ROSAH Syndrome — Comprehensive Disease Characteristics Report

Disease: ROSAH Syndrome (Retinal dystrophy, Optic nerve edema, Splenomegaly, Anhidrosis, and Headache) **MONDO:** MONDO:0013999 · **OMIM:** #614979 · **Orphanet:** ORPHA:313800 · **Causal gene:** *ALPK1* (HGNC:20917)

Summary

ROSAH syndrome is an ultra-rare, autosomal dominant **systemic autoinflammatory disease** caused by heterozygous gain-of-function missense variants in *ALPK1* (alpha-kinase 1). First delineated in 2019 in five unrelated families, the syndrome is named for its cardinal features — **R**etinal dystrophy, **O**ptic nerve edema, **S**plenomegaly, **A**nhidrosis, and **H**eadache — but is now understood to be a far broader multisystem inflammatory disorder. The defining molecular lesion is a recurrent variant, c.710C>T (p.Thr237Met), with a second recurrent allele p.Tyr254Cys and additional rarer variants (p.Ser277Phe, p.His735Pro, p.Thr237Ala). Mechanistically, wild-type ALPK1 is a cytosolic innate-immune receptor that senses the bacterial metabolite ADP-heptose and signals through TIFA–TRAF6 to activate NF-κB. The ROSAH variants are **neomorphic**: they alter the kinase's ligand specificity so it becomes aberrantly activated by endogenous host nucleotide sugars (e.g., UDP-mannose, ADP-ribose), producing constitutive NF-κB plus type I/II interferon signaling in the absence of any infection.

Clinically, the disease presents in **early childhood** with near-universal, frequently blinding bilateral ocular disease (optic disc edema, cone-rod retinal dystrophy resembling retinitis pigmentosa, low-grade uveitis/vitritis, and macular edema) accompanied by variable systemic features: splenomegaly (often with cytopenias), anhidrosis/hypohidrosis, migrainous headache, short dental roots, recurrent fever, deforming arthritis, premature basal-ganglia/brainstem mineralization on MRI, and a risk of AA (reactive) amyloidosis with renal failure. Expressivity is strikingly variable even within a single family; some individuals (notably with p.Thr237Ala) have a predominantly or exclusively ocular phenotype.

Therapeutically, cytokine blockade — particularly **IL-6 receptor inhibition with tocilizumab** — best controls systemic and intraocular inflammation and can reverse macular edema and optic-disc swelling, but **retinal/optic neurodegeneration frequently progresses despite immunosuppression**, suggesting a degenerative component partly uncoupled from controllable inflammation. The first selective ALPK1 inhibitor, **DF-003**, has been designed for oral dosing and is advancing toward the clinic. The same gene, mutated somatically at a different residue (p.Val1092Ala), drives the skin tumors spiradenoma and spiradenocarcinoma, placing ROSAH within an *ALPK1*/NF-κB "gain-of-function" allelic series.

Section 1 — Disease Information

Overview. ROSAH syndrome is a monogenic, autosomal dominant, systemic autoinflammatory disorder with prominent ophthalmologic involvement. Although the acronym (Retinal dystrophy, Optic nerve edema, Splenomegaly, Anhidrosis, Headache) captures the cardinal features originally described, the condition is now recognized as a broad autoinflammatory disease with ocular, hematologic, neurologic, dermatologic, dental, rheumatologic, and renal manifestations.

Key identifiers (verified via EBI OLS / MONDO and mygene.info):

Resource	Identifier
MONDO	MONDO:0013999 ("retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache syndrome")
OMIM (phenotype)	#614979
Orphanet	ORPHA:313800
UMLS	C4749914
GARD	0017411
MedGen	1662266
Causal gene *ALPK1*	HGNC:20917; NCBI Gene 80216; Ensembl ENSG00000073331; gene OMIM 607347; UniProt Q96QP1; cytoband **4q25**

Synonyms / alternative names: ROSAH syndrome; Retinal dystrophy–optic nerve edema–splenomegaly–anhidrosis–headache syndrome; ALPK1-associated autoinflammatory disease. A related "ROSAH-like" presentation restricted to ophthalmologic features has been reported (PMID: 39847428).

Information source. Knowledge for this entry is derived from **aggregated disease-level resources** (OMIM, Orphanet, MONDO) combined with **individual-patient clinical reports and cohorts** (e.g., the n=27 cohort of Kozycki et al. 2022 and numerous case series). It is not derived from a single EHR dataset.

Section 2 — Etiology

Primary cause — genetic. ROSAH is caused by heterozygous **gain-of-function missense variants in *ALPK1***. The founding variant c.710C>T (p.Thr237Met) segregated with disease across five unrelated families (PMID: 30967659). The disorder is autosomal dominant with variable expressivity.

> *"We found the heterozygous missense variant in the α-kinase gene, ALPK1, (c.710C>T, [p.Thr237Met]), segregated with disease in all five families."* — PMID: 30967659

Genetic risk factors. The disease is essentially monogenic; the causal alleles are the risk factors. Recurrent variants: **p.Thr237Met** (most common) and **p.Tyr254Cys**; additional reported alleles include **p.Ser277Phe**, **p.His735Pro**, and **p.Thr237Ala** (the latter associated with a milder, largely ocular phenotype). No susceptibility loci or polygenic contributions have been defined.

Environmental / modifier factors. No environmental exposure is required to cause disease. However, the **inflammatory context modulates the pathway**: IFN-γ "licenses" (primes/amplifies) the ALPK1/TIFA axis in human monocytes (PMID: 39868044), and concurrent gram-negative infection (supplying ADP-heptose) could in principle further activate even wild-type ALPK1. These represent plausible gene-environment / cytokine-context interactions that may contribute to episodic flares and variable expressivity, though this remains inferred rather than demonstrated in patients.

Protective factors. None established. No protective alleles or lifestyle factors are known for this ultra-rare Mendelian disease.

Section 3 — Phenotypes

ROSAH has a near-universal, early-onset ocular core with variable multisystem involvement. Onset is typically **pediatric (early childhood)**; penetrance for ocular disease appears high/near-complete, but expressivity varies even within families.

Phenotype	Type	HPO suggestion	Frequency / notes
Bilateral optic disc / nerve edema	Clinical sign	HP:0000543 (optic disc edema)	Near-universal; often presenting feature
Cone-rod retinal dystrophy (RP-like)	Clinical sign	HP:0000541 / HP:0000510	Near-universal; progressive; rod function often more reduced than cone (PMID: 41046116)
Low-grade uveitis / vitritis, vitreous opacities	Clinical sign	HP:0000554 (uveitis)	Common; persistent vitreous inflammatory opacities
Macular edema	Clinical sign	HP:0040049	Common; may respond to steroid/anti-VEGF/IL-6 blockade
Progressive vision loss / blindness	Symptom	HP:0000618 / HP:0000572	Major morbidity driver
Glaucoma / acute angle-closure (short axial length)	Clinical sign	HP:0000501	Reported subset (PMID: 41880066)
Keratoconus, dry eye	Clinical sign	HP:0000563 / HP:0000517	Newly described ocular-surface features (PMID: 41880066)
Splenomegaly	Physical manifestation	HP:0001744	Characteristic; often with cytopenias/pancytopenia (HP:0001876)
Anhidrosis / hypohidrosis	Clinical sign	HP:0000970	Characteristic
Headache / migraine	Symptom	HP:0002076	Common; sometimes with meningeal enhancement
Short / abnormal dental roots	Physical manifestation	HP (dental root anomaly)	Characteristic dental feature
Recurrent fever	Symptom	HP:0001945	Inflammatory feature
Deforming arthritis / arthralgia	Clinical sign	HP:0002758	Inflammatory feature

Phenotype	Type	HPO suggestion	Frequency / notes
Premature basal-ganglia/brainstem mineralization	Imaging/ laboratory	HP:0002452 (basal ganglia calcification)	On MRI (PMID: 35868845)
AA (reactive) amyloidosis → renal failure	Laboratory/ clinical	HP:0011035 / HP:0000121	Serious complication (PMID: 41880066)
Recurrent infections	Clinical sign	HP:0002719	Reported subset
Urticaria	Clinical sign	HP:0000988	Listed among MONDO features

> *"Nearly all patients exhibited at least one feature consistent with inflammation including recurrent fever, headaches with meningeal enhancement and premature basal ganglia/ brainstem mineralisation on MRI, deforming arthritis and AA amyloidosis."* — PMID: 35868845
>
> *"The clinical manifestations were relatively homogeneous, prominently presenting with juvenile onset oculopathy and splenomegaly."* — PMID: 31939038

Quality-of-life impact. Progressive, often irreversible vision loss is the dominant QoL burden. Systemic inflammation (fever, arthritis) and complications such as amyloidosis/renal failure add substantial morbidity. No formal EQ-5D/SF-36 studies exist for this rare disease.

Section 4 — Genetic / Molecular Information

Causal gene. *ALPK1* (alpha-kinase 1), HGNC:20917, NCBI Gene 80216, Ensembl ENSG00000073331, UniProt Q96QP1, cytoband **4q25**. ALPK1 is a cytosolic serine/threonine alpha-kinase that functions as an innate-immune receptor.

Pathogenic variants.

Variant (protein)	cDNA	Type	Classification	Notes
p.Thr237Met	c.710C>T	Missense	Pathogenic	Recurrent founding allele; multiple ancestries
p.Tyr254Cys	—	Missense	Pathogenic	Second recurrent allele (Kozycki 2022)
p.Ser277Phe	—	Missense	Likely pathogenic	Strong neomorphic activation (PMID: 39626775)
p.His735Pro	—	Missense	VUS → likely pathogenic	pCS/ROSAH case (PMID: 42640550)
p.Thr237Ala	—	Missense	Pathogenic	Milder, largely ocular phenotype (PMID: 41046116)

- **Variant class:** all reported ROSAH alleles are **missense**, clustering in/near the kinase/ligand-binding region.
- **Allele frequency:** absent/extremely rare in gnomAD (consistent with highly penetrant disease alleles).
- **Origin: germline** for ROSAH (de novo capable, given recurrence across diverse ancestries). The same gene mutated **somatically** at a different residue (p.Val1092Ala) causes spiradenoma (PMID: 31101826).
- **Functional consequence: gain of function / neomorphic** — constitutive NF-κB activation; not loss of function.

> *"The majority of the cohort carried the p.Thr237Met mutation but we also identified a new ROSAH-associated mutation, p.Tyr254Cys."* — PMID: 35868845

Modifier genes / epigenetics / chromosomal abnormalities. No specific modifier genes or epigenetic mechanisms have been established for ROSAH, and there are no associated chromosomal abnormalities (this is a single-nucleotide-variant disease). IFN-γ cytokine priming (PMID: 39868044) acts as a functional modifier of pathway output.

Section 5 — Environmental Information

ROSAH is a Mendelian disorder with no required environmental cause. Relevant non-genetic contributors are **inflammatory/cytokine context** rather than toxins or lifestyle:

- **Infectious / PAMP context:** Wild-type ALPK1 is the sensor for bacterial **ADP-heptose** (CHEBI), a gram-negative LPS-biosynthesis metabolite (PMID: 30111836, PMID: 31075211). While ROSAH variants are activated without infection, microbial ADP-heptose could further amplify signaling.
- **Cytokine priming:** IFN-γ licenses the ALPK1/TIFA pathway (PMID: 39868044), a plausible trigger for flares.
- **Lifestyle factors:** none identified.

Section 6 — Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

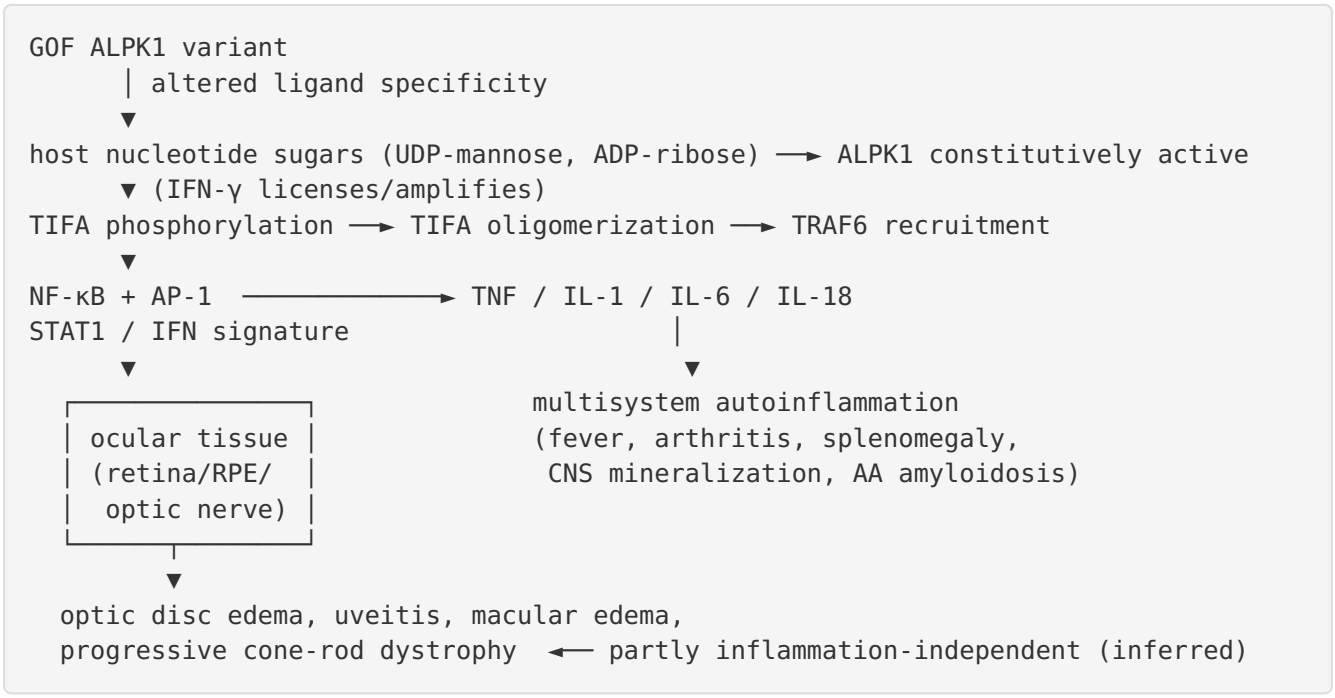
1. A heterozygous **gain-of-function missense variant in *ALPK1*** (e.g., p.Thr237Met, p.Tyr254Cys, p.Ser277Phe) **alters the kinase's ligand-binding pocket**, changing its specificity for allosteric nucleotide-sugar activators.
2. The altered pocket **leads to** aberrant activation of ALPK1 by **endogenous host metabolites** (UDP-mannose, ADP-ribose; also GDP-mannose for p.Ser277Phe) — i.e., activation *without* microbial ADP-heptose (PMID: 39626775, PMID: 39580356).
3. Constitutively active ALPK1 **phosphorylates TIFA**, which **results in** TIFA oligomerization.
4. Oligomerized TIFA **recruits TRAF6**, which **leads to** activation of the **NF-κB** and **AP-1** transcription factors (PMID: 32591860, PMID: 30111836).
5. *(Branch, inferred amplification)* **IFN-γ licenses/primes** the same pathway, amplifying signaling in monocytes (PMID: 39868044).
6. NF-κB/AP-1 activation **results in** chronic production of proinflammatory cytokines (**TNF, IL-1, IL-6, IL-18**) and, in parallel, **STAT1 phosphorylation and a type I/II interferon gene-expression signature** (PMID: 35868845).
7. Systemic cytokine excess **leads to** multisystem autoinflammation → recurrent fever, deforming arthritis, splenomegaly, meningeal enhancement, premature basal-ganglia/brainstem mineralization, and (chronically) **AA amyloidosis** with renal failure.

8. *(Branch — tissue-specific)* ALPK1 is expressed in **retina, RPE, and optic nerve**, localizing to the **photoreceptor connecting-cilium basal body**; local inflammation plus a possible ciliogenesis/degenerative component **results in** optic-nerve edema, uveitis, macular edema, and progressive **cone-rod retinal dystrophy** — the latter frequently progressing *despite* inflammation control, implying a partly inflammation-independent neurodegenerative arm (inferred; PMID: 30967659, PMID: 42773882).

Supporting detail

- **Molecular pathways:** ALPK1 → TIFA → TRAF6 → **NF-κB** (GO:0038061, NIK/NF-κB signaling) and AP-1; innate-immune TLR-like signaling (GO:0002224); JAK-STAT/interferon (STAT1).
- **Cellular processes:** chronic inflammation, cytokine secretion; GSDMD-mediated **pyroptosis** implicated in related ALPK1/retinal contexts (PMID: 41006430); defective **ciliogenesis** in patient fibroblasts (PMID: 30967659).
- **Protein dysfunction: neomorphic gain of function** — altered specificity for allosteric nucleotide-sugar activators rather than misfolding/aggregation (PMID: 39580356).
- **Immune involvement:** autoinflammation with combined NF-κB and interferon signatures.
- **Subcellular localization (GO CC):** ciliary basal body (GO:0036064), centriole (GO:0005814), microtubule-organizing center (GO:0005815), spindle pole during metaphase.

> *"Patients' primary samples and in vitro assays with mutated ALPK1 constructs showed immune activation with increased NF-κB signalling, STAT1 phosphorylation and interferon gene expression signature."* — PMID: 35868845
>
> *"...the mechanism of ADP-heptose sensing by alpha-protein kinase 1 (ALPK1) and its downstream signaling pathway that involves the proteins TIFA and TRAF6 and induces the activation of NF-κB and the secretion of inflammatory cytokines."* — PMID: 32591860
>
> *"In contrast to wild-type ALPK1, which is activated specifically by bacterial ADP-heptose, ALPK1[Ser277Phe] is also activated by the human metabolites UDP-mannose and ADP-ribose."* — PMID: 39626775



Section 7 — Anatomical Structures Affected

- **Primary organs: eye** (UBERON:0000970) — retina (UBERON:0001782), retinal pigment epithelium, optic nerve (UBERON:0000941), macula, cornea (UBERON:0000964); **spleen** (UBERON:0002106).
- **Secondary / systemic:** skin/sweat glands (anhidrosis), **brain** (basal-ganglia/brainstem mineralization; meningeal enhancement), joints (deforming arthritis), teeth (short dental roots), **kidney** (AA amyloidosis → renal failure), bone marrow/hematologic (cytopenias).
- **Body systems:** visual/ophthalmic, hematologic/reticuloendothelial, nervous, integumentary, musculoskeletal, renal.
- **Cell types (CL):** retinal cone cell (CL:0000573), retinal rod cell (CL:0000604), retinal pigment epithelial cell (CL:0002586), sweat gland cell (CL:0000650), monocytes/macrophages (effectors of autoinflammation).
- **Subcellular (GO CC):** ciliary basal body (GO:0036064), centriole (GO:0005814), MTOC (GO:0005815), cytosol.
- **Lateralization:** ocular disease is **bilateral**; splenomegaly is left-sided/midline per anatomy.

> *"ALPK1 was notably expressed in retina, retinal pigment epithelium, and optic nerve, with immunofluorescence indicating localization to the basal body of the connecting cilium of the photoreceptors, and presence in the sweat glands."* — PMID: 30967659

Section 8 — Temporal Development

- **Onset:** typically **pediatric / early childhood**; ocular symptoms are frequently the presenting and sometimes the exclusive early feature. Some cases show subtle signs in infancy (e.g., hand abnormalities by 18 months; PMID: 41269507).
- **Onset pattern: chronic / insidious**, with superimposed episodic inflammatory flares (fever).
- **Progression: progressive**, particularly the retinal degeneration, which advances like retinitis pigmentosa. Systemic inflammation can be episodic/relapsing.
- **Disease course / duration: chronic, lifelong**.
- **Remission:** inflammatory manifestations can enter treatment-induced remission with cytokine blockade; **retinal/optic degeneration generally does not remit** and may progress despite therapy.
- **Critical period:** early diagnosis and anti-inflammatory intervention before irreversible retinal/optic damage represents the key window of opportunity (PMID: 41880066, PMID: 40201710).

Section 9 — Inheritance and Population

- **Inheritance: autosomal dominant**, heterozygous gain-of-function.
- **Penetrance / expressivity:** high/near-complete penetrance for ocular disease; **markedly variable expressivity**, including intrafamilial (e.g., mother–daughter pair with very different courses, PMID: 42773882; p.Thr237Ala with ocular-only phenotype, PMID: 41046116).
- **De novo / recurrence:** recurrent identical missense alleles across diverse ancestries indicate recurrent, de-novo-capable mutations rather than a single founder effect.

- **Epidemiology: ultra-rare.** Only ~18 patients were reported by 2020 (PMID: 31939038); the largest single cohort is n=27 (PMID: 35868845). Cumulative literature remains on the order of tens of families worldwide. **No formal prevalence or incidence has been established.**
- **Population demographics:** reported across US/European, Chinese, Polish, Italian, and Brazilian ancestries, consistent with recurrent alleles rather than population-specific founders. No strong sex skew documented.

> *"Up to date, 18 patients of ROSAH syndrome have been reported."* — PMID: 31939038

Section 10 — Diagnostics

- **Genetic testing (confirmatory):** molecular confirmation of a pathogenic *ALPK1* variant via **whole-exome sequencing** (most common diagnostic route), targeted/retinal-dystrophy gene panels, or single-gene *ALPK1* sequencing. Advocacy exists for including *ALPK1* on panels for optic neuropathies, retinal disorders, and unexplained arthropathy (PMID: 41269507).
- **Ophthalmic work-up:** fundus photography, **OCT / OCT-angiography** (macular edema, ellipsoid-zone loss), **fundus autofluorescence** (hyperautofluorescent ring around disc), **full-field ERG** (rod > cone dysfunction), visual fields, fluorescein angiography (lack of capillary closure; preretinal neovascularization) — PMID: 41046116, PMID: 40069099.
- **Systemic work-up:** abdominal ultrasound (splenomegaly); CBC (cytopenias/pancytopenia); inflammatory markers; **brain MRI** (meningeal enhancement, basal-ganglia/brainstem mineralization); renal assessment and tissue biopsy if amyloidosis suspected.
- **Clinical criteria:** diagnosis rests on the characteristic combination of optic disc edema, uveitis, and retinal degeneration plus systemic features, **confirmed by *ALPK1* genetic testing** (PMID: 40201710).
- **Differential diagnosis:** retinitis pigmentosa / inherited retinal dystrophies, uveitis of other causes, Cogan's syndrome (ROSAH can masquerade as pediatric Cogan's; PMID: 42640550), lupus nephritis (renal ROSAH masquerade; PMID: 42112140), other autoinflammatory syndromes (e.g., CAPS/NLRP3).

> *"A diagnosis of ROSAH syndrome... can be made by targeted genetic sequencing of the ALKP1 gene."* — PMID: 40201710

Section 11 — Outcome / Prognosis

- **Survival / mortality:** not systematically quantified; the disease is chronic and disabling rather than rapidly fatal, but **AA amyloidosis → renal failure/dialysis dependence** is a serious, potentially life-limiting complication (PMID: 41880066).
- **Morbidity / function:** dominated by **progressive, often irreversible vision loss / blindness**; additional morbidity from arthritis, recurrent fever, cytopenias, and renal disease.
- **Complications:** amyloidosis with renal failure, glaucoma (including acute angle-closure), vitreous hemorrhage, recurrent infections, cytopenias.
- **Recovery potential:** inflammation is often controllable; **retinal/optic neurodegeneration generally does not recover** once established — inflammatory and degenerative processes appear to progress at least partly independently (PMID: 42773882).
- **Prognostic factors:** early diagnosis and timely anti-inflammatory therapy before irreversible retinal damage are the key favorable factors; advanced retinal degeneration at diagnosis predicts poor visual outcome despite treatment.

Section 12 — Treatment

Pharmacotherapy — cytokine blockade (mainstay).

Agent	Target (NCIT class)	Effect	Evidence
Tocilizumab	IL-6 receptor antagonist	Best control of **intraocular** inflammation; reduces macular edema & optic-disc swelling; improves systemic inflammation	PMID: 35868845, PMID: 41269507, PMID: 41880066
Anti-TNF (e.g., adalimumab)	TNF inhibitor	Suppresses systemic inflammation, improves QoL; limited ocular benefit	PMID: 35868845
Anti-IL-1 (e.g., anakinra)	IL-1 inhibitor	Suppresses systemic inflammation; limited ocular benefit	PMID: 35868845
Methotrexate / rituximab	Conventional/B-cell immunosuppression	Generally ineffective for ocular degeneration	PMID: 41269507, PMID: 41880066

> *"While anti-TNF and anti-IL-1 therapies suppressed systemic inflammation and improved quality of life, anti-IL-6 (tocilizumab) was the only anticytokine therapy that improved intraocular inflammation (two of two patients)."* — PMID: 35868845

Targeted therapy (upstream, investigational). DF-003, a selective ALPK1 inhibitor with pharmacokinetics suitable for once-daily oral dosing, targets the TIFA/TRAF6/NF-κB axis (PMID: 40925900).

> *"Here, we report the design of an ALPK1 inhibitor, DF-003, with pharmacokinetic properties suitable for daily oral dosing."* — PMID: 40925900

Local ocular / supportive measures. Intravitreal dexamethasone and **anti-VEGF** (transient macular-edema benefit, ~6 weeks; PMID: 40069099); **splenectomy** resolves recurrent fever in selected patients (PMID: 41880066); renal replacement therapy for amyloidosis-related failure.

Important caveat. Across multiple reports, **immune suppression controls inflammation but does not reliably prevent retinal degeneration or restore lost vision** (PMID: 40201710, PMID: 42773882).

Section 13 — Prevention

- **Primary prevention:** none — this is a genetic disease; no vaccination or risk-factor modification prevents it.
- **Secondary prevention / early detection:** early genetic diagnosis (including *ALPK1* on retinal/optic-neuropathy and autoinflammatory panels) to enable prompt anti-inflammatory therapy before irreversible ocular damage (PMID: 40270650, PMID: 41269507).
- **Tertiary prevention:** cytokine blockade to prevent systemic complications (amyloidosis, deforming arthritis); monitoring for renal amyloidosis; ophthalmologic surveillance for glaucoma/edema.
- **Counseling: genetic counseling** for autosomal dominant inheritance (50% transmission risk); options include prenatal/preimplantation testing given known familial variants.
- **Screening:** cascade genetic testing of at-risk relatives once a familial variant is identified.

Section 14 — Other Species / Natural Disease

- **Orthologous gene:** mouse *Alpk1* (ortholog of human *ALPK1*, NCBI Gene 80216). The ALPK1–TIFA–TRAF6–NF-κB ADP-heptose-sensing pathway is evolutionarily conserved.
- **Natural disease in other species: no naturally occurring ROSAH-equivalent disease** has been described in companion animals or wildlife (OMIA has no established ROSAH entry).
- **Comparative biology:** ADP-heptose/ALPK1 innate immunity is conserved; ALPK1-TIFA signaling controls intestinal stem-cell regeneration in mouse models (PMID: 40651470), illustrating conserved physiological roles.
- **Zoonotic potential:** not applicable (non-infectious genetic disease).

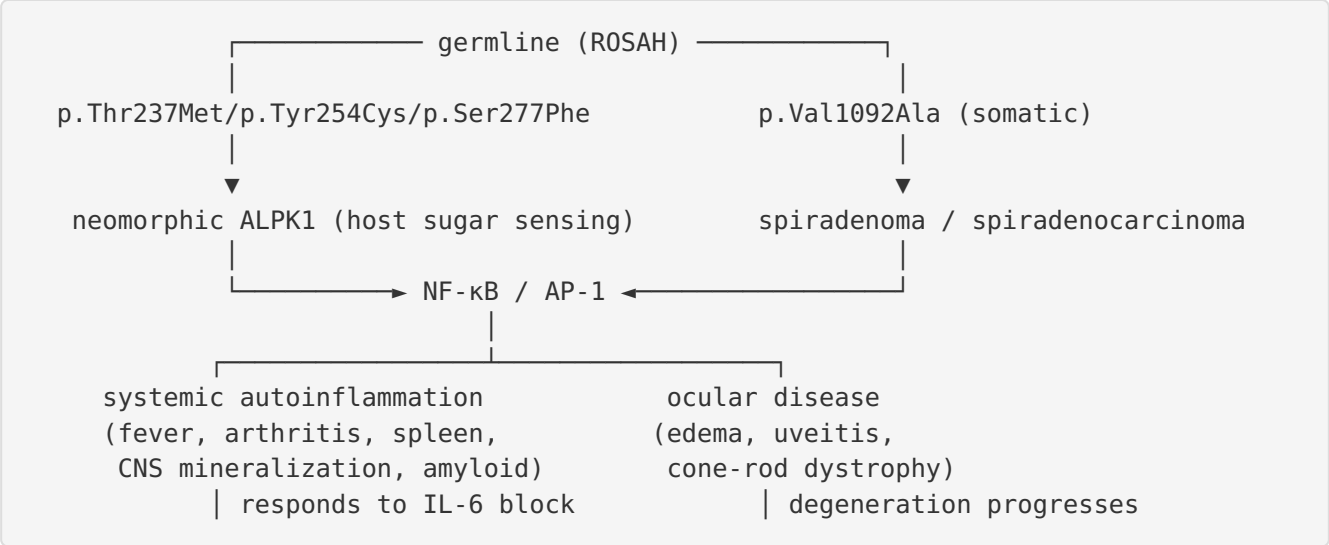
Section 15 — Model Organisms

- **Knock-in mouse:** Kozycki et al. (2022) generated an *Alpk1* knock-in mouse carrying the ROSAH mutation as an in-vivo model of the autoinflammatory phenotype (PMID: 35868845).

- **Cellular / in-vitro models:** patient-derived fibroblasts (showed defective ciliogenesis; PMID: 30967659); **ALPK1-knockout HEK-Blue NF-κB/AP-1 reporter cells** for quantifying variant activity and screening VUS (PMID: 39600975); transfected-cell NF-κB/AP-1 assays establishing gain-of-function/altered specificity (PMID: 39626775, PMID: 39580356).
- **Phenotype recapitulation:** the knock-in mouse enables study of the **inflammatory** arm; cellular assays faithfully reproduce **constitutive/neomorphic NF-κB activation**.
- **Limitations:** models of the **retinal-degeneration** arm and long-term ocular neurodegeneration are less developed; capturing the human ocular phenotype in rodents remains a gap.

Mechanistic Model / Interpretation

ROSAH is best understood as a **neomorphic kinase disease converging on NF-κB-driven autoinflammation plus a partly separable ocular neurodegeneration**. The unifying molecular theme — shared with somatic *ALPK1*-driven spiradenoma — is aberrant NF-κB activation from a gain-of-function/altered-specificity *ALPK1* allele. Upstream (causal) events are the germline mutation and the resulting constitutive ALPK1→TIFA→TRAF6 signaling; downstream (effector) events are cytokine excess (IL-6, TNF, IL-1, IL-18), the interferon signature, and the end-organ consequences. The ocular phenotype has two plausible contributors: (i) local inflammation in ALPK1-expressing retina/RPE/optic nerve, and (ii) a possible cilium-related degenerative process (defective ciliogenesis; connecting-cilium basal-body localization). The clinical observation that IL-6 blockade reverses inflammation but not degeneration argues that arm (ii) is at least partly inflammation-independent — the single most important mechanistic and therapeutic gap.


germline (ROSAH)
p.Thr237Met/p.Tyr254Cys/p.Ser277Phe
p.Val1092Ala (somatic)
neomorphic ALPK1 (host sugar sensing)
spiradenoma / spiradenocarcinoma
NF-κB / AP-1
systemic autoinflammation
(fever, arthritis, spleen,
CNS mineralization, amyloid)
responds to IL-6 block
ocular disease
(edema, uveitis,
cone-rod dystrophy)
degeneration progresses

Evidence Base

PMID	Role in this report
30967659	Founding paper: *ALPK1* p.Thr237Met in 5 families; tissue localization; ciliogenesis defect
35868845	n=27 cohort; autoinflammatory mechanism; p.Tyr254Cys; tocilizumab ocular benefit; knock-in mouse
32591860	Defines normal ALPK1-TIFA-TRAF6-NF-κB axis
30111836	ALPK1 as cytosolic receptor for bacterial ADP-heptose
39626775	p.Ser277Phe neomorphic activation by host UDP-mannose/ADP-ribose
39580356	Altered-specificity mechanism unifying ROSAH and spiradenoma
31101826	Somatic *ALPK1* hotspot driving spiradenoma/spiradenocarcinoma
39868044	IFN-γ licenses the ALPK1/TIFA pathway (modifier)
40925900	DF-003 selective ALPK1 inhibitor
31939038	Juvenile oculopathy + splenomegaly; ultra-rare epidemiology
41046116	Ocular manifestations; p.Thr237Ala milder/ocular-only
42773882	Intrafamilial variability; inflammation vs degeneration uncoupling
41880066	Reactive amyloidosis; novel ocular features; IL-6 systemic benefit
40201710	Diagnosis by *ALPK1* sequencing; degeneration progresses despite therapy
41269507	Tocilizumab anatomical benefit; p.Tyr254Cys
39600975	NF-κB/AP-1 reporter assay for variant functional testing
42640550	*ALPK1* p.His735Pro; ROSAH as Cogan's-syndrome mimic
42112140	Renal ROSAH masquerading as lupus nephritis
40069099	Anti-VEGF transient benefit; vitreous hemorrhage phenotype

Limitations and Knowledge Gaps

1. **Ultra-rarity:** With only tens of reported families, epidemiologic parameters (prevalence, incidence, sex ratio, penetrance estimates, survival) are uncertain and largely qualitative.
2. **Ocular neurodegeneration mechanism:** It remains unresolved whether retinal/optic degeneration is driven primarily by local inflammation, a cilium/ciliogenesis defect, or an independent neurodegenerative process; the apparent uncoupling of inflammation control from degeneration progression is clinically observed but mechanistically unexplained.
3. **Genotype–phenotype correlation:** Why p.Thr237Ala yields a mild/ocular-only phenotype while p.Thr237Met and p.Tyr254Cys cause full multisystem disease is not fully understood.
4. **Treatment evidence:** Therapeutic data derive from small cohorts and case reports, not controlled trials; no therapy is proven to halt vision loss.
5. **Model limitations:** Current models capture inflammation better than the ocular phenotype.

Proposed Follow-up Experiments / Actions

1. **Natural-history registry** to quantify penetrance, progression rates, visual outcomes, and amyloidosis risk across *ALPK1* genotypes.
2. **Mechanistic dissection of the ocular arm:** retinal organoids/iPSC-RPE and refined knock-in mice to test whether vision loss is inflammation-dependent, cilium-dependent, or neurodegenerative — directly informing whether upstream ALPK1 inhibition (DF-003) can protect vision where cytokine blockade fails.
3. **Clinical evaluation of DF-003** and head-to-head comparison with tocilizumab for ocular endpoints.
4. **Structural studies** (crystallography/cryo-EM/AlphaFold) of mutant ALPK1 bound to host nucleotide sugars to enable variant-selective inhibitor design sparing normal innate immunity.
5. **Functional classification pipeline** using the NF-κB/AP-1 reporter assay (PMID: 39600975) to reclassify *ALPK1* VUS and support genetic diagnosis.
6. **Biomarker development** (interferon signature, serum amyloid A) for monitoring disease activity and treatment response.

Report compiled from 27 reviewed publications and 9 confirmed findings. Evidence sources span human clinical cohorts/case reports, in-vitro reporter and biochemical assays, and a knock-in mouse model. Primary genetic and mechanistic claims are anchored to PMIDs 30967659, 35868845, 32591860, 39626775, and 39580356.
