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Case Report

Prenatal ultrasound findings of X-linked congenital cataracts: case report and description of a novel variant

Yanyan Zheng, Liang Li, Ling Wang, Chaoxue Zhang

Department of Ultrasound, First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui, China

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Abstract: Congenital cataracts, an important cause of permanent visual loss in children, are predominantly caused by hereditary factors. Genetic variants reportedly cause approximately 50% of congenital cataracts. The literature mainly describes cases of autosomal dominant inheritance diagnosed after birth, and minimal information is available concerning the prenatal diagnosis of X-linked congenital cataracts. Prenatal ultrasound is the primary method for diagnosis of congenital cataracts, whereas the diagnostic value of prenatal genetic testing remains controversial; however, such testing is reportedly essential for determination of disease etiology. Here, we describe a 33-year-old multigravida woman with a singleton pregnancy who was referred to our center at 24 weeks for routine prenatal examination; ultrasound imaging revealed bilateral cataracts in the male fetus. Genetic testing revealed a pathogenic variant in exon 11 of the OCRL inositol polyphosphate-5-phosphatase (*OCRL*) gene in the fetal sample, with the potential to cause the X-linked recessive genetic disease Dent disease 2 (Online Mendelian Inheritance in Man [OMIM]: 300555) or the X-linked recessive genetic disorder Lowe's syndrome (OMIM: 309000). We provide a comprehensive family history and our findings in a gross examination of the stillborn fetus. So, ultrasound imaging provides important information that can guide the diagnosis of congenital cataracts. When congenital cataracts are detected by prenatal ultrasound, a detailed family history should be obtained. We recommend genetic testing of the fetus and the family members to determine the etiology.

Keywords: Prenatal ultrasonography, X-linked, cataract, congenital, case report

Introduction

The prevalence of congenital cataracts reportedly ranges from 1 to 6 cases per 10,000 live births [1]. Genetic variants reportedly cause 30% of unilateral cataracts and 50% of bilateral cataracts in an autosomal dominant, recessive, or X-linked manner [2, 3]; other causes (e.g., inflammation and infections) have also been documented [4, 5]. Benacerraf et al. [6] were the first to report the identification of congenital cataracts by prenatal ultrasound. Congenital cataracts can occur as an isolated disorder or as the characteristic feature of a syndrome [1]. For example, congenital cataracts are present in patients with Lowe syndrome, an X-linked disorder that primarily affects the lens, kidney, and brain [7]. Based on extensive research concerning early identification of congenital cataracts, prenatal ultrasound has become the preferred approach for prenatal diagnosis (**Table 1**) [8-15]. Congenital cataracts often appear with other disorders, such as microphthalmia. Because patients with congenital cataracts may have normal-sized eyes, isolated cataracts can easily be overlooked during an ultrasound examination. Here, we describe a unique case in which X-linked recessive congenital cataracts were diagnosed prenatally using ultrasound and genetic testing. The gene responsible for this manifestation, OCRL inositol polyphosphate-5-phosphatase (*OCRL*), exhibited a variant at site 129562444 in the X chromosome.

Case description

A 33-year-old multigravida woman (gravida 2, para 0) with a singleton pregnancy was referred to our center at 24 weeks of gestation for a routine prenatal examination of a male fetus. Ultrasound imaging at our center showed that

Table 1. Cases of prenatal diagnosis of congenital cataracts reported in PubMed in the past 20 years

Sex	Ultrasound findings	Genetic details	Family history	Year of publication	Ref.
Male	Bilateral cataracts Enlarged posterior fossa	Xq25q26.1 (128155802-128789721) × 0.4	No	2017	[8]
Male	Bilateral cataracts	(c755A>G [P.Lys252Arg]) in *CRYBB1*	No	2020	[9]
-	Bilateral cataracts Unilateral cataract Unilateral cataract Unilateral cataract Bilateral cataracts (all other manifestations of MPS)	-	Yes	2004	[10]
Male	Microretrognathia; nasal anteversion; wide forehead; atrioventricular septum defect; renal hypoplasia; postaxial hexadactyly	AR; chrom. 11; *DHCR7*	No	2008	[11]
Male	Congenital bilateral cataracts	Semi-dominant; chrom. X	No	2007	[12]
Male	Congenital bilateral cataracts	Semi-dominant; chrom. X	No	2003	[13]
Male	Bilateral cataracts and microphthalmia	-	No	2009	[14]
-	Bilateral cataracts	*CRYBB2*, *CRYBB3*	Yes	2016	[15]

Abbreviations: AR, Autosomal Recessive; chrom., chromosome; CRYBB1, Crystallin Beta B1; CRYBB2, Crystallin Beta B2; CRYBB3, Crystallin Beta B3; DHCR7, 7-Dehydrocholesterol Reductase; MPS, Mucopolysaccharidoses; Ref., Reference.

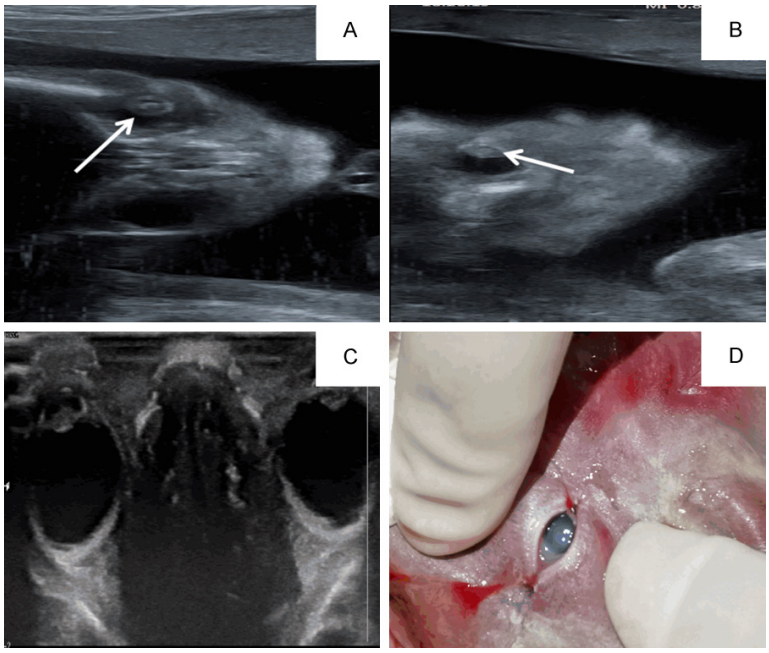

Figure 1. A and B. Prenatal high-frequency ultrasound showing dot-like and cluster-like echogenicities in bilateral lenses (the white arrow). C. High-frequency ultrasound after induced labor showed dot-like and cluster-like echogenicities in bilateral lenses. D. Lens opa cification was observed after labor induction.

the fetus had bilateral cataracts. Fetal growth, amniotic fluid volume, and Doppler findings were normal; no other structural defects were noted. Hyperechogenic lenses were observed by high-resolution ultrasound (**Figure 1A** and **1B**).

Discussion with the mother revealed that during her previous pregnancy (at the age of 29 years), a congenital cataract had been identified in the male fetus and labor had been induced to terminate the pregnancy at 22 weeks of gestation. Subsequently, she had completed a divorce and began a new marriage; she had been married to her current husband for 2 years at the time of the ultrasound examination. The mother denied a family history of congenital cataracts. The ultrasound findings were suggestive of X-linked recessive disease caused by a maternal genetic variant (**Figure 2**). Prenatal amniocentesis showed normal copy number variant sequencing and karyotyping findings. Further genetic testing of the fetus and parents was performed via high-throughput whole-exome sequencing technology and the Verita Trekker® variant locus detection system (Berry Genomics). Data were analyzed using the Enliven® annotation and interpretation system for variant sites. The results revealed a pathogenic variant in *OCRL* in the fetal sample, with the potential to cause the X-linked recessive genetic disease Dent disease 2 (Online Mendelian Inheritance in Man [OMIM]: 300555) or the X-linked recessive genetic disorder Lowe's syndrome (OMIM:

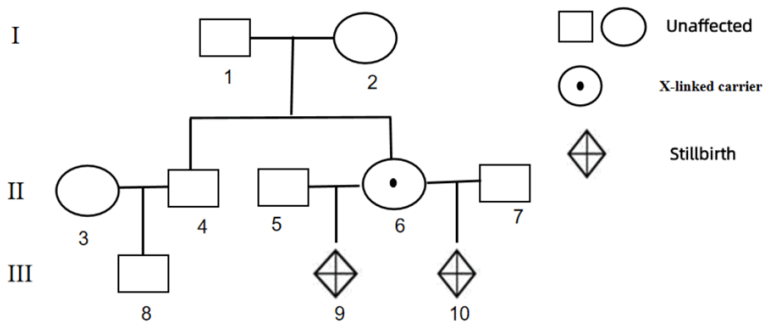

Figure 2. Family tree of the mother and fetus (fetus is shown in line III, number 10).

309000). A heterozygous variant was present in the mother, whereas the wild-type sequence was present in the father, leading to a hemizygous offspring. Moreover, the fetus's clinical features were consistent with the congenital cataract phenotype. In addition to cataracts, this genotype has been associated with clinical phenotypes such as intellectual disability and renal Fanconi syndrome [8]. The single nucleotide variant and insertion-deletion results are shown in **Table 2** and **Figure 3**.

After multidisciplinary counseling, the parents decided to terminate the pregnancy. Abortion was performed by induction of labor; lens opacification was observed during gross examination of the fetus. Bilateral congenital cataracts were confirmed by postpartum high-frequency ultrasound, consistent with prenatal ultrasound findings (**Figure 1C** and **1D**). Both prenatal and postpartum ultrasound findings revealed normal-sized eyes and lens opacification, with dot-like and cluster-like echogenicities.

Discussion

Many genetic variants can cause congenital cataracts; 8.3% to 25% of congenital cataracts are inherited, and variants in crystallin genes cause disease in half of the affected patients [16]. Importantly, the transparency and refractive index of the human lens are controlled by the concentrations of crystallins; changes in crystallins can lead to the formation of cataracts. Genetic testing and prenatal ultrasound have become the primary methods for diagnosis of congenital cataracts. High-throughput whole-exome sequencing has gradually been implemented for the detection of congenital cataracts [2, 3]. There has been considerable progress in efforts to map new cataract loci and identify the corresponding genes. Causative genes (e.g., crystallin-alpha A, crystallin-alpha B, crystallin-beta B1, and crystallin-beta B2) have been identified in approximately 40 of 60 mapped loci. However, there is increasing evidence that each variant can cause extensive differences in cataract morphology and severity, both within and among families [9, 12]. Thus, genetic or environmental factors presumably modify the primary variant associated with cataract onset. The present case differed from previously reported cases in a few aspects. The mother's history was unique in that congenital cataracts occurred in two singleton pregnancies with different fathers; however, genetic testing was not recommended during prenatal consultation for the first pregnancy. To our knowledge, this is the first report of congenital cataract diagnosis based on prenatal ultrasound findings in combination with high-throughput whole-exome sequencing. Additionally, a diagnosis of an X-linked recessive genetic disease caused by a genetic variant was suspected based on the mother's family history and remarriage. In addition to cataracts, the genetic variant identified in this case is associated with other clinical phenotypes, including intellectual disability and renal Fanconi syndrome [8].

Nevertheless, prenatal ultrasound remains an important, non-invasive, and convenient examination method for the diagnosis of fetal cataracts. Transvaginal ultrasound can be used to diagnose congenital cataracts as early as 14 to 16 weeks of gestation [17]. Three types of congenital cataracts have been identified via prenatal ultrasound: type 1, homogeneous hyperechogenicity in the lens; type 2, hyperechogenic spots in the lens; and type 3, irregular or crenated hyperechogenic borders (double ring sign) [18]. In our case, both prenatal and postpartum ultrasounds showed normal-sized eyes and a hyperechogenic spot in the lens, suggesting a type 2 cataract; these findings emphasize the importance of prenatal ultrasound in establishing the final diagnosis of congenital cata-

Table 2. Single nucleotide variant and insertion-deletion detection results

Gene	Variant site	Gene subregion	HGVS	Variant type	Heterozygosity	Variation rating	Diseases/genetic patterns
OCRL	ChrX: 129562444	Exon 11	NM_000276.4:c.1000c>T:p.R334*	Stop-gain	Fetus: Hemizygous Mother: Heterozygous Father: Wild-type	Pathogenic	Dent disease 2, XLR; Lowe syndrome, XLR

Abbreviations: ChrX, X Chromosome; HGVS, Human Genome Variation Society Variant Description; OCRL, OCRL Inositol Polyphosphate-5-Phosphatase; XLR, X-linked Recessive. Note: Reference database: Human Genome 38 (HG38/GRCh38). This case report was written in accordance with the guidelines of the American Society for Medical Genetics and Genomics. The loci associated with phenotype and high likelihood of disease were selected and reported according to genetic pattern, age at onset, population frequency, and hazard prediction filter. These results are only provided for clinical reference.

Figure 3. Sequencing chromatogram showing single nucleotide variant and insertion-deletion findings. A hemizygous c.1000C>T variant is present in the OCRL inositol polyphosphate-5-phosphatase (*OCRL*) gene from the fetus (20Y00182), a heterozygous c.1000C>T variant is present in the mother (20Y00182MU0), and no variant is present in the father (20Y00182FU0). These findings suggest that the variant was provided by the mother.

racts. A final diagnosis of hemizygous X-linked recessive genetic disease was established; the causative gene, *OCRL*, exhibited a variant in exon 11 (at site 129562444 in the X chromosome [NM_000276.4:c.1000c>T:p.R334*]).

According to the Human Gene Mutation Database, there are approximately 250 pathogenic variants in *OCRL*, with ≥90% in exons 10-18 and exons 19-23. In our case, the variant was located in exon 11. Although congenital cataracts have been associated with variants in *OCRL*, there have been no reports regarding a prenatal diagnosis of congenital cataracts associated with variants in exon 11 (NM_000276.4:c.1000c>T:p.R334*) [19, 20]. Previous reports indicate that both frameshifts and splicing variants in or near the Rho GTPase activating protein (RhoGAP)-like domain and the 5-phosphatase domain in *OCRL* variants are associated with severe clinical manifestations [21-23]. Furthermore, the presence of a heterozygous variant in the asymptomatic mother and a hemizygous variant in the affected fetus suggests X-linked recessive inheritance. The autopsy findings of congenital cataracts were consistent with the presence of a variant in *OCRL* and X-linked recessive inheritance. Congenital cataracts, an important cause of amblyopia and blindness in children, are usually detected after birth or in early childhood; early surgery and optical rehabilitation are often indicated [24, 25]. Bilateral lens resection is the preferred treatment and is indi-

cated earlier for type 1 cataracts than for type 2 cataracts. Overall, early detection and diagnosis are important for improving the prognosis of affected patients.

Conclusions

Ultrasound imaging provides important information that can guide the diagnosis of congenital cataracts. When congenital cataracts are detected by prenatal ultrasound, a detailed family history should be obtained. We recommend genetic testing of the fetus and the parents to determine the etiology. Treatment during pregnancy should be provided after detailed counseling regarding ultrasound findings, etiology, possible complications, and risks in subsequent pregnancies. Notably, substantial advances in sequencing technology and molecular biology research have led to the arrival of third-generation *in vitro* fertilization. Thus, carrier women with X-linked congenital cataracts can now choose genetically normal fertilized eggs for uterine implantation, which may help to reduce the risk of congenital cataracts in their offspring.

Disclosure of conflict of interest

None.

Address correspondence to: Chaoxue Zhang, Department of Ultrasound, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Shushan District, Hefei 230022, Anhui, China. Tel: +86-0551-69118322; Fax: +86-0551-69118322; E-mail: zcxay@163.com

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