



CASE REPORT

**REVISED** Case Report: Atypical Cornelia de Lange Syndrome  
 [version 2; referees: 1 approved, 2 approved with reservations]

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**v2** First published: 31 Jan 2014, 3:33 (doi: [10.12688/f1000research.3-33.v1](https://doi.org/10.12688/f1000research.3-33.v1))  
 Latest published: 27 May 2015, 3:33 (doi: [10.12688/f1000research.3-33.v2](https://doi.org/10.12688/f1000research.3-33.v2))

**Abstract**

Cornelia de Lange Syndrome (CdLS) (also called Bushy Syndrome or Amsterdam dwarfism), is a genetic disorder that can lead to several alterations. This disease affects both physical and neuropsychiatric development. The various abnormalities include facial dysmorphia (arched eyebrows, synophrys, depressed nasal bridge, long philtrum, down-turned angles of the mouth), upper-extremity malformations, hirsutism, cardiac defects, and gastrointestinal alterations. The prevalence of this syndrome is approximately one per 15,000. Ultrasound is not the perfect means to diagnose CdLS, however, many abnormalities can be detected prenatally by scrupulous image observation. We report an atypical CdLS case characterized by increased nuchal translucency in the first trimester, normal karyotype, saddle nose, micrognathia with receding jaw, low set ears, facies senilis, arthrogryposis of the hands, absence of the Aranzio ductus venous, dilatation of gallbladder and bowel, a unique umbilical artery, increased volume of amniotic fluid, and intrauterine growth retardation ending with the interruption of pregnancy.

**Open Peer Review**

Referee Status:

	Invited Referees		
	1	2	3
<b>version 2</b> published 27 May 2015	<b>REVISED</b>	report	report
<b>version 1</b> published 31 Jan 2014	report		report

- 1 **Jinglan Liu**, Drexel University USA
- 2 **Laird Jackson**, Drexel University USA
- 3 **Orkun Çetin**, Istanbul Suleymaniye Birth and Gynecology Training and Research Hospital Turkey

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**How to cite this article:** Leanza V, Rubbino G and Leanza G. **Case Report: Atypical Cornelia de Lange Syndrome [version 2; referees: 1 approved, 2 approved with reservations]** *F1000Research* 2015, 3:33 (doi: [10.12688/f1000research.3-33.v2](https://doi.org/10.12688/f1000research.3-33.v2))

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**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Competing interests:** No competing interests were disclosed.

**First published:** 31 Jan 2014, 3:33 (doi: [10.12688/f1000research.3-33.v1](https://doi.org/10.12688/f1000research.3-33.v1))

**REVISED Amendments from Version 1**

Sections of text, in the Discussion in particular, have been modified according to the suggestions of the reviewers.

See referee reports

**Introduction**

Cornelia de Lange Syndrome (CdLS) is a genetic disorder that can lead to several alterations. It affects both physical and neuropsychiatric development. The several abnormalities include facial dysmorphism (arched eyebrows, synophrys, depressed nasal bridge, long philtrum, down-turned angles of the mouth), upper-extremity malformations, hirsutism, cardiac defects, and gastrointestinal alterations<sup>1</sup>. The prevalence of this syndrome is approximately one per 15,000<sup>2</sup>. Many markers have to be considered. Nuchal translucency (NT) measurement during the first trimester screening between 11 and 14 weeks gestation has now been clearly identified as a marker for aneuploidies and in particular for trisomy 21. Even in the absence of aneuploidy, increased foetal nuchal translucency has been shown to be a marker for foetal heart malformations and several other foetal defects linked to genetic syndromes when the measure exceeds the 95<sup>th</sup> percentile (3–5 mm)<sup>3</sup>. When conventional karyotyping is normal, enlarged NT is a strong marker for adverse pregnancy outcome, associated with miscarriage or intrauterine death). Unspecified genetic syndromes involving developmental delay may only emerge after birth and become evident after the first years of life. Several abnormalities have been reported in fetuses with enlarged NT: the majority are cardiac defects, diaphragmatic hernia, exomphalos, body stalk anomaly, skeletal defects, certain genetic syndromes (such as congenital adrenal hyperplasia), foetal akinesia, deformation sequence, Noonan syndrome, Smith-lemli-Opitz syndrome and spinal muscular atrophy<sup>4</sup>. The saddle nose, characterized by a markedly depressed bridge has been described in AIDS embryopathy, Christ-Siemans-Touraine syndrome, various deletion syndromes, foetal trimethadione syndrome, Laron-type dwarfism, leprechaunism, multiple epiphyseal dysplasia, otospondylomegalepiphyseal dysplasia (OSMED) syndrome, relapsing polychondritis, thanatophoric dwarfism, Wegener's granulomatosis, and various conditions that are further characterized by gargoyle-like faces. Micrognathia is a malformation of the foetal face characterized by a small mandible. Micrognathia may be idiopathic but is more commonly associated with many different syndromes. Retrognathia (recession of the chin) is assessed through the measurement of the inferior facial angle, as defined on a mid-sagittal view. With routine ultrasound, the recessed chin may be observed on a profile of the face. Yet, this diagnosis is often missed during a routine ultrasound examination. The mandible is known to grow significantly during the third trimester. If mandibular alteration is suspected, particular attention should be paid to the growth of the chin throughout the remainder of the pregnancy. Conditions associated with micrognathia include chromosomal abnormalities, neuromuscular abnormalities, single-gene disorders, and other syndromes. The prognosis of foetal micrognathia is poor, even in chromosomally normal fetuses. Frequent malformations associated with micrognathia are: Pierre Robin sequence (micrognathia, cleft palate, or both)<sup>5</sup>; Cerebrocostomandibular syndrome (diagnosed on the basis of micrognathia, a posterior cleft palate defect, and characteristic

rib gap abnormalities); Cornelia de Lange syndrome, (underdeveloped chin with tetralogy of Fallot, intrauterine growth restriction, and an abnormal right hand)<sup>6</sup>; hypochondrogenesis type II and Caffey disease.

**Case report**

We report a case of a healthy 31-year-old, gravida 2, para 1 at 30 weeks of gestation that was admitted to S. Bambino University Hospital in Catania for ultrasound examination. Ultrasounds revealed nuchal oedema, saddle nose, micrognathia with receding jaw, low set ears, facies senilis at 3D ultrasounds, arthrogryposis of the hands, absence of Aranzio's ductus venous, dilation of gallbladder and bowel, single one umbilical artery, increased volume of amniotic fluid. Intrauterine growth retardation was associated as well. (Figure 1) Micrognathia was evident on midsagittal and 3D scan. The biparietal diameter was 68 mm, femur length 47 mm, suggesting foetal growth restriction. Pulsed Doppler sonography showed normal middle cerebral artery and umbilical artery pulsatility indices. The obstetric history revealed increased nuchal translucency thickness (NT) at 11 weeks (4 mm, > 95 centile). No genetic alterations were found at the amniocentesis carried out during 16<sup>th</sup> week of pregnancy (normal karyotype of 46, XX). Morphological ultrasound at 22 weeks of pregnancy was not able to detect the syndrome. A further ultrasound examination at 29 weeks (Figure 2) of pregnancy pointed out a foetal dysmorphism and the pregnant woman asked for our consultation.

Soon after, interruption of pregnancy occurred. The autopsy showed a foetus with a weight between the 5<sup>th</sup> and the 10<sup>th</sup> percentile and a dysmorphic syndrome with malformation features amenable to CdLS (Figure 3). The foetus had a typical dysmorphic face, hirsutism, rhizomelic limb, bilateral camptodactyly, single transverse palmar crease, proximal and very short inches with hypoplasia of 1<sup>st</sup> metacarpal and single phalanx, II-III membranous syndactyly of feet, right diaphragmatic hernia, bilateral cryptorchidism, microcephaly, numerous nodules of heterotopic cerebellar vermis, single umbilical artery and hypotrophic placenta devoid of inflammatory lesions.



**Figure 1.** 30<sup>th</sup> week face profile with ultrasound.



**Figure 2.** 29<sup>th</sup> week face aspect with 3D ultrasound.



**Figure 3.** Aspect of the new born (facies senilis).

### Discussion and conclusion

CdLS is a multisystem malformation syndrome recognized primarily on the basis of the morphological characteristics (malformations of the cranial, cardiac, gastrointestinal, and skeletal systems)<sup>7</sup>. However, there is wide clinical variability of disorders, with milder phenotypes that may be difficult to ascertain on the basis of physical features. In certain cases the diagnosis may be missed when ultrasound examination is not performed accurately. Criteria to detect CdLS are not standardized. The main alterations are as follows<sup>9</sup>:

- Facial abnormalities (synophrys, long eyelashes, microcephaly, anteverted nostrils)

- Cardiac defects (defects of ventricles or atria, aortic or pulmonary stenoses, tetralogy of Fallot, atrioventricular canal, single ventricle, aorto-pulmonary window, truncus arteriosus communis)
- Abnormalities of upper limbs (ectrodactyilia and monodactylism)
- Gastrointestinal alterations (diaphragmatic hernia)
- Musculoskeletal malformation
- Intrauterine growth retardation

Ultrasound detection of eyelashes is considered a clue for prenatal diagnosis of CdLS, but it can be missed in clinical practice<sup>10</sup>. CdLS is considered a cohesinopathy. Mutations in cohesin, or its regulators, cause a spectrum of human developmental syndromes. Cohesinopathy disorders include both CdLS and Roberts Syndrome. The discovery of novel roles for chromatid cohesion proteins in regulating gene expression led to the idea that cohesinopathies are caused by dysregulation of multiple genes downstream of mutations in cohesin proteins. Consistent with this idea, there is an altered expression of developmental genes and an incomplete overlap among dysregulated genes in different components of the cohesin apparatus<sup>11</sup>. CdLS is considered a dominantly inherited congenital malformation disorder, caused by mutations in the cohesin-loading protein *NIPBL* for nearly 60% of individuals. In humans, the multi-subunit complex cohesin is made up of *SMC1*, *SMC3*, *RAD21* and a *STAG* protein. These form a ring structure that is proposed to encircle sister chromatids to mediate sister chromatid cohesin; it also has a key role in genetic regulation. In CdLS cell lines an altered transcription with either *NIPBL* or *HDAC8* mutations has been found<sup>12</sup>. The proteins produced from mutated genes interfere in the foetal development. Within cells, these proteins help regulate the structure and organization of chromosomes and are involved in the repair of damaged DNA. They also regulate the activity of certain genes in the developing limbs, face, and other parts of the body. Researchers are looking for additional changes in the *NIPBL*, *SMC1A* and *SMC3* genes, as well as mutations in other genes, that may be responsible for this condition. The majority of cases result from new gene mutations and occur in people with no family history. CdLS can be prenatally diagnosed in a family with a known mutation in a CdLS gene. The characteristic ultrasonographic profile may allow for prenatal diagnosis of CdLS in subsequent pregnancies for couples with a prior child with CdLS in whom a mutation has not been identified or when there are unexplained signs of foetal abnormality during pregnancy, such as oligo- or polyhydramnios, a low maternal serum PAPP-A level and/or increased NT, foetal growth retardation, or structural anomalies consistent with CdLS<sup>13</sup>. Data from mutational testing on known CdLS genes (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8*) are important in the diagnosis of the typical syndrome. Indeed, the article published by Clark *et al.* (2012)<sup>13</sup> recommends molecular analysis of CdLS genes to prenatal diagnosis of CdLS. In our case data from mutational testing on known CdLS genes (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8*) was negative and so we consider this a case of atypical CdLS. Mutations in *NIPBL* are not present in all cases and they account for about 60% of CdLS; while mutations in *SMC1A* and *SMC3* only for a small percentage<sup>14</sup>. In some cases the diagnosis is made prenatally

in other cases the syndrome is diagnosed after childbirth. Currently, there are no definitive prenatal screening measures that lead to the diagnosis of CdLS<sup>13</sup>. Fewer than 1% of individuals diagnosed with CdLS have an affected parent<sup>14</sup>. Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical examination for features of CdLS as well as the plotting of the growth parameters and the molecular genetic testing for *NIPBL* mutation compared to the one identified in the proband. In our atypical Cornelia de Lange syndrome case molecular tests, conducted on the blood samples of the parents in a sequential manner of for *NIPBL*, *SMC1A*, *SMC3*, *RAD21* and *HDAC8*, were negative. The diagnosis is indicated when there is a major longitudinal deficiency defect of the upper limb, severe prenatal and postnatal growth retardation, and severe mental retardation. Features used to make the correct diagnosis include penciled and arched eyebrows, a high set/short anteverted nose, a long flat philtrum, a thin upper lip, downturned corners of the mouth, and micrognathia. Characteristics that are misleading include full or flat brows, a prominent nasal bridge or bulbous tip, and/or a normal or prominent chin. The genetic tests with positive results confirm the presence of the syndrome while the negative results do not exclude it. Indeed, mutations in *NIPBL*, *SMC1A* and *SMC3* are not present in all cases of CdLS as in our case. Less than 1% of individuals diagnosed with CdLS have an affected parent<sup>14</sup>. As genetic and biochemical tests are unreliable at present, antenatal detection depends upon identification of some aspects of the phenotype in the foetus using ultrasound imaging<sup>15,16</sup>. When the syndrome is not recognized during

pregnancy, the newborn may survive with a low quality of life and, thus, medical team could become involved in surgical procedures<sup>17</sup>. Each malformation causes an impact in the psychological sphere of both the individual and the family<sup>18</sup>. Last but not the least, the failure of an early diagnosis may lead to medical-legal issues<sup>19–21</sup>.

## Consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient and her husband.

## Author contributions

LV: conception and design. RG: performed the ecography and drafted the article. All authors revised the manuscript for intellectual content and approved the final manuscript for publication.

## Competing interests

No competing interests were disclosed.

## Grant information

The author(s) declared that no grants were involved in supporting this work.

## Acknowledgements

Special thanks to Professor Salvatore Sciarretta and Andreea Olteanu for their precious help in revising the English version of this work.

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# Open Peer Review

Current Referee Status:



## Version 2

Referee Report 10 December 2015

doi:10.5256/f1000research.4647.r4026



**Orkun Çetin**

Obstetrics and Gynecology, Istanbul Suleymaniye Birth and Gynecology Training and Research Hospital, Istanbul, Turkey

I appreciate your work and thank you for your effort. However I have some considerations to be clarified.

1. The manuscript needs a light sub-edit for the English.

2. The authors made the final diagnosis only with the clinical findings. However, there were not any photos that confirmed CdLS. If possible, the autopsy photos should be added to the manuscript.

The manuscript could be accepted after minor revisions.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

Referee Report 28 May 2015

doi:10.5256/f1000research.4647.r8779



**Laird Jackson**

Department of Obstetrics and Gynecology, Drexel University, Philadelphia, PA, USA

The authors have responded appropriately to the earlier comments except in one instance. It may be due to language differences but the term "unreliable" should not be used to describe the genetic tests referred to in the paper. The tests are "reliable" if performed properly; in that they do or do not demonstrate a copy-number change (if by microarray) or a point mutation (if by some means of genome sequencing). What the authors intend to say is that a negative test (i.e. one that does not demonstrate a molecular change), is not equivalent to ruling out the clinical diagnosis. So they might simply say that the molecular tests are only "conclusive" in about 60-70% of the clinically recognized cases.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

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**Version 1**

Referee Report 14 April 2014

doi:10.5256/f1000research.1212.r4483

**Laird Jackson**

Department of Obstetrics and Gynecology, Drexel University, Philadelphia, PA, USA

I agree with the report and comments of [Dr Jinglian Liu](#), who has also reviewed this article. The case report is interesting in its detail of the prenatal ultrasound examination and observations, but completely fails its responsibility to connect those observations to appropriate use of contemporary molecular diagnostic opportunities. As such, this article fails the medical community by not accepting the opportunity to connect their useful prenatal morphological observations to detectable objective molecular findings.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

Referee Report 14 February 2014

doi:10.5256/f1000research.1212.r3450

**Jinglan Liu**

Department of Pediatrics, Drexel University, Philadelphia, PA, USA

This manuscript describes a fetus with clinical features suggestive of Cornelia de Lange Syndrome (CdLS).

My comments are as follows:

1. Data from mutational testing on known CdLS genes (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, and *HDAC8*) would be important for this case. The article published by [Clark \*et al.\* \(2012\)](#) which was also cited by the authors, recommends molecular analysis of CdLS genes to prenatal diagnosis of CdLS.
2. The authors should compare prenatal findings in the current case with what described in the article by [Clark \*et al.\* \(2012\)](#). Without molecular testing data, I would like to see a table demonstrating the current case presenting prenatal clinical features consistent with what has been documented in the literature by studying a larger cohort of probands.
3. In the discussion, in the beginning of first paragraph, the authors claim that CdLS is diagnosed primarily by morphological characteristic and cited a paper published in 1933. At present, the diagnosis criteria of CdLS cannot be the same as what was 90 years ago, particularly with the identification of specific gene mutations in CdLS probands. Please re-phrase this part, and cite updated references.

4. In the end of the discussion, what does it mean “genetic tests are not reliable”? As a matter of fact, molecular testing has become a widely accepted concept and a popular diagnostic approach for individuals with congenital anomalies.

Minor things:

1. OMIM numbers of CdLS and disease genes should be given.
2. Please double check the spelling and eliminate typographic errors, also, some terms are not accurately used. Below is listed some examples of those errors:
  - Abstract – “kariotype” -> “karyotype”
  - Introduction – “psychical” - > I’d like to use “neuropsychiatric”
  - 2<sup>nd</sup> paragraph in case report – “dimorphism” -> “dysmorphism”
  - 2<sup>nd</sup> paragraph in discussion – “cohesion” -> “cohesin”
  - 2<sup>nd</sup> paragraph in discussion – please italicize the gene names “NIPBL” and “HDAC8”
  - 2<sup>nd</sup> paragraph in discussion – “familiarity” ? What does it mean? Why not change to “no family history”

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

Author Response 01 Sep 2014

**vito leanza, Italy**

1. *“Data from mutational testing on known CdLS genes (NIPBL, SMC1A, SMC3, RAD21, and HDAC8) would be important for this case. The article published by Clark et al. (2012) which was also cited by the authors, recommends molecular analysis of CdLS genes to prenatal diagnosis of CdLS.”*

In our case report, data from mutational testing on known CdLS genes (*NIPBL, SMC1A, SMC3, RAD21, and HDAC8*) are negative, indeed it was called atypical Cornelia de Lange Syndrome (CdLS).

Mutations in *NIPBL* are not present in all cases and they account for about 60% of CdLS; mutations in *SMC1A* and *SMC3* account for a small percentage (Deardorff et al., 2011).

2. *“The authors should compare prenatal findings in the current case with what described in the article by Clark et al. (2012). Without molecular testing data, I would like to see a table demonstrating the current case presenting prenatal clinical features consistent with what has been documented in the literature by studying a larger cohort of probands.”*

Cornelia de Lange Syndrome (CdLS) is a multisystem developmental disorder

characterized by growth retardation, cognitive impairment, external and internal structural malformations, and characteristic facial features. Currently, there are no definitive prenatal screening measures that lead to the diagnosis of CdLS. (Clark *et al.* 2012).

In our case (atypical CdLS) increased nuchal translucency in the first trimester, normal karyotype, saddle nose, micrognathia with receding jaw, low set ears, facies senilis, arthrogryposis of the hands, absence of the Aranzio ductus venous, dilatation of gallbladder and bowel, a unique umbilical artery, increased volume of amniotic fluid, and intrauterine growth retardation were found.

Fewer than 1% of individuals diagnosed with Cornelia de Lange syndrome have an affected parent.

Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical examination for features of CdLS, complete with plotting of growth parameters and molecular genetic testing if the NIPBL mutation has been identified in the proband. In our atypical Cornelia de Lange syndrome molecular tests of parents were negative.

3. *"In the discussion, in the beginning of first paragraph, the authors claim that CdLS is diagnosed primarily by morphological characteristic and cited a paper published in 1933. At present, the diagnosis criteria of CdLS cannot be the same as what was 90 years ago, particularly with the identification of specific gene mutations in CdLS probands. Please re-phrase this part, and cite updated references."*

Diagnosis is based on clinical findings. High-resolution ultrasound examination to follow growth and to evaluate the limbs, heart, diaphragm, palate, and other organs or structures affected in CdLS is fundamental. Reported prenatal ultrasound findings include: increased nuchal translucency in the first trimester [Sekimoto *et al.*, 2000; Huang & Porto, 2002]; Growth failure, which typically presents in the second trimester; and the typical *in utero* facial profile of a fetus with CdLS consisting of micrognathia, a prominent upper lip, and a depressed nasal bridge with somewhat anteverted nares [Ranzini *et al.*, 1997; Boog *et al.*, 1999; Urban & Hartung, 2001].

4. *"In the end of the discussion, what does it mean "genetic tests are not reliable"? As a matter of fact, molecular testing has become a widely accepted concept and a popular diagnostic approach for individuals with congenital anomalies."*

Genetic tests are not reliable when negative. On the contrary when positive they are important for syndrome.

Indeed, mutations in NIPBL are not present in all cases and they account for about 60% of CdLS; mutations in SMC1A and SMC3 account for a small percentage (Deardorff *et al.*, 2011).

Minor things:

These minor things are easy to correct. I thank the first referee for his clarifications.

**Competing Interests:** No competing interests were disclosed.



