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NLM Citation: Kozycki C, Kastner D, Huryn L, et al. *ALPK1*-Related Autoinflammatory Disease. 2024 Jun 27. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

ALPK1-Related Autoinflammatory Disease

Synonym: ROSAH Syndrome

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Created: June 27, 2024.

Summary

Clinical characteristics

ALPK1-related autoinflammatory disease (*ALPK1*-AD) is characterized by clinical findings that can include intraocular inflammation, retinal degeneration, recurrent fever, deforming arthritis, and headaches. Anhidrosis/hypohidrosis, dental caries, short dental roots, and hyposalivation are common. While most adults have ophthalmologic manifestations, vision loss is not universal. Although significant intrafamilial variability can occur, most individuals with *ALPK1*-AD exhibit at least one clinical or laboratory feature (such as episodic low-grade fever or episodic elevation of serum markers of inflammation such as C-reactive protein). To date, 41 individuals from 19 families with a pathogenic variant in *ALPK1* have been described.

Diagnosis/testing

The diagnosis of *ALPK1*-AD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *ALPK1* identified by molecular genetic testing.

Management

Treatment of manifestations: Supportive treatment involves the following: intraocular inflammation management; low vision services; systemic inflammation management (such as a rheumatologist); dental care of enamel defects; and orthodontic procedures for individuals with short dental roots.

Surveillance: Regular monitoring by specialists treating the ophthalmologic findings, systemic inflammatory disease, and systemic and dental manifestations of anhidrosis/hypohidrosis.

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Genetic counseling

ALPK1-AD is inherited in an autosomal dominant manner. If a parent of the proband has the *ALPK1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Once the *ALPK1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

ALPK1-related autoinflammatory disease (*ALPK1*-AD) **should be suspected** in a proband with the following clinical, laboratory, and imaging findings and family history.

Clinical findings

- **Ophthalmologic findings** (which vary between and within families) include the following:
  - Optic nerve edema (elevation) is often present on initial evaluation even in early childhood (i.e., age <10 years). Can be observed on fundoscopic evaluation and on measurement of retinal nerve fiber layer thickness obtained by optical coherence tomography (OCT).
  - Intraocular inflammation (uveitis, retinal vasculitis)
    - Limited data suggest that it is often present in adolescence and early adulthood.
    - Slit lamp examination and dilated fundoscopic examination can identify signs of ocular inflammation. Additional testing, including OCT and fluorescein angiography (FA), can further investigate cystoid macular edema and retinal vascular leakage, respectively.
  - Retinal dystrophy (degeneration)
    - Timing of onset varies.
    - Signs of retinal dystrophy (including retinal atrophy, vascular attenuation, and pigment migration) can be identified on fundus examination and retinal fundus autofluorescence (FAF) imaging.
    - Electroretinogram (ERG) can identify early changes in photoreceptor function before signs of retinal dystrophy are observed on examination.
- **Recurrent low-grade, non-infectious fever.** Fever episodes typically last <24 hours before resolving spontaneously.
- **Episodic malaise.** "Flu-like" episodes that last a few days. These seem to be more prominent in individuals with splenomegaly and cytopenias.
- **Episodic abdominal pain.** Typically, gastroesophageal reflux disease and constipation
- **Joint involvement.** Arthralgia (discomfort) in small and large joints and deforming arthritis of the hands (affecting the proximal interphalangeal and distal interphalangeal joints)
- **Headaches.** Some individuals experience daily headaches, which can have migraine-like qualities including sensitivity to light.
- **Splenomegaly** can present with abdominal fullness and/or cytopenias or be identified on screening of asymptomatic individuals. Some individuals develop massive splenomegaly with weight exceeding 3 kilograms. Pathology at the time of splenic resection typically reveals red pulp congestion.
- **Anhidrosis/hypohidrosis,** which can manifest as difficulty tolerating hot temperatures (including easy flushing)
- **Dental findings** include enamel defects / multiple dental caries and short dental roots.
- **Dry mouth** caused by decreased salivary flow. Includes difficulty tolerating dry foods (e.g., crackers or pretzels) without simultaneously drinking liquids and the need to drink water during the night.
- **Inability of women to lactate** after childbirth

Laboratory findings

- Transient (cyclical) cytopenias with absolute neutrophil count occasionally dropping below 1,000 cells/µL and platelets occasionally dropping below 100,000 cells/µL
- Intermittently elevated C-reactive protein (CRP) ranging from mild (>10 mg/L) to severe (>100 mg/L)
- The risk of AA amyloidosis (previously known as secondary [AA] amyloidosis) is unknown; however, it was noted on biopsy of one individual who presented with renal dysfunction [C Kozycki, personal observation].

Imaging findings. On brain MRI, meningeal enhancement and premature basal ganglia / brain stem mineralization/calcifications can be observed in the absence of extrapyramidal symptoms such as parkinsonism or involuntary movements.

Family history may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations) or the proband may have a *de novo ALPK1* pathogenic variant and represent a simplex case (i.e., a single occurrence in a family). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ALPK1*-AD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ALPK1* identified by molecular genetic testing (see Table 1).

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 can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *ALPK1* 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 sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. For individuals with elevated optic nerves and retinal degeneration, single-gene testing is a preferable first step, as this constellation of features has not been associated with other inherited retinal disorders and targeted testing may save time and money.

Sequence analysis of *ALPK1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Typically, if no variant is detected by the sequencing method used, the next step would be gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder and would not be expected given the gain-of-function mechanism of disease causation.

A primary immunodeficiency or inherited retinal degeneration multigene panel that includes *ALPK1* 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 used for each gene vary by laboratory and are likely to change over time. (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

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 *ALPK1*-Related Autoinflammatory Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ALPK1	Sequence analysis [3]	All variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date [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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Kozycki et al [2022] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. To date such variants have not been identified as a cause of this disorder and would not be expected given the gain-of-function mechanism of disease causation.

Clinical Characteristics

Clinical Description

ALPK1-related autoinflammatory disease (*ALPK1*-AD) is characterized by clinical findings that can include intraocular inflammation, retinal degeneration, recurrent fever, deforming arthritis, and headaches. Anhidrosis/hypohidrosis with associated findings of enamel and caries, short dental roots, and hyposalivation are common. Most adults have ophthalmologic manifestations; however, vision loss is not universal [Kozycki et al 2022].

Although significant intrafamilial variability can occur, most individuals with *ALPK1*-AD exhibit at least one clinical or laboratory feature (e.g., episodic elevation of serum markers of inflammation such as C-reactive protein).

To date, 41 individuals from 19 families with a pathogenic variant in *ALPK1* have been described [Williams et al 2019, Zhong et al 2020, Jamilloux et al 2021, Hecker et al 2022, Kozycki et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports (see Table 2).

Table 2. *ALPK1*-Related Autoinflammatory Disease: Frequency of Select Features

Feature	Frequency	Comment
Optic nerve elevation	++	Present on initial eval for most persons
Retinal degeneration	++	When present, onset is typically by age 30 yrs.
Ocular inflammation	+	Uveitis ± retinal vasculitis, cystoid macular edema
Headaches	++	
Recurrent fever	++	Can be low grade & last <24 hours
Episodic malaise	++	
Joint involvement	++	
Splenomegaly	++	
Episodic abdominal pain	+	
Anhidrosis/hypohidrosis	++	
Dry mouth	++	Caused by decreased salivation
Enamel defects / multiple dental caries	++	
Short dental roots	++	
Inability to lactate	++	

Based on Kozycki et al [2022]
++ often present; + rarely present

Ocular manifestations include optic disc edema, retinal degeneration, and signs of ocular inflammation including uveitis, retinal vasculitis, and cystoid macular edema. Initial ophthalmologic examination may be prompted by subjective visual changes. However, in those with a family history of retinal disease, early evaluation may reveal ocular involvement prior to development of subjective changes.

Systemic inflammation. Most individuals reported to date have findings consistent with systemic inflammation including headaches, recurrent fever, malaise, joint pain, episodic abdominal pain, and transient cytopenias. The fevers are often low grade and brief, lasting less than 24 hours before resolving spontaneously.

Joint pain and arthritis can affect both small and large joints, including hands, wrists, elbows, spine, knees, ankles, and feet. Reported gastrointestinal involvement includes episodic abdominal pain, gastroesophageal reflux disease, dysphagia, constipation, and ileus. Abdominal discomfort can also occur in the setting of massive splenomegaly.

Although recurrent headaches are common, cognitive deficits have only been reported in individuals who have other unrelated neurologic issues.

Dental abnormalities include multiple dental caries and short dental roots. Dysfunctional production of saliva, sweat, and breast milk are also common features in individuals with *ALPK1*-AD.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

To date, all individuals with an *ALPK1* pathogenic variant have had at least one clinical feature or laboratory finding consistent with *ALPK1*-AD. However, the highly variable clinical manifestations of *ALPK1*-AD require that clinicians examining heterozygous family members obtain a thorough medical history and perform a

detailed physical examination to ensure that they correctly identify individuals as clinically affected or unaffected (C Kozycki, personal obervations).

Nomenclature

ALPK1-AD is also referred to as ROSAH syndrome. ROSAH is an acronym for the following findings associated with *ALPK1*-AD: *r*etinal dystrophy, *o*ptic nerve edema, *s*plenomegaly, *a*nhidrosis, and migraine *h*eadache.

Prevalence

ALPK1-AD is rare. To date, 41 individuals from 19 families have been reported in the literature (see Clinical Description).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous *ALPK1* germline pathogenic variant.

Sporadic tumors occurring as single tumors in the absence of any other findings of *ALPK1*-AD frequently contain a somatic *ALPK1* pathogenic variant that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Blau syndrome (OMIM 186580) – an autosomal dominant autoinflammatory disorder caused by pathogenic variants in *NOD2* – is associated with arthritis and uveitis and can be considered in the differential diagnosis of *ALPK1*-related autoinflammatory disease (*ALPK1*-AD). However, the erythematous maculo-micropapular fine, scaly skin rash characteristic of Blau syndrome has not been described in *ALPK1*-AD. Additionally, while individuals with Blau syndrome can develop some degree of disc edema in the setting of panuveitis, the edema is usually not as severe as the edema that occurs in individuals with *ALPK1*-AD.

Management

No clinical practice guidelines for *ALPK1*-related autoinflammatory disease (*ALPK1*-AD) have been published. In the absence of established clinical practice guidelines, the authors offer the recommendations discussed in this section based on their collective experience in working with more than 15 families over a period of five years.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ALPK1*-AD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *ALPK1*-Related Autoinflammatory Disease: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Ophthalmic	Ophthalmologic eval	• By specialists in uveitis & retinal disorders &/or ophthalmic genetics • Determine need for referral to low vision services.
Systemic	By rheumatologist	Experience in managing systemic inflammation recommended
Anhidrosis/ Hypohidrosis	Assess severity of hypohidrosis, incl episodes of hyperthermia.	Evaluate for history of heat intolerance & anhidrosis.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Dental abnormalities	• Dental prophylaxis • Fluoride application • Full series of radiographs to evaluate infections of dental roots	As needed to inform treatment planning
Oral medicine / Clinical oral pathology	• Evaluate for dry mouth. • Educate re salivary hypofunction.	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *ALPK1*-AD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support

ALPK1-AD = ALPK1-related autoinflammatory disease; MOI = mode of inheritance

Treatment of Manifestations

There is no cure for *ALPK1*-AD. Supportive treatment to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *ALPK1*-Related Autoinflammatory Disease: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Ophthalmic	Depending on extent of inflammation, consider immunomodulating therapy w/guidance of ophthalmologist experienced in mgmt of intraocular inflammation.	
	Low vison services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Headaches	Experience is too limited to provide definitive recommendations.	
Fatigue	Consider immunomodulating therapy w/guidance of provider experienced in mgmt of systemic inflammation.	
Splenomegaly	Provide anticipatory guidance on potential risk of rupture after minimal trauma.	
Anhidrosis/ Hypohidrosis	• During hot weather: access to adequate water supply & cool environment (e.g., air conditioning, wet T-shirt, &/or spray bottle of water) • Skin care products for mgmt of dry skin, eczema, & rashes assoc w/certain outdoor exposures (e.g., swimming)	Some persons may benefit from cooling vests.

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Enamel defects/ caries	• 2-3x/day brushing w/fluoridated dentifrice, daily high-fluoride oral rinse/mouthwash, or use of custom fluoride trays • 2-3x per year dental prophylaxis incl professional fluoride application	For teeth w/enamel hypoplasia or abnormal crown morphology, consider coverage of crowns to protect from further structural loss due to occlusal forces & abrasion.
Short dental roots	Care should be taken when considering orthodontic procedures in persons w/short dental roots.	• Because short roots have limited anchorage value over which to distribute the orthodontic force, consider enhancing anchorage value (e.g., adding more teeth in the anchored unit). • Because of reduced root support, use of headgear on taurodont molars is contraindicated.
Hyposalivation	Therapeutics (e.g., saliva substitutes) to maintain oral lubrication & ↓ risk of dental caries	• Fluoride treatments per treating dentist • Consider other approaches to prevent dental caries such as pit & fissure sealants.
Inability to lactate	Provide anticipatory guidance regarding this possibility	

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *ALPK1*-Related Autoinflammatory Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
Ophthalmologic inflammation	• Dilated eye exam w/OCT & FA • Consider ERG to evaluate retinal function.	Based on initial findings; likely every 6 mos to 1 yr
Systemic autoinflammatory disease	Per treating clinician	Per treating clinician
Anhidrosis/ Hypohidrosis	Assess severity & treatment response for hypohidrosis.	Annually &/or as needed
Dental	• Dental exam to monitor (1) existing treatments & (2) tooth & maxillary/mandibular development • To provide anticipatory guidance for parents & continued interventions as needed	Every 6-12 mos beginning at age 1 yr
Family/Community	Assess family need for social work support or follow-up genetic counseling if new questions arise (e.g., family planning.	As needed

ERG = electroretinogram; FA = fluorescein angiography; OCT = optical coherence tomography

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 may benefit from initiation of treatment with targeted immunomodulatory therapy.

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

Pregnancy Management

To date, there is no evidence that a pregnant woman or fetus with *ALPK1*-AD is at increased risk of adverse outcomes.

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

ALPK1-related autoinflammatory disease (*ALPK1*-AD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with *ALPK1*-AD have an affected parent.
- Some individuals diagnosed with *ALPK1*-AD have the disorder as the result of a *de novo ALPK1* pathogenic variant.
- If 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 evaluate their genetic status and inform recurrence risk assessment.
- 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.
- The family history of some individuals diagnosed with *ALPK1*-AD may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated 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 the sibs of inheriting the pathogenic variant is 50%.
- Intrafamilial variability may be observed among heterozygous family members. Affected family members may present with variable clinical features, and ophthalmologic involvement is not always present.

- If the *ALPK1* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *ALPK1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low but still increased over that of the general population because of the possibility of failure to recognize manifestations in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *ALPK1*-AD has a 50% chance of inheriting the *ALPK1* 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 *ALPK1* 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.

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ALPK1* 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 and preimplantation genetic testing. While most centers would consider use of prenatal and preimplantation genetic 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.

- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org
- **National Headache Foundation**
  Phone: 888-NHF-5552; 888-643-5552

Email: info@headaches.org
www.headaches.org

- **The Vision of Children Foundation**
  Phone: 858-314-7917
  www.visionofchildren.org

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. ALPK1-Related Autoinflammatory Disease: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ALPK1	4q25	Alpha-protein kinase 1	ALPK1	ALPK1

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 ALPK1-Related Autoinflammatory Disease (View All in OMIM)

607347	ALPHA KINASE 1; ALPK1
614979	RETINAL DYSTROPHY, OPTIC NERVE EDEMA, SPLENOMEGALY, ANHIDROSIS, AND MIGRAINE HEADACHE SYNDROME; ROSAH

Molecular Pathogenesis

ALPK1 encodes alpha-protein kinase 1 (ALPK1), which is expressed in a wide range of cells. Although the complete role of ALPK1 in cellular function is still being investigated, it has been shown to act as an intracellular sensor for bacterial metabolites [Zhou et al 2018]. Specifically, the N-terminal domain of ALPK1 binds bacterial sugars, including ADP-beta-D-manno-heptose (ADP-heptose). On activation, the kinase domain of ALPK1 phosphorylates TRAF-interacting protein with fork head-associated domain (TIFA), leading to enhanced NF-κB signaling. To date, *ALPK1* pathogenic variants associated with autoinflammation have been restricted to the ligand-sensing domain [Kozycki et al 2022].

Of note, 40 of the 41 individuals identified in the literature with *ALPK1*-related autoinflammatory disease to date are heterozygous for pathogenic variant p.Thr237Met (see Table 7).

Mechanism of disease causation. Gain of function

Table 7. *ALPK1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_025144.4 NP_079420.3	c.710C>T	p.Thr237Met	Most common pathogenic variant to date

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.

Chapter Notes

Author Notes

Dr Christina Kozycki runs a clinical and translational research program focused on *ALPK1*-related autoinflammatory disease (*ALPK1*-AD). In her work, she strives to improve clinical care for individuals living with *ALPK1*-AD and leverage insights gained from caring for these individuals to drive basic science research that can further elucidate the role of ALPK1 in human biology. As part of this work, her team is actively engaged in the evaluation of *ALPK1* variants of uncertain significance. Dr Kozycki would be happy to communicate with persons who have any questions regarding diagnosis or treatment of *ALPK1*-related autoinflammatory disease.

Dr Kozycki is currently following individuals with *ALPK1*-AD in the natural history protocol Familial Mediterranean Fever and Related Disorders: Genetics and Disease Characteristics (NCT00001373).

Acknowledgments

We express our greatest gratitude to patients and their families who have entrusted us with their care and dedicated their time and tissues to advancing our understanding of this rare disease.

Revision History

- 27 June 2024 (bp) Review posted live
- 2 June 2023 (ck) Original submission

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