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Ophthalmic Manifestations of KIF11-Associated Microcephaly With or Without Chorioretinopathy, Lymphedema, or Intellectual Disability: A Case Report of a Novel Variant

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 39-year-old
Final Diagnosis: KIF11-associated chorioretinopathy
Symptoms: Decrease vision and nyctalopia
Clinical Procedure: —
Specialty: Ophthalmology
Objective: Rare disease

Background: Mutations in the kinesin family member 11 (KIF11) gene have been recently identified in several families worldwide. This gene plays a crucial role in cell division, chromosomal positioning, and separation. KIF11 mutations are associated clinically with microcephaly with or without chorioretinopathy, lymphedema, or intellectual disability (MCLMR). It is an autosomal dominant disorder with reduced penetrance, and few reports in the literature describe its phenotypic associations.

Case Report: We present the case a 39-year-old man from the Kingdom of Saudi Arabia with a known history of nyctalopia who was diagnosed with retinitis pigmentosa in early childhood. He experienced a profound decrease in visual acuity in both eyes, accompanied by a severely reduced rod response and mixed cone responses on full-field electroretinography. Fundus examination in both eyes showed a pale disc, diffuse retinal atrophy extensively involving the macula, mild blood vessel attenuation, pigment clumping with bone spicules, islands of peripheral and mid-peripheral chorioretinal atrophy, and lattice degeneration at the periphery. Optical coherence tomography revealed outer retinal atrophy with loss of the ellipsoid zone. Targeted next-generation sequencing using a vision/retinal dystrophy gene panel identified a heterozygous frameshift variant in KIF11 (NM_004523.4: c.535del; p.(Ser179Leufs*16)), classified as likely pathogenic according to ACMG/AMP/ClinGen SVI guidelines. The variant was absent from population databases (gnomAD, ESP, 1000 Genomes) and, to the best of our knowledge, has not been previously reported in the literature. The patient was diagnosed with KIF11-related MCLMR syndrome, presenting with microcephaly and chorioretinal atrophy.

Conclusions: Mutations in KIF11 are uncommon. Due to its reduced penetrance, individuals with this mutation may present mainly with microcephaly with or without chorioretinopathy, lymphedema, intellectual disability, or even without any clinical features. Early diagnosis of the disease is crucial for multidisciplinary management and genetic counseling.

Keywords: lymphedema • microcephaly • retinal dystrophies • ophthalmology • chorioretinopathy • KIF11 protein, human • genetic predisposition to disease • case reports

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/952957

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Introduction

Mutations in the kinesin family member 11 (KIF11) gene are extremely rare. These mutations have been recently linked to the development of microcephaly with or without chorioretinopathy, lymphedema, or intellectual disability (MCLMR). This condition is inherited in an autosomal dominant (AD) fashion with reduced penetrance, and few cases have been reported worldwide [1]. Different variants have been identified in reported cases, including missense, nonsense, frameshift, and splice-site mutations [1]. The gene is responsible for various tasks in cell division, including chromosomal positioning and separation, bipolar spindle establishment during mitosis, regulation of axonal branching and growth cone motility, and cell motility [2].

Patients with KIF11 mutations associated with MCLMR usually share some phenotypic features. The most common shared features are, as the name of the disease suggests, microcephaly, chorioretinopathy, lymphedema, and mild to moderate intellectual disability. Dysmorphic features include an upslanting palpebral fissure, a broad nose, a thin upper lip with a long philtrum, and large ears [1].

The typical phenotypic ocular association is chorioretinopathy, characterized by islands of macular and extramacular chorioretinal atrophy, pigment clumping, and attenuation of blood vessels [3]. To our knowledge, only one reported case in the Kingdom of Saudi Arabia (KSA) involving a KIF11 mutation and MCLMR syndrome exists. Alahmadi G et al reported a case of a 10-year-old girl complaining of poor vision since the age of four, with microcephaly, intellectual disability, lymphedema, and chorioretinal atrophy. The diagnosis of MCLMR syndrome with a novel variant was ultimately made [4].

KIF11-related chorioretinopathy can closely mimic retinitis pigmentosa (RP) and other inherited retinal dystrophies, leading to diagnostic confusion and delayed molecular confirmation. The novelty of the present report is 2-fold: (1) we describe a previously unreported KIF11 variant (p.(Ser179Leufs*16)), and (2) we highlight an RP-like retinal dystrophy phenotype and microcephaly in the absence of lymphedema. This case underscores the importance for ophthalmologists of considering KIF11 testing in patients with an apparent "RP-like" dystrophy, particularly when associated systemic features (eg, microcephaly or intellectual disability) are present, as an accurate genetic diagnosis guides multidisciplinary management and genetic counseling.

Case Report

Before writing this report and after the patient's presentation to our clinic, Institutional Review Board (IRB) approval was obtained from Imam Abdulrahman Bin Faisal University (IRB: 2024-01-542). Written informed consent was obtained from the patient, who agreed to publication of this case report without recognizable facial photography. Here, we present a 39-year-old male who presented to our clinic with a concern of poor vision, especially at night, since early childhood. The patient had previously been diagnosed with retinitis pigmentosa (RP) with no history of ocular intervention. There was no known family history of retinal dystrophy or visual impairment. He had 4 healthy siblings, and his parents were consanguineous with non-significant medical histories. His past medical history was unremarkable except for glucose-6-phosphate dehydrogenase (G6PD) deficiency and a nasal septum deviation surgery. There was no history of hearing loss, seizures, behavioral changes, or learning difficulties. He did not recall

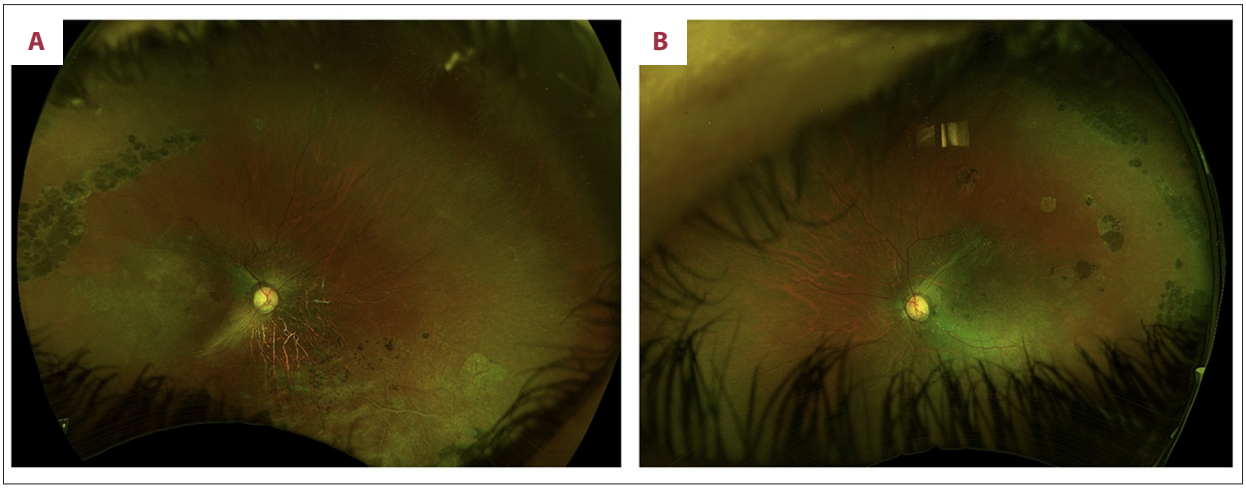

Figure 1. Color fundus photograph of both eyes. Both images (**A, B**) show clear media, total optic disc pallor, diffuse retinal atrophic changes involving the macula, peripheral and mid-peripheral islands of chorioretinal atrophy, peripheral lattice degeneration, and bone spicules, more prominent in photo **A** than **B**.

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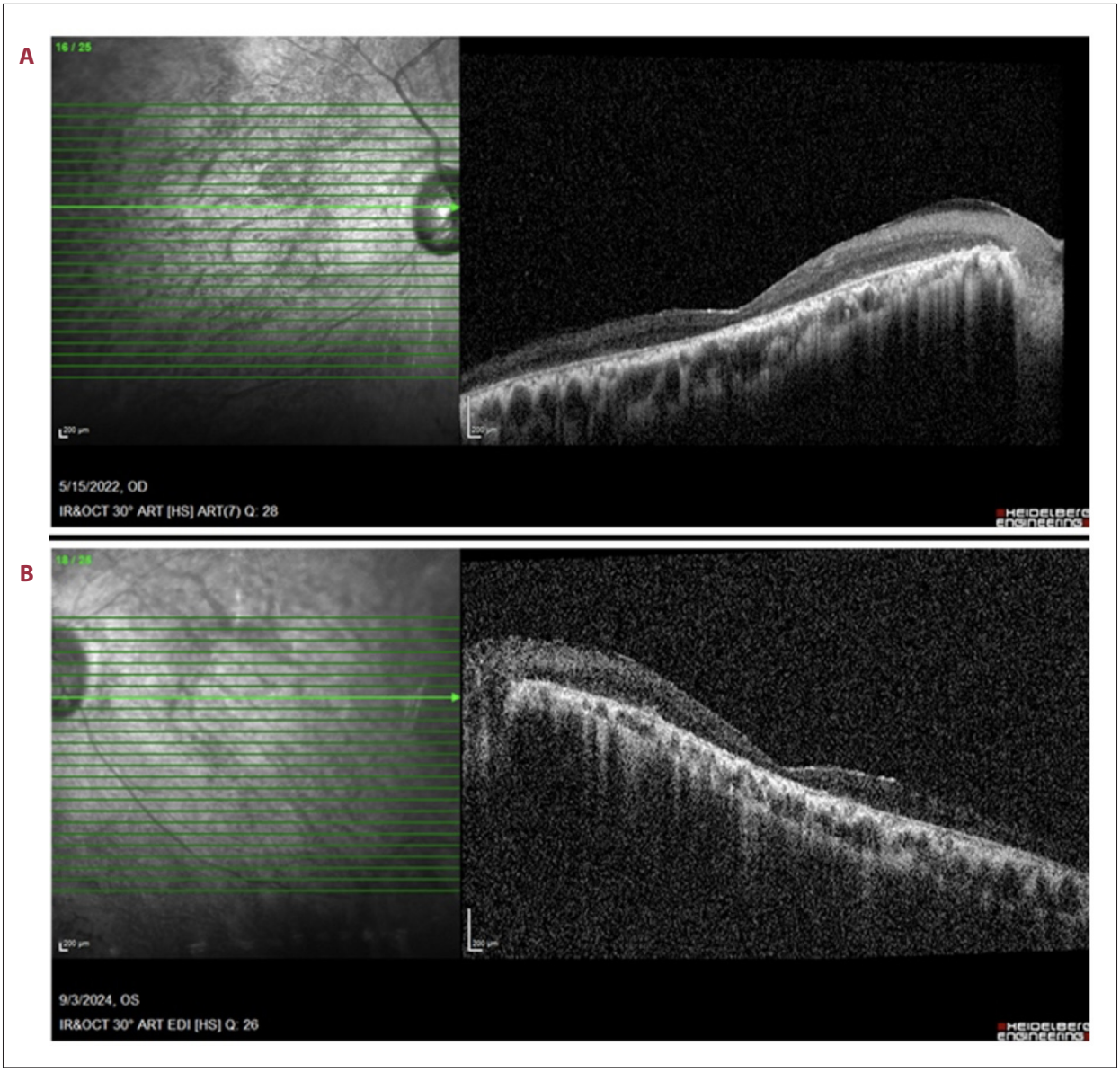

Figure 2. Optical coherence tomography of the posterior pole. Images **A** (right eye) and **B** (left eye) show outer retinal atrophy with no evidence of macular edema. There is loss of the ellipsoid zone and thinning of the outer nuclear layer.

any perinatal history or milestone delays; however, he only had a middle-school education.

His uncorrected vision with the Snellen chart was 20/400 in the right eye and counting fingers at three feet in the left eye at presentation. The right eye refraction was -4.25-1.25 × 20, which corrected his vision to 20/320. The left eye refraction was -2.00-0.50 × 150, with a corrected vision of 20/250. Slit-lamp examination showed an unremarkable anterior segment in both eyes, with normal intraocular pressure. The posterior segment examination showed clear vitreous, total optic disc pallor, and blood vessel attenuation. The retina showed diffuse atrophy, more extensive within the macula, pigment clumps with bone spicules, islands of peripheral and mid-peripheral chorioretinal atrophy, and peripheral lattice degeneration (**Figure 1**). Optical coherence tomography (OCT) demonstrated diffuse outer retinal atrophy, with loss of the ellipsoid zone and thinning of the outer nuclear layer. Central macular thickness measured 198 µm in the right eye and 192 µm in the left eye (**Figure 2**). Full-field electroretinography (ERG) was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Scotopic (rod) responses were severely reduced (barely detectable), and photopic (cone) and 30-Hz flicker responses were markedly reduced, consistent with a generalized rod–cone dystrophy.

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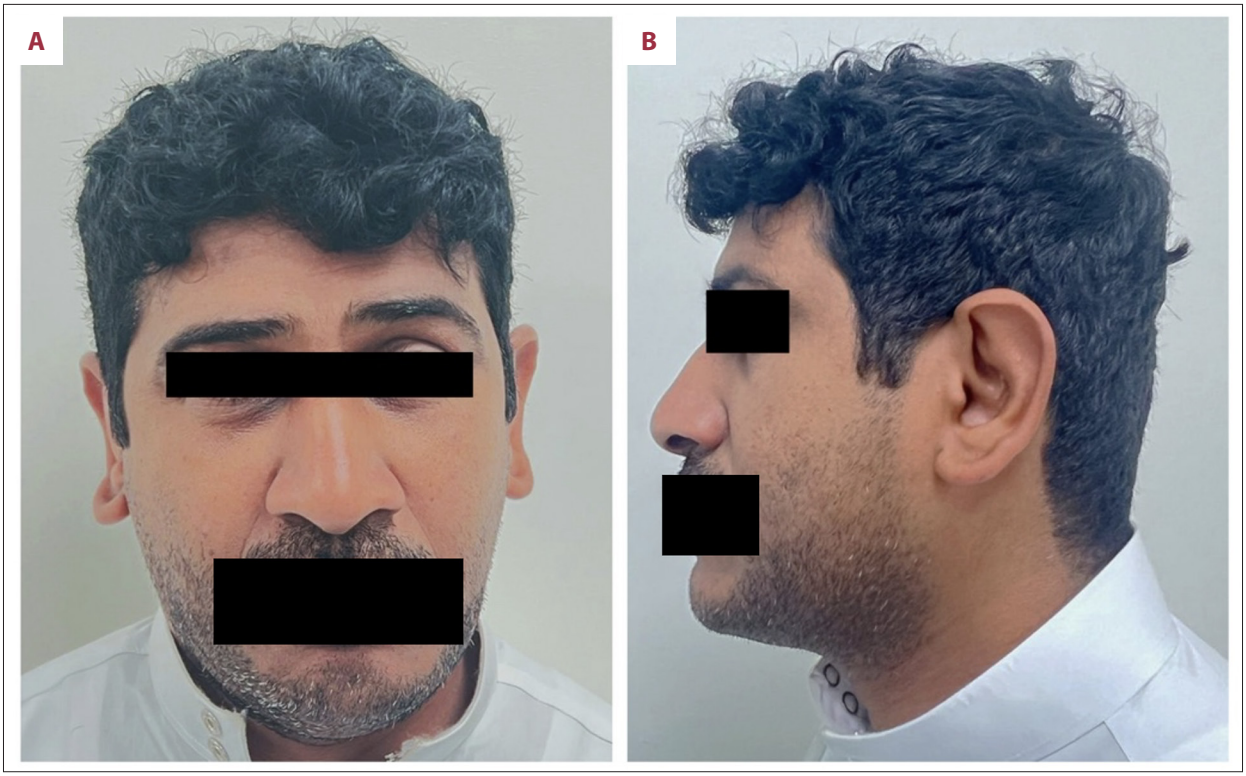

Figure 3. Photographs of the frontal and side views of the face and head. Both photos show microcephaly, large protruding ears, a wide nose, and a short mouth-to-nose distance. Photo **A** shows a wide nose, and Photo **B** shows a sloping forehead.

Table 1. Summary of abnormal anthropometric features and their measurements.

Measurement	Value
Ear height, width, and protrusion	6.4 (-1.33 SD), 3.5 (+0.75 SD), and 1.6 cm (-0.67 SD)
IPD	6.5 cm
Palpebral fissure	11 mm (+1.5 SD)
Mouth-to-nose distance	2.6 cm (-1.5 SD)
Nose height and width	5.5 cm (0.0 SD), and 5.4 cm (+3.8 SD)
Upper lip thickness	0.5 cm (-2.5 SD)
Mouth-to-chin distance	3.7 cm (-2.17 SD)
Eyebrow height, length, and thickness	1.1 cm (-2.33 SD), 3.6 cm (-2.33 SD), and 0.6 cm (-2.0 SD)
Mouth width	6 cm (+2 SD)

Note: IPD, interpupillary distance; SD, standard deviation.

Physical examination showed normal weight and height (69 kg and 167 cm) and an occipital-frontal circumference (OFC) of 48 cm (-3.2 SD). Additional findings included no limb edema or atrophy, no overlapping toes, and no pointed chin or café-au-lait spots. He had a high-arched palate, an upslanting palpebral fissure, a broad nose, a thin upper lip with a long philtrum, and a sloping forehead (**Figure 3**). Most of his facial anthropometric features were abnormal (**Table 1**).

Blood investigations were performed, including a complete blood count (CBC), chemistry tests, liver function tests, and renal function tests, all of which were within normal ranges. Molecular genetic testing was performed at a clinical reference laboratory using a targeted next-generation sequencing (NGS) panel for inherited vision disorders, together with NGS-based copy-number variant (CNV) analysis. Analysis identified a heterozygous frameshift variant in the KIF11 gene, NM_004523.4: c.535del;

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p.(Ser179Leufs*16), predicted to create a reading-frame shift starting at codon 179 in exon 5 (of 22) and to lead to premature truncation. The variant was absent from population databases, including gnomAD, ESP (Exome Sequencing Project), and the 1000 Genomes Project. In silico pathogenicity predictions were not applicable because of the frameshift nature of the variant. The variant was classified as likely pathogenic according to ACMG/AMP/ClinGen SVI guidelines, and the interpretation was reported as consistent with a genetic diagnosis of autosomal dominant microcephaly with or without chorioretinopathy, lymphedema, or impaired intellectual development (MCLMR; OMIM #152950). No other clinically relevant variants were detected. Parental targeted testing was recommended to establish whether the variant arose de novo or was inherited; however, parental testing was not performed, and the inheritance status of the variant thus could not be determined. Genetic counseling was offered to the patient and family. To the best of our knowledge, this variant has not been previously reported.

Discussion

Our patient presented with chorioretinal features previously described in MCLMR syndrome, caused by mutations in the KIF11 gene [1]. Given the combination of diffuse chorioretinal atrophy, bone-spicule pigmentation, and severely reduced ERG responses, the phenotype initially raised suspicion for classic retinitis pigmentosa; however, the associated microcephaly and the identification of a likely pathogenic KIF11 variant place this case within the spectrum of KIF11-associated chorioretinopathy, best described as an "RP-like" retinal dystrophy rather than classic RP [3]. In addition to typical findings, several other retinal features have been described in KIF11-associated retinopathy, including retinal folds, persistent hyaloid artery, and retinal detachment. KIF11 mutations have been reported in a subset of patients with familial exudative vitreoretinopathy (FEVR), although the precise proportion varies between cohorts [3].

Other ocular phenotypic features include myopia, hyperopia, astigmatism, angle-closure glaucoma, cataract formation, disc pallor, nystagmus, and microphthalmia [3].

Genetic testing in our patient revealed a novel variant of the KIF11 gene. In Saudi Arabia, there was only 1 other report of this gene mutation, in which Alahmadi et al reported a case of a 10-year-old girl with a history of microcephaly, lymphedema, chorioretinal dysplasia, and intellectual disability. Her retinopathy was in the form of outer retinal atrophy, attenuated blood vessels, and lacunar chorioretinal atrophy in both eyes. The authors reported a new variant mutation linked to their case: a heterozygous frameshift mutation with a different amino acid change (p.Val620Thrfs*6) [4].

Although MCLMR syndrome is extremely rare and is most commonly an AD condition, an autosomal recessive (AR) case has been reported by Rosa et al, who described the case of a 7-year-old boy who was initially diagnosed with congenital toxoplasmosis. After further examination and workup, the diagnosis was revised to AR MCLMR syndrome [5].

Malvezzi et al studies 15 families affected by MCLMR, identifying several point mutations of the KIF11 gene. Although multiple mutations have been identified in the KIF11 gene, they were all linked to MCLMR syndrome [6].

From a genotype–phenotype perspective, frameshift variants such as in our patient are predicted to cause loss of function through nonsense-mediated decay or truncation of the motor domain, which is consistent with haploinsufficiency as the proposed disease mechanism for autosomal dominant MCLMR. Reduced penetrance and variable expressivity are well recognized in KIF11-related disease and likely explain why some carriers, including apparently unaffected parents, have negative or unremarkable family histories despite transmitting the condition [1,6]. In our patient, the parents were consanguineous but clinically healthy, and targeted parental testing was not performed; the inheritance status of the variant (de novo vs inherited from an asymptomatic carrier parent) thus could not be established. This is acknowledged as a limitation of the present report, and targeted parental and at-risk family testing was recommended to the family for definitive genetic counseling.

Most of the reported cases of MCLMR syndrome shared the typical posterior segment findings of peripheral retinal changes, RPE clumping, and chorioretinal atrophy with blood vessel attenuation. Microcephaly was found in most of the reported cases, which is also consistent with our report. However, lymphedema, prominent ears, broad nose, upslanting palpebral fissure, and other facial features have been inconsistently reported [6].

Conclusions

KIF11 mutations are very rare; the clinical presentation may vary among patients due to reduced penetrance. In this report, we describe a case of MCLMR syndrome with microcephaly, chorioretinopathy, and intellectual disability, without lymphedema. Genetic testing revealed a novel variant in the KIF11 gene. Identifying the clinical features of this rare mutation may help better understand this disease, improve management of the clinical course, and guide genetic counseling of other family members.

Department and Institution Where Work Was Done

King Fahad Hospital of the University, Alkhobar, Saudi Arabia.

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Consent for Publication

Written informed consent was obtained from the patient, who agreed to publish this report, including the unrecognizable facial photography, after covering the eyes and the mouth.

Ethics approval

Ethics approval was obtained from Imam Abdulrahman Bin Faisal University (IRB: 2024-01-542).

AI Disclosure

During the preparation of this work, the corresponding author utilized ChatGPT, DeepL, and Grammarly to enhance writing style, ensure text consistency, and check for grammar and spelling errors. After using these tools and services, the authors reviewed and edited the content as necessary, and they take full responsibility for the publication's content.

Abbreviations

KIF11, kinesin family member 11; **MCLMR**, microcephaly with or without chorioretinopathy, lymphedema, or intellectual disability; **AD**, autosomal dominant; **KSA** – Kingdom of Saudi Arabia; **IRB**; institutional review board; **RP**, retinitis pigmentosa; **G6PD**, glucose-6-phosphate dehydrogenase; **OCT**, optical coherence tomography; **ERG**, electroretinogram; **OFC**, occipital-frontal circumference; **CBC**, complete blood count; **FEVR**, familial exudative vitreoretinopathy; **AR**, autosomal recessive; **ISCEV**, International Society for Clinical Electrophysiology of Vision; **NGS**, next-generation sequencing; **CNV**, copy-number variant; **ACMG/AMP**, American College of Medical Genetics and Genomics/Association for Molecular Pathology.

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