

# Incidence of *TNFRSF1A* mutations in German children: epidemiological, clinical and genetic characteristics

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**Objective.** TNF receptor 1-associated periodic syndrome (TRAPS) is a rare disease belonging to the heterogeneous group of hereditary periodic fever (HPF) syndromes. By their monogenic origins, the HPF syndromes are clearly differentiated from other periodic inflammatory episodes occurring in autoimmune, neoplastic and infectious diseases. We aim to determine the incidence of TRAPS and the spectrum of mutations in the *TNFRSF1A* gene, and to give a brief survey of clinical signs.

**Methods.** A prospective surveillance of children with TRAPS was conducted in Germany during a time period of 3 years (2003–06). Monthly inquiries were sent to 370 children's hospitals by the German Pediatric Surveillance Unit (Clinic-ESPED, n1) and to 23 laboratories (Laboratory-ESPED, n2). Inclusion criteria were *TNFRSF1A* mutation-positive patients  $\leq 16$  years of age, more than three self-limiting episodes of fever  $>38.5^{\circ}\text{C}$ , and increased inflammation markers. Clinical, epidemiological and genetic data were evaluated via questionnaires.

**Results.** Of the 23 cases included, 19 were identical in 20 clinical and 22 laboratory reports. The incidence of TRAPS in German children was estimated to be  $\sim 5.6$  per  $10^7$  person-years. In 20 TRAPS patients of the Clinic-ESPED, median age of onset and duration of fever periods were 6 (range 1–16) years and 6.3 (range 2–24) days, respectively. Main symptoms were arthralgia, abdominal pain, lymphadenopathy, headache and skin involvement. The R92Q substitution was found in 19 (83%) of 23 cases.

**Conclusion.** The incidence of TRAPS is low and corresponds to 6–10 newly diagnosed patients  $\leq 16$  years per year in Germany.

**KEY WORDS:** TNF receptor 1-associated periodic syndrome, Hereditary periodic fever, Autoinflammatory disease, ESPED, *TNFRSF1A* gene, Mutation.

## Introduction

Hereditary periodic fever (HPF) syndromes are rare autoinflammatory diseases (AIDs) characterized by (i) recurrent episodes of inflammation with acute attacks of fever variably associated with serosal, synovial and/or cutaneous inflammation, usually in a self-limiting manner and (ii) a mostly monogenic origin [1–3]. Patients often remain undiagnosed for years and undergo extensive diagnostic investigations. Amyloidosis is the most severe, life-threatening complication [4].

TNF receptor 1-associated periodic syndrome (TRAPS) was first described in 1982 in a large Irish family and was originally called familial Hibernian fever [5]. It is due to autosomal dominantly inherited mutations in exons 2–4 or 6 of the *TNFRSF1A* gene on chromosome 12p13.2, which encodes the 55-kDa receptor for TNF- $\alpha$  [6]. Genetic testing has become an important adjunct in the diagnosis of HPF [7, 8]. The growing list of mutations and polymorphisms is frequently updated in INFEVERS, a mutational database accessible on the World Wide Web at <http://fmf.igh.cnrs.fr/infevers> [9, 10].

Fever is one of the most common symptoms in paediatric practice. Since genetic testing has become available, a large cohort of children has been tested for HPF. TRAPS is an increasingly

recognized disease entity prompting genetic testing. However, mutation screening for TRAPS is not very cost effective [11]. Its incidence is unknown and the clinical picture has never been analysed in a population-based sample. Therefore, we estimated the incidence of TRAPS and analysed the clinical picture in a paediatric population-based sample with two methods for case ascertainment.

## Methods

### Study design

A prospective, national active surveillance of symptomatic children with TRAPS was conducted in Germany from July 2003 to June 2006. This TRAPS survey was part of a national epidemiological survey on HPF in Germany by the German Paediatric Surveillance Unit for rare pediatric diseases (ESPED), which is a well-established tool [12, 13]. Monthly inquiries were sent to 370 children's hospitals and paediatric rheumatological outpatient clinics (Clinic-ESPED, n1) and to all 23 laboratories performing genetic analyses for HPF (Laboratory-ESPED, n2).

### Case definition

The criteria for case definition include: age  $\leq 16$  years, confirmed *TNFRSF1A* mutation, more than three self-limiting episodes of fever  $>38.5^{\circ}\text{C}$  and increased inflammation markers.

Newly diagnosed patients with a mutation in the *TNFRSF1A* gene were added to the database, and epidemiological, clinical and genetic information was evaluated using questionnaires for hospitals and laboratories. The return rates were 97% for the monthly report cards of Clinic-ESPED and  $>90\%$  for the questionnaires sent for validation of the reports and for clinical data. In the Laboratory-ESPED, all required information was asked on the monthly inquiry with return rates of 98%.

For each patient, the following data were documented in the Clinic-ESPED (n1): unique identification number, number and town of reporting clinic, core data [gender, date of birth (month/year) and time of diagnosis (month/year)], history (consanguinity, ethnic origin and affected relatives), symptoms

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Submitted 1 November 2008; revised version accepted 24 April 2009.

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(description of fever episodes, skin, joint, abdominal, neurological and bone involvement, lymphadenopathy, serositis, amyloidosis, trigger and rare observations), genetic analysis, medications (NSAIDs, corticosteroids, colchicine, etanercept and other treatment); and in the Laboratory-ESPED (n2): fulfilled case definition, core data [gender, date of birth (month/year) and time of diagnosis (month/year)], reporting institution (children's hospitals and paediatric private practices), patient or relative, genetic analysis and laboratory method [sequencing of exons 2–5, intron 2, intron 4 and the intron/exon junctions ( $n=1$ ), sequencing of exons 2–7 ( $n=2$ ) and sequencing of exons 2–4, 6 and 7 ( $n=27$ )].

### Incidence calculation

The number of cases reported to both independent data sources ( $n1 \cap n2$ ) and the remaining cases of  $n1$  and  $n2$  were used to determine the total number of definite TRAPS cases. The identification of cases reported to both ESPED surveys was possible by using the core data (see above) of the patients. The total number of cases as numerator was estimated as  $\sum(n1+n2) - (n1 \cap n2)$  with representation of a 95% CI, assuming a Poisson distribution. This strategy gives a conservative estimate of the total number of cases without making any assumptions regarding dependencies between the sources. For calculation of the incidence per person-years in the complete population of German children  $\leq 16$  years of age, data of the Federal Office of Statistics were used as denominator (www.destatis.de).

### Statistical analysis and data protection

Frequency measurements were performed by descriptive analysis of each variable. Because of their seemingly non-Gaussian distribution, continuous data are given preferentially as medians and ranges. Discrete variables are described with proportional values.

Personal data were pseudonymized and analysed anonymously. They were stored in an anonymized fashion for scientific research work. With the information kept in the data bank, it was impossible to retrieve the identity of individuals. Data were also guarded against foreign access. The study has been approved by the ethics committee at the University of Düsseldorf. Parents and patients were instructed by an information letter.

## Results

### Incidence of newly diagnosed TRAPS

A total of 156 cases of HPF and among them 20 (12.8%) cases of TRAPS were registered in Clinic-ESPED (n1) between 2003 and 2006. Altogether, 23 cases in different families fulfilled the inclusion criteria as TRAPS patients and had been recorded in at least one of the two surveillance systems ( $n1$  or  $n2$ ). Out of these, 19 (83%) had been identified in both sources ( $n1 \cap n2$ ). One case had been documented only in Clinic-ESPED ( $n1$ ) and three cases only in Laboratory-ESPED ( $n2$ ). Laboratory-ESPED ( $n2$ ) detected seven additional *TNFRSF1A* mutation carriers, who did not fulfil the criteria of the case definition. This included symptomatic patients without periodic fever as well as asymptomatic children and relatives, respectively. Thus, the total number of carriers increased to 30, representing 25 families.

We have used the number of cases fulfilling the inclusion criteria for each of the two sources together with the children population for the years 2003–06 to determine the incidence of TRAPS per person-year in Germany, which was  $\sim 5.6$  per  $10^7$  person-years (95% CI: 3.6, 8.5 per  $10^7$  children) (Table 1). Since TRAPS is a genetic disorder precluding recovery and unlikely to result in premature death before the age of 16 years, the prevalence of TRAPS in children under the age of 16 years may be calculated by multiplying incidence per  $10^7$  person-years by 16, yielding an estimate of 8.96 (95% CI: 5.76, 13.60) per  $10^6$  children in this age group.

The following sections outline the distribution of clinical and genetic parameters recorded in the two surveillance systems.

### Clinical presentation of TRAPS patients

Full clinical information was available for 20 out of the 23 cases according to the case definition. These 20 datasets of TRAPS children (Table 2) recorded in the Clinic-ESPED survey [male ( $n=13$ ) 65%; female ( $n=7$ ) 35%] showed a median age of onset of 6 (range 1–16) years. An affected parent was present in four (20%) patients and an asymptomatic mother with a mutation in one individual. Countries of origin were Germany ( $n=16$ , 80%), Turkey ( $n=3$ , 15%) and Italy ( $n=1$ , 5%). The median duration of fever periods was 6.3 (range 2–24) days. Two patients had previously been misdiagnosed as systemic onset juvenile idiopathic arthritis or SLE. Therapeutic strategies differed considerably. Thirteen (65%) patients were treated with corticosteroids, 7 (35%) with NSAIDs, 3 (15%) with etanercept and 1 (5%) with colchicine. Three (15%) children did not receive drug treatment.

### Genetics

Altogether, *TNFRSF1A* mutations were identified by genetic analysis in 30 individuals (Table 3). These included symptomatic and asymptomatic patients as well as relatives. Twenty-three of 30 cases fulfilled the inclusion criteria and were diagnosed as TRAPS ( $n=22$ , 96%) and HIDS/TRAPS ( $n=1$ , 4%). Two (9%) of 23 patients presented with the c.193-14G→A exchange, and one (4%) individual each was heterozygous for C29Y and H105P. The R92Q substitution was found in 19 (83%) of 23 cases fulfilling the ESPED inclusion criteria and represented 26 (87%) of the 30 mutations found in the *TNFRSF1A* gene. Interestingly, a subgroup of 1 (4%) of 23 and 3 (10%) of 30 children carried an additional mutation in a second HPF gene.

## Discussion

For the first time, the incidence of an HPF syndrome in children was estimated by two surveillance systems. In addition, the clinical picture of TRAPS was analysed in a population-based sample. Our prospective epidemiological Clinic-ESPED survey found 156 newly diagnosed HPF patients including 20 (12.8%) with TRAPS. Data of both Clinic- and Laboratory-ESPED showed 23 cases of TRAPS and revealed the incidence in children to be  $\sim 5.6$  per  $10^7$  person-years (95% CI: 3.6, 8.5 per  $10^7$  children). The most prevalent *TNFRSF1A* variant was R92Q ( $n=19$ , 83%). Thus, clinically manifested TRAPS is a rare condition in children of age  $\leq 16$  years in the Caucasian population studied.

TABLE 1. Incidence of TRAPS (95% CI)

	7/2003–6/2004	7/2004–6/2005	7/2005–6/2006	Total number
Newly diagnosed symptomatic TRAPS cases	6	10	7	23
Population of children $\leq 16$ years of age	13 863 624	13 572 071	13 284 656	40 720 351
Incidence per 10 000 000 person-years	4.3	7.4	5.3	5.6
95% CI	1.6–9.4	3.5–13.6	2.1–10.8	3.6–8.5

TABLE 2. Clinic-ESPED: clinical and genetic characteristics of 20 new diagnosed TRAPS patients reported between 2003 and 2006

Case	Age at onset of attacks, years	Age of diagnosis, years	Origin	Duration of fever episode, days	Mutation in the TNFRSF1A gene	Abdomen			Joint			Skin and muscle			Chest			Head			General			Fare observations	Drugs
						Abdominal pain	Diarrhoea	Vomiting	Arthralgia	Arthritis	Skin involvement	Myalgia	Pleuritis	Pericarditis	Chest pain	Pleuritis	Headache	Conjunctivitis	Lymphadenopathy	Trigger factors	Only fever				
1	10	10	German	14	R92Q																			c	
2	1	1	German	7	R92Q																				c
3	1	4	German	6	R92Q																				c
4	14	14	Turkish	20	R92Q																				c
5	10	11	German	4,5	R92Q																				N
6	1	2	German	6,5	R92Q																				N
7	4	16	German	10	R92Q																				N
8	12	13	German	14	R92Q																				cNe
9	7	10	German	4	R92Q																				Ncol
10	5	5	German	3	R92Q																				c
11	2	2	German	3	R92Q																				c
12	6	13	German	24	R92Q																				cN
13	1	2	Turkish	14	R92Q																				cN
14	1	2	Turkish	2	R92Q																				c
15	1	2	Italian	4	R92Q																				ce
16	7	7	German	7	H105P																				no
17	4	4	German	7	C29Y																				no
18	3	4	German	3	c.193-14→GA																				no
19	12	12	German	5	c.193-14G→A																				cN
20	1	8	German	5	R92Q + V377I/S378P (MVK)																				no
																									c

c: corticosteroids; N: NSAID; e: etanercept; col: colchicine.

TABLE 3. Spectrum of mutations in the *TNFRSF1A* gene in symptomatic or asymptomatic children in Germany

Mutations in the <i>TNFRSF1A</i> gene	All cases reported in n1+n2
R92Q	23
<i>TNFRSF1A</i> pR92Q; <i>MEFV</i> pM694V	2
c.193-14G→A	2
C29Y	1
H105P	1
<i>TNFRSF1A</i> pR92Q; <i>MVK</i> pV377I/S378P	1
Total number	30

Underreporting is a potentially critical issue pertaining to our data. Underascertainment is likely since not all cases might either be hospitalized or see a paediatric specialist and be diagnosed. However, underreporting within this setting appears to be low since three cases were identified by the laboratories only. The reason may be a high alertness to the study, since there had been a number of educational articles and presentations regarding the issue of HPF during the preceding years and during the course of this study. As there is not yet a functional test available to diagnose TRAPS, we used a case definition that included symptomatic disease with fever. With this definition, asymptomatic mutation carriers and patients without fever are not detected. It remains uncertain whether all R92Q patients reported in this study can unequivocally be classified as TRAPS. In fact, only a long-term follow-up may finally tell us if they will behave like 'real' TRAPS patients.

A French study group investigated 394 patients with recurrent inflammatory syndromes to characterize the frequency, clinical signs and genotypic features of TRAPS. These patients were mostly adults with a high suspicion of TRAPS or patients with the clinical suspicion of FMF. *TNFRSF1A* mutations were found in 28 (7.1%, 6 children and 22 adults) of 394 patients. R92Q ( $n=12$ , 43%) and P46L ( $n=10$ , 36%) were the most frequent alterations [14]. Gattorno *et al.* [11] published 92 (40%) patients with a mutation in the *MEFV*, *MVK* or *TNFRSF1A* gene in a screening group of 228 adults and children with periodic attacks of fever and at least two of the following symptoms during the attack (lymphadenopathy, splenomegaly, gastrointestinal and/or musculoskeletal manifestations, skin involvement and chest pain). *TNFRSF1A* mutations were detected in 22 (24%) of 92 cases, and 13 (59%) of 22 cases carried the R92Q variant [11].

The *TNFRSF1A* R92Q substitution is the most frequent TRAPS-associated variant, resulting in a mild phenotype and a heterogeneous clinical picture [3, 11, 14, 15]. The mutation has a low penetrance, present in symptomatic TRAPS patients as well as in asymptomatic controls, and occurs with an allele frequency of ~3% in a German control population and of ~1% in an Irish and a North American control population [16, 17]. The phenotypic manifestation of R92Q may depend on other linked or unlinked modifying genes and/or on modifying environmental factors. Indeed, this variant has been hypothesized to have an influence on the susceptibility to inflammation (e.g. early arthritis) [17, 18].

Our understanding of the pathogenesis of TRAPS is still limited and it is controversial whether R92Q is indeed a disease-causing mutation or not. With our study, we are unable to test whether R92Q is indeed the sole disease-causing mutation in the children who fulfilled our inclusion criteria or if there are additional genetic or environmental factors contributing to disease manifestation in R92Q mutation carriers. Ravet *et al.* [15] identified 34 R92Q-positive adults and a total of five families in which segregation with disease occurred to a limited extent. Determination of penetrance was complicated by the fact that, in two of the five families, an *MEFV* mutation was also present in symptomatic carriers of the R92Q exchange [15]. Kämpfel *et al.*, in contrast, found an R92Q-positive parent in 11 (55%) out of 20 patients,

who suffered from multiple sclerosis and a late-onset form of TRAPS without fever. Nine (82%) of these 11 parents were symptomatic, pointing to a higher penetrance of the R92Q mutation in affected family members than reported in other studies [19]. The discrepancies concerning R92Q prevalence in asymptomatic parents may be related to differences in inclusion criteria and populations examined (e.g. adults vs children, fever vs other symptoms). Hence, the lack of widely accepted and standardized diagnostic criteria for TRAPS, either functional or clinical, presents a considerable problem for the comparability of results.

Given the relatively high frequency of R92Q in the white population, it is not surprising that compound heterozygosity involving this variant is quite frequently observed. The coexistence of mutations in two different AID genes (*MEFV*, *MVK*, *NLRP3*/*CIAS1* and *TNFRSF1A*) in a single subject therefore has been also reported. Hoffmann *et al.* [20] separately presented our case with compound heterozygosity for the mevalonate kinase mutations V377I and S378P carrying the *TNFRSF1A* R92Q variant, who showed a disproportionately severe mevalonate kinase deficiency but a mild phenotype. Simon *et al.* [21] have performed a clinical and genetic analysis of HPF patients (HIDS:  $n=64$ , TRAPS:  $n=15$  and FMF:  $n=8$ ) and detected 5 (6%) of 87 subjects with mutations in other autoinflammatory genes (HIDS/TRAPS and FMF/TRAPS) [21].

The heterogeneity of periodic autoinflammatory syndromes is further illustrated by the absence of mutations in the coding region of the *TNFRSF1A* gene in some families with clinically indistinguishable phenotypes [22–24]. Additionally, with the advent of genetic testing for AID, the clinical phenotypes and the ethnic distribution of each of these syndromes have turned out to be much more variable than anticipated [21]. The presence of TRAPS in populations of Turkish and Italian ancestry and the short duration of the inflammatory attacks can lead to the false diagnosis of FMF [14]. Moreover, the diagnosis of TRAPS is difficult to establish given the fact that there is a vast array of possible clinical manifestations but no functional test.

Interestingly, Gattorno *et al.* [11] developed a diagnostic score and a flow chart for the molecular analysis of HPF. Onset at young age, positive family history of periodic fever, thoracic pain, abdominal pain, diarrhoea and oral aphthosis were found to be independently correlated with a positive genetic test result. These variables were combined in a linear score, whose ability to predict a positive result on genetic testing was validated in an independent dataset. Perhaps, this guideline could help paediatricians and geneticists in the diagnostic evaluation of children with periodic fever. It could also optimize the molecular analyses by suggesting the order in which the genes should be screened. Additional information is available on the World Wide Web at <http://www.printo.it/periodicfever> [11].

## Conclusion

This is the first systematic approach to estimate the incidence of an HPF syndrome in Germany. The incidence of TRAPS is very low, calculated as 5.6 cases per  $10^7$  person-years for the period 2003–06. This corresponds to 6–10 newly diagnosed young patients per year in Germany. The *TNFRSF1A* R92Q substitution is the prevailing TRAPS variant. The relatively high frequency of this mutation in the reference population indicates that the clinical manifestation requires additional genetic or environmental factors causing the disease. The rarity of HPF and the limited diagnostic significance and prognostic value of associated mutations in children with fever of unknown origin currently does not appear to justify genetic screening in all children with fever. Only if there is a typical pattern of symptoms (e.g. periodicity and urticarial rash) or a positive family history for HPF, genetic analyses are warranted.

### Rheumatology key messages

- The incidence of TRAPS is very low.
- The incidence of *TNFRSF1A* mutations is calculated as 5.6 cases per 10<sup>7</sup> person-years.
- The *TNFRSF1A* R92Q substitution is the prevailing TRAPS variant.

### Acknowledgements

The authors thank U. Göbel and B. Heinrich from the ESPED registry. They gratefully acknowledge the helpful discussions with and comments made by Oliver Weiergräber (Forschungszentrum Jülich, Germany). The authors also thank the following colleagues for their collaboration: Clinic-ESPED: E. Weissbarth-Riedel (Hamburg); D. Föll, D. Viemann (Münster); G. Reutter (Nürnberg); D. Schewe, V. Grote, F. Hoffmann, G. Notheis (München); C. Rietschel (Frankfurt); D. Fürsich (Weiden i.d. Opf); M. Richter (Garmisch-Partenkirchen); N. Tzaribachev (Tübingen); K. Minden (Berlin); Laboratory-ESPED: S Burwinkel (Department of Molecular Medicine, Bernhard Nocht Institute for Tropical Medicine, Hamburg); and H. Ruebsamen (Department of Clinical Chemistry – Grosshadern, University of Munich, Munich).

*Disclosure statement:* T.N. has received honoraria from and is a consultant for Wyeth, Abbott, Octapharma and CSL Behring. All other authors have declared no conflicts of interest.

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