ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2025;96(4):525-530
DOI: 10.32641/andespediatr.v96i4.5532

CLINICAL SERIE

Clinical and molecular findings in Cornelia de Lange syndrome. Case series

Hallazgos clínicos y moleculares en el síndrome de Cornelia de Lange. Serie de casos

Gustavo Keilhold[a], Antonio Cárdenas Tadich[a], Carmen Ludeña[a], Maykol Araya Castillo[b], Martina Keilhold[c], Michele Callea[d,e], Francisco Cammarata-Scalisi[a]

[a]Servicio de Pediatría, Hospital Regional de Antofagasta. Antofagasta, Chile.
[b]Laboratorio Clínico. Hospital Regional de Antofagasta. Antofagasta, Chile.
[c]Interna de Medicina, Universidad Andrés Bello. Santiago, Chile.
[d]Postgraduate Program in Oral Surgery, University of Florence. Florence, Italy.
[e]Doctoral Program in Molecular Genetics and Biotechnology, Graduate School, University of Nova Gorica, Nova Gorica, Slovenia.

Received: December 2, 2024; Approved: March 16, 2025

What do we know about the subject matter of this study?

Cornelia de Lange syndrome (CdLS) is a rare, congenital genetic disorder with a very heterogeneous clinical phenotype, so it is necessary to recognize it early to ensure a multidisciplinary and individualized approach, in addition to providing timely family genetic counseling.

What does this study contribute to what is already known?

It describes the clinical presentation of six patients diagnosed with CdLS, all originally from and residing in the Antofagasta Region, underlining the importance of their clinical follow-up. It also describes its main etiopathogenic cause, which highlights three heterozygous variants in the NIPBL gene and one in the SMC3 gene, not previously described in the literature.

Abstract

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder caused by pathogenic variants in genes related to the regulation of cohesin transcription. It presents a very heterogeneous clinical phenotype, with wide variability in severity. **Objective:** To describe the clinical and molecular findings in patients diagnosed with CdLS. **Patients and Method:** Observational and descriptive study conducted in patients with CdLS evaluated between April 1, 2020, and April 1, 2024, at the Clinical Genetics Unit, Pediatrics Service, of the *Hospital Regional de Antofagasta*. The diagnostic algorithm suggested by the first international consensus statement for CdLS was used, and the results of the genetic studies were analyzed **Results:** Six patients aged 0–17 years were included; 4 were male. Global developmental delay and/or intellectual disability, the presence of synophrys, abnormalities of the nose and lips, and hypertrichosis were confirmed in all patients. Heterozygous variants in the *NIPBL* gene were found in 5/6 patients (83.33%), all classified as pathogenic and associated with cases of classic

Keywords:
Cornelia de Lange;
Synophrys;
NIPBL;
Genetic Counseling

Correspondence:
Francisco Cammarata-Scalisi
francocammarata19@gmail.com

Edited by:
Luisa Schonhaut Berman

How to cite this article:Andes pediatr. 2025;96(4):525-530. DOI: 10.32641/andespediatr.v96i4.5532

CdLS. Four of the variants described in this study have not been previously reported in the literature. **Conclusions:** Neurological alterations, facial dysmorphism, and hypertrichosis were present in all patients studied. Heterozygous pathogenic variants in the *NIPBL* gene represented the main etiopathogenic cause, allowing for timely family genetic counseling.

Introduction

The Cornelia de Lange syndrome (CdLS; OMIM# 122470, 300590, 610759, 614701, 300882, 620568)[1-5], is a rare genetic disorder caused by pathogenic variants in genes related to the regulation of cohesin transcription (table 1)[1,6]. It presents a very heterogeneous clinical phenotype with wide variability in severity[1-3,6,7], characterized by prenatal and/or postnatal growth retardation[1-5], developmental and intellectual disorder[1-5,7], epilepsy[2], autism spectrum disorder[1,2], behavioral disorders[1-4], anxiety, attention deficit hyperactivity[1], self-injurious behaviors[1,2], myopia, hearing loss, and feeding difficulties[2]. Craniofacial malformations are distinctive and include microbrachycephaly[2,3,5], arched eyebrows[3], synophrys, long eyelashes, depressed nasal bridge, short nose with anteverted nostrils, long philtrum, thin upper lip[2,3], downturned corners of the mouth[2], delayed tooth eruption[3], small, widely spaced or missing teeth, high arched palate, and micrognathia[2,3]. Other common findings include upper limb reduction defects ranging from complete absence of the forearms to subtle phalangeal anomalies[1-3,5,7], hypertrichosis[2], and multisystem abnormalities such as congenital heart disease (septal defects)[2], as well as gastrointestinal[8], renal[9], and genital abnormalities[2]. The natural history of the disease includes multiple chronic conditions, so it is essential to properly plan and address the follow-up of affected individuals[5].

CdLS was described by pediatrician Cornelia de Lange in 1933 in two unrelated girls with similar clinical features[10]. Meinecke and Hayek in 1990[11] reported that Vrolik in 1849 and Brachmann in 1916 described cases with a similar phenotype[12,13]. The first case in Chile was published in 1968, although previously Núñez and Urrizola had presented a case at the *Sociedad de Pediatría de Concepción*[14]. Broitman et al[15] in 1980 presented a series of four clinical cases. The estimated incidence is between 1 in 10,000-30,000 live births[2-5] and may be higher due to undetected mild cases[2].

CdLS is caused by haploinsufficiency of gene variants encoding components of the cohesin complex or proteins that regulate its loading and recycling[8]. It is associated with pathogenic variants in the *NIPBL* gene (OMIM *608667), in approximately 60-70% of cases, and presents with a classic phenotype[1,2,4]. On the other hand, variants in the genes *SMC1A* (OMIM *300040), *SMC3* (OMIM *606062), *RAD21* (OMIM *606462), *HDAC8* (OMIM *300269)[1,4], and *MAU2* (OMIM *614560)[9] are responsible for 10-15% of cases[1,4], and in 15% of cases, there is no molecular diagnosis[9]. Carriers of variants in the genes *SMC1A*, *SMC3*, *RAD21*, *BRD4* (OMIM *608749), and *ANKRD11* (OMIM *300269) predominantly present with the non-classical or atypical form[1], while pathogenic variants in the *HDAC8* gene have been associated with classical and non-classical forms[1,2].

The objective of this study is to describe the clinical and molecular findings in patients diagnosed with CdLS.

Patients and Method

Observational and descriptive study conducted in patients with clinical diagnosis and molecular confirmation of CdLS evaluated at the Clinical Genetics Polyclinic in the Pediatrics Service of the *Hospital Regional de Antofagasta*, from April 01, 2020, to April 01, 2024. Through a data collection instrument previously reviewed and approved by two experts, family and personal history were recorded, and genealogy was constructed in each case. The diagnostic algorithm suggested by the first international consensus statement for CdLS[16] was used, in which a score is assigned based on the presence of cardinal or suggestive characteristics in the patient, and the total score determines the corresponding classification (table 2). The results of the genetic studies (panel for CdLS and related disorders or exome sequencing) were also analyzed. Legal guardians provided consent for genetic studies, data analysis and presentation, as long as the identification of the patients involved is protected.

Results

Six patients aged 0 to 17 years were included, all from the Antofagasta Region, four of whom were male. In all cases, the affected individual was the only one in their family, and there was no reported history of parental consanguinity.

In the two cases with the highest score according to the diagnostic algorithm suggested by the first con-

Table 1. Inheritance pattern, genes and locus described according to the type of SCdL[1-6]

Type	Inheritance pattern	OMIM	Gene	Locus	OMIM
CdLS 1	AD	122470	*NIPBL*	5p13.2	608667
CdLS 2	XLD	300590	*SMC1A*	Xp11.22	300040
CdLS 3	AD	610759	*SMC3*	10q25.2	606062
CdLS 4	AD	614701	*RAD21*	8q24.11	606462
CdLS 5	XLD	300882	*HDAC8*	Xq13.1	300269
CdLS 6	AD	620568	*BRD4*	19p13.12	608749

CdLS: Cornelia de Lange syndrome; OMIM: Online Mendelian Inheritance in Man; AD: Autosomal dominant; XLD: X-linked dominant.

sensus statement, prenatal diagnosis revealed growth restriction and upper limb reduction defect, suggesting the diagnosis of CdLS. Among the cardinal features, the presence of synophrys and/or thick eyebrows, nasal and lip abnormalities was observed in all cases. Among the suggestive features, global developmental delay and/or intellectual disability, as well as hypertrichosis, were also described in all patients (table 2). Additionally, recurrent infections were described in four cases, with respiratory infections being the most common, and attention-deficit/hyperactivity disorder was described in 3/5 cases, among the most frequent alterations.

Heterozygous variants in the *NIPBL* gene were found in 5/6 patients (83.33%), classified as pathogenic, and two of these were nonsense type (patients 1 and 3). The case with the highest score according to the diagnostic algorithm suggested by the consensus statement (patient 5) presented an intronic variant that was initially classified as of uncertain significance. Following familial variant studies of healthy parents, which showed that it was a *de novo* variant in the patient, and with predictive studies, this variant could be reclassified as pathogenic (table 3). The only variant of uncertain significance found in these cases was of the *SMC3* gene and corresponded to the only case of non-classical CdLS. Of the six variants described, four were not previously described in the literature (table 3).

Table 2. Diagnostic algorithm suggested by the Consensus Statement[10], in the patients studied.

	Score	1	2	3	4	5	6
Cardinal features							
Synophrys and/or thick eyebrows	2	+	+	+	+	+	+
Short nose, concave nasal ridge and/or upturned nasal tip	2	+	+	+	+	+	+
Long and/or smooth philtrum	2	+	+	-	-	+	+
Thin upper lip vermilion and/or downturned corners of mouth	2	+	+	+	+	+	+
Hand oligodactyly and/or adactyly	2	+	+*	-	-	+	-
Congenital diaphragmatic hernia	2	-	-	-	-	+	-
Suggestive features							
Global developmental delay and/or intellectual disability	1	+	+	+	+	+	+
Prenatal growth retardation	1	+	+	+	+	+	-
Postnatal growth retardation	1	+	+	+	+	+	-
Microcephaly (prenatally and/or postnatally)	1	+	+	-	+	+	-
Small hands and/or feet	1	+	-	+	-	+	-
Short fifth finger	1	-	-	-	-	-	-
Hirsutism	1	+	+	+	+	+	+
Total	-	16	15	11	11	18	10

≥ 11 points, of which at least 3 are cardinal: classic CdLS; 9 or 10 points, of which at least 2 are cardinal: non-classic CdLS. 4–8 points, of which at least 1 is cardinal: molecular testing for CdLS indicated. < 4 points: insufficient to indicate molecular testing for CdLS. *Unilateral left.

Table 3. Gene variants found in the patients studied

Patient	Sex	Gene	Variant	Zygosity	Classification	Reference
1	M	*NIPBL*	c.3406G>T (p.Glu1136*)	Heterozygous	Pathogenic	-
2	M	*NIPBL*	Deletion (Exons 2-32)	Heterozygous	Pathogenic	17
3	F	*NIPBL*	c.3316C>T (p.Arg1106*)	Heterozygous	Pathogenic	18
4	M	*NIPBL*	c.64+1G>A (splice donor)	Heterozygous	Pathogenic	-
5	F	*NIPBL*	c.6249+5G>A (Intronic)	Heterozygous	Pathogenic	-
6	M	*SMC3*	c.2752_2754del (p.Asp918del)	Heterozygous	Variant of uncertain significance	-

F: Female; M: Male.

Discussion

In this study, variants in the *NIPBL* gene were the main cause of CdLS and in all cases corresponded to the classic type. The variant found in the *SMC3* gene has been classified as of uncertain significance and corresponded to the only case of non-classical CdLS; however, the patient presented all the facial cardinal features (tables 2 and 3). Patients with pathogenic variants in the *NIPBL*, *RAD21*, *SMC3*, and *BRD4* genes present an autosomal dominant inheritance pattern, while individuals with variants in the *SMC1A* and *HDAC8* genes show an X-linked inheritance pattern[3,6]. Less than 1% of individuals with CdLS with an autosomal dominant inheritance pattern inherit the variant from an affected parent, whereas X-linked variants are usually *de novo*[3]. The hypothesis of germline mosaicism has also been described[6]. All the cases in our study were new in their families, with an autosomal dominant inheritance pattern, an important aspect to know at the time of family genetic counseling.

Pathogenic nonsense variants in the *NIPBL* gene result in a more severe phenotype. Nonsense variants and deletions without a change in reading frame in the *NIPBL*, *SMC1A*, and *SMC3* genes result in a milder form of the disease. Pathogenic nonsense variants and in-frame deletions in the HEAT domain of the NIPBL protein result in a severe phenotype, suggesting that the gene, variant type, and protein domain are important in determining the phenotype[7]. Patients carrying pathogenic nonsense variants in the *NIPBL* gene (1 and 3) had scores of 16 and 11 points, respectively, according to the diagnostic algorithm suggested by the consensus statement, while the highest scoring patient[5] had an intronic variant that was reclassified as pathogenic (tables 2 and 3). The literature mostly presented genotype and phenotype information from North American and European population groups[7], so the local description of the clinical-molecular characteristics of CdLS is necessary to know the form of presentation in the region and to be able to compare it with subsequent national or Latin American studies.

Classical CdLS most commonly arises from variants that form part of the structural and/or regulatory units involved in the function of the highly conserved multiprotein cohesin complex[1-4,6], a cellular machinery responsible for numerous biological processes essential for cell survival, such as regulation of sister chromatid cohesion, DNA repair[2-4,6], DNA replication, centrosome duplication[2], maintenance of genomic stability and organization[4,9], and regulation of gene expression[1-3,6,9]. Non-classic or milder CdLS phenotypes are often attributed to variants in genes encoding structural units of the cohesin complex (*SMC1A*, *RAD21*, *SMC3*) or cohesin-associated proteins (*ANKRD11*, *BRD4*, among others)[1,6]. However, cell lines from individuals with CdLS do not present cohesion defects, but a global dysregulation of gene expression is observed, which may be considered responsible for the disease phenotype[4].

Recently, variants have also been identified in the genes *STAG1* (OMIM *604358), *KMT2A* (OMIM *159555), *SETD5* (OMIM *615743), *HDAC2* (OMIM *605164), *MAU2* (OMIM *614560), *ZMYND11* (OMIM *608668), *MED13L* (OMIM *608771), *PHIP* (OMIM *612870), and *EP300* (OMIM *602700) that cause CdLS or a similar phenotype[7]. Pathogenic variants in the *ANKRD11* gene previously known to cause KBG syndrome have been identified in patients with a CdLS-like phenotype, so additional causative genes

and epigenetic mechanisms will continue to be identified within the spectrum[2].

Most cases of CdLS are clinically diagnosed at birth. However, certain phenotypic features allow prenatal detection during second and third trimester ultrasound, such as growth restriction in the second trimester, increased nuchal translucency in the first trimester, plus typical facial features including micrognathia, a prominent upper lip, and a depressed nasal bridge with anteverted nostrils[2]. In this series, prenatal diagnosis of CdLS was suggested in two cases in the presence of intrauterine growth restriction and upper limb reduction defect.

In 2018, the first international consensus statement describing a scoring system to classify the severity of the syndrome was published[16], based on a detailed diagnostic algorithm based on the combination of cardinal and suggestive features, and can be easily followed by pediatricians upon suspicion of the diagnosis[9]. A score ≥ 11 confirms the clinical diagnosis of classic CdLS, even in the absence of a molecular diagnosis[4]. In this case series, this statement was used to describe the phenotypic variability of the patients studied (table 2). Clinical follow-up should be multidisciplinary, early, and individualized in these patients, given the involvement of different systems and severity of the phenotype.

In particular, most of these genes have previously been associated with neurodevelopmental disorders that share partial phenotypic overlap with CdLS, such as Rubinstein-Taybi syndrome (OMIM #180849, #613684), KBG syndrome (OMIM #148050), Coffin-Siris syndrome (OMIM #135900), Wiedemann-Steiner syndrome (OMIM #605130), Kabuki syndrome (OMIM #147920, #300867)[3,4], and CHOPS syndrome (OMIM #616368)9, which represent the main differential diagnoses.

Conclusions

We presented a series of six CdLS cases, five of which correspond to the classic type, in which neurological abnormalities, facial dysmorphisms, and hypertrichosis were present in all the patients studied. All classic CdLS were associated with heterozygous pathogenic variants in the *NIPBL* gene, representing the main etiological cause, as described in the literature, and required for timely family genetic counseling. Three variants in this gene had not been previously described, highlighting the molecular findings of CdLS in the patients studied in the Antofagasta Region. This represents the first case series in the country with molecular confirmation.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. Ng R, O'Connor J, Summa D, Kline AD. Neurobehavioral and developmental profiles: genotype-phenotype correlations in individuals with Cornelia de Lange syndrome. Orphanet J Rare Dis. 2024;19(1):111. doi: 10.1186/s13023-024-03104-1.
2. Iftikhar A, Barnes K, Figueroa M, Francis AP. Early prenatal diagnosis of Cornelia de Lange's syndrome with whole-exome sequencing: A case report. AJP Rep. 2024;14(1):e31-3. doi: 10.1055/s-0043-1776149.
3. Conti B, Rinaldi B, Rimoldi M, et al. Chung-Jansen syndrome can mimic Cornelia de Lange syndrome: Another player among chromatinopathies? Am J Med Genet A. 2023;191(6):1586-92. doi: 10.1002/ajmg.a.63164.
4. Parenti I, Kaiser FJ. Cornelia de Lange syndrome as paradigm of chromatinopathies. Front Neurosci. 2021;15:774950. doi: 10.3389/fnins.2021.774950.
5. Selicorni A, Mariani M, Lettieri A, Massa V. Cornelia de Lange syndrome: From a disease to a broader spectrum. Genes (Basel). 2021;12(7):1075. doi: 10.3390/genes12071075.
6. Tehrani Fateh S, Mohammad Zadeh N, Salehpour S, et al. Comprehensive review and expanding the genetic landscape of Cornelia-de-Lange spectrum: insights from novel mutations and skin biopsy in exome-negative cases. BMC Med Genomics. 2024;17(1):20. doi: 10.1186/s12920-024-01798-7.
7. Seymour H, Feben C, Nevondwe P, et al. Mutation profiling in South African patients with Cornelia de Lange syndrome phenotype. Mol Genet Genomic Med. 2024;12(1):e2342. doi: 10.1002/mgg3.2342.
8. Foglia M, Guarrera L, Kurosaki M, et al. The *NIPBL*-gene mutation of a Cornelia de Lange syndrome patient causes deficits in the hepatocyte differentiation of induced Pluripotent Stem Cells via altered chromatin-accessibility. Cell Mol Life Sci. 2024;81(1):439. doi: 10.1007/s00018-024-05481-z.
9. Ascaso Á, Arnedo M, Puisac B, et al. Cornelia de Lange spectrum. An Pediatr (Engl Ed). 2024;100(5):352-62. doi: 10.1016/j.anpede.2024.04.012.
10. de Lange C. *Sur un type nouveau de degenerescence (typus Amstelodamensis).* Arch Med Enfants. 1933;36:713-9.
11. Meinecke P, Hayek H. Brief historical note on the Brachmann-de Lange syndrome: A patient closely resembling the case described by Brachmann in 1916. Am J Med Genet. 1990;35:449-50. doi: 10.1002/ajmg.1320350328.
12. Brachmann W. A case of symmetrical monodactyly, representing ulnar deficiency, with symmetrical antecubital webbing and other abnormalities, (dwarfism, cervical ribs, hirsutism) Jarb Kinder Phys Erzie. 1916;84:225-35.
13. Vrolik W. *Tabulae ad illustrandam embryogenesin hominis et mammalium tam naturalem quam abnormem.* Amstelodami; London, UK: 1849.
14. Oroz J, Duarte J. Síndrome Cornelia de Lange. Pediatría (Chile)1968;11:125.
15. Broitman H, Heredia F, Campos D. Síndrome Cornelia de Lange. Rev Chilena Pediatr.1980;51(1):55-8.
16. Kline AD, Moss JF, Selicorni A, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018;19(10):649-66. doi: 10.1038/s41576-018-0031-0.
17. Gervasini C, Parenti I, Picinelli C, et al. Molecular characterization of a mosaic *NIPBL* deletion in a Cornelia de Lange patient with severe phenotype. Eur J Med Genet. 2013;56(3):138-43. doi: 10.1016/j.ejmg.2012.
18. Nizon M, Henry M, Michot C, et al. A series of 38 novel germline and somatic mutations of *NIPBL* in Cornelia de Lange syndrome. Clin Genet. 2016;89(5):584-9. doi: 10.1111/cge.12720.