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Ocular characteristics of a 6-year-Old boy with molybdenum cofactor deficiency type B

Wenjia Yan [1], Li Huang [1], Limei Sun, Xiaoyan Ding [*]

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, 510000, China

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ABSTRACT

Purpose: To report a rare case of Molybdenum Cofactor Deficiency with novel ocular manifestations.
Observations: This is a case study of a 6-year-old boy who initially presented with conjunctival hyperemia and ocular pain of the left eye. Medical history revealed refractory convulsion, global developmental delay, microcephaly, feeding difficulties, aphasia, and spastic quadriplegia, as well as pathogenic *MOCS2* mutations, indicating the diagnosis of molybdenum cofactor deficiency (MoCD). This case report highlights detailed ocular manifestations of late-onset MoCD-B, ectopia lentis of bilateral eyes, spherophakia, hyperemia, secondary glaucoma, cyclodialysis, and retinal detachment of the left eye, which will help further understanding of MoCD.
Conclusions and importance: MoCD as a rare genetic disease is tend to be easily neglected. The ophthalmic examination could provide important evidence for early diagnosis.

1. Introduction

Molybdenum cofactor deficiency (MoCD) is a rare autosomal recessively inherited disease characterized by neurological deterioration, intractable seizures, facial dysmorphism, microcephaly, and feeding difficulties.[1] Due to the disfunction of molybdenum cofactor-dependent enzymes (including sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase), toxic metabolites accumulate and cause neurodegeneration, subsequently leading to severe disability and early death. Laboratory abnormalities of MoCD include low serum and urinary uric acid levels, a positive urinary sulfite test, and elevated urinary xanthine, hypoxanthine, and *S*-sulfonylcysteine levels.[1]

Four genes, *MOCS1*, *MOCS2*, *MOCS3*, and *GPHN*, play a role in molybdenum cofactor biosynthesis.[2] *MOCS1* gives rise to an intermediate metabolite of the synthesis chain of the molybdenum cofactor, cyclic pyranopterin monophosphate (cPMP). Mutations in *MOCS1* are responsible for more than 50% of the reported cases and lead to MoCD-A.[3,4] Mutations in *MOCS2* and *MOCS3*, which participate in the formation of molybdopterin,[4] cause MoCD-B. Mutations in *GPHN* intervene in the last step of the formation of the molybdenum cofactor and induce MoCD-C, with only two cases reported so far.[5,6] The relationship of these four genes has been well illustrated by Jochen Reiss.[2] The *MOCS2* gene is located in the long arm of chromosome 5 and consists of seven exons. It encodes the large and small subunits of heterodimeric molybdopterin (MPT) synthase, which converts the precursor to molybdopterin.[2] To the best of our knowledge, the ocular features due to *MOCS2* mutations has not be well documented. Therefore, the aim of this report is to explore the ocular manifestations of *MOCS2*-associated MoCD.

2. Case report

A 6-year-old Chinese Han boy was referred to our hospital with the symptoms of conjunctival hyperemia and ocular pain of the left eye for 10 days. He was born from the first pregnancy by vaginal delivery at the gestational age of 40 weeks with a birth weight of 3600 g. Perinatal conditions, as well as newborn metabolic screening, were unremarkable. The history of trauma was denied. The family history of consanguineous marriage, miscarriages, metabolic disorders, and neurological diseases was negative. He had distinctive facial dysmorphic features, a long philtrum, a broad nasal bridge, prominent cheek, and retrognathia (Fig. 1). At the age of 4 months, the boy debuted with refractory

Abbreviations: MoCD, molybdenum cofactor deficiency; cPMP, cyclic pyranopterin monophosphate; MRI, magnetic resonance imaging; MPT, molybdopterin; UBM, ultrasound biomicroscopy; ERG, electroretinogram; FFA, fundus fluorescein angiography.

* Corresponding author. Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, 510000, China.
E-mail address: dingxiaoyan@gzzoc.com (X. Ding).

[1] These authors contributed equally to this work as co-first authors.

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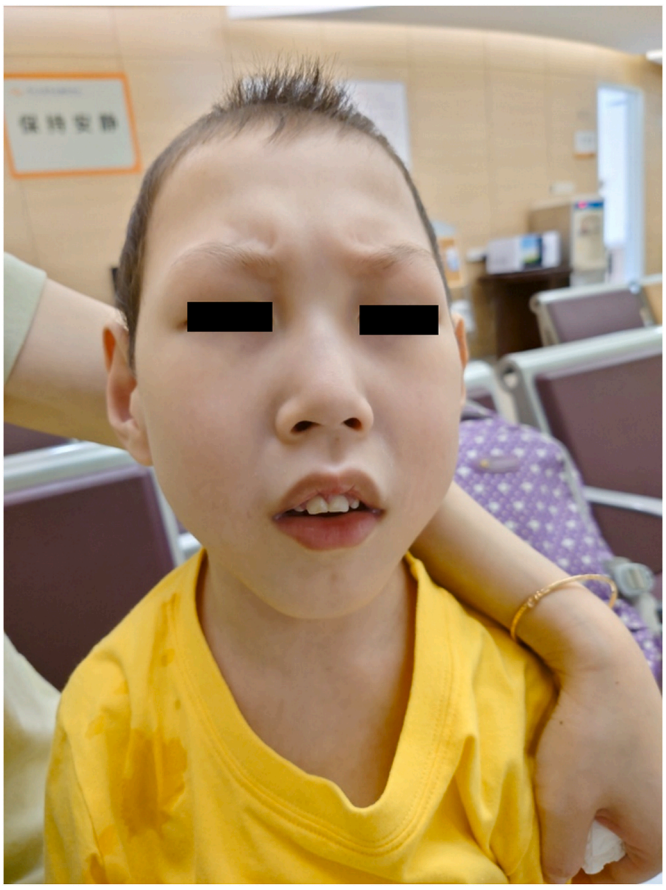

Fig. 1. Facial features of the patient showing a long philtrum, a broad nasal bridge, prominent cheek, and retrognathia. Permission for the use of the picture from his mother has been granted.

convulsions. Symmetric subcortical cystic leukomalacia and an enlarged cisterna magna were revealed by brain magnetic resonance imaging (MRI). Bilateral spontaneous subluxation of the lens was also detected at the age of 4 months. During the subsequent growth and development, the child showed global developmental delay, microcephaly (a head circumference of 39 cm at the age of 6 years), feeding difficulties (unable to chew and swallow), aphasia, and spastic quadriplegia (unable to sit and stand). Whole exome sequencing revealed a known homozygous mutation, c.16C>T(p.Q6*), in the *MOCS2* gene,[7] which was inherited from his parents (in heterozygous state). The typical clinical features and the pathogenic *MOCS2* mutation confirmed the diagnosis of MoCD-B.

Visual acuity was not available due to lack of cooperation. Intraocular pressure (IOP) was 15.7 mmHg for the right eye and 47.3 mmHg for the left eye, measured with a Goldmann applanation tonometer. Lens dislocation of the right eye was detected under handheld slit-lamp examination. Ocular examination of the left eye revealed moderate conjunctival hyperemia, corneal edema, and hyphema (Grade I: less than 33% anterior chamber filling) by slit-lamp examination, which was presented as a high-density mass in the anterior chamber in ultrasound biomicroscopy (UBM, Avsion Ultrasound Platform, Quantel Medical, Rue du Bois Joli Cournon d'Auvergne, France). UBM also revealed subluxation lens, spherophakia, and cyclodialysis of the left eye. Retinal detachment was shown in the B-scan ultrasonography of the left eye (Fig. 2). RetCam imaging (RetCam, Clarity Medical Systems Inc., Pleasanton, CA, USA) showed ectopia lentis of the right eye falling into the vitreous cavity; however, fundus fluorescein angiography is unremarkable (Fig. 3). Axial length was 23.52 mm in the right eye and was not measured in the left eye due to retinal detachment. Electroretinogram (ERG, LKC Technologies, Gaithersburg, MD, USA) was performed in the right eye and revealed generally unremarkable cone and rod responses, indicating that this disease does not affect the function of photoreceptors(Fig. 4). The significant reduced cone and rod responses in the left eye, could be secondary to retinal detachment. The patient was diagnosed with ectopia lentis in both eyes, spherophakia, hyperemia, secondary glaucoma, cyclodialysis, and secondary retinal detachment in the left eye.

A combination of 0.2% brimonidine tartrate eye drops (ALPHAGAN, Allergan Sales LLC, Irvine, CA), brinzolamid and timolol maleate eye drops (AZARGA, Alcon Laboratories Inc, Fort Worth, TX) twice daily for the left eye was used to control the IOP. On the third day following admission, the patient's IOP of left eye decreased to 17.5 mmHg, and the ocular pain relieved. Considering the possibility of eyeball atrophy, lensectomy or anterior chamber irrigation was not performed for the left eye. The dislocation of right lens was in a steady state and did not cause complications, thus we suggested his parent to follow-up regularly.

3. Discussion

MoCD is considered as an incurable and lethal disease that results in progressive neurological damage and early childhood death in most cases.[8] According to Konstantin Mechler et al., the median age at the onset of the disease was 1 day, and the median survival age was 36 months.[9] The natural history of ophthalmic development in MoCD is difficult to ascertain by reviewing most reported cases for at least two reasons. First, the lack of treatment for this disease resulted in a high mortality rate in the neonatal period, making it impossible to perform a serial ophthalmic examination. Second, few of these reports were coauthored by an ophthalmologist, and few patients were comprehensively examined by an ophthalmologist. Thus, no systemic ophthalmic review of this genetic disease has been documented.

To date, 39 MOCD-B patients with 33 different *MOCS2* gene variants have been reported,[4,5,7,8,10–26] including this one reported in our study. We reviewed the detail clinical and genetic data of each patient and verified the variants carefully. The data of 25 patients with confirmed pathogenic *MOCS2* mutations were summarized in Table 1.[2–20] Of the total 18 children with adequate clinical data, 15(83%) children had symptom onset immediately after birth and 3(17%) children had symptom onset 1 month after birth. Seizures were found in 16 (89%) patients, with their occurrence in 14(88%) patients in the neonatal period and in other 2(12%) patients 1 month later. All reported children had delayed motor milestones. Facial dysmorphism, including puffy cheeks, microcephaly, microphthalmia, broad nasal bridge, and long philtrum, was observed in 10 (56%) patients, and 10 (56%) patients experienced feeding difficulties.

Among 13 patients with available ocular signs and examinations, ocular symptoms were found in 3 (23%) patients. Of the 7 patients who were followed up for less than 1 year, only 1 was found to have bilateral ectopia lentis. Among 6 patients who were followed up for more than 1-year, positive ocular manifestations were noted in 3 (50%) patients, including bilateral ectopia lentis, spherophakia, hyperopia, and retinal detachment. These three patients with abnormal ocular manifestations were spared from ocular signs right after birth, indicating a progressive neurological pathology. In the case with hyperopia, the patient's developmental status was generally age-appropriate and no lens dislocation was found. The hyperopia in the mild case might be physiological.

We presented a MoCD-B case with a comprehensive ocular evaluation. Lens dislocation is a characteristic feature and is reported in about half of patients who survived the neonatal period. Subluxation of the binocular lens occurred on this patient at the age of 4 months. On examination, it was noted that the right eye had already progressed to lens luxation. The left eye with lens luxation, as well as spherophakia, was reported once[27] and resulted in hyphema and secondary glaucoma. From reviewing previous cases, ectopia lentis were the earliest detected

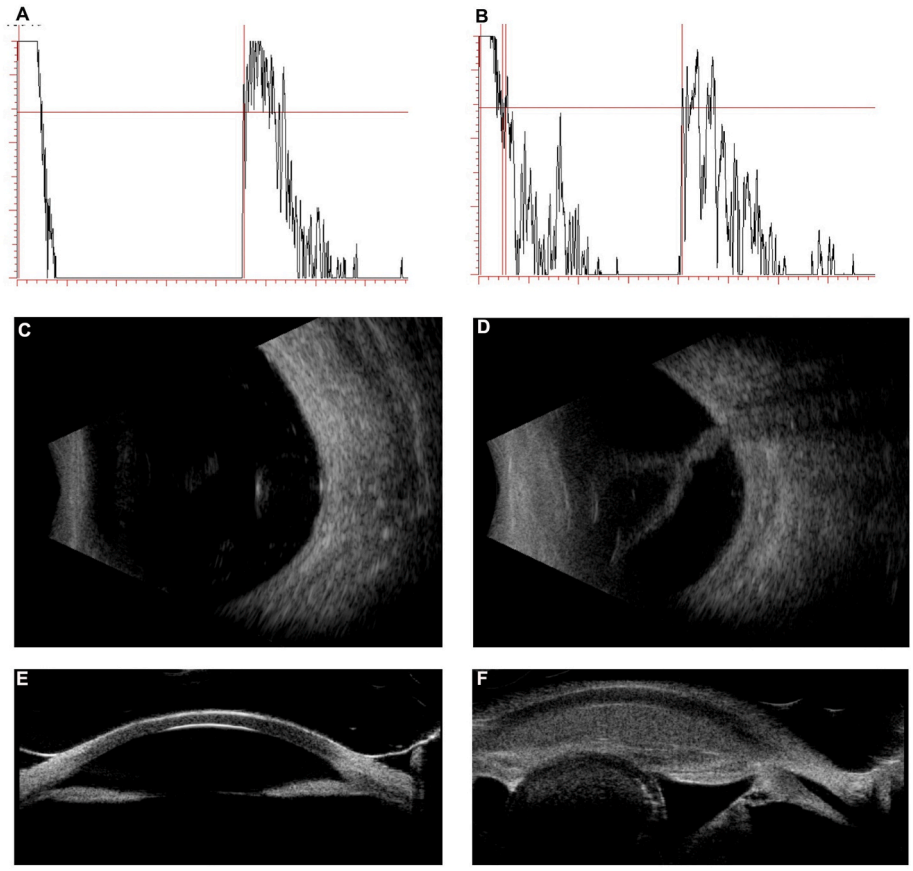

Fig. 2. The A scan, B scan, and ultrasound biomicroscopy (UBM) of the patient. (A) A scan, (C) B scan, and (E) UBM of the right eye revealed lens luxation into the vitreous. (B) A scan, (D) B scan, and (F) UBM of the left eye revealed lens subluxation, retinal detachment, cyclodialysis, and hyphemia.

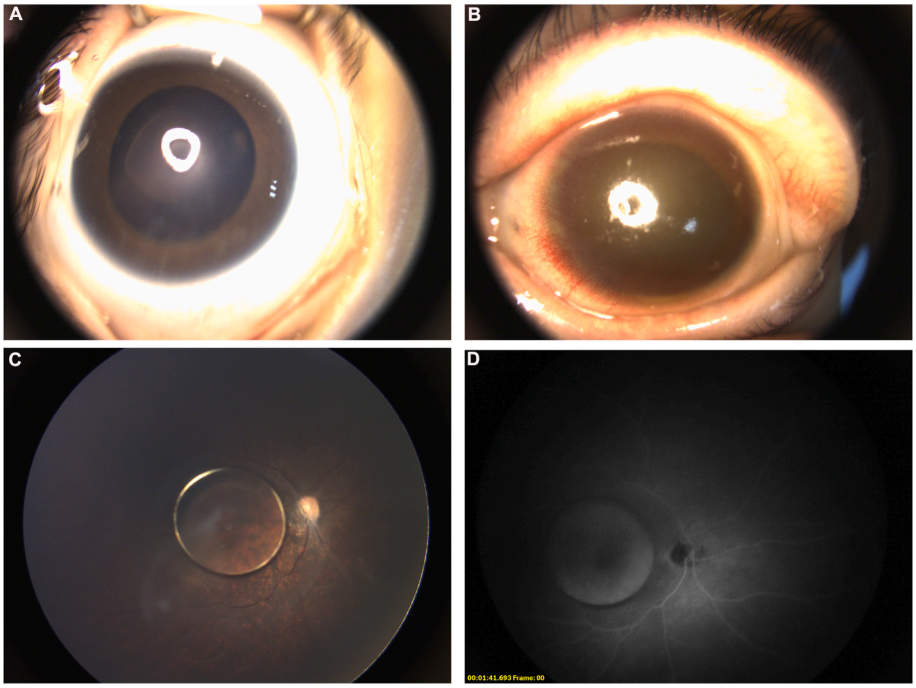

Fig. 3. RetCam and fundus fluorescein angiography (FFA) of the right eye of the patient. (A) A clear cornea, anterior chamber, and aphakia of the right eye are shown. (B) Conjunctival congestion, corneal edema, and hyphemia of the left eye are shown. (C) The lens luxation into the vitreous of the right eye is clearly revealed. (D) The FFA of the right eye revealed lens luxation and normal retinal vessels.

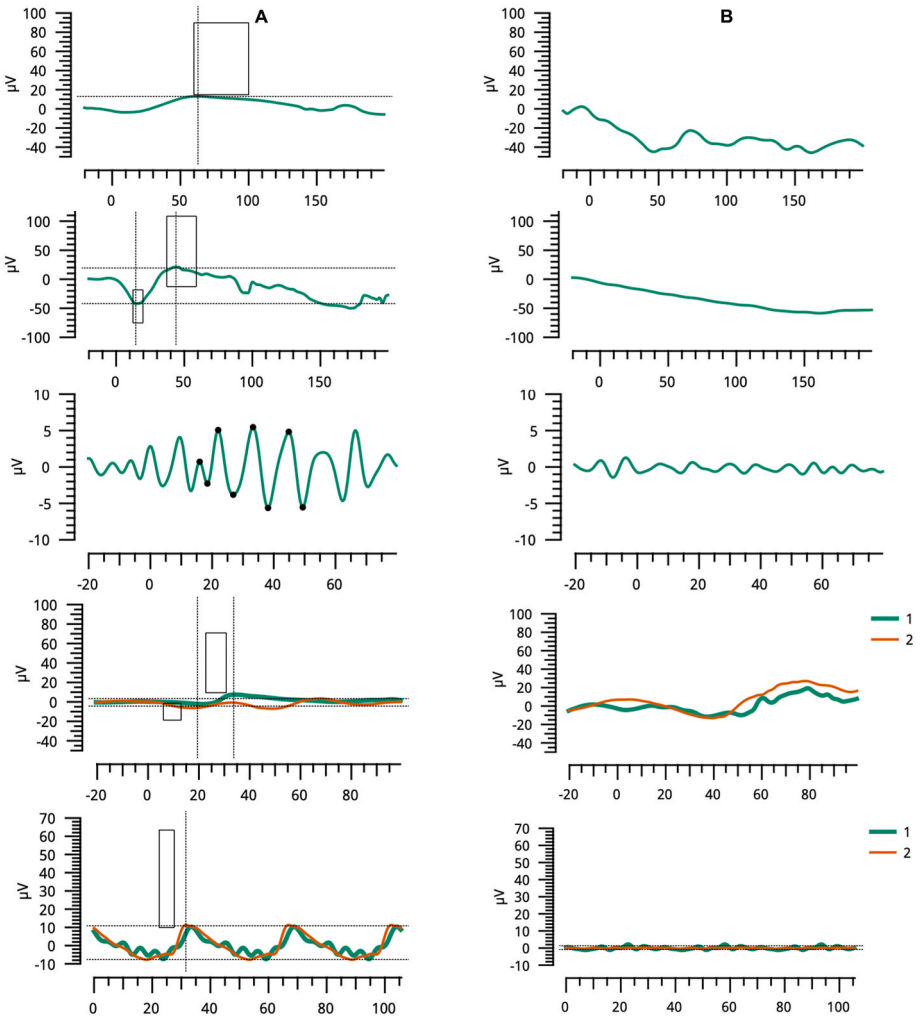

Fig. 4. Electroretinogram of the patient. (A) Relatively normal cone and rod responses of the right eye are shown. (B) Extinguished cone and rod responses are shown.

ocular characteristic in most patients. Interestingly, in two cases with spherophakia, lens dislocation developed after spherophakia. Rossella Parini[27] speculated that the deficiency of sulfite oxidase may impair the zonular fibers. This result in the modification of the lens shape, producing spherophakia with anterior chamber obstruction, and subsequently lead to lens dislocation. Summarizing previous cases, ectopic lens and spherophakia are considered to be primary findings in MoCD, while glaucoma, hyphemia, and cyclodialysis might be secondary. Retinal detachment has not been described in MoCD patients until now. Due to a limited number of cases, we are unable to determine whether retinal detachment is a consequence of MoCD or a secondary result. Further follow-up and study are required.

Theoretically, all types of MoCD result in the dysfunction of the same enzymes. There might not be a substantial clinical difference between the different subtypes of MoCD from a pathophysiological point of view. An atypical mild phenotype of late-onset MoCD has been recognized, and to date, 13 patients have been reported.[28] These late-onset patients generally have a longer life expectancy. Furthermore, patients with *MOCS1* mutation have been treated with a stable injectable form of cPMP,[28] and according to Schwahn and Van Spronsen, the prognosis is promising,[29] early diagnosis and treatment lead to a longer survival of MoCD-A patients. The ophthalmic examination could provide important evidence for early diagnosis because the biochemical abnormality may be easily missed on routine newborn metabolic screening. The finding of ectopia lentis in an infant with refractory seizures is highly suggestive of this disease. However, it remains unknown to what extent the metabolism disorder impairs the visual system and how it could be prevented and treated. Visual function as an important part affecting the quality of life of patients deserves more attention, and ophthalmic serial examination should be performed as far as possible.

4. Conclusions

Patient with MoCD-B may present the ocular manifestations as ctopia lentis, spherophakia, hyperemia, secondary glaucoma, cyclodialysis, and retinal detachment. Carefully evaluation of the ocular findings can help early diagnosis of MoCD.

Patient consent

Consent to publish this case report has been obtained from the guardian of this patient in writing. Collection and evaluation of protected patient health information adhered to the ethical principles of the 2013 amended Declaration of Helsinki.

Conflict of interest disclosures

The authors declare no conflict of interest.

Table 1
Genetic and Clinical features of MoCD patients with *MOCS2* mutations.

Reference	Case	Sex	Age of onset	Last follow-up	Status	NM_	Exon	Mutation type	DNA changes	Amino acid changes	Ocular manifestations	Clinical findings
Reiss et al.[10]	1	NA	Neonatal	NA	Hom	NM_176806.4	1	Missense	c.3G>A	–	NA	Seizures, Facial dysmorphism
	2	NA	Neonatal	NA	Hom	NM_176806.4	3	Insertion	c.252dup	p.Ile85Hisfs*2	NA	Seizures, Facial dysmorphism
	3	NA	Neonatal	NA	Hom	NM_004531.5	5	Deletion	c.533_536del	p.Gly178Alafs*16	NA	Seizures, Facial dysmorphism
Johnson et al.[7]	4	F	11 month	5 years	Hetero	NM_176806.4	1	Nonsense	c.16C>T	p.Gln6*	Hyperopia	Macrocephaly, Hypotonia
					Hetero	NM_176806.4	1	Missense	c.19G>T	p.Val7Phe		
Reiss and Johnson[4]	5	NA	NA	NA	Hom	NM_176806.4	2	Missense	c.45T>A	p.Ser15Arg	NA	NA
	6	NA	NA	NA	Hom	NM_176806.4	2	Nonsense	c.88C>T	p.Gln30*	NA	NA
	7	NA	NA	NA	Hom	NM_176806.4	2	Nonsense	c.106C>T	p.Gln36*	NA	NA
	8	NA	NA	NA	Hom	NM_004531.5	4	Missense	c.413C>T	p.Ala138Val	NA	NA
Leimkühler et al.[11]	9	NA	NA	NA	Hom	NM_176806.4	2	Nonsense	c.33T>G	p.Tyr11*	NA	NA
Hahnewald et[12]	10	M	Neonatal	Infancy	Hom	NM_176806.4	1a	Frameshift	c.-8_15del	p.Met1fs	None	Seizures, Feeding difficulties
Per et al.[14]	11	M	Neonatal	Infancy	Hom	NM_176806.4	2	Nonsense	c.130C>T	p.Arg44*	None	Seizures, Hypotonia
Sie et al.[16]	12	M	Neonatal	Infancy	Hom	NM_176806.4	3	Nonsense	c.220C>T	p.Gln74*	None	Facial dysmorphism, Feeding difficulties, Seizures, Facial dysmorphism
Reiss and Hahnewald[5]	13	NA	NA	NA	Hom	NM_176806.4	3	Nonsense	c.220C>T	p.Gln74*	NA	NA
	14	NA	NA	NA	Hom	NM_004531.5	5	Nonsense	c.501del	p.Glu168Lysfs*27	NA	NA
Vijayakumar et al.[8]	15	NA	Neonatal	NA	Hom	NM_004531.5	3	Missense	c.226G>A	p.Gly76Arg	NA	Seizures, Facial dysmorphism
	16	NA	Neonatal	NA	Hom	NM_004531.5	3	Missense	c.226G>A	p.Gly76Arg	NA	Seizures, Facial dysmorphism
Kikuchi et al.[18]	17	M	Neonatal	2 years	Hetero	NM_176806.4	3	Stoploss	c.265T>C	p.*89Glnext*3	None	Seizures, Feeding difficulties, Developmental delay
					Hetero	NM_176806.4	3	Stoploss	c.266A>G	p.*89Trpext*3		
Megahed et al.[20]	18	F	Neonatal	6 years	Hom	NM_176806.4	1	Missense	c.3G>A	–	None	Developmental delay, Facial dysmorphism
Zaki et al.[21]	19	F	12 Months	5.5 years	Hom	NM_176806.4	1	Missense	c.3G>A	–	None	Seizures, Feeding difficulties
Yoganathan et al.[22]	20	M	Neonatal	9 months	Hom	NM_176806.4	3	Missense	c.218T>C	p.Leu73Pro	None	Seizures, Feeding difficulties
Pinar Arican et al.[23]	21	M	Neonatal	Infancy	Hom	NM_004531.4	1a	Missense	c.-9G>A	5 prime UTR	None	Seizures, Facial dysmorphism, Feeding difficulties
Edward Jin Lee[25]	22	F	Neonatal	9 years	Hetero	NM_004531.5	5	Missense	c.493T>C	p.Trp165Arg	Bilateral ectopia lentis	Seizures, Developmental delay, Feeding difficulties, Microcephaly, Xanthine stones,
					Hetero	NM_004531.5	5	Deletion	c.539_540del	p.Lys180Argfs*31		
Yuanyuan Lin[26]	23	F	Neonatal	Infancy	Hom	NM_176806.4	2	Deletion	c.168del	p.Phe57Leufs*195	None	Seizures, Feeding difficulties
Aleksandra Jezela-Stanek[24]	24	M	Neonatal	Infancy	Hom	NM_004531.5	5	Deletion	c.472_477del	p.Leu158_Lys159del	None	Seizures, Feeding difficulties
This case	25	M	4 Months	6 years	Hom	NM_176806.4	1	Nonsense	c.16C>T	p.Gln6*	Ectopia lentis, Spherophakia, Retinal detachment, Hyphema, Secondary glaucoma Cyclodialysis	Seizures, Developmental delay, Facial dysmorphism, Feeding difficulties, Microcephaly

Abbreviations: F = female; M = male; NA= Not available; Hom = Homozygote; Hetero = Heterozygote.

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Authorship

Pro. Xiaoyan Ding conceptualized the study, critically reviewed and revised the manuscript. Dr. Wenjia Yan collected the clinical data of the patient and drafted the initial manuscript. Dr. Li Huang coordinated manuscript drafting, reviewed and revised the manuscript. Dr. Limei Sun carried out the initial analyses and coordinated in drafting the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors attest that they meet the current ICMJE criteria for authorship.

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