Case Report

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Pathogenic Variants in *TUBGCP6* of Familial Microcephaly and Chorioretinopathy

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Abstract:

Microcephaly and chorioretinopathy type 1 (MCCRP1) is an autosomal recessive syndrome characterized by severe microcephaly, facial dysmorphisms, chorioretinopathy, and developmental delays. This rare condition is caused by homozygous or compound heterozygous pathogenic variants in the Tubulin Gamma Complex Component 6 (*TUBGCP6*) gene. We present 2 siblings from a non-consanguineous family in Indonesia diagnosed with MCCRP1. Both had a history of intrauterine growth retardation (IUGR) and were born with microcephaly and low birth weight. They exhibited developmental delays and hyperactive behavior. Facial dysmorphisms included upslanting palpebral fissures, strabismus, long philtrum, and a low anterior hairline. Ophthalmologic examination revealed chorioretinopathy in both siblings, while

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cardiac and hearing evaluations were normal. Microarray analysis revealed no likely pathogenic copy number variants (CNVs). Whole exome sequencing (WES) was performed on DNA from the siblings and their parents. The variant analysis identified a paternal pathogenic splice variant c.2066-6A>G and a maternal pathogenic nonsense variant c.3393G>A in the *TUBGCP6* gene (NM_020461.4) in both siblings, indicating a compound heterozygous variant. This is the first case report of familial MCCRP1 in Indonesia, presenting both clinical features and genetic analysis of the *TUBGCP6* gene.

Keywords: autosomal recessive, chorioretinopathy, MCCRP1, microcephaly, *TUBGCP6* gene

Introduction

Microcephaly is a condition characterized by a head circumference that is significantly smaller than average, either present at birth (primary or congenital microcephaly) or developing later in life (postnatal or acquired microcephaly). It is defined as having a head circumference more than 2 standard deviations below the mean for a person's gender and age, affecting approximately 2% of the human population[1]. The prevalence is 1.53 cases per 10,000 births in Europe[2] and 14.5% in neonates in Thailand[3]. Genetic factors contribute to 50% of microcephaly cases, followed by perinatal injury at 45%, and postnatal injury at 3%[4]. Research studies have demonstrated that genetic testing and chromosomal microarray analysis can ascertain an underlying genetic cause of microcephaly in approximately 15.3% to 52% of cases[4].

Autosomal recessive microcephaly and chorioretinopathy type 1 (MCCRP1; OMIM #251270) is a rare syndrome caused by homozygous or compound heterozygous pathogenic variants in the Tubulin Gamma Complex Component 6 (*TUBGCP6*) gene in band q13.33 of chromosome 22. This syndrome is characterized by severe microcephaly, psychomotor developmental delay, ophthalmologic abnormality, dysmorphic features, and often includes short stature[5,6].

Here, we present a case study involving 2 siblings with pathogenic variants in the *TUBGCP6* gene. This report encompasses a comprehensive analysis of the genetic and clinical findings, as well as a detailed account of the genetic counseling provided to the family.

Case report

We present 2 siblings from an Indonesian family referred by the Indonesian Rare Disorders Community for free chromosomal microarray (CMA) testing, offered by the Prodia Laboratory. The siblings, an 11-year-old female and a 7-year-old male, both exhibited microcephaly. The family reported no consanguinity or other instances of microcephaly. Pedigree over 3 generations shows no history of similar complaints, indicating that the inheritance pattern is likely autosomal recessive. Informed consent was obtained for clinical data, genetic testing, and documentation.

The prenatal history of the daughter revealed intrauterine growth restriction (IUGR). She was delivered at 37 weeks via cesarean section with a birth weight of 1.5 kilograms (kg) (<1st percentile) and a head circumference of 25 centimeters (cm) (<1st percentile). Developmental delays included walking at 18 months, first words at 2 years, and writing difficulties by 5 years. She is hyperactive, with visual issues, and attends a specialized school. She began menstruating at 10 years old. The daughter presented with a head circumference of 43.5 cm (<-2 standard deviation (S.D.)), indicating microcephaly, height 140 cm (>10th percentile), and weight 31.4 kg (10th percentile). Dysmorphic features include short philtrum, upslanting palpebral fissures, prominent ears, strabismus, low anterior hairline, and

clitoromegaly, though 17–hydroxyprogesterone levels were normal (Figure 1A). Currently, she attends a religious school because she has learning difficulties and cannot attend an ordinary kindergarten. She exhibits hyperactive behavior comparable to that of a 3–year–old child. She has been menstruating since the age of 10.

The son also had IUGR, delivered at 37 weeks with a birth weight of 2.2 kg (1st percentile) and a head circumference of 30 cm (<1st percentile). Developmental delays included walking at 18 months and single words at 6 years. He is non–verbal, hyperactive, and struggles to communicate. He also presented with microcephaly, with a head circumference of 40 cm (<–2 S.D.). In addition, he had a height of 110 cm (>1st percentile) and a weight of 17.5 kg (>1st percentile). Dysmorphic features include upslanting palpebral fissures, a short philtrum, and a low anterior hairline (Figure 1B). Additional anomalies in the lower extremities include clinodactyly and a sandal gap. Genital examination revealed normal phallus length and the external urethral meatus at the tip of the phallus. Gonadal examination using an orchidometer found both gonads palpable, with the right gonad sized at 1–2 milliliters (mL) and the left gonad less than 1 (mL), suspected to be dysgenesis.

He was able to lift his head independently at 6 months, began crawling at 13 months, and took his first steps at 18 months. He demonstrated scribbling on paper at 3 years of age and was able to stack blocks at 5. The boy first articulated "mama" or "dada" at 4 years and was able to say a single word at 6 years. Currently, he is unable to count numbers or write. To express his needs, he points to desired objects. While walking, he sometimes bumps into

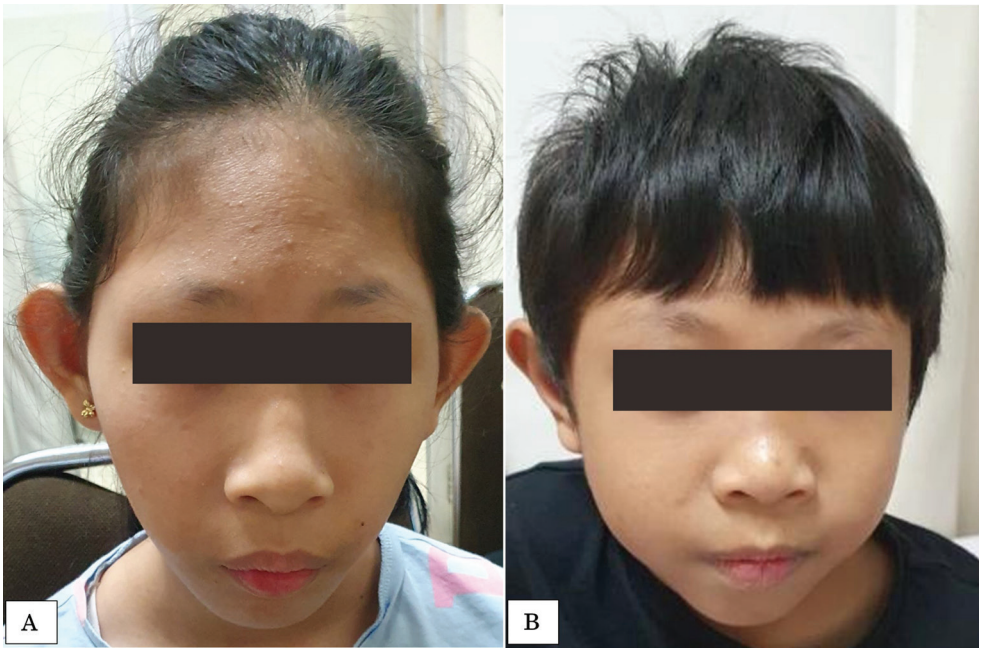

Figure 1 Dysmorphology of both daughter and son. (A) Facial dysmorphisms show upslanting palpebrae, a short philtrum, strabismus, prominent ears, and a low anterior hairline. (B) Facial dysmorphisms show upslanting palpebrae, a short philtrum, strabismus and a low anterior hairline.

objects around him, just like his sibling. His interactions with peers are limited, likely due to his restricted communication abilities.

Ophthalmological evaluations of both siblings revealed retinal abnormalities, esotropia, and central retina thinning. The daughter's visual acuity was 0.1S–3.00D 0.25 no better correction (nbc) in the right eye and 0.3 no change (nc) in the left. Ocular alignment tests showed 30° esotropia. Fundoscopy revealed papillary atrophy and thinning of the papillomacular bundle (Figure 2A). Optical coherence tomography (OCT) showed central retinal thickness (CRT) <100 micrometers (μm), hyperreflective spots temporal to the fovea, and thinning of the inner and outer nuclear layers (Figure 2B and C). These findings indicate hereditary retinal dystrophy with intermittent esotropia.

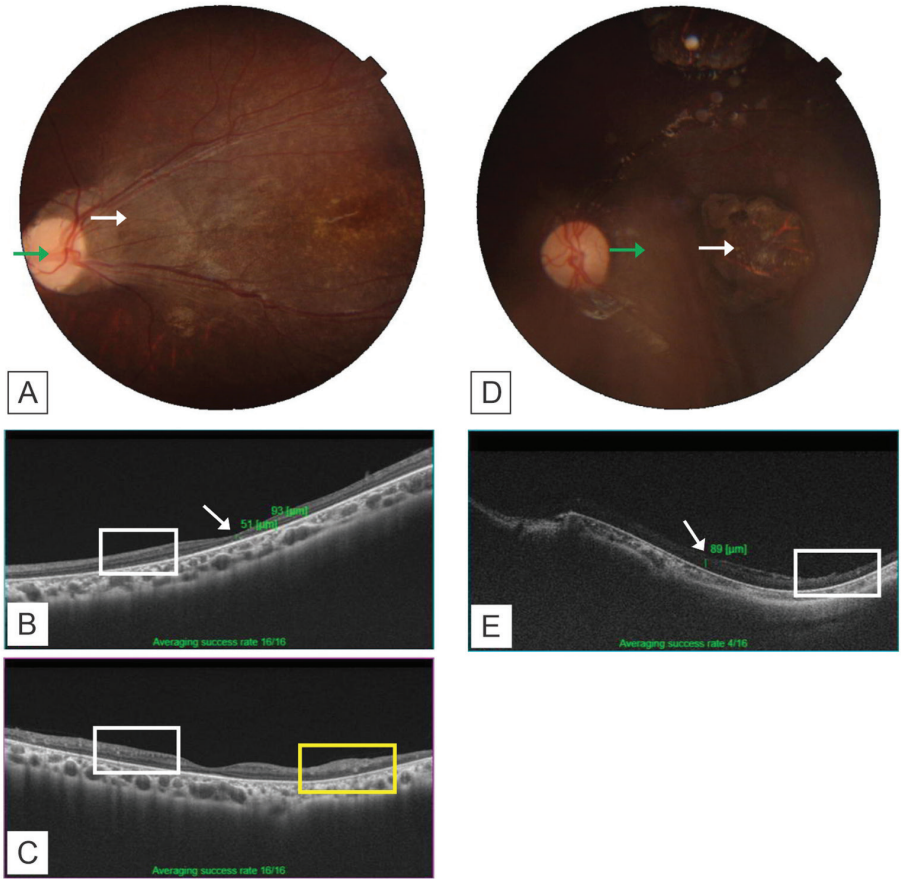

Figure 2 (A) The daughter's ophthalmology examination revealed papillary atrophy (green arrow) and papillomacular thinning (white arrow). (B and C) optical coherence tomography (OCT) revealed central retinal thickness (CRT) <100 μm (white arrow) with hyperreflective spots temporal to the fovea (white box) and thinning of the inner and outer nuclear layers (yellow box). (D) The son's ophthalmology examination revealed papillomacular bundle thinning (green arrow) and geographic retinal pigment epithelium (RPE) layer loss (white arrow). (E) OCT revealed CRT <100 μm (white arrow) and thinning of the inner and outer nuclear layers (white box).

The boy's visual acuity was ½ / 60, with normal ocular alignment (Hirschberg test 0°). Fundoscopy revealed thinning in the papillomacular bundle, macular atrophy, and geographic retinal pigment epithelium (RPE) loss near the temporal fovea and superior equator (Figure 2D). OCT showed CRT <100 µm, hyperreflective spots in the outer retina temporal to the fovea, and thinning of the inner and outer nuclear layers (Figure 2E). Despite unmeasurable vision due to non-cooperation, he could play with a mobile phone and watch television. Findings indicate hereditary retinal dystrophy.

Cardiac and hearing examinations yielded normal results for both siblings. CMA analysis found no pathogenic copy number variants. Further WES analysis in both siblings identified a paternally inherited, heterozygous, pathogenic variant in the *TUBGCP6* gene (Chr22(GRCh37):g.50662855T>C NM_020461.4:c.2066-6A>G r.spl?)[7] as well as a maternally inherited heterozygous, pathogenic nonsense variant in the same gene (Chr22 (GRCh37):g.50659395C>T NM_020461.4:c.3393G>A p.(Trp1131*), indicating a bi-allelic gene defect (compound heterozygous). However, the variant inherited from the mother was not found in the American College of Medical Genetics and Genomics (ACMG). Pathogenic variants (stop loss, missense, truncating, and splice variants) in the *TUBGCP6* gene have been described as causative for recessive 'microcephaly and chorioretinopathy type 1' (MCCRP1, OMIM #251270)[5]. Post-test counseling informed the parents of a 25% recurrence risk and discussed options for future pregnancies, including preimplantation genetic testing.

Discussion

Pathogenic variations in *TUBGCP6* can lead to disruptions that cause an autosomal recessive neurodevelopmental disease characterized by a deficiency in neural migration. It can appear as primary microcephaly, either with or without structural brain abnormalities. These disruptions are associated with poor centriole biogenesis, which is crucial for cell division and brain growth, emphasizing the gene's important role in neurodevelopment[8]. The *TUBGCP6* [OMIM *610053] gene encodes gamma-tubulin complex protein 6 (GCP6), which is part of the eukaryotic y tubulin complex[9]. GCP6, along with GCP4 and GCP5, is known to play important roles in the assembly of the γ-tubulin ring complex (y-TuRC) and the regulation of its activity[9]. A multiprotein y-TuRC at the microtubule organizing center (MTOC) is essential for initiating microtubule formation throughout the process of cell division[9]. *TUBGCP6* is highly expressed in brain tissues, specifically in astrocytes and excitatory neurons[10]. It is widely known that astrocyte differentiation corresponds with brain size. *TUBGCP6* is also present in the cerebellum, cerebral cortex, olfactory area, hippocampal formation, amygdala, basal ganglia, thalamus, hypothalamus, midbrain, and pons and medulla[10]. The extensive presence of the *TUBGCP6* gene in various parts of the brain indicates the importance of its protein in the normal development and functioning of the brain.

Whole Exome Sequencing (WES) with subsequent analysis of the gene panel for Intellectual Disability (version DG-3.8) in these siblings has identified compound heterozygous pathogenic variants in the *TUBGCP6* gene, which provides an explanation for their disorder. The discovery of a splice variant and a nonsense variant in both siblings highlights the importance of genetic variants in the development of microcephaly and related physical characteristics. The splice variant domain of c.2066-6A>G is located between the Grip1 domain and the tandem repeat region. A splicing mutation in the father may cause exon skipping where the specific exon may be excluded from the final mRNA transcript. This mutation can lead to incorrect removal of an exon, truncated protein, and lost protein activity[11]. This variant has been previously reported

in a pair of siblings, where RNA studies demonstrated that it leads to the crea-tion of cryptic splice sites, resulting in out-of-frame transcripts. This alteration is expected to produce a truncated protein[12].

The c.2066-6A>G variant is classified as likely pathogenic and known to be associated with microcephaly and chorioretinopathy, typically without cerebral MRI abnormalities. The c.2066-6A>G variant has been identified in both maternal as well as paternal carriers[12,13]. Moreover, based on information in the Genome Aggregation Database (gnomAD; v4.1.0), the allele frequency of the c.2066-6A>G variant is 0.00008909 (4 out of 44,900 alleles) in the East Asian population, which is slightly higher than the total allele frequency of 0.00006567. There are no homozygotes for this variant in gnomAD. The nonsense variant c.3393G>A [p.(Trp1131*)] is not present in gnomAD (v4.1.0). A nonsense variant c.3392G>A causing the same premature stop as in this patient [(p.Trp1131*)] was described previously by Hanany et al.[14] in a patient with Syndromic Chorioretinopathy.

In 1966, McKusick was the first to report cases with the combination of microcephaly and retinal abnormalities, involving 8 affected individuals from 2 families[5]. Later, Puffenberger et al. (2012) identified a homozygous stop-loss variant in the *TUBGCP6* in one of these families[15]. To date, the total number of published cases is 16, as shown in Supplementary Table 1.

Ophthalmological findings in these siblings are similar to the previously reported cases. Retinal abnormalities were consistently present in nearly every case[5]. These retinal issues are attributed to the absence of secondary capillary layers in the deep and peripheral retina, resulting in angiogenesis problems. This avascularity subsequently leads to the clinical manifestations of the disease. The association of microcephaly with visual impairments, especially retinal abnormalities, along with developmental delays, points to genetic factors that may play a role[15]. These patients were not diagnosed genetically until they joined the Indonesian Rare Disorders screening program. To the best of our knowledge, these are the first cases in Indonesia and the 17th case worldwide.

These findings not only highlight the significance of the *TUBGCP6* gene in neurodevelopment but also underscore the necessity of genetic counselling for families with a rare ge-netic disease. In this study, the diagnosis was made possible through Whole Exome Sequencing (WES), which played a critical role in identifying the pathogenic variant, establishing the pattern of inheritance, and providing accurate genetic counseling. This study provides insight-ful data on *TUBGCP6*-associated disorders in Indonesia, which are also rare globally. It contributes to the limited knowledge on these rare conditions and emphasizes the importance of ongoing research and targeted therapeutic strategies, especially for familial microcephaly.

Conclusion

These cases underscore the critical role of *TUBGCP6* in neurodevelopment and the importance of genetic counselling for rare disorders. The findings highlight the necessity of early diagnosis, family education, and targeted therapeutic interventions for patients with rare genetic diseases. This report contributes to the global understanding of MCCRP1 and expands the knowledge of its phenotypic spectrum in Indonesia.

Supplementary materials

The supporting information can be downloaded at https://doi.org/10.6084/m9.figshare.29277734.v1

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Supplementary Table 1 Clinical findings and genetic characteristics of published *TUBGCP6*–associated cases

Case number	Reported by	Variant	Type of variant	Identity	Clinical findings	Ocular finding
1	This study	c.2066–6A>G r.spl?; c.3393G>A p.(Trp1131*)	Splice site; nonsense	Female, 11–year–old	Microcephaly and developmental delay. Facial dysmorphism, clitoromegaly	Strabismus, chorioretinopahty
				Male, 7–year–old	Microcephaly and developmental delay. Facial dysmorhpism, clinodactyly, sandal gap	Strabismus, chorioretinopahty
2	McKusick et al. (1966)	N/A	N/A	Two families, eight individuals	Microcephaly, short stature, developmental delay, and seizure. Exaggerated deep tendon reflex	Nystagmus, strabismus, chorioretinopathy
3	Cantu et al. (1977)			One family, three individuals	Microcephaly, short stature, developmental delay, and seizure. Cutis marmorata	Nystagmus, chorioretinopathy
4	Abdel–Salam et al. (2000)			Male, 12–year–old and female 9–year–old	Microcephaly, short stature, developmental delay, and seizure. Facial dysmorphism, skeletal abnormalities, bilateral UDT (male)	Nystagmus, chorioretinopathy
5	Xie et al. (2022)			One family, one individual	Developmental delay and seizure	N/A
6	Puffenberger et al. (2012)	c.[5458T>C]; p.[Ter1820Gly]	Substitution; stop loss	Two families	Microcephaly, short stature, developmental delay, and seizure. Facial dysmorphism	Chorioretinopathy
7	Martin et al. (2014)	c.[4333insT]; p.[His1445LeufsTer*24]	Indel; Frameshift insertion	3–year–old	Microcephaly, short stature, and developmental delay. Lower limb spasticity, achilles contractures	Nystagmus, chorioretinopathy
		c.[2215C>T]; [2546A>G]; p.[Arg739Ter]; p.[Glu849Gly]	Substitution SNV; nonsense and missense	3–year–old	Microcephaly, short stature, and developmental delay. Triphalangeal thumbs. Small ASD and VSD	Chorioretinopathy
		c.[3565G>T]; [3163C>T]; p.[Gly1189Ter]; p.[His1055Tyr]	Substitution SNV; nonsense and missense	16–year–old	Microcephaly, short stature, and developmental delay. Mild kyphosis and lordosis. Multiple pigmented nevi. Increased tone, decreased, strength. Behavior– Aggressive and self–injurious behaviors	Nystagmus, chorioretinopathy
				9–year–old	Microcephaly, short stature, and developmental delay. Facial dysmorphism – cutis marmorata. Mild lumbar lordosis	Glaucoma, nystagmus, chorioretinopathy
8	Hull et al. (2019)	c.[2066–6A>G]; [4485–21A>C]; r.[2065_2066ins2066–1_2066–5]	Substitution SNV; intronic and intronic	Male, 17–year–old and female, 14–year–old (siblings)	Microcephaly, developmental delay, and seizure	Chorioretinopathy

Supplementary Table 1 (continued)

Case number	Reported by	Variant	Type of variant	Identity	Clinical findings	Ocular finding
9	Shurygina et al. (2019)	c.C3163T: p.H1055Y; c.G3565T: p.G1189X	Substitution; SNV; nonsense and missense	Male, 17–year–old	Microcephaly, short stature, and developmental delay. Facial dysmorphism. fifth finger clinodactyly. Constipation. Behavioral – Aggressive and self–injurious behaviors	Nystagmus, cataract chorioretinopathy
				Female, 24–year–old	Microcephaly, short stature, and developmental delay. Facial dysmorphism, secondary amenorrhea, urinary incontinence, constipation, mild kyphosisand lordosis, multiple pigmented nevi, increased muscletone	Nystagmus, chorioretinopathy
10	Kolbjer et al. (2021)	c.[1050C>A]; [589T>C]; p.[Cys350*]; [Ser197Pro]	Substitution; SNV; nonsense and missense	Male, 5–year–old	Microcephaly, short stature, developmental delay, and seizure	Nystagmus, strabismus chorioretinopathy
11	Chen et al. (2022)	p.Tyr613Ter; p.Glu1368Lys	Substitution SNV; nonsense and missense	4–year–old	Microcephaly, short stature, and developmental delay.	N/A
12	Wang et al. (2023)	c.[2066–6A>G]; c.[4485–31_4485–22delGCCCGCCCTG]	Substitution SNV; intronic indel Intronic and intronic	One family, one individual	Developmental delay. Vesicoureteral reflux	Retinal detachment
13	Sengillo et al. (2023)	c.2215C>T (p.Arg739Ter); c.4108+1G>A	Nonsense; splice site	Male, 4–month–old	Microcephaly and developmental delay	Nystagmus, chorioretinopathy
14	Wilson et al. (2023)	c.[4626+1C>T] [2155C>T]; p.[?] [Arg719Ter]	Substitution SNV; splicing and nonsense	Female, 2–year–old	Microcephaly, short stature, and developmental delay. Facial dysmorphism, single transverse palmar crease, bilateral clinodactyly. Small PFO and LVH	Glaucoma. chorioretinopathy
		c.[1587del] [2066–6A>G]; p.[Cys529fsTer25] [?]	Indel and substitution SNV; frameshift and intronic	Female, 3–year–and–8–month–old	Microcephaly and developmental delay. Facial dysmorphism, absent right thumb, hypoplastic left thumb, bilateral sandal gap. VSD, PDA, PFO	Nystagmus, strabismus, chorioretinopathy
		c.[1833+1G>A]; [4003_4017dup15]; p.[?]; [Gly1335_1339dup]	Substitution SNV+ indel; splicing and frameshift	Male, 4.5–year–old	Microcephaly and developmental delay	Cataract, chorioretinopathy
		c.[1690C>T] [2066–6A>G]; p.[Arg564Ter] [Asp689ValfsTer2]	Substitution SNV; nonsense and intronic	Fetus	Microcephaly. Facial dysmorphism, cerebellar hypoplasia, sloping forehead, fixed limb flexion	Not applicable

Supplementary Table 1 (continued)

Case number	Reported by	Variant	Type of variant	Identity	Clinical findings	Ocular finding
15	Pal et al. (2024)	c.[5275_5285del] 405 bp deletion p.[Pro1759Alafs*68] [?]	Indel + SV; frameshift deletion and SV	Female, 6-year-old and sibling fetus	Microcephaly, short stature, and developmental delay. Facial dysmorphism.	Chorioretinopathy

ASD=atrial septal defect, CRT=central retinal thickness, CSF=cerebrospinal fluid, ERG=electroretinography, IUGR=intrauterine growth restriction, LVH=left ventricular hypertrophy, OCT=optical coherence tomography, PDA=patent ductus arteriosus, PFO=patent foramen ovale, RPE=retinal pigment epithelium, SNV=single nucleotide variant, SV=structural variant, UDT=undescended testes, VSD=ventricular septal defect.

Two additional cases (Schmidt, 1967; Koch, 1968) were identified but not included due to unavailable full texts.