Received: 10 July 2022 | Revised: 12 December 2022 | Accepted: 16 December 2022

DOI: 10.1111/cge.14286

CLINICAL GENETICS WILEY

SHORT REPORT

ROSAH syndrome mimicking chronic uveitis

Christine Fardeau[1] | Munirah Alafaleq[1,2] | Claire-Marie Dhaenens[3] | Hélène Dollfus[4] | Isabelle Koné-Paut[5] | Olivier Grunewald[3] | Jean-Baptiste Morel[1] | Cherif Titah[6] | David Saadoun[7] | Patrice Olivier Lazeran[8] | Isabelle Meunier[9]

[1]Department of Ophthalmology, Reference Center for Rare Diseases, La Pitié-Salpêtrière Hospital, Paris-Sorbonne University, Paris, France

[2]Ophthalmology Department, Imam Abdulrahman Bin Faisal University, King Fahad Hospital of the University, Dammam, Saudi Arabia

[3]University Lille, Inserm, CHU Lille, U1172-LilNCog-Lille Neuroscience & Cognition, Lille, France

[4]Institut de Génétique médicale d'Alsace, CARGO Reference Center for Rare Diseases in Genetic Ophthalmology, University Hospital of Strasbourg, Strasbourg, France

[5]Paediatric Rheumatology Department and CEREMAIA, Bicetre Hospital, APHP, University of Paris Sud Saclay, Bures-sur-Yvette, France

[6]Department of Ophthalmology, Hôpital Fondation Rothschild, Paris, France

[7]Department of Internal Medicine and Clinical Immunology, Reference Centre for Systemic Auto-Immune Diseases, La Pitié-Salpêtrière Hospital, Paris-Sorbonne University, Paris, France

[8]Department of Ophthalmology, Clinique des Cévennes, Annonay, France

[9]Department of Ophthalmology, Reference Centre for Genetic Sensory Diseases, Hôpital Gui de Chauliac, Montpellier University, Montpellier, France

Correspondence
Christine Fardeau, Department of Ophthalmology, Reference Center for Rare Diseases, La Pitié-Salpêtrière Hospital, Paris-Sorbonne University, Paris, France.
Email: christine.fardeau@aphp.fr

Abstract

To suggest a unique missense variant candidate based on long-term ophthalmological changes and associated systemic signs described in five patients from two unrelated families affected by an autosomal dominant multi-systemic disorder including Retinal dystrophy, Optic nerve oedema, Splenomegaly, Anhidrosis and migraine Headaches, called ROSAH syndrome, related to a unique missense variant in *ALPK1* gene. Observational longitudinal follow-up study of unrelated families. Clinical analysis of ophthalmological and systemic examinations was performed, followed by genetic analysis, including targeted Next Generation Sequencing (NGS) and Whole-Genome Sequencing (WGS). The ophthalmological phenotype showed extensive optic nerve swelling associated with early macular oedema and vascular leakage. The main associated systemic manifestations were recurrent fever, splenomegaly, anhidrosis, mild cytopenia, anicocytosis and hypersegmented polynuclear cells. WGS, shortened in the second family by the gene candidate suggestion, revealed in all patients the heterozygous missense variant c.710C>T; p.(Thr237Met) in *ALPK1*. The primary morbidity in ROSAH syndrome in this cohort appeared ophthalmological. Comprehensive, detailed phenotype changes aided by the advancement in genetic testing could allow an early genetic diagnosis of ROSAH syndrome and targeted treatment. The unique missense variant may be suggested as a target of gene correction therapy.

KEYWORDS
alpha-protein kinase 1, cone-rod dystrophy, macular oedema, papillary oedema, retinal dystrophy, ROSAH syndrome, uveitis

1 | INTRODUCTION

Retinal dystrophies (RD) are a group of inherited degenerative disorders. Despite the good performances of Next Generation Sequencing (NGS) of targeted RD genes (PMID 30718709), the use of Whole-Exome Sequencing (WES) and Whole-Genome Sequencing (WGS) combined with clinical analysis has improved the diagnosis of rare syndromic retinal dystrophies.

WGS led to the recent identification of *the ALPK1* gene as the cause of the systemic ocular disorder called ROSAH syndrome due to its clinical features, including familial autosomal dominant Retinal dystrophy, Optic nerve oedema, Splenomegaly, Anhidrosis and migraine Headaches syndrome.[1,2]

We report the ophthalmological changes, systemic features, and genetic analysis in patients from two unrelated families treated with bilateral chronic posterior uveitis.

2 | MATERIAL AND METHODS

This longitudinal observational follow-up study included five patients from two unrelated families.

A complete clinical and ophthalmological work-up was performed, including auto-immune, infectious, storage disease and genetic studies. In addition, detailed ophthalmological tests were displayed in Data S1.

2.1 | Ethics and consents

The current study was approved on November 10, 2021, by an institutional review board at Montpellier University Hospital (IRB ID:202100959). The study was conducted in compliance with good clinical practice and followed the tenets of the Declaration of Helsinki. Informed written consents were obtained according to the French bio-ethics law n°2011-814, decree 2013-527, from patients and the parents of minors. In addition, written photo consent was obtained from each involved patient.

2.2 | Molecular analysis

Genetic analysis used different NGS panels, including primary genes known to be associated with autosomal dominant inherited Retinal dystrophies and was unsuccessful in identifying the causal pathogenic variant. With current knowledge of novel syndromes from Chronic infantile neurological cutaneous articular (CINCA) to ROSAH syndromes, WGS were required to identify the pathogenic variant previously reported in ROSAH syndrome. Sanger sequencing was used to confirm the results obtained from WGS. High-quality genomic DNA samples were randomly fragmented by Covaris Technology. Detailed methods are shown in the Data S1.

3 | RESULTS

The main clinical and biological features at admission and therapeutic responses are summarized in Table 1.

3.1 | First family

3.1.1 | Patient 1: The proband

An 11-year-old boy presented with a bilateral decrease in his visual acuity (VA) to 20/200 in the right eye (RE) and 20/80 in the left eye (LE). Anterior segment examination was not remarkable. Vitreous examination showed vitreous cells graded as 1+ in both eyes. Fundus examination showed an optic nerve head swelling and macular oedema in both eyes (Figure 1).

Cerebral Magnetic Resonance Imaging (MRI) showed normal ventricles and optic pathways. Lumbar puncture was normal. Magnetic resonance spectroscopy showed a very high choline peak suggesting degradation of myelin. The patient has undergone a lumbo-peritoneal shunt at the age of 10 years for chronic bilateral papilledema along with campimetric worsening abnormalities.

Ten years later, VA was 20/2000 RE and 20/125 LE. Fundus examination revealed intra-retinal peripapillary exudates in the RE and superficial flame-shaped haemorrhage in the LE on the optic nerve head swelling, with annular macular pigmented changes.

Associated main systemic signs were recurrent fever at 39.5°C every 6–8 weeks, splenomegaly, eczema, anhidrosis and thin hair. At the age of 18 years, he developed a severe *Epstein Barr Virus* (EBV) infection.

3.1.2 | Patient 2: Proband's brother

The youngest brother was admitted on the same day at the age of 6 years. At admission, VA was 20/20 in both eyes. Fundus exam showed vitreous 0.5+ cells, bilateral papillary oedema in both eyes, and fine flame-shaped haemorrhages on the margins of papillary swelling. Brain MRI and lumbar pressure were normal. Main associated signs were recurrent fever spikes, headaches, lower back pain, splenomegaly, anhidrosis, nail dystrophy, thin hair, and dental problems. Ten years later, VA was 20/200 RE and 20/125 LE. The fundus showed optic nerve swelling, and OCT showed macular cysts.

3.1.3 | Patient 3: Proband's father

Fifty-year-old presented decreased visual acuity since the age of 7 years and chronic bilateral papilledema. He was admitted the same day at the age of 50 years with legal blindness. He had chiasmata

TABLE 1 Main clinical and biological signs at admission of patients diagnosed with ROSAH syndrome

Ophthalmological signs								Systemic signs				Biological results				
Patient Gender Age	Family history Papillary oedema Uveitis	BCVA RE LE	Fundus	Posterior pole Auto Fluorescence	Macular OCT	Visual field	Recurrent fever	Migraines Age of onset	Splenomegaly Age of initial diagnosis	Severe EBV infection history	Anhidrosis	Blood count	Blood smear	Anti-nuclear antibodies	Others autoantibodies	Treatments Clinical response
Family 1 Proband M 11 years old	Present	20/200 20/80	Extensive papillary oedema	Hyperautofluorescent ring surrounding a large hypoautofluorescent macular area	Macular oedema changing towards atrophy	Coecocentral scotoma	Present	Present 10 years Increased in febrile period	Present 5 years	Present	Present	Low platelet count 100 000/mm^3 Normal Bone marrow	Poikilocytosis Hyper segmented polynuclear cells	Present 1/2560 DFS[1] 70 aspect	Negative	Prednisone Colchicine Azathioprine GC intravitreal injections No clinical effect. Only prednisone >40 mg/j provided Increased VA
Family 1 Proband' Brother M 6 years old	Present	20/20 20/20	Extensive papillary oedema	Hyperautofluorescent ring surrounding a large hypoautofluorescent macular area	Macular oedema changing towards atrophy	Enlarged Mariotte spot changing towards coecocentral scotoma	Present	Present In childhood Increased in febrile period	Present 5 years	Absent	Present	Low platelet count 100 000/mm^3 Normal Bone marrow	NA[2]	Present 1/160	Negative	Prednisone Colchicine Mycophenolate mofetil Adalimumab: strong reaction at the injecting site: STOP Anakinra: worsened clinical conditions Infliximab + azathioprine + prednisone 10 mg/d ongoing for partial response on arthralgia No ophthalmological response
Family 1 Proband' Father M 50 years old	Present	1/200 1/100	Extensive papillary oedema	Large hypoautofluorescent macular area	Macular oedema changing towards atrophy	NA	present	Present 10 years Increased in febrile period	Present NA	NA	Present	Platelets 100 000–150 000/mm^3 Leukopenia Normal Bone Marrow	Anisocytosis anisochromia, poikilocytosis Hyper segmented polynuclear cells	NA	Negative	Prednisone for 16 years No clinical systemic benefit Worsening ocular signs
Family 2 Proband M 14 years old	Present	20/20 1/200	Extensive papillary oedema	Hyperautofluorescent ring surrounding papillary oedema	Macular oedema in LE	Enlarged Mariotte spot in RE NA in LE	Absent	Absent	Present 10 years	Absent	Present	Low count in normal range Normal Bone Marrow	Poikilocytosis	1/160	Negative	Prednisone Anakinra for 5 months Adalimumab and MTX for 32 months Tocilizumab for 12 months No clinical or ophthalmological benefit. Only prednisone 40 mg/d showed Improved retinal vascular leakage
Family 2 Proband' Father M 43 years old	Present	20/20 20/20	Extensive papillary oedema	Hyperautofluorescent ring surrounding papillary oedema	Normal	Enlarged Mariotte spot	Present	Present Teenage years Increased in febrile period	Present 18 years Splenectomy 20 years	Present	Present	Normal Normal Bone Marrow	Howell-Jolly corpus	Negative	Negative	Anakinra efficient on arthralgia Canakinumab inefficient on arthralgia Absent ophthalmological changes

Abbreviations: BCVA, best corrected visual acuity; DFS, dense fine speckled; GC, glucocorticoid; NA, not applicable by missing data.

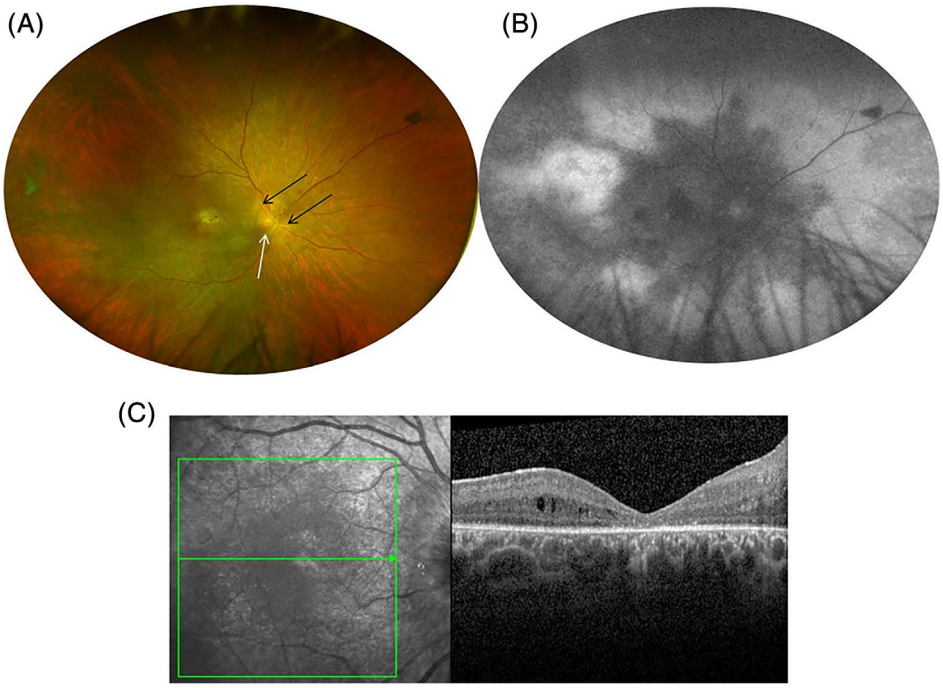

FIGURE 1 Proband's brother in the family 1. A 16-year-old boy showed a BCVA at 20/200 in RE and 20/125 in LE. (A) LE retinography showing papillary oedema showing blurred optic nerve head edge (white arrow), prepapillary sheathed arteries (black arrows), centromacular atrophy following chronic intraretinal cysts. (B) LE posterior pole autofluorescence showing large macular hypoautofluorescence area surrounded by hyperautofluorescent ring. (C) LE horizontal central OCT scan showing foveal atrophy associated with intra nuclear layer cysts, and thickened peripapillary area [Colour figure can be viewed at wileyonlinelibrary.com]

decompression at the age of 10 years. The main associated signs were diarrhoea, weekly fever, and splenomegaly.

3.1.4 | Wide work-up results

Immune work-up showed in the three patients a platelet count at about 140 000/mm^3 and poikilocytosis. The C-reactive protein (CRP) was normal outside of feverish periods. Infectious serologies were negative. Lysosomal diseases were ruled out, in particular Gaucher disease and Niemann-Pick. The leukocyte activity of acid sphingomyelinase was normal. The search for lymphadenopathy, infectious, autoimmune or tumour causes was negative.

3.1.5 | Genetic analysis

Genetic analysis was carried out in 2003, 2007 and 2011 identified no variant in genes associated with retinitis pigmentosa, cone-rod dystrophy or hereditary fevers, particularly TNF receptor-associated periodic syndrome (*TNFRSF1A*). In addition, no causal variants were found for familial Mediterranean fever (*MEFV*), *NLRP3*, which is responsible for *CINCA* syndrome, or mevalonate kinase deficiency (*MVK*).

A variant of unknown significance was identified in exon 4 of *NOD2* but was further excluded as it did not segregate with the disease.

The heterozygous missense variant c.710C>T, p.(Thr237Met) located in exon 9 of *ALPK1* (NM_025144.4) was identified by WGS in both children of the first family and the other unrelated boy and his father. The c.710C>T variant is rare because not present in the gnomAD database. It is highly conserved, and the physicochemical distance between threonine and methionine is high (Grantham distance of 81), with a CADD score of 22.9. This variation is considered likely pathogenic (SNV4) according to the ACMG (*American College of Medical Genetics and Genomics*) 2015 classification criteria three and was previously reported to cause ROSAH syndrome.[1–3]

3.1.6 | Treatment

Treatment was started by acetazolamide (250 mg three times a day) followed by systemic prednisone, successively associated with methotrexate, azathioprine, colchicine, anakinra, adalimumab and infliximab. Although Anakinra worsened the ophthalmological picture, infliximab was effective on recurrent fever while not affecting VA and retinal features.

3.1.7 | Patient 4: Unrelated boy

Fourteen-year-old boy complained of visual loss in the left eye since early childhood, initially related to a bilateral non-granulomatous posterior uveitis showing bilateral diffuse papillary oedema and posterior pole inferior exudation in the left eye (Figure 2). Associated systemic signs were splenomegaly, homogeneous hepatomegaly and polar kidney cyst. Familial history included: (1) father with no visual complains but exhibiting bilateral papillary oedema, associated with recurrent unexplained fever and splenomegaly for which a splenectomy was performed; (2) great paternal father had uveitis and chronic bilateral papillary oedema associated with hepatosplenomegaly and polycystic kidney lesions. Visual acuity was preserved until his death related to a rectal carcinoma.

A comprehensive immune and infectious work-up was negative. The brain MRI showed a stable hyper signal in white matter in the parahippocampus gyrus with no contrast enhancement. Medullar MRI and spinal fluid analysis were normal.

Treatments included prednisone successively associated with anakinra, adalimumab, methotrexate, and tocilizumab. No significant ophthalmological response was seen. Immunosuppressive agents, including

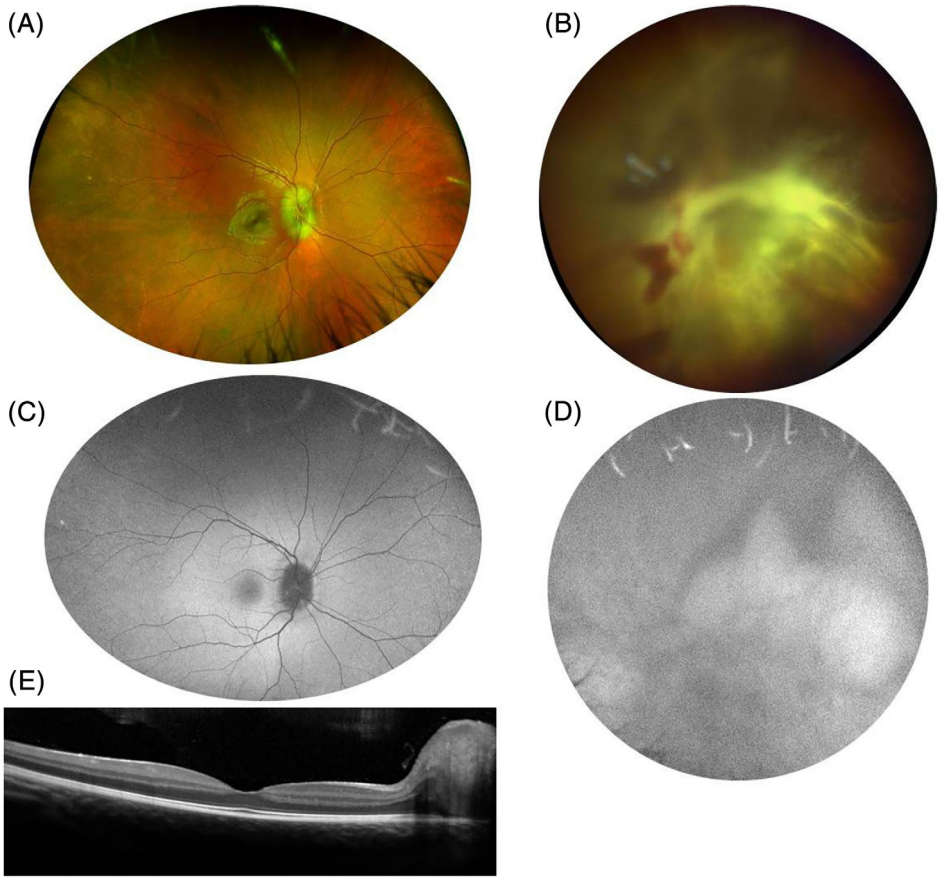

FIGURE 2 Proband in the family 2. A 14-year-old boy showed a BCVA at 20/20 in RE and light perception in LE. (A) RE retinography showed papillary oedema. (B) LE retinography showed exudative chronic papillomacular detachment and peripapillary intra retinal haemorrhages. (C, D) Posterior pole autofluorescence showed hyperfluorescent ring in the RE and large hyperfluorescent area corresponding to exudative detachment. (E) RE showing papillary oedema [Colour figure can be viewed at wileyonlinelibrary.com]

tocilizumab, were stopped because: the left eye was considered beyond therapeutic level, the right eye had a stable uncomplicated papillary oedema and the possible risk of onset of severe EBV infection in teenage years period.

The genetic investigations ruled out enzyme deficiency diseases: (*negative mevalonic aciduria, no deficiency in CD70 and negative CGH array*). However, the combination of ophthalmological, systemic signs and familial history suggested ROSAH syndrome and *ALPK1* as candidate genes. So in the following weeks, the heterozygous missense variant c.710C>T, p.(Thr237Met) located in exon 9 of *ALPK1* was identified by the NGS genes panel in both the child and father.

4 | DISCUSSION

The current study confirms the association of a unique variant missense in ALPK1 as a guide diagnosis of ROSAH using the WGS.

Different genomic technologies lead to the diagnosis of ROSAH syndrome in identifying the causing variant in *ALPK1* in five unrelated families.[1,2] The patients reported in this study presented similar ophthalmological features to those described in a cohort of 27 patients that included the second currently presented family.[3] The fascinating study provides the rates of clinical signs showing that optic disc elevation appeared frequent. Detailed initial data and treatment response are shown in Table 1.

The earliest clinical features in the current cohort were optic nerve head oedema, migraines, anhidrosis and splenomegaly. In addition, severe slow visual loss occurred in all eyes of the three first-family patients. In contrast, it occurred in only one eye of the second family proband of whom father and grandfather exhibited bilateral papillary chronic oedema and preserved visual acuity in both eyes.

ALPK1 is an alpha-protein kinase belonging to a class of atypical protein kinases, which could have a critical role in centrosome and cilia biology. Given the centrosomal, spindle poles and primary cilia localization of *ALPK1*, Williams et al. hypothesized that abnormal cilia function may be due to *ALPK1* pathogenic variant, p.(Thr237Met).[1] Moreover, *ALPK1* has been shown as a component in apical protein transport in Golgi network vesicles. The centrosomal cilia function of *ALPK1* could suggest abnormalities in the primary cilia, including photoreceptors cells and RPE polarity, induced by *ALPK1* variant. Abnormalities of the blood smear, noticed at the admission (shown in Table 1), could belong to ROSAH syndrome, and could be related to the centrosomal cilia function of *ALPK1*. Splenomegaly which is frequently found in ROSAH syndrome raises the question of the level of expression of ALPK1 in the spleen.

On the other hand, *ALPK1* is a cytosolic innate immune receptor for bacterial ADP-heptose, which triggers activation of the inflammatory NFkappaB signalling pathway. This process subsequently induces the expression of pro-inflammatory cytokines such as TNF alpha, IL1 beta, IL6, and IL8.[4]

Elevated plasma TNFalpha level was found in untreated patients. IL6, MCP1, soluble IL2 receptor alpha and IL10 were also frequently elevated.[3,5] Moreover, the variant has been shown to cause gain-of-function of *ALPK1* with activation of NF-kB.[3]

Hecker et al. described a patient affected by ROSAH syndrome exhibiting visual loss related to uveitis associated with papillary oedema. Multiple treatment approaches were successively used including rituximab, JAK inhibitors (baricitinib and tofacitinib), ustekinumab and intercurrent glucocorticosteroid noticed to be ineffective. Increasing expression of TNFalpha and IL6 were shown in myeloid cells, suggesting that *ALPK1* p.Thr237Met mutation might trigger auto-inflammation in a TNFalpha and IL6-dependant manner. Anti-TNF adalimumab in association with low dose corticosteroid and COX-2 inhibition with etoricoxib improved arthritis.[5]

Jamilloux et al. described a ROSAH family corresponding to the first family currently described in this paper. Initial ophthalmological signs, associated therapeutic sequences, and response have been added to Table 1.[6]

Zhong et al. presented two unrelated ROSAH patients, showing increased plasma TNFalpha levels. One patient was treated with adalimumab, but visual acuity deteriorated.[7]

Several ophthalmological elements were considered auto-immune uveitis mechanisms, such as chronic macular oedema (CME), fluorescein leakage in retinal angiography, and cells in vitreous noted at 1+ on the Sun scale. However, these three elements are compatible with the diagnosis of retinal dystrophy.

The various known process implications of *ALPK1* may interact with the ocular phenotype occurrence. On the one hand, the activated NFkappaB could induce increased pro inflammatory cytokines expression, that are known to be able to damage several components of the inner retinal blood barrier (RBB).[8] The RBB breakdown could take part in ophthalmological signs that have been treated as chronic uveitis for years. On the other hand, the centrosomal cilia function of *ALPK1* could suggest abnormalities in photoreceptor primary cilia induced by *ALPK1* variant,[1] which could lead to the dystrophic retinal damage unresponsive to immunosuppressive treatments.

5 | CONCLUSION

Comprehensive, detailed phenotype changes aided by the advancement in genetic testing could allow an early genetic diagnosis of ROSAH syndrome and targeted treatment. In addition, the unique missense variant may be suggested as a target of gene correction therapy.

AUTHOR CONTRIBUTIONS

Conception or design of the work: Christine Fardeau, Munirah Alafaleq, and Isabelle Meunier. *Data collection*: Christine Fardeau, Munirah Alafaleq, Claire-Marie Dhaenens, Hélène Dollfus, Isabelle Koné-Paut, Olivier Grunewald, Jean-Baptiste Morel, Cherif Titah, David Saadoun, Patrice Olivier Lazeran, and Isabelle Meunier. *Data analysis and interpretation*: Christine Fardeau, Munirah Alafaleq, Claire-Marie Dhaenens, Isabelle Koné-Paut, and Isabelle Meunier. *Drafting the article*: Christine Fardeau, Munirah Alafaleq, Claire-Marie Dhaenens, Isabelle Koné-Paut, and Olivier Grunewald. *Critical revision of the article*: Munirah Alafaleq, Claire-Marie Dhaenens, Isabelle Koné-Paut, Olivier Grunewald, and Isabelle Meunier. *Final approval of the version to be published*: Christine Fardeau, Munirah Alafaleq, Claire-Marie Dhaenens, Hélène Dollfus, Isabelle Koné-Paut, Olivier Grunewald, Jean-Baptiste Morel, Cherif Titah, David Saadoun, Patrice Olivier Lazeran, and Isabelle Meunier.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Christine Fardeau https://orcid.org/0000-0003-1935-2711

REFERENCES

1. Williams LB, Javed A, Sabri A, et al. ALPK1 missense pathogenic variant in five families leads to ROSAH syndrome, an ocular multisystem autosomal dominant disorder. *Genet Med*. 2019;21(9):2103-2115.
2. Tantravahi SK, Williams LB, Digre KB, et al. An inherited disorder with splenomegaly, cytopenias, and vision loss. *Am J Med Genet A*. 2012;158A(3):475-481.
3. Kozycki CT, Kodati S, Huryn L, et al. Gain-of-function mutations in ALPK1 cause an NF-κB-mediated autoinflammatory disease: functional assessment, clinical phenotyping and disease course of patients with ROSAH syndrome. *Annals Rheum Dis*. 2022;81:1453-1464.
4. Zhou P, She Y, Dong N, et al. Alpha-kinase 1 is a cytosolic innate immune receptor for bacterial ADP-heptose. *Nature*. 2018;561(7721):122-126.
5. Hecker J, Letizia M, Loescher BS, Siegmund B, Weidinger C. Early onset of TNFα-driven arthritis, auto-inflammation, and progressive loss of vision in a patient with ALPK1 mutation. *J Clin Immunol*. 2022;42(4):880-884.
6. Jamilloux Y, Mathis T, Grunewald O, et al. ALPK1 gene mutations drive autoinflammation with ectodermal dysplasia and progressive vision loss. *J Clin Immunol*. 2021;41(7):1671-1673.
7. Zhong L, Wang J, Wang W, et al. Juvenile onset splenomegaly and oculopathy due to germline mutation in ALPK1. *J Clin Immunol*. 2020;40(2):350-358.
8. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: beyond the surface. *Prog Retin Eye Res*. 2018;63:20-68.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fardeau C, Alafaleq M, Dhaenens C-M, et al. ROSAH syndrome mimicking chronic uveitis. *Clinical Genetics*. 2023;103(4):453-458. doi:10.1111/cge.14286