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TNF Receptor-Associated Periodic Fever Syndrome

Synonyms: TNF Receptor-Associated Periodic Syndrome (TRAPS), Tumor Necrosis Factor Receptor-Associated Periodic Syndrome

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Summary

Clinical characteristics

TNF receptor-associated periodic fever syndrome (TRAPS) is characterized by episodes of inflammation typically occurring every four to six weeks and lasting between five and 25 days. Flares may be prompted by stress, infection, trauma, hormonal changes, and vaccination. Symptoms may include fever, abdominal pain, arthralgia, myalgia, migratory rash, and eye inflammation, with variable severity. Symptoms often begin in early childhood (median age 4.3 years), though symptom onset can occur later in life. During a flare, acute-phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A are typically elevated. Generally, acute-phase reactants stabilize between flares but may remain somewhat elevated even in the absence of clinical symptoms. AA amyloidosis, the most severe sequela of TRAPS, can largely be avoided with adequate treatment. Proteinuria and kidney failure occur in 80%-90% of affected individuals with amyloidosis, while intestinal, thyroid, myocardium, liver, and spleen deposits are less common.

Diagnosis/testing

The diagnosis of TRAPS is established in a proband with at least one suggestive clinical feature and a heterozygous pathogenic (or likely pathogenic) variant in *TNFRSF1A* identified by molecular genetic testing.

Management

Treatment of manifestations: Interleukin-1 (IL-1) inhibitors (anakinra or canakinumab) are considered first-line therapies. Another treatment option is the use of TNF inhibitors (most commonly etanercept), which may be considered in refractory situations. The use of corticosteroids may be useful as needed during an acute attack but is not sufficient for long-term management or for preventing amyloidosis. Standard treatment (including low-

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vision services) by an ophthalmic subspecialist may be considered in those who experience retinal infarcts and/or optic nerve damage.

Prevention of secondary manifestations: IL-1 inhibitors and the TNF inhibitor etanercept control the severity of disease flares and are effective in preventing AA amyloidosis.

Surveillance: Complete physical examination with blood pressure and other vital signs, full skin examination, assessment for the presence of lymphadenopathy and hepatosplenomegaly, and musculoskeletal evaluation should be performed yearly, or more frequently if clinically indicated. The following are also recommended on an annual basis (or more frequently if indicated): measurement of CRP, ESR, serum level of AA amyloid, fibrinogen, haptoglobin, and complete blood count with differential, liver and renal function tests, urinalysis, quantitative immunoglobulins, QuantiFERON® to screen for tuberculosis (for those on biologic treatment), ophthalmologic evaluation, and assessment of the Autoinflammatory Diseases Activity Index (AIDAI). Imaging of the abdomen to assess for splenomegaly/hepatomegaly may also be considered if there are findings of serum AA amyloid or suspected spleen or liver enlargement on physical exam.

Agents/circumstances to avoid: For affected individuals managed with continuous biologic agents, consideration should be given to whether live-attenuated versus non-live vaccines should be administered. Data on the effect of live-attenuated vaccines is limited, and risks/benefits should be considered. It should be noted that affected individuals may have severe, paradoxical reactions that have been associated with anti-TNF monoclonal antibodies.

Pregnancy management: To date, no pattern of birth anomalies with either the anti-IL-1 or TNF inhibitor medication classes has been reported. The use of corticosteroids during human pregnancy has been associated with an increased risk of cleft lip with or without cleft palate in exposed fetuses.

Genetic counseling

TRAPS is inherited in an autosomal dominant manner. Most individuals diagnosed with TRAPS have an affected parent. Each child of an individual with TRAPS has a 50% chance of inheriting the *TNFRSF1A* pathogenic variant. Once the *TNFRSF1A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Many clinical diagnostic criteria for TNF receptor-associated periodic fever syndrome (TRAPS) have been proposed. A classification system that incorporates molecular genetic testing and clinical features has been found to have a sensitivity of 95%, a specificity of 99%, and an accuracy of 99% [Gattorno et al 2019] (see Establishing the Diagnosis).

Suggestive Findings

TRAPS **should be considered** in individuals with the following clinical, supportive laboratory, and family history findings.

Clinical findings

- Recurrent or chronic systemic inflammation causing:
  - Prolonged and recurrent episodes of fever, typically occurring every four to six weeks and lasting from five to 25 days;
  - Abdominal pain;
  - Chest pain;
  - Arthralgia;

- Myalgia;
- Migratory erythematous rash;
- Eye inflammation manifesting as conjunctivitis, periorbital edema, and periorbital pain.

- Poor response to colchicine therapy

Supportive laboratory findings during a febrile episode:

- Leukocytosis, typically characterized by an absolute leukocyte count in the 9,000-12,000/mm^3 range, with an increased absolute neutrophil count of 7,000-9,000/mm^3 (reference range typically 1,500-7,200/mm^3)
- Elevated erythrocyte sedimentation rate and/or C-reactive protein
- Extremely high levels of serum amyloid A

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of TRAPS **is established** in a proband with [Gattorno et al 2019]:

- At least one of the following clinical features:
  - Duration of the flare (i.e., period of fevers and related symptoms) longer than seven days
  - Myalgia
  - Migratory rash
  - Periorbital edema
  - Suggestive family history

  AND

- A heterozygous pathogenic (or likely pathogenic) variant in *TNFRSF1A* identified by molecular genetic testing (see Table 1).

In the absence of the identification of a pathogenic (or likely pathogenic) variant in *TNFRSF1A*, at least two of the above clinical features are highly suggestive of the diagnosis, with a sensitivity of 95%, a specificity of 99%, and an accuracy of 99% [Gattorno et al 2019].

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *TNFRSF1A* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome or genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with periodic fevers and autoinflammatory conditions are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and supportive laboratory findings suggest the diagnosis of TRAPS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TNFRSF1A* is performed first to detect almost exclusively pathogenic missense variants located in the extracellular domain of *TNFR1* (see Molecular Genetics). Note: Nonsense and splice site pathogenic variants and small pathogenic indels have been found in a very few affected individuals. Single-exon, multiexon, or whole-gene deletions/duplications of *TNFRSF1A* have not been reported in TRAPS.
- **A periodic fever multigene panel** that includes *TNFRSF1A* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing panels vary by laboratory and they need to be periodically updated. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from other inherited disorders characterized by periodic fever, genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in TNF Receptor-Associated Periodic Fever Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TNFRSF1A	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Cudrici et al [2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gene-targeted deletion/duplication analysis has not identified any deletions/duplications in *TNFRSF1A*. This gene is intolerant to loss-of-function variants, and single-exon, multiexon, or whole-gene deletions/duplications are not reported in TRAPS.

Clinical Characteristics

Clinical Description

To date, more than 200 individuals have been identified with a pathogenic variant in *TNFRSF1A* [Cudrici et al 2020]. As a periodic fever syndrome, TNF receptor-associated periodic fever syndrome (TRAPS) is characterized by episodes of inflammation typically occurring every four to six weeks and lasting between five and 25 days. Flares may be prompted by stress, infection, trauma, hormonal changes, and vaccination. Symptoms may include fever, abdominal pain, arthralgia, myalgia, migratory rash, and eye inflammation, with variable severity. Symptoms often begin in early childhood (median age 4.3 years), though symptom onset can occur later in life, especially in those with mild or somatic pathogenic variants (see Molecular Genetics). During a flare, acute-phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A are typically elevated. Generally, acute-phase reactants stabilize between flares but may remain somewhat elevated even in the absence of clinical symptoms. Symptom severity does not appear to correlate with sex.

Table 2. TNF Receptor-Associated Periodic Fever Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Fever	96%	Periodic in nature & generally longer in duration than in persons w/other periodic fever syndromes
Abdominal pain	70%	
Arthralgia	69%	
Myalgia	69%	
Maculopapular/ migratory rash	60%	
Conjunctivitis	37%	
Periorbital edema	28%	
Chest pain	33%	

Fever occurs in the majority (~96%) of individuals with TRAPS at some point in time. Febrile episodes typically occur every four to six weeks, and these flares are typically much longer in duration than in individuals with other hereditary periodic fever syndromes [Cudrici et al 2020].

Pain in individuals with TRAPS is typically caused by inflammation in the surrounding tissues. It can affect the abdomen, bones and joints, chest, muscles, scrotum, and eye. Pain may migrate with rashes throughout a flare and often affects the same areas of the body. Abdominal pain during flares is noted in most (~70%) individuals with TRAPS; however, it is not always accompanied by other gastrointestinal symptoms such as nausea or diarrhea.

Gastrointestinal (GI) findings affect around 70% of individuals with TRAPS during flares. They generally consist of broad pain as a result of serositis, but symptoms like diarrhea, constipation, vomiting, aseptic peritonitis, and GI bleeding can occur. In some cases, splenomegaly and/or hepatomegaly may be noted outside of a flare, especially in cases of untreated AA amyloidosis.

Ophthalmologic findings including conjunctivitis and periorbital edema during a flare are seen in about 50% of affected individuals. Periorbital edema, in the context of other symptoms, appears to be a distinguishing feature of TRAPS compared to other periodic fever syndromes. Ocular findings are caused by inflammation in and around the eye and generally resolve with treatment [Lachmann et al 2014, Maccora et al 2021].

Skin/mucocutaneous findings are common features and often migrate with myalgias in the arms and legs throughout the course of a flare. Inflammation of the fascia of a muscle (fasciitis) has been also reported. Histologically, skin lesions often contain nonspecific perivascular infiltrates of lymphocytes and monocytes. Types of skin findings include the following:

- Maculopapular/migratory rashes consisting of both flat and raised lesions on the skin. In individuals with TRAPS, the rash frequently migrates distally down the limbs as a flare progresses. This rash is typically not itchy.
- Urticarial rashes (also known as hives) that are raised and often itchy.
- Erysipelas-like erythema consisting of raised rashes typically affecting the lower limbs. Such rashes may be warm to the touch and can be quite tender.

Mucocutaneous findings such as pharyngitis and aphthous stomatitis have been reported in a number of individuals with TRAPS [Cudrici et al 2020].

AA amyloidosis is the most severe sequela of TRAPS but can largely be avoided with adequate treatment (see Management). AA amyloid is produced during acute-phase reaction, and development of amyloidosis has been associated with a number of inflammatory conditions including other autoinflammatory diseases. Amyloid buildup is caused by misfolding of the serum amyloid A protein during periods of inflammation. This misfolded protein is unable to be cleaved and excreted, and it deposits in the organs. Proteinuria and kidney failure occur in 80%-90% of affected individuals with amyloidosis, while intestinal, thyroid, myocardium, liver, and spleen deposits are less common.

Lymphadenopathy is present in about 15% of individuals with TRAPS and can include enlarged cervical lymph nodes (often painless) as well as generalized lymphadenopathy.

Cardiac findings. Inflammation of the pericardium may lead to pericarditis and chest pain. This finding is present in about 30% of individuals with TRAPS.

Respiratory findings are generally rare, but around 2% of affected individuals report persistent cough and 1% report recurrent pneumonia. The link between respiratory findings and TRAPS remains unclear.

Neurologic findings in individuals with TRAPS are rare, but headaches and seizures have been reported in some affected individuals [Cudrici et al 2020].

Genotype-Phenotype Correlations

Most pathogenic variants in *TNFRSF1A* are missense variants affecting the cysteine residues, which are important for protein folding and intracellular trafficking. Generally, people with these pathogenic variants have more severe symptoms and are more likely to have AA amyloidosis if left untreated. Missense variants at residues that do not affect protein folding (see Molecular Genetics, Low-Penetrance Variants) may play a role in inflammation but do not lead to the severe symptoms seen with pathogenic variants affecting cysteine residues.

Penetrance

Most individuals with severe pathogenetic variants in *TNFRSF1A* (such as c.236C>T; p.Thr79Met or those at cysteine residues) have at least some manifestations of the disease.

There are a few notable low-penetrance variants in *TNFRSF1A*. Individuals with these low-penetrance variants typically either have mild symptoms or may not experience symptoms at all, in which case they are generally not considered to have TRAPS (see Molecular Genetics, Low-Penetrance Variants).

Nomenclature

TRAPS was initially referred to as familial Hibernian fever.

Prevalence

An estimated 1:1,000,000 individuals worldwide have TRAPS [Zegarska et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TNFRSF1A*.

Differential Diagnosis

Table 3. Hereditary Disorders of Interest in the Differential Diagnosis of TNF Receptor-Associated Periodic Fever Syndrome (TRAPS)

Gene	Disorder	MOI	Key Features
MEFV	Familial Mediterranean fever (FMF)	AR (AD [1])	Recurrent short episodes of inflammation & serositis incl fever, peritonitis, synovitis, pleuritis, & (rarely) pericarditis
NLRP3	Familial cold autoinflammatory syndrome 1 (FCAS1) (OMIM 120100)	AD	Cold-induced attacks of fever, rash, & arthralgia but no deafness or amyloidosis
	Muckle-Wells syndrome (MWS) (OMIM 191900)	AD	Urticaria, deafness, & renal amyloidosis
	Chronic infantile neurologic cutaneous & articular (CINCA) / neonatal-onset multisystem inflammatory disease (NOMID) (OMIM 607115)	AD	Neonatal onset of persistent & migratory skin rashes, chronic meningitis, recurrent fevers, & progressive hearing loss w/o renal amyloidosis
MVK	Hyperimmunoglobulin D & periodic fever syndrome (HIDS) (OMIM 260920)	AR	Recurrent attacks of fever, abdominal pain, & arthralgia often brought on by stress or vaccination
RIPK1	Cleavage-resistant *RIPK1*-induced autoinflammatory (CRIA) syndrome (OMIM 618852)	AD	Persistent fevers, lymphadenopathy, oral ulcers, tonsillitis, headaches, & hepatomegaly/splenomegaly
TTR	Hereditary transthyretin amyloidosis	AD	Amyloidosis w/progressive neuropathy, cardiomyopathy, nephropathy, & vitreous opacities; more likely than TRAPS to have CNS amyloid

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance
1. FMF is usually inherited in an autosomal recessive manner, although some studies have suggested that some heterozygotes manifest a spectrum of findings from classic FMF to mild FMF.

Acquired disorders of interest in the differential diagnosis of TRAPS

- Infection (viral, bacterial, or parasitic)
- Malignancy
- Behçet syndrome
- Inflammatory bowel disease
- Adult-onset Still disease

Management

Clinical practice guidelines for the management of monogenic autoinflammatory conditions, including TNF receptor-associated periodic fever syndrome (TRAPS), have been published; see ter Haar et al [2015] (full text; log in or purchase required) and Soriano et al [2020] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with TRAPS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with TNF Receptor-Associated Periodic Fever Syndrome

System/Concern	Evaluation	Comment
Rheumatologic	History & physical exam for signs/symptoms of systemic inflammation, fevers, serositis/pain, & join involvement	Consider referral to rheumatologist to initiate biologic therapies (see Table 5).
	Assessment of inflammatory markers (serum CRP & ESR), kidney & liver function, [1] CBC w/differential, serum immunoglobulins, & urinalysis for proteinuria	• To assess for inflammatory markers &/or evidence of end-organ damage • Imaging of abdomen to assess for splenomegaly/ hepatomegaly may also be considered if there are findings of serum AA amyloid or suspected spleen or liver enlargement on physical exam.
Skin	Full skin exam to assess for rashes	Consider consultation w/dermatologist for mgmt of rashes.
Eye	Consultation w/ophthalmologist	For eval of ptosis, abnormal eye movements, retinal infarcts, optic nerve damage
Renal	In addition to serum renal function tests [1] & urinalysis, serum level of AA amyloid	If AA amyloidosis is present, consider endocrinologist & cardiologist consultations depending on degree of organ involvement.
	Consultation w/nephrologist	If there are signs/symptoms of renal involvement
Cardiac	If serum AA amyloid is ↑, echocardiogram to assess for pericarditis or amyloid deposition in heart	Consider referral to cardiologist.
Endocrinologic	If serum AA amyloid is ↑, perform thyroid function tests. [2]	Consider referral to endocrinologist.
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of TRAPS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CBC = complete blood count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MOI = mode of inheritance; TRAPS = TNF receptor-associated periodic fever syndrome

1. Renal function testing may include serum blood urea nitrogen, creatinine, cystatin-C, and electrolytes; liver function testing may include assessment of serum aspartate aminotransferase, alanine transaminase, protein, and albumin.

2. Thyroid function tests may include serum thyroid-stimulating hormone, free T4, and/or T4.

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with TNF Receptor-Associated Periodic Fever Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Recurrent or chronic systemic inflammation [1]	Anti-IL1 therapy: • Anakinra 1.5 mg/kg/day w/titration as needed • Canakinumab 2 mg/kg every 4 or 8 wks	• Considered first-line treatment & is generally more effective than anti-TNF inhibitors. • ~90% of persons w/TRAPS respond to IL-1 inhibition.
	TNF inhibitors (typically etanercept)	• Etanercept is the most effective anti-TNF, whereas monoclonal antibodies have been assoc w/severe, paradoxical reactions. • In general IL-1 inhibition is considered first line, but etanercept may be considered in refractory cases. • Affected persons w/infrequent attacks may only require as-needed dosing during disease flares.
	Corticosteroids (e.g., prednisone 1 mg/kg/day)	May be useful as needed during an attack but not sufficient for long-term mgmt or in preventing amyloidosis.
Retinal infarcts / Optic nerve damage [2]	Ophthalmic subspecialist	Low-vision clinic &/or community vision services / OT / mobility services
	Low-vision services	• Children: through early intervention programs &/or school district • Adults: low-vision clinic &/or community vision services / OT / mobility services

IL = interleukin; OT = occupational therapy; TNF = tumor necrosis factor

1. The use of nonsteroidal anti-inflammatory (NSAID) medication has not resulted in a benefit for most affected individuals [Author, personal observation].

2. These findings may not be reversible even when anti-inflammatory treatments are initiated or even subsequently optimized.

Prevention of Secondary Manifestations

Interleukin-1 (IL-1) inhibitors and the TNF inhibitor etanercept are effective in preventing AA amyloidosis and can also control the severity of disease flares [Cudrici et al 2020].

Surveillance

In addition to a complete physical examination (performed annually or sooner if clinically indicated) with blood pressure and other vital signs, full skin examination, assessment for the presence of lymphadenopathy and hepatosplenomegaly, and musculoskeletal evaluation, the evaluations outlined in Table 6 are recommended.

Table 6. Recommended Surveillance for Individuals with TNF Receptor-Associated Periodic Fever Syndrome

System/Concern	Evaluation	Frequency
Rheumatologic	• Measure acute-phase reactants incl CRP, ESR, serum level of AA amyloid, fibrinogen, haptoglobin, & CBC w/ differential. [1] • Assess w/Autoinflammatory Diseases Activity Index (AIDAI). [2]	Annually or more frequently if indicated
Gastrointestinal	• Liver function tests [3] • Imaging of abdomen to assess for splenomegaly/ hepatomegaly may also be considered if there are findings of serum AA amyloid or suspected spleen or liver enlargement on physical exam.	
Renal	Measurement of renal function [4] & urinalysis [5]	
Eyes	Ophthalmologic exam for ptosis, abnormal eye movements, retinal infarcts, optic nerve damage	
Infectious/ Immunologic	Measure quantitative serum immunoglobulins.	
	Screen for tuberculosis, typically by QuantiFERON® measurement.	For any affected person on biologic treatment, as risk of infection may be ↑

CBC = complete blood count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MOI = mode of inheritance; TRAPS = TNF receptor-associated periodic fever syndrome

1. To assess for leukocytosis and elevated neutrophil count, thrombocytosis, and normochromic anemia, which may be related to secondary chronic inflammation.

2. This checklist reviews 12 symptoms and provides an assessment of whether an affected individual is experiencing frequent disease activity that may require optimization of the treatment regimen or if the affected individual is fairly well controlled in terms of their autoimmune symptoms.

3. Liver function testing may include assessment of serum aspartate aminotransferase, alanine transaminase, protein, and albumin.

4. Renal function testing may include serum blood urea nitrogen, creatinine, cystatin-C, and electrolytes.

5. To assess for proteinuria

Agents/Circumstances to Avoid

For affected individuals managed with continuous biologic agents, consideration should be given to whether live-attenuated versus non-live vaccines should be administered. Data on the effect of live-attenuated vaccines are limited, and risks/benefits should be considered. Before undertaking any live vaccinations, individuals should discuss the risk/benefit of receiving such vaccines. It should be noted that affected individuals may have severe, paradoxical reactions that have been associated with anti-TNF monoclonal antibodies.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Evaluations can include the following:

- Targeted molecular genetic testing if the pathogenic variant in the family is known;
- If the pathogenic variant in the family is unknown, clinical assessment (history and physical exam for signs/symptoms of systemic inflammation), full skin examination for rashes, ophthalmology evaluation, assessment of inflammatory markers (serum C-reactive protein and erythrocyte sedimentation rate), complete blood count with differential, serum immunoglobulins, creatinine, blood urea nitrogen, urinalysis for proteinuria, and serum level of AA amyloid can be considered.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Information regarding the safety of the use of IL-1 inhibitors in human pregnancy is limited. Retrospective analyses suggest that anakinra and canakinumab are effective treatments in pregnant women with familial Mediterranean fever and other autoinflammatory diseases with low risk to the fetus [Youngstein et al 2017, Gunn et al 2018, Venhoff et al 2018, Weber et al 2022]. To date, no pattern of birth anomalies with either the anti-IL-1 or TNF inhibitor medication classes has been reported. The use of corticosteroids during human pregnancy has been associated with an increased risk of cleft lip with or without cleft palate in exposed fetuses. Medications should be discussed with a health care provider during pregnancy or when planning to conceive [Youngstein et al 2017].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TNF receptor-associated periodic fever syndrome (TRAPS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with TRAPS have an affected parent.
- Some individuals diagnosed with TRAPS have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with TRAPS caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Note: Mosaicism for a *TNFRSF1A* pathogenic variant has been reported [Rowczenio et al 2016, Kontzias et al 2019]. A parent with somatic and germline mosaicism for a *TNFRSF1A* pathogenic variant may be mildly/minimally affected.

- The family history of some individuals diagnosed with TRAPS may appear to be negative because of failure to recognize the disorder in affected family members, reduced penetrance, variable expressivity, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to each of the sibs is 50%.
- If the proband has a known *TNFRSF1A* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the small possibility of parental mosaicism. Mosaicism for a *TNFRSF1A* pathogenic variant has been reported [Rowczenio et al 2016, Kontzias et al 2019].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with TRAPS has a 50% chance of inheriting the *TNFRSF1A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *TNFRSF1A* pathogenic variant in the family.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TNFRSF1A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Tumor necrosis factor receptor-associated periodic syndrome
- **Autoinflammatory Alliance**
  Phone: 415-831-8782
  Email: karen@autoinflammatory.org
  www.nomidalliance.org
- **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
  1 AMS Circle
  Bethesda MD 20892-3675
  Phone: 877-226-4267 (toll-free); 301-565-2966 (TTY)
  Fax: 301-718-6366
  Email: niamsinfo@mail.nih.gov
  www.niams.nih.gov
- **Eurofever Registry**
  Paediatric Rheumatology International Trials Organisation (PRINTO)
  Largo Gaslini, 5
  Genova 16147
  Italy
  Phone: +39 010 382854; +39 010 393425
  Fax: +39 010 393324; +39 010 4211018
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  Eurofever Project

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. TNF Receptor-Associated Periodic Fever Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TNFRSF1A	12p13.31	Tumor necrosis factor receptor superfamily member 1A	TNFRSF1A database The registry of TNFRSF1A sequence variants	TNFRSF1A	TNFRSF1A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for TNF Receptor-Associated Periodic Fever Syndrome (View All in OMIM)

142680	PERIODIC FEVER, FAMILIAL, AUTOSOMAL DOMINANT; FPF
191190	TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 1A; TNFRSF1A

Molecular Pathogenesis

TNFRSF1A encodes a TNF cell membrane-coupled receptor (TNFR1) that is expressed on a wide range of cells and serves several functions including induction of cytokine secretion, increased expression of adhesion molecules on leukocytes and endothelial cells, and leukocyte activation. Receptor activation also leads to a specific negative feedback mechanism called shedding, whereby the receptor is cleaved by a protease and the extracellular part of the receptor is released in a soluble form into the extracellular space, where it can act as a competitive inhibitor of TNFR1/p55 [McDermott et al 1999, Simon et al 2001].

Disease-causing genetic variants are predominantly found in the extracellular domain of TNFR1 and affect protein folding – often through interruption of hydrogen and disulfide bonds – which in turn affects receptor structure and cell surface expression. Mutated proteins are then unable to be shed and accumulate in the cells, leading to endoplasmic stress, upregulation of unfolded protein response (UPR), and increased production of mitochondrial reactive oxygen species [Cudrici et al 2020]. The autoinflammatory phenotype of TNF receptor-associated periodic fever syndrome (TRAPS) results from a combination of cellular defects that ultimately upregulate the expression of proinflammatory cytokines and chemokines. In mutated leukocytes with heightened inflammatory state, a trivial trigger can lead to an uncontrolled inflammatory response.

Mechanism of disease causation. Undefined; leads to an enhanced inflammatory response

***TNFRSF1A*-specific laboratory technical considerations.** Two variant-numbering systems exist for TRAPS in the literature. In initial reports, the first 29 amino acids encoding the signal peptide were subtracted from variant/protein numbering; however, by consensus, the main transcript isoform numbering should start with Met 1 (e.g., variant c.123T>G [p.Asp41Glu] has been reported as p.Asp12Glu). Both nomenclature systems are still used in the literature for TRAPS. For clarification, both nomenclatures are reported in the Infevers database.

Table 7. Notable *TNFRSF1A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_001065.4 NP_001056.1	c.176G>A	p.Cys59Tyr (Cys30Tyr)	More severe pathogenic variant w/↑ risk of AA amyloidosis
	c.236C>T	p.Thr79Met (Thr50Met)	Most common pathogenic variant; affects important hydrogen bond & protein folding; considered a severe pathogenic variant.
	c.241T>C	p.Cys81Arg (Cys52Arg)	More severe pathogenic variant w/↑ risk of AA amyloidosis
	c.242G>T	p.Cys81Phe (Cys52Phe)	More severe pathogenic variant w/↑ risk of AA amyloidosis

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions.

Low-Penetrance Variants

Low-penetrance variants in *TNFRSF1A* (e.g., c.123T>G [p.Asp41Glu], c.224C>T [p.Pro75Leu], c.398G>A [p.Arg104Gln], c.362G>A [p.Arg121Gln], c.370G>A [p.Val124Met]). While the prevalence of these variants appears to be enriched in individuals with autoinflammatory and TRAPS-like features, their clinical significance remains uncertain. Functional studies have shown that these variants do not behave in the same manner as pathogenic variants, such as those impacting cysteine residues [Bulua et al 2011]. Typically, individuals with a low-penetrance variant have milder symptoms (if any), and such variants are often inherited from an asymptomatic parent.

Chapter Notes

Author Notes

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