Case Report

New Phenotype in Two Siblings with Familial *FLVCR1* Mutation: Neurotrophic Keratopathy

Betül Dertsiz Kozan, Mehmet Fuat Alakuş, Hamza Polat

University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital, Clinic of Ophthalmology, Diyarbakır, Türkiye

Abstract

The feline leukemia virus subgroup C receptor (*FLVCR1*) gene plays a role in heme, choline, and ethanolamine transport. In biallelic pathogenic *FLVCR1* variants, macrocytic anemia may be associated with childhood- or adult-onset neurodegeneration of the retina, spinal cord, and peripheral nervous system. In patients with *FLVCR1* variants, optic atrophy and retinitis pigmentosa are previously described ocular findings, but neurotrophic keratopathy has not been reported. In this study, we describe two patients with homozygous novel likely pathogenic variants in terms of their clinical findings, including neurotrophic keratopathy. On examination, the 2-year-old sister had bilateral central corneal clouding, leukoma, absent corneal reflexes, normal fundus findings, and protruding ears. The 5-year-old sister exhibited significant bilateral corneal leukoma and scarring, optic disc pallor, absent corneal reflexes, and autoamputation-like defects on the fingertips of both hands. Next-generation sequencing analysis of the 5-year-old patient revealed a homozygous likely pathogenic c.160dup p.Arg54ProfsTer36 variant of the *FLVCR1* gene that was not listed in the GnomAD, ESP6500, ExAC, or Clinvar databases. *FLVCR1* mutations can disrupt choline transport and therefore acetylcholine production. Acetylcholine increases cGMP in the cornea, promoting epithelial growth. A lack of this neurotransmitter in the cornea leads to epithelial destruction. The development of neurotrophic keratopathy in this patient and her sibling may be a new phenotypic feature of this novel variant.

Keywords: *FLVCR1*, neurotrophic keratopathy, neuropathy, optic atrophy

Cite this article as: Dertsiz Kozan B, Alakuş MF, Polat H. New Phenotype in Two Siblings with Familial *FLVCR1* Mutation: Neurotrophic Keratopathy. Turk J Ophthalmol. 2025;55:287-290

Address for Correspondence: Betül Dertsiz Kozan, University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital, Clinic of Ophthalmology, Diyarbakır, Türkiye

E-mail: dr.dertsiz@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0667-2866

Received: 19.05.2025 **Accepted:** 30.07.2025

DOI: 10.4274/tjo.galenos.2025.05043

Introduction

The feline leukemia virus subgroup C receptor (*FLVCR*) gene plays a role in the transport of heme, choline, and ethanolamine. Biallelic pathogenic *FLVCR1* variants have been associated with NEDMISH (neurodevelopmental disorder with microcephaly, absent speech, and hypotonia) syndrome, which is characterized by macrocytic anemia, childhood- or adult-onset neurodegeneration of the retina, spinal cord, and peripheral nervous system, as well as a milder phenotype called retinopathy-sensory neuropathy syndrome.[1] Ocular pathologies such as optic atrophy or retinitis pigmentosa have been reported in both syndromes.[2,3] In this study, we describe clinical findings including neurotrophic keratopathy in two homozygous carriers of a novel, likely pathogenic variant.

Case Reports

Two sisters, 2 and 5 years of age, presented to the ophthalmology outpatient clinic with complaints of whiteness in the eyes. The patients' parents were cousins. Despite an unremarkable prenatal history, both patients were being followed for global developmental delay and had reportedly never achieved the key milestones of sitting, walking, or speaking. They exhibited marked hypotonia and the parents reported multiple hospitalizations due to frequent infection. As the patients had no pain perception, they had widespread skin ulcers and scars on the tongue and fingers.

On physical and ophthalmologic examination, the 2-year-old girl exhibited leukoma in both corneas and protruding ears (Figure 1). There was no epithelial involvement in corneal fluorescein staining, the fundus was normal (Figure 2), and corneal reflex could not be elicited. The 5-year-old girl had significant leukoma and scarring in both corneas (Figure 3), corneal fluorescein staining revealed unilateral epithelial

involvement, bilateral optic disc pallor (Figure 4), and corneal reflex could not be elicited. Partial auto-amputation of the finger tips was observed in both hands (Figure 5). The demographic and clinical characteristics of the cases are summarized in Table 1. The 5-year-old girl died 8 months later. The family history included two other girls with similar clinical complaints who had died previously.

Next-generation sequencing analysis in the 5-year-old patient revealed a homozygous likely pathogenic *FLVCR1* variant (c.160dup p.Arg54ProfsTer36) that was not reported in the databases. For molecular analysis, 2 mL of peripheral blood was collected in EDTA tubes and stored at -20 °C. Genomic DNA was isolated from peripheral blood leukocytes using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocols. All coding exons and exon-intron boundaries of 4,493 genes were amplified using the Clinical Exome Solution v2 kit (SOPHiA Genetics, Boston USA). The prepared library was sequenced on the Illumina NextSeq platform (Illumina Inc., San Diego, CA, USA). Together with clinical findings, the data were analyzed using Sophia DDM data analysis software (Sophia Genetics, Boston USA) (Figure 6).

Discussion

FLVCR1 gene variants exhibit a broad and pleiotropic phenotypic spectrum, ranging from adult neurodegeneration to severe developmental disorders with variable anemia and skeletal malformations. Different phenotypes of this rarely reported gene defect have been recognized over time, and the genetic tests performed vary according to the phenotype.

FLVCR1 gene mutations can disrupt transport of choline, which plays an important role in methyl group metabolism

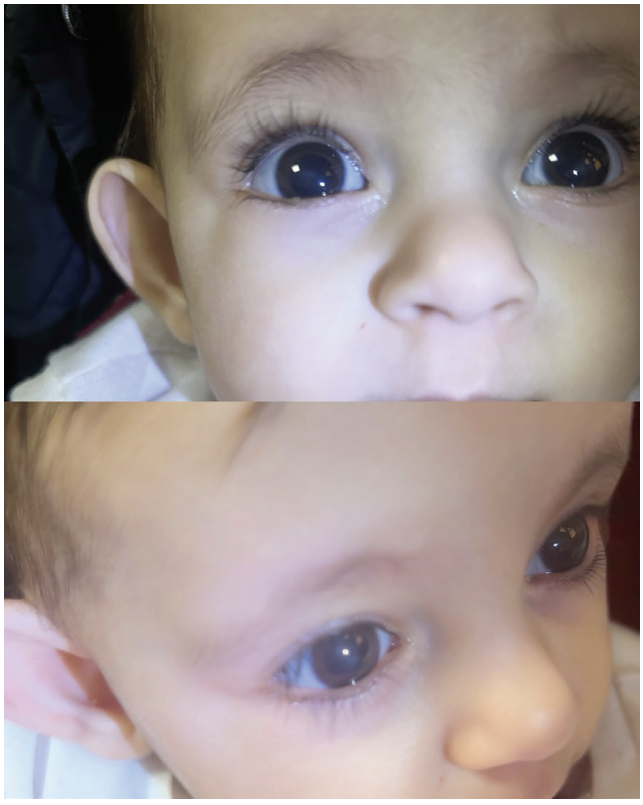

Figure 1. The 2-year-old female patient, corneal leukoma and protruding ears

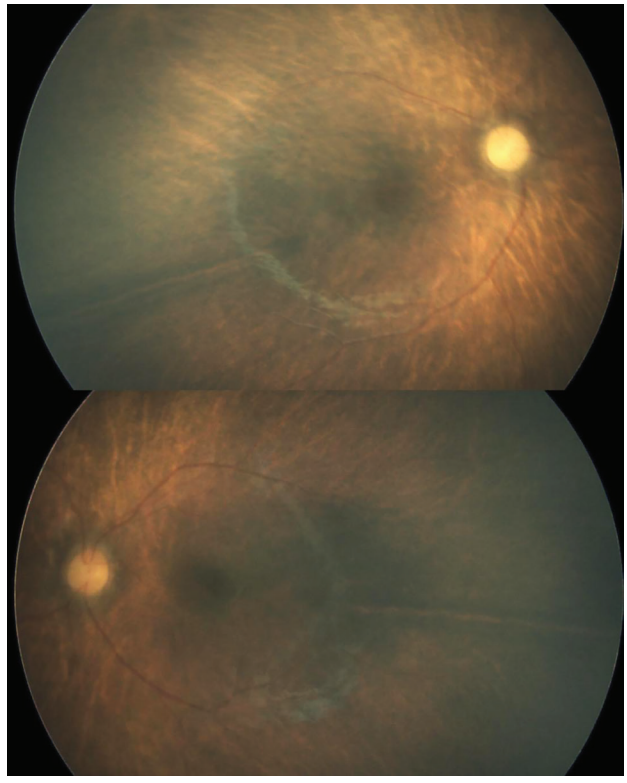

Figure 2. The 2-year-old female patient, normal fundus appearance

Figure 3. The 5-year-old female patient, significant leukoma and corneal scar

and the synthesis of phosphatidylcholine and acetylcholine via the Kennedy pathway. Choline is essential for normal neurodevelopment.[4] Maternal choline deficiency has been reported to impair hippocampal development and neuronal and retinal progenitor cell proliferation and differentiation in mouse embryos.[5,6] Ethanolamine cannot be synthesized by humans and is a precursor to phosphatidylethanolamine synthesis via the Kennedy pathway.[7] Phosphatidylethanolamine and phosphatidylcholine are membrane phospholipids required for membrane integrity, cell division, and mitochondrial respiratory function. These molecules are vital and their deficiency results in early death.

Damage to the dense corneal nerve endings from the long posterior ciliary nerves play a fundamental role in the pathophysiology of keratopathy. Studies have shown that these sensory neurons directly affect the integrity of the corneal

Figure 4. The 5-year-old female patient, defects in the fingertips

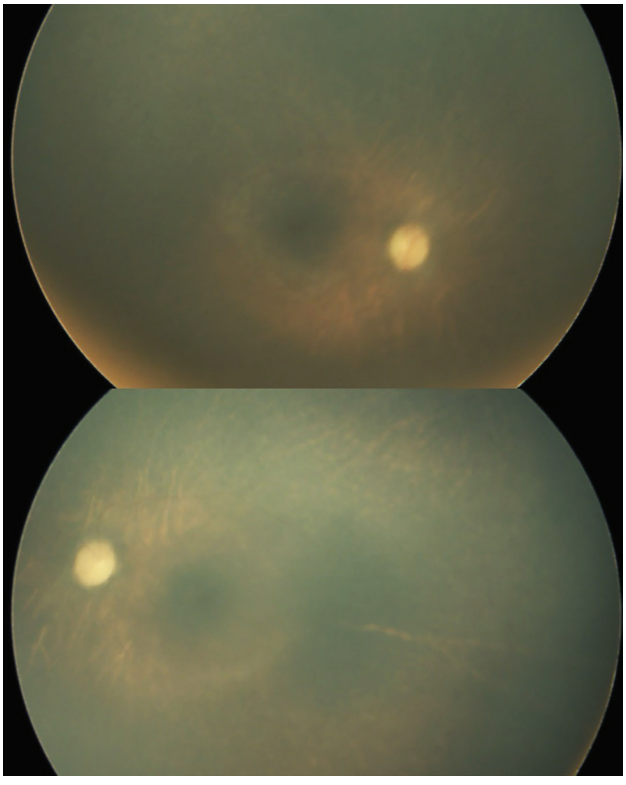

Figure 5. Five-year-old female patient, bilateral optic atrophy

Table 1. Demographic and clinical characteristics		
	Patient 1	**Patient 2**
Age (years)	2	5
Sex	Female	Female
Corneal findings	Bilateral leukoma	Bilateral leukoma, left scar
Fluorescein staining	None	Left +
Corneal reflex	Absent	Absent
Fundus	Normal	Bilateral optic disc pallor
Additional findings	Protruding ears	Autoamputation of digits

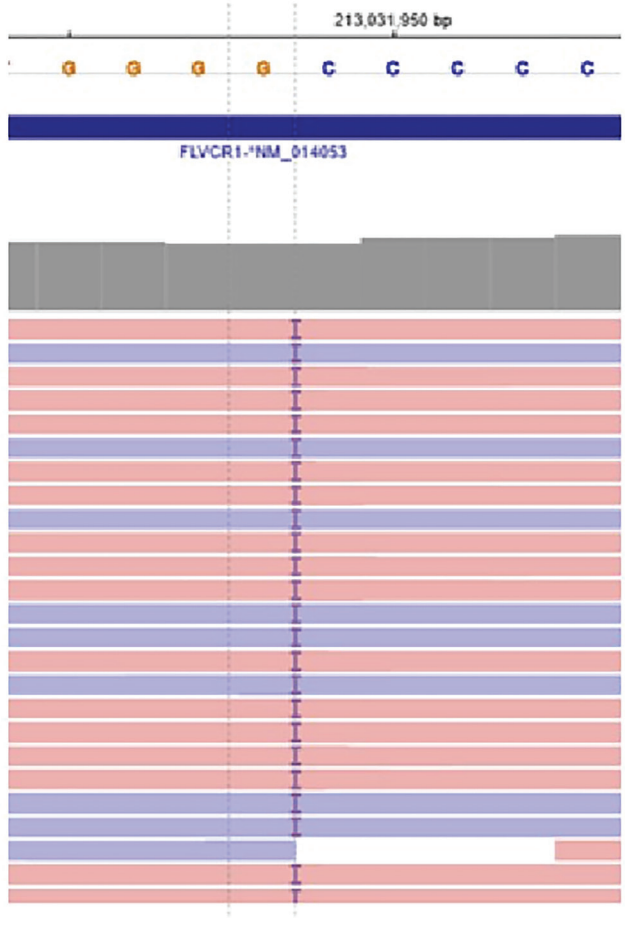

Figure 6. Integrated genomic imager variant visualization

epithelium. In the presence of neuronal destruction, the epithelial cells swell, lose their microvilli, and produce abnormal basal laminae. This can slow or stop mitosis, leading to epithelial defects.[8] Although Cochet-Bonnet esthesiometer and in vivo confocal microscopy can be used for the objective assessment of corneal neuropathy, these could not be performed in our cases because they were not available in our clinic and the patients were not cooperative. However, these tests are recommended in similar cases.

Disrupted choline transport due to *FLVCR1* mutation results in inability to produce acetylcholine. The presence of this neurotransmitter in the cornea increases cGMP and promotes epithelial growth, whereas its deficiency leads to epithelial destruction, resulting in keratopathy. Microtrauma, infection, nerve damage, and various other factors inhibit cell mitosis, leading to recurrent epithelial erosion and ulceration. Loss of the corneal epithelial barrier leads to the development of stromal edema in areas of epithelial erosion.[8]

Our patient was found to carry a homozygous p.Arg54ProfsTer36 variant, which was not previously reported in the GnomAD, ESP6500, ExAC and Clinvar databases. These cases are distinguished from retinopathy-sensory neuropathy by the absence of retinitis pigmentosa and ataxia. Considering that *FLVCR1*-associated phenotypes arise from loss-of-function mutations, the frameshift nature of the novel variant identified in our patient evaluated in the context of the clinical findings support its classification as likely pathogenic. The development of neurotrophic keratopathy in this patient and her sibling may be a new phenotypic feature of this novel variant.

Genetic testing to identify specific causative pathogenic variants is important to confirm the diagnosis and provide appropriate genetic counseling to affected families. Identifying specific genetic defects allows for predictive testing of at-risk relatives and enables informed decisions about surveillance and preventive measures.

Ethics

Informed Consent: Written consent was obtained from the parent of the patients.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.D.K., M.F.A., H.P., Concept: B.D.K., M.F.A., H.P., Design: B.D.K., M.F.A., H.P., Data Collection or Processing: B.D.K., M.F.A., H.P., Analysis or Interpretation: B.D.K., M.F.A., H.P., Literature Search: B.D.K., M.F.A., H.P., Writing: B.D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Calame DG, Wong JH, Panda P, Nguyen DT, Leong NCP, Sangermano R, Patankar SG, Abdel-Hamid MS, AlAbdi L, Safwat S, Flannery KP, Dardas Z, Fatih JM, Murali C, Kannan V, Lotze TE, Herman I, Ammouri F, Rezich B, Efthymiou S, Alavi S, Murphy D, Firoozfar Z, Nasab ME, Bahreini A, Ghasemi M, Haridy NA, Goldouzi HR, Eghbal F, Karimiani EG, Begtrup A, Elloumi H, Srinivasan VM, Gowda VK, Du H, Jhangiani SN, Coban-Akdemir Z, Marafi D, Rodan L, Isikay S, Rosenfeld JA, Ramanathan S, Staton M, Oberg KC, Clark RD, Wenman C, Loughlin S, Saad R, Ashraf T, Male A, Tadros S, Boostani R, Abdel-Salam GMH, Zaki M, Mardi A, Hashemi-Gorji F, Abdalla E, Manzini MC, Pehlivan D, Posey JE, Gibbs RA, Houlden H, Alkuraya FS, Bujakowska K, Maroofian R, Lupski JR, Nguyen LN. Biallelic variation in the choline and ethanolamine transporter FLVCR1 underlies a severe developmental disorder spectrum. Genet Med. 2025;27:101273.
2. Rajadhyaksha AM, Elemento O, Puffenberger EG, Schierberl KC, Xiang JZ, Putorti ML, Berciano J, Poulin C, Brais B, Michaelides M, Weleber RG, Higgins JJ. Mutations in FLVCR1 cause posterior column ataxia and retinitis pigmentosa. Am J Hum Genet. 2010;87:643-654.
3. Kuehlewein L, Schöls L, Llavona P, Grimm A, Biskup S, Zrenner E, Kohl S. Phenotypic spectrum of autosomal recessive retinitis pigmentosa without posterior column ataxia caused by mutations in the FLVCR1 gene. Graefes Arch Clin Exp Ophthalmol. 2019;257:629-638.
4. Ioannidis NM, Rothstein JH, Pejaver V, Middha S, McDonnell SK, Baheti S, Musolf A, Li Q, Holzinger E, Karyadi D, Cannon-Albright LA, Teerlink CC, Stanford JL, Isaacs WB, Xu J, Cooney KA, Lange EM, Schleutker J, Carpten JD, Powell IJ, Cussenot O, Cancel-Tassin G, Giles GG, MacInnis RJ, Maier C, Hsieh CL, Wiklund F, Catalona WJ, Foulkes WD, Mandal D, Eeles RA, Kote-Jarai Z, Bustamante CD, Schaid DJ, Hastie T, Ostrander EA, Bailey-Wilson JE, Radivojac P, Thibodeau SN, Whittemore AS, Sieh W. REVEL: an ensemble method for predicting the pathogenicity of rare missense variants. Am J Hum Genet. 2016;99:877-885.
5. Siepel A, Bejerano G, Pedersen JS, Hinrichs AS, Hou M, Rosenbloom K, Clawson H, Spieth J, Hillier LW, Richards S, Weinstock GM, Wilson RK, Gibbs RA, Kent WJ, Miller W, Haussler D. Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. Genome Res. 2005;15:1034-1050.
6. Cooper GM, Stone EA, Asimenos G; NISC Comparative Sequencing Program; Green ED, Batzoglou S, Sidow A. Distribution and intensity of constraint in mammalian genomic sequence. Genome Res. 2005;15:901-913.
7. Schubach M, Maass T, Nazaretyan L, Röner S, Kircher M. CADD v1.7: using protein language models, regulatory CNNs and other nucleotide-level scores to improve genome-wide variant predictions. Nucleic Acids Res. 2024;52:D1143-D1154.
8. Ruiz-Lozano RE, Hernandez-Camarena JC, Loya-Garcia D, Merayo-Lloves J, Rodriguez-Garcia A. The molecular basis of neurotrophic keratopathy: diagnostic and therapeutic implications. A review. Ocul Surf. 2021;19:224-240.