



Early Prenatal Diagnosis of Cornelia de Lange's Syndrome with Whole-Exome Sequencing: A Case Report

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Abstract

Keywords

- ▶ Cornelia de Lange's syndrome
- ▶ prenatal diagnosis
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- ▶ prenatal ultrasound
- ▶ cohesinopathies

Cornelia de Lange's syndrome (CDLS) is a multisystem genetic syndrome characterized by well-defined physical, intellectual, and behavioral characteristics. The diagnosis of CDLS is typically done clinically after birth; however, recent studies have demonstrated the ability to use prenatal ultrasound and whole-exome sequencing to diagnose CDLS prenatally. Here we present a prenatal case in which multiple fetal anomalies were identified on ultrasound at 20 weeks of gestation. Use of whole-exome sequencing allowed for successful diagnosis of CDLS in this fetus prenatally.

Cornelia de Lange's syndrome (CDLS; OMIM# 122470, 300040, 300269, 300590, 300882, 606062, 606462, 608667, 608749, 610759, 614701) is a genetically and clinically heterogeneous disorder with physical, behavioral, intellectual, and cognitive characteristics. First described in 1933 by pediatrician Cornelia de Lange, the prevalence is estimated to be between 1 in 10,000 and 1 in 30,000 live births, and possibly higher due to undetected mild cases.^{1,2} The classic phenotype encompasses distinct facial features including synophrys, long eyelashes, depressed nasal bridge, short nose with anteverted nares, long philtrum, thin lips, downturned corners of the mouth, and micrognathia. It also

includes growth retardation, upper limb reduction defects ranging from complete absence of the forearms to subtle phalangeal abnormalities, hypertrichosis, feeding difficulties, small or absent teeth, microcephaly, and neurocognitive delay.³ In addition, the phenotype can vary significantly due to the heterogeneity of the disease. Other common features include cardiac abnormalities (septal defects), hearing loss, myopia, genital anomalies, seizures, high-arched palate, autism, and self-injurious behaviors. A consensus statement was released in 2018 outlining the clinical diagnostic criteria for CDLS and categorizing it into cardinal features and suggestive features.³ The majority of cases of CDLS are

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diagnosed clinically after birth; however, certain phenotypic features allow for early prenatal detection during the second and third trimester ultrasound. A prior study found that two-thirds of cases of CDLS with major malformations were not detected by routine prenatal ultrasound.⁴ The typical in utero facial profile of a fetus with CDLS consists of micrognathia, a prominent upper lip, and a depressed nasal bridge with somewhat anteverted nares.⁵ It may also present with growth failure in the second trimester and an increased nuchal translucency (NT) in the first trimester.⁶

The genes known to cause classic CDLS include *NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *BRD4*, and *HDAC8*.⁷ These genes encode proteins that form structural and/or regulatory components of the cohesin complex. The cohesin complex is a multiprotein, evolutionarily conserved complex that plays a stabilizing role during cell cycling by holding sister chromatids together prior to segregation. It is also involved in double-strand deoxyribonucleic acid (DNA) break repair, DNA replication, centrosome duplication, chromatin architecture, and transcriptional regulation.⁸ *NIPBL* forms a dimer with another protein Mau2 sister chromatid cohesion factor (*MAU2*) that loads the cohesin complex onto sister chromatids (OMIM# 614560).

Recently pathogenic variants in *ANKRD11* previously known to cause KBG syndrome were identified in patients with CDLS-like phenotype, and as the classic CDLS is broadened to a spectrum disorder additional causative genes and epigenetic mechanisms have and will continue to be identified within the spectrum.

Whole-exome sequencing (WES) is a powerful diagnostic tool that interrogates the exons of all known genes, using bioinformatics, and ideally with parental DNA, to search for pathogenic variants associated with a clinical phenotype. Although WES has been available since 2012, it has not been widely incorporated into prenatal care due to multiple challenges including high costs, lack of insurance coverage, consenting for American College of Medical Genetics and Genomics (ACMG) secondary findings, specimen requirements, and result turnaround time. In 2019, a prospective study on use of WES for fetal structural anomalies demonstrated an additional diagnostic rate of 30% in fetuses with three (3) or more anomalies above routine chromosomal microarray.⁹ The benefits of providing a definitive genetic diagnosis of ultrasound abnormalities are self-evident in terms of improved decision-making for pregnancy management, reproductive decision-making for current and future pregnancies, recurrence risk, and testing options.

Case

This is a 37-year-old Latino woman gravida 2 para 0–0–1–0 with a past medical history of hypertension on labetalol and low-dose daily aspirin for preeclampsia prevention. She has a history of an uncomplicated first trimester pregnancy loss. She was referred at 13 weeks of gestation to genetic counseling due to a positive first trimester screen with increased NT thickness. Her first trimester screen was positive for trisomy 21 and 18 with risks of 1/6 and 1/24, respectively. Fetal NT measured

6.44 mm; pregnancy-associated plasma protein-A (PAPP-A) was 0.53 multiples of median (MOM) and human chorionic gonadotropin (HCG) was 0.70 MOM. The patient's noninvasive prenatal screen was low risk for trisomy 21, 18, 13, and sex chromosome aneuploidy. The patient was counseled on invasive diagnostic testing via chorionic villus sampling (CVS) or amniocentesis. She was also advised to consider an early anatomical ultrasound at 16 weeks of gestation and complete anatomical ultrasound at 20 weeks of gestation as well as a fetal echocardiogram. The patient underwent amniocentesis at 17 weeks resulting in normal chromosome analysis and normal microarray results, specifically negative for Noonan's syndrome. Her anatomy ultrasound at 20 weeks showed early onset growth restriction with the fetus measuring 18 weeks and multiple anomalies including shortened long bones, clenched fists, bilateral clubfeet with high suspicion of polydactyly, cerebellar hypoplasia, abnormal calvarium, micrognathia, low-set ears, single umbilical artery, and possible ventral septal defect (VSD). The patient was offered WES testing and counseled on options for continuation versus termination of pregnancy given the anomalies seen on ultrasound. The patient ultimately decided to terminate the pregnancy. WES was positive for CDLS due to heterozygous *NIPBL* pathogenic variant c.1713 1716delACAA. This variant was not found in parental DNA and therefore likely de novo; however, gonadal mosaicism cannot be excluded.

Discussion

CDLS is a rare disorder with variable phenotypic presentation commonly caused by a sporadic, de novo dominant mutation. We present a case in which CDLS was diagnosed prenatally at an early gestational age with the aid of WES. Increased NT found at 13 weeks allowed for early referral to genetic counseling and the ability to follow the proposed algorithm as described by Clark et al to achieve a prenatal diagnosis of CDLS.¹⁰ Ultrasound results showed some characteristic phenotypes of CDLS as described in prior studies, including growth restriction, limb defects, micrognathia, and increased NT.^{7,8} Micrognathia and severe bilateral limb deformities were also noted in our case and very strongly associated with a mutation in *NIPBL*.¹¹ Other typical characteristics were not visualized including synophrys, short nose with depressed nasal bridge and anteverted nares, long and smooth philtrum, and thin upper lip and downturned corners of the mouth.⁶ These characteristics may have been present, but better appreciated via volumetric ultrasound. Although it is difficult to diagnose CDLS based only on ultrasound findings, prenatal ultrasound can be used as a tool to aid early diagnosis. Coupled with the technology of WES, the diagnosis of CDLS can be made prior to the third trimester. It can also aid in determining a patient's recurrence risk of fetal anomalies in future pregnancies.

This case revealed a mutation in the *NIPBL* gene, which is present in approximately 60% of patients with CDLS. Studies have shown that *NIPBL* mutations lead to more severe phenotype for growth retardation and development delay compared with other gene mutations. Although the exact

function of *NIPBL* is unclear, it is strongly expressed in the heart, skeletal muscle, and thymus, and is vital for adequate development in the embryo.¹²

Conclusion

We present a case in which CDLS was diagnosed at an early gestational age. Fetal anomalies were detected using prenatal ultrasound, raising suspicion for an underlying genetic abnormality in the fetus. WES was subsequently used to come to a definitive diagnosis of CDLS. This case supports the suggestion that the CDLS genes be added to the broad multigene panels for fetuses with growth retardation and structural anomalies to aid in the diagnosis of CDLS in the prenatal period.⁵

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Conflict of Interest

None declared.

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