenopathy (16.6%), transit disorders (21.4%), seritis (27%), amyloidosis (9.52%), rhinolaryngeal disorders (10.7%), periocular oedema (9.5%) and conjunctivitis (6%). In all, 36 (42.9%) patients had familial TRAPS and 48 (57.1%) were sporadic cases.

In all, 56 (66.6%) patients were Caucasian (Belgian, Czech, French, Armenian, Luxemburgian and Dutch), 16 (19%) were Arabs from Maghreb (Maghreb comprises Morocco, Algeria and Tunisia), 8 (9.5%) were Mediterranean (Jewish Italian, Portuguese and Spanish), 3 (3.5%) were native African and 1 (1.2%) patient was Indian (table 2).

The mean age at the first episode of fever was 15.7 years, with 9 days as the mean duration of episodes. In all, 46

patients had one episode per month, 27 had two or more episodes per month.

Patients with the P46L TNFRSF1A substitution

The P46L mutation was found in 13 (9 women and 4 men) unrelated patients, including 9 of Maghrebian origin ($p < 0.001$). In all patients, the disease was considered to be sporadic ($p < 0.001$). The mean age at the first episode of fever was 22.4 years, with 7.5 days as the mean duration of the episode. Six patients had one episode a month and four patients had two or more episodes a month. We do not have enough information about the frequency of the episodes for the three remaining patients. We did not find any significant difference between this group and group B, except for lymphadenopathy, which was significantly more frequent in group C ($p = 0.003$).

In two families, several patients appeared to be affected with inflammatory symptoms. For the first family, the patient genotyped P46L/N was symptomatic and presented with moderate fever, diarrhoea, nodes, aseptic meningitis, arthralgia and pseudo-erysipelas. His mother, genotyped N/N, presented with arthralgia, recurrent inflammatory episodes with unknown diagnosis, and his father, genotyped P46L/N, was asymptomatic. In the second family, the patient

Table 2 Ethnicity

Mutations	Caucasian	Maghrebian	Mediterranean	Native African	Indian	Total
Group A	28	3	2	1	NR	34
Group C	1	9	1	2	NR	13
Group B	27	4	5	NR	1	37
Total	56	16	8	3	1	84

NR, not reported.

genotyped P46L/N presented with fever, arthro-myalgia, urticaria, lymphadenopathy, pharyngeal manifestations and periorbital oedema. His mother was asymptomatic, but genotyped P46L/N. His father and his paternal aunt had N/N genotypes, but the paternal aunt presented flares of fever, pleurisy, arthralgia, pharyngitis and skin manifestations without a known diagnosis.

Patients with the R92Q TNFRSF1A substitution

The R92Q mutation was found in 34 (17 women and 17 men) unrelated patients, including 27 with a sporadic presentation. In all, 28 patients were Caucasians, 3 were Maghrebians, 2 were Mediterraneans and 1 was native African (table 2).

Among the clinical signs of patients with TRAPS carrying a substitution R92Q, abdominal pain was less frequent in the R92Q group than in the known mutations group ($p = 0.029$). A marked difference was seen in the age of onset and duration of fever in the R92Q group compared with the known mutations group (table 1). We found only five families, including 10 patients, in which segregation occurred to some extent (table 3).

In the first and the second families, penetrance was incomplete because the father in the first family and the mother in the second, genotyped R92Q/N, were asymptomatic. In the fourth family, there was suspicion of incomplete penetrance because the nephew, genotyped R92Q/N, was asymptomatic but the father's genotype was unknown; he had had amyloidosis some years before.

In the fifth family, the patient and his stepbrother, genotyped R92Q/N, were symptomatic. Genotypes of asymptomatic parents were unknown. We found an *MEFV* heterozygotic V726A mutation both in the father and in the son in the first family. Another *MEFV* heterozygotic mutation, A744S, was found in the third family, but only in the father.

In another family, R92Q does not seem to segregate with the inflammatory disease. Indeed, the patient genotyped R92Q/R92Q was symptomatic and presented fever and abdominal pain. The patient's mother and brother, genotyped R92Q/N, were asymptomatic, and father and paternal uncle were symptomatic with skin manifestations and fever, genotyped R92Q/N and N/N, respectively.

Laboratory investigations

Acute-phase response markers, C reactive protein, erythrocyte sedimentation rate and fibrinogen were increased in all patients during episodes. Plasma TNF and soluble TNF receptor levels were measured during episodes of fever in six patients with known mutations (three patients with T50M, two patients with C30S and one with R92W). In these six patients, TNF levels were high, whereas soluble TNF receptor levels were normal. One patient with R92Q substitution presented a high concentration of TNF and TNF receptors during episodes of fever (table 4).

Treatments

Among 84 patients selected, 34 had a daily continuous treatment and 5 had a treatment restricted to episodes, including non-steroidal anti-inflammatory drugs, aspirin and morphine chlorhydrate (table 5).

In all, 25 patients were treated with colchicine and 4 patients seemingly showed a good response, with total disappearance of fever. No definite difference in efficacy of colchicine was found between the three groups.

Glucocorticoids are able to decrease the severity of symptoms, both acutely and chronically, in most patients. Azathioprine, ciclosporin, cyclophosphamide and TNF inhibitors were tried empirically but were not found to be beneficial; no statistical analysis was carried out.

None of the patients were treated with chlorambucil, intravenous methylprednisolone, immunoglobulins, dapsone, methotrexate or thalidomide.

DISCUSSION

Around 50 mutations in the *TNFRSF1A* gene have so far been reported to be associated with TRAPS. A large proportion of the mutations observed are substitutions of cysteine residues that are clearly associated with a typical TRAPS phenotype. By contrast, the status of two non-cysteine substitutions remains a topic of discussion.¹²⁻¹⁸ In our study, we discussed the specific status of these two specific substitutions.

In our series, the clinical presentation of patients with P46L appeared to be milder, as age at onset was greater, episodes were shorter, amyloidosis was absent, and none of these patients had been treated with corticosteroid and TNF inhibitors. Intriguingly, peripheral lymph nodes were more frequent in these patients during episodes of fever, without other specific manifestations.

We did not find familial cases in the P46L group. Indeed, two patients presented with familial history of recurrent inflammation, but in both families P46L is not segregated with the inflammatory disorder. P46L had been reported previously at a frequency of 2–3% in patients with TRAPS.^{10-12,18} This frequency is as high as 15.5% in our study. In several control populations, P46L was present at a frequency of around 1%.^{4,13,19} It was detected in 1 of 170 northern-European control chromosomes and in 3 of 156 African American control chromosomes, at a combined gene frequency of 1.2%.¹² However, the frequency of P46L in other populations seems to be considerably higher. We previously found that in the general population of Arabs from Maghreb, P46L was present with an allele frequency of 2.9%.¹³ Moreover, in sub-Saharan African populations, P46L was reported recently with an unexpected allele frequency of 9.8%, suggesting a north-to-south gradient.⁹

It is important to note that the origin of most of our patients with P46L is Maghrebian, a population in which the frequency of this substitution is high. Taking into account all

Table 4 Levels of tumour necrosis factor and tumour necrosis factor receptors 1 and 2 during crisis

	TNF* (pg/ml)	TNFR1† (ng/ml)	TNFR2‡ (ng/ml)	Mutation
Patient 1	40	1.1	NR	T50M/N
Patient 2	29	0.4	NR	T50M/N
Patient 3	33	0.6	NR	T50M/N
Patient 4	27	0.7	1.8	C30S/N
Patient 5	24	1.2	NR	R92W
Patient 6	40	0.9	4	C30S/N
Patient 7	8.8	49	9.6	R92Q

NR, not reported; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor.

*TNF during crisis (normal <13 pg/ml); †TNFR1 during crisis (normal 0.8–1.9 ng/ml); ‡TNFR2 during crisis (normal 2–6.6 ng/ml).

Table 5 Treatments

Mutations			
Patients	R92Q	P46L	Other mutations
Basic treatment	11 Colchicine: 4 CE 4 PE 3 NE 1 TNF α inhibitor+ glucocorticoid	6 Colchicine:4 PE 2CE	8 Colchicine:7 NE 1 PE 1 Glucocorticoids + azathioprine or ciclosporin + colchicine 5 Glucocorticoids 1 Cyclophosphamide + NSAIDs 2 Colchicine + glucocorticoids 1 TNF α inhibitor 1 NSAID*
Treatment of fever	2 NSAIDs	1 Aspirin 1 Morphin chlorhydrate	1 NSAID*
Treated or not treated	14:21	8:6	18:20
Total	34	14	37

CE, completely effective; NE, not effective; NSAID, non-steroidal anti-inflammatory drugs; PE, partially effective; TNF α , tumour necrosis factor α .

*Same patient treated with cyclophosphamide.

our available data, we believe that in the Maghrebian population, P46L is a polymorphism rather than a mutation.

In group A, the R92Q phenotype seems to be more heterogeneous. In our series, the clinical phenotype appears to be milder compared with group B, as age at onset of episodes is higher and duration of attacks is shorter ($p = 0.01$ and $p = 0.01$, respectively). Symptoms associated with episodes seem to be different, as abdominal pain is less frequent during episodes ($p = 0.029$). Moreover, in this group, some patients presented with recurrent pericarditis or headache with aseptic meningitis as the only clinical symptom. In addition, patients with R92Q require to be treated with steroids or immunosuppressive agents less often. Globally, patients with R92Q thus appear to have a milder phenotype than group B patients.

These results are in agreement with those of Hull *et al*'s⁹ study, which included 50 patients, with a median age at onset of 23 years in patients with R92Q and of 7 years in patients with other mutations. Clinically, patients with R92Q seem to present with a less typical phenotype than patients with other *TNFRSF1A* mutations. Rashes were generally less typical and ranged from large macular erythematous patches to urticaria-like lesions. Similarly, not all the symptoms were present to the same degree, and symptoms range in duration from several days to the more typical week-long episodes.⁹

We found only two cases of amyloidosis amyloid A in patients with R92Q, with no marked difference in group B. TRAPS mutations that result in cysteine substitutions show a higher probability of developing life-threatening amyloidosis (24% *v* 2% for non-cysteine residue substitutions).⁹

Most of our patients with R92Q (27/37; 79%) appeared to be sporadic cases. The remaining patients belonged to six families. In five of these families, the penetrance of R92Q appears incomplete. In the last family, R92Q is not segregated with the disease; this may be linked to another gene responsible for the inflammatory disease.

The frequency of R92Q substitution in control populations was estimated at around or below 1%, a frequency compatible with the status of a low-penetrance mutation.^{12–13} However, some recent results suggest that R92Q could be implicated in other inflammatory disorders.^{19–23} In fact, R92Q has been found at a frequency of 5.2% in a cohort of patients with early arthritis and in a series of patients with Behçet's disease; it was markedly associated with extracranial deep vein thrombosis.^{19–22} In a series of patients with juvenile idiopathic arthritis, R92Q was more frequent in patients with amyloidosis.²⁴

R92Q was reported in a patient with inflammatory panniculitis, without the canonical signs of the TRAPS phenotype.²⁰ All these results would suggest that R92Q is a low-penetrance mutation associated with the TRAPS

phenotype. R92Q is also probably a non-specific factor in other inflammatory diseases. Its role as a factor favouring secondary amyloidosis and its implication in some vascular processes need to be established by further research.

Interpreting the results of the *TNFRSF1A* genotype requires a comparison with clinical signs and ethnic background. The frequencies of R92Q and P46L in some populations do not allow us to systematically attribute inflammatory symptoms to these sequence variations. Moreover, the absence of segregation of these sequence variations with the disease in some families suggests the existence of other genes underlying auto-inflammatory syndromes.

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