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Review Article

A Review on Cornelia De Lange Syndrome

Chothave Pradnya, DR.Bhangale Charushila

Department of Pharmaceutical Chemistry , Pravara Rural Education Society's College of Pharmacy (For Women) , Chincholi, Nashik, Maharashtra, India.

A B S T R A C T

Cornelia de Lange Syndrome (CdLS) is a rare genetic condition that affects multiple body systems. It is marked by distinctive facial features, delayed growth, limb differences, and a wide range of cognitive and behavioral challenges. First identified in 1933 by Dutch pediatrician Cornelia de Lange, the syndrome occurs in roughly 1 in 10,000 to 30,000 live births. The severity of CdLS varies widely, from classic, clearly recognizable cases to milder or atypical forms with subtler features. The disorder is mainly caused by mutations in genes related to the cohesin complex—such as NIPBL, SMC1A, SMC3, RAD21, HDAC8, BRD4, ANKRD11, and MAU2—which disrupt gene regulation, DNA repair, and oxidative stress responses, though basic sister chromatid cohesion is usually intact. Individuals with CdLS may display a combination of facial and limb abnormalities, growth restriction, intellectual disability, behavioral difficulties, and problems involving organs such as the heart, digestive system, kidneys, eyes, and reproductive organs. Mosaicism is relatively common and can influence the severity and variability of symptoms, sometimes making diagnosis more challenging. Genetic testing through targeted gene panels or exome sequencing is key for diagnosis, with careful selection of tissue samples to detect mosaic variants. Prenatal diagnosis is possible in families at risk or when ultrasound findings raise suspicion, but interpretation can be complex. Managing CdLS requires a multidisciplinary approach, including nutritional support, surgical interventions, medications for seizures or behavioral concerns, and ongoing therapies such as physical, occupational, and speech therapy. Despite advances in genomic research, some cases remain unexplained, underscoring the complexity of this condition.

Keywords: Cornelia de lange syndrome, Biological functions, Dysmorphia, Visceral defects, Mosaicism, Prenatal diagnosis, Treatment.

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*Address for Correspondence:

Chothave Pradnya, Department of Pharmaceutical Chemistry , Pravara Rural Education Society's College of Pharmacy (For Women) , Chincholi, Nashik, Maharashtra, India.

INTRODUCTION

Cornelia de Lange Syndrome (CdLS) is a rare, complex genetic disorder listed in the Online Mendelian Inheritance in Man (OMIM) database under entries 122470, 300590, 300882, 610759, and 614701. It affects multiple body systems and is characterized by distinctive physical features, developmental delays, and behavioral challenges. The syndrome is named after Dutch pediatrician Cornelia de Lange, who first described it in two infants in 1933. CdLS occurs in approximately 1 in 10,000 to 1 in 30,000 live births. The classic form of the disorder can often be recognized at birth by experienced pediatricians and genetic specialists due to its characteristic facial features, growth delays, and limb abnormalities. However, not all individuals display the full spectrum of features. The condition ranges widely in severity, from classic cases with obvious signs to milder or atypical forms with subtle facial or limb differences. Advances in genome-wide testing have helped identify genetic variants in cohesin-related genes, such as NIPBL, SMC1A, SMC3, RAD21, HDAC8, and others, which are central to CdLS. Yet, genetic findings have revealed complexity, as some individuals with mutations in these genes may show atypical features or resemble other developmental syndromes. Overall, CdLS is best understood as a spectrum disorder, with the classic phenotype at one end and milder or atypical forms at the other, all linked to dysfunction in cohesin-related pathways, though not all cohesinopathies result in CdLS.(1,2)

History of Cornelia de Lange Syndrome (CdLS)

The earliest documented case resembling CdLS was reported in 1916 by Winfried Robert Clemens Brachmann, a German physician. He described a 19-day-old infant who died of malnutrition and pneumonia, noting several unusual physical features, including ulnar limb defects, excessive hair growth, and abnormal facial characteristics such as a widened forehead. Brachmann's observations highlighted the uniqueness of the case, but his research was interrupted due to military service during World War I.The condition was later more thoroughly described in 1933 by Dutch pediatrician Cornelia Catharina de Lange, after whom the syndrome is now named. De Lange, one of the early female physicians in the Netherlands, observed two unrelated infants with strikingly similar features, including distinctive facial traits, growth delays, and limb abnormalities. She referred to the condition as "typus Amstelodamensis". Her early reports focused on both somatic and behavioral characteristics, though at the time intellectual disability was assessed through observation rather than formal testing.

De Lange conducted detailed examinations, including microscopy of blood and urine, skull X-rays, and autopsies, noting brachycephaly, limb malformations, and characteristic hand and foot shapes. She described hands and feet as small and chubby, with short fingers, curved little fingers, and proximally positioned thumbs, which she compared to those of primates. The similarity between her first and second patients reinforced her suspicion of a genetic basis for the disorder.In 1938, De Lange published a follow-up report on a series of five cases, including additional patients from other reports. She documented neurological and radiographic findings, as well as detailed observations from autopsies, including microscopic abnormalities in the cerebral hemispheres and rare peritoneal findings. These meticulous studies provided early insight into the phenotypic and anatomical features of the syndrome.Later, in 1985, John Marius Opitz recognized the historical significance of Brachmann's work, suggesting that the eponym "Brachmann-de Lange syndrome" be used to honor both physicians, though the name Cornelia de Lange syndrome (CdLS) remains widely accepted.(3,4,5)

Biological functions that are disturbed in Cornelia de Lange Syndrome

In Cornelia de Lange syndrome (CdLS), sister chromatid cohesion itself remains unaffected, meaning the exact molecular basis of the disorder is still not fully understood. However, several key biological processes have been found to function abnormally in CdLS, such as gene transcription, RNA formation, DNA repair, and the body's response to oxidative stress. The cohesin complex—along with its loading protein NIPBL and the insulator protein CTCF—plays an essential role in regulating how enhancers and promoters interact to form topologically associating domains (TADs) within the genome. Studies have shown that in CdLS, cohesin tends to bind more frequently to promoter and nearby regions, and this binding is often linked to actively transcribed genes. Furthermore, cells from CdLS patients carrying pathogenic variants in the SMC1A gene or having reduced NIPBL expression display a distinct pattern of gene expression changes compared to normal cells.(6,7).

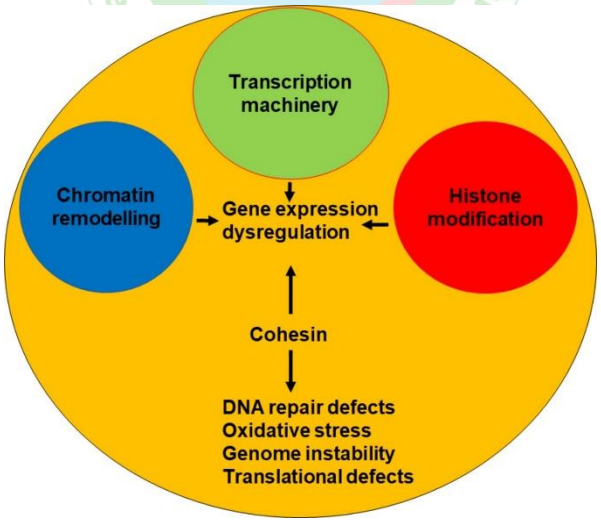
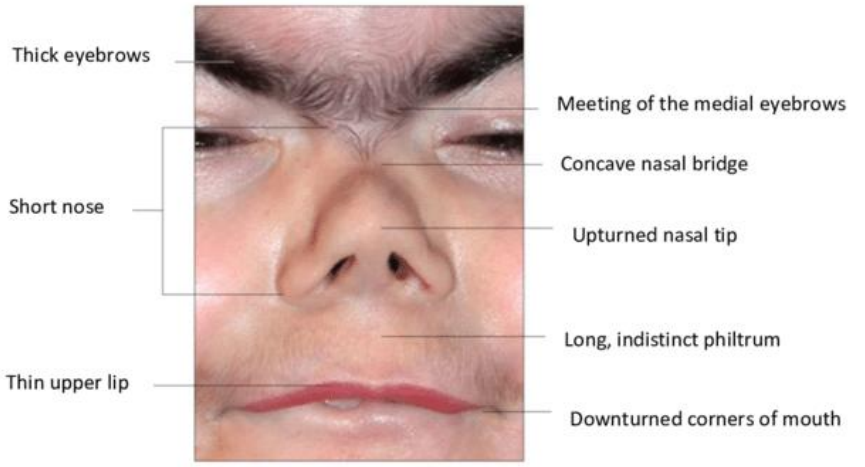


Figure 1: Cohesin malfunction in Cornelia de Lange syndrome (CdLS) disrupts gene regulation. It affects key processes like chromatin remodeling, histone modification, and transcription, leading to issues such as DNA repair defects, oxidative stress, and genome instability.

Clinical characteristics

Cornelia de Lange syndrome (CdLS) presents with a wide range of clinical features, varying from mild to severe forms. The severe or classic type is marked by distinct facial characteristics, growth restriction beginning before birth and continuing throughout life (typically below the 5th percentile), excess body hair (hypertrichosis), and upper limb abnormalities, which can range from minor finger deformities to missing digits.Typical facial features include joined eyebrows (synophrys), thick or highly arched eyebrows, long eyelashes, a short nasal bridge with upturned nostrils, small and widely spaced teeth, and a small head size (microcephaly).People with milder forms of CdLS show less severe issues with growth, cognition, and limb development but often retain the characteristic facial appearance. Intellectual ability in CdLS can vary widely,

with IQ scores ranging from below 30 to around 102 (average of 53). Many individuals also display autistic traits and self-injurious behaviors.Other common health issues include heart defects (such as septal anomalies), digestive problems, hearing impairment, short-sightedness (myopia), and underdeveloped or undescended genitalia (cryptorchidism or hypoplasia).(8)



Clinical Presentations of CdLS:

Dysmorphia

Facial abnormalities are the most consistent and recognizable features of Cornelia de Lange Syndrome (CdLS). Common characteristics include a short neck, low hairline at the back of the head, prominent or hirsute forehead, arched eyebrows with a unibrow (synophrys), and sometimes drooping eyelids (ptosis). Individuals often have long, thick eyelashes, low-set ears, a flattened midface, a short nose, and an elongated area between the nose and upper lip (philtrum).Oral features frequently include a thin upper lip with downward-turned corners, a high palate, widely spaced teeth, and a small jaw (micrognathia). About 20% of individuals have a cleft palate, most of which are submucous.

Limb abnormalities are also common. Hands and feet may be small, and upper limb reduction defects can range from shortened first metacarpal bones, proximally positioned thumbs, short or curved fingers (brachydactyly and clinodactyly), to missing fingers or forearm bones. More than half of individuals have single palmar creases, and about one-third have more severe upper limb malformations, such as oligodactyly, ulnar deficiency, or absent forearms. Lower limbs are usually less affected. Some individuals may also experience radial head dislocation, fused radius and ulna (radioulnar synostosis), or limited elbow extension.Additional findings include excessive hair growth (hirsutism) on the face, back, and limbs and cutis marmorata (a marbled skin appearance) in roughly half of affected individuals.(9)

Growth and Development in Cornelia de Lange Syndrome (CdLS)

Individuals with CdLS typically have small, proportionate stature that begins before birth, often noticeable in the late second trimester. At birth, their size measurements are usually below the 10th percentile and can fall below the 5th percentile during early childhood, although their growth generally follows standard growth patterns. Specialized CdLS growthcharts are available to monitor their development. By adulthood, both height and weight remain well below the 3rd percentile, and the average head circumference is around 49 cm, reflecting significant microcephaly.

Developmentally, delays and intellectual disabilities are common. Speech and language skills are often the most affected, while visual-spatial memory and perceptual skills tend to be better preserved. Intellectual functioning usually ranges from mild to moderate impairment, though cases with borderline normal or severe intellectual disability are also reported. Learning continues throughout life without regression, and early intervention programs have been shown to improve developmental outcomes, making ongoing support crucial.

Visceral Defects in Cornelia de Lange Syndrome (CdLS)

CdLS affects multiple organ systems, and feeding difficulties are common in infancy and early childhood. These challenges often lead to gastroesophageal reflux disease (GERD), which usually requires medical treatment and, in many cases, surgical intervention. Other gastrointestinal issues frequently reported include pyloric stenosis, diaphragmatic hernia, intestinal malrotation, and an increased risk of volvulus.Approximately 25% of individuals with CdLS have congenital heart defects, most commonly ventricular septal defects (VSD) or atrial septal defects (ASD), though other cardiac anomalies can also occur. Kidney problems may also arise, including vesicoureteral reflux, pelvic dilation, and renal dysplasia, leading to impaired renal function.The most serious complications and leading causes of death in CdLS are primarily gastrointestinal in nature, such as diaphragmatic hernia in infancy, followed by aspiration pneumonia related to GERD or volvulus later in life.(10)

Behavioral and Neurological Issues in Cornelia de Lange Syndrome (CdLS)

Almost all individuals with CdLS experience behavioral challenges, which are often influenced or worsened by physical health problems. Common behaviors include self-injury, obsessive-compulsive tendencies, attention deficit disorder (with or without hyperactivity), short attention span, depression, and traits associated with autism spectrum disorder. Social and environmental interactions vary widely between individuals, with some engaging more effectively than others.Seizures are the most frequent neurological complication in CdLS. While no specific EEG pattern has been identified, seizures generally respond well to standard treatments. Sleep disturbances are also common.

Brain imaging studies often reveal enlarged ventricles (especially in the basal cisterns), white matter atrophy in the frontal lobes, and underdevelopment of the brainstem and cerebellar vermis. Structural abnormalities of the brain, defective myelination, and neurofibrillary tangles have also been observed in post-mortem studies.Muscle tone can be variable, with both hypertonicity (increased muscle tension) and hypotonia (reduced muscle tone) reported. Many individuals with CdLS appear to have a high pain threshold, likely related to poorly understood peripheral nerve differences.(11)

Findings in Other Organ Systems in Cornelia de Lange Syndrome (CdLS)

Individuals with CdLS can have eye abnormalities, with almost all showing peripapillary pigmentation. Common eye issues include high myopia (nearsightedness), drooping eyelids (ptosis), blepharitis, and mild microcornea. Less frequent problems include nasolacrimal duct obstruction and nystagmus, while cataracts, glaucoma, and other eye malformations are rare.Hearing and balance issues are also common, including sensorineural or conductive hearing loss, recurrent ear infections (otitis media), and sinusitis.Orthopedic problems beyond the upper limb abnormalities can include hip dislocation or dysplasia, scoliosis, tight Achilles tendons, and delayed bone development.Genital abnormalities are frequently observed. In males, these may include undescended testicles (cryptorchidism), small penis (micropenis), and hypospadias, while females may have small labia majora. Most individuals experience normal puberty, though it may be slightly delayed in some cases. Behavioral challenges, especially self-injury and anxiety, often become more pronounced during adolescence. Fertility is generally normal in individuals with milder forms of CdLS.

The long-term natural history of CdLS is not well understood, but there is some evidence suggesting premature aging. There does not appear to be a significant increase in cancer risk, though rare cases such as liver hemangioendothelioma and Wilm's tumor have been reported. Low platelet counts (thrombocytopenia) have also been noted consistently in some individuals.(12)

Genetic Causes of Cornelia de Lange Syndrome (CdLS)

NIPBL is the most frequently affected gene in CdLS, with variants identified in about 70% of cases. Loss-of-function mutations generally lead to more severe symptoms, while missense variants are often associated with milder features. Small deletions within NIPBL and mosaic variants also contribute to the disorder. Although classic CdLS is most often linked to NIPBL mutations, individuals with variants in other causative genes can also display a classic phenotype.

SMC1A, an X-linked gene encoding a core component of the cohesin complex, accounts for roughly 5% of cases. Mutations in SMC1A usually lead to non-classic CdLS, characterized by fuller eyebrows, a rounder face, and a less pronounced shortening of the nasal bridge. About 40% of affected individuals may show a phenotype resembling Rett syndrome rather than CdLS. Females tend to be less severely affected due to X-chromosome inactivation, and mosaic variants have been reported in asymptomatic parents.

SMC3 variants are rare and usually involve missense mutations, as loss-of-function mutations are likely not tolerated. Individuals with SMC3 variants may show atypical CdLS features or isolated intellectual disability and congenital anomalies.

RAD21 variants are also uncommon and typically result in a non-classic CdLS phenotype. Both truncating and missense mutations have been reported, though some missense variants appear in individuals without CdLS, making genotype–phenotype correlations difficult.

BRD4, a protein associated with chromatin regulation, has been implicated in a few cases with atypical CdLS. Mutations in BRD4 can disrupt its interaction with NIPBL, which may underlie the disease mechanism, but the number of reported cases is too small to define a typical phenotype.

HDAC8 is an X-linked gene with mutations reported in both classic and non-classic CdLS. Affected individuals can have additional distinctive features, such as a large anterior fontanel, widely spaced eyes (orbital hypertelorism), and cheerful personalities. Female carriers may be variably affected depending on which X chromosome is inactivated.

ANKRD11 variants have been identified in a small number of individuals with non-classic CdLS, showing overlapping facial and minor CdLS features.

Other genes occasionally associated with CdLS-like features include EP300, AFF4 (linked to CHOPS syndrome), NAA10, and TAF6. In these cases, the phenotype is often limited or atypical, and individuals may not meet the full clinical criteria for CdLS.

Overall, CdLS is a genetically heterogeneous disorder primarily involving cohesin-related genes, with variability in severity and phenotype depending on the specific gene and type of mutation.(13)

Mosaicism

Mosaicism is quite common in Cornelia de Lange syndrome (CdLS). Around 15–20% of individuals who show classic symptoms of the condition have mosaic mutations in the NIPBL gene, which often cannot be detected in blood cells (lymphocytes). In some rare cases,

people with CdLS may also have mosaic variants in genes such as SMC3, RAD21, or SMC1A.It is believed that mosaicism contributes to differences in the severity of symptoms seen among individuals, although this has not yet been proven scientifically. Interestingly, researchers have observed selection against blood cells carrying faulty HDAC8, meaning that such abnormal cells may not survive. Similarly, cases where NIPBL variants are absent inblood but present in other tissues suggest that the body may favor normal cells in the blood while allowing mosaic variants to exist in other tissues.

To accurately detect mosaicism, the most reliable method is testing DNA from uncultured fibroblasts (skin cells). However, when that's not possible, DNA from buccal swabs (cheek cells), cultured fibroblasts, bladder cells, skin biopsies, or surgical tissue samples can also be used, as these approaches have increased the chances of identifying mosaic variants in CdLS.(14)

Sister Chromatid Cohesion Defects Are Unlikely to Cause CdLS

The cohesin complex plays several important roles in the cell, including holding sister chromatids together during cell division, repairing DNA, and regulating gene expression. Because the genes mutated in Cornelia de Lange Syndrome (CdLS) are involved in cohesin function, scientists initially thought that the developmental problems in CdLS might result from defects in sister chromatid cohesion or from delays in the cell cycle.However, research so far does not clearly support this idea. Studies using cells derived from CdLS patients generally show no obvious cohesion defects. In one study, only a small proportion of cells in about 40% of patient cell lines exhibited minor cohesion problems, while another study found none at all. Interestingly, cells from patients with NIPBL or SMC1A mutations do show mild problems with DNA repair, suggesting that while cohesion itself may not be severely disrupted, at least one of cohesin's critical functions is somewhat impaired.(15)

Molecular Diagnosis

Cornelia de Lange syndrome (CdLS) can be confirmed through genetic testing that identifies a harmful (pathogenic) change in one of the five main genes responsible for the disorder — NIPBL, SMC1A, SMC3, RAD21, and HDAC8 — all of which are linked to the cohesin complex. In addition, newer research has revealed three more genes (BRD4, ANKRD11, and MAU2) that may also contribute to the condition, though with less certainty.

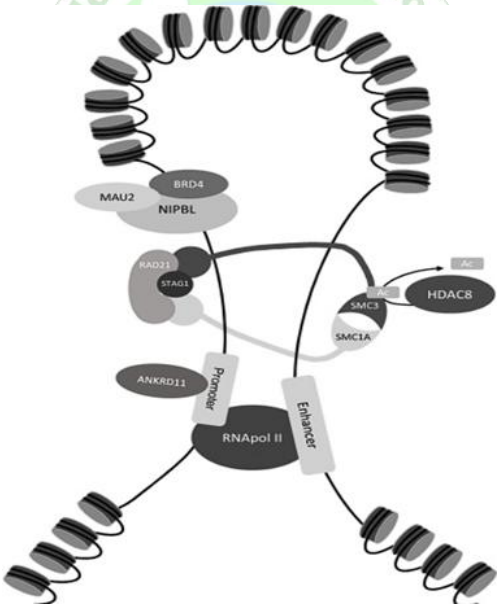


Figure 2 : The cohesin complex and its partner proteins help regulate how genes are switched on and off. Proteins such as SMC1A, SMC3, RAD21, NIPBL, MAU2, BRD4, HDAC8, and ANKRD11 work together to shape the DNA into loops, bringing key control regions—enhancers and promoters—closer together so genes can function correctly. When any of theseproteins are altered or disrupted, gene regulation is disturbed, which can lead to Cornelia de Lange syndrome (CdLS).

The cohesin complex itself is a critical molecular structure composed of several proteins, including SMC1A, SMC3, and RAD21, whichform its core ring, and regulatory proteins like NIPBL and HDAC8. NIPBL plays a key role in loading cohesin onto DNA, while HDAC8 helps release it when needed. This complex performs several essential functions in the body, such as maintaining chromosome organization, ensuring genome stability, and most importantly, regulating gene expression.More than 60% of CdLS cases are caused by mutations in the NIPBL gene, which affects how genes are switched on or off across the body. Because of this widespread disruption in gene regulation, CdLS is often described as a "transcriptomopathy" — a disorder resulting from abnormal global gene expression, explaining its wide range of symptoms and severity among individuals.Recent advances in high-throughput sequencing technologies have made it easier to identify new genes involved in CdLS, particularly in patients who show mild or atypical features. For instance, ANKRD11 helps regulate gene transcription, while MAU2 and BRD4 interact directly with NIPBL, providing further insight

into the disease's complexity.Due to the genetic and clinical variability seen in CdLS, especially in non-classic or mild cases, diagnosing the condition can sometimes be challenging. Therefore, next-generation sequencing (NGS) is recommended as a first step, since it allows simultaneous analysis of multiple genes. Nowadays, doctors often use gene panels that include CdLS-related and neurodevelopmental genes, or clinical exome sequencing, which can assess thousands of genes at once. As sequencing technologies become faster, cheaper, and more automated, whole-exome or even whole-genome sequencing may soon become the standard diagnostic tool.

If these tests fail to detect any abnormalities, an array comparative genomic hybridization (CGH) test may be performed to look for chromosomal changes or copy number variations. However, in about 10–13% of patients, the presence of somatic mosaicism (where not all cells carry the same genetic variant) can make detection difficult. In such cases, testing other tissues like oral mucosa or skin fibroblasts using more sensitive molecular techniques is advised.If the diagnosis remains unclear even after these steps, whole-exome sequencing of the patient along with both parents (known as trio sequencing) can be done. Comparing the child's genetic variants with those of the parents helps identify new or rare disease-causing mutations.Despite significant advances, some CdLS cases still remain genetically unexplained, suggesting that yet-undiscovered genes or mechanisms may be responsible for the syndrome in these individuals.(16,17)

Prenatal Diagnosis of Cornelia de Lange Syndrome (CdLS)

Prenatal testing for CdLS is primarily considered in three situations: if a previous child in the family has CdLS, if a known genetic alteration in a CdLS-related gene exists in the family, or, more commonly, when prenatal ultrasound reveals features suggestive of CdLS in a fetus with no family history. Among 73 reported cases with prenatal findings, the most frequent sign was symmetric intrauterine growth restriction (IUGR) starting in the second trimester, observed in about 80% of cases. Limb anomalies were noted in 66% of fetuses (possibly reflecting selection bias), and roughly 50% had abnormal facial features such as micrognathia and a prominent maxilla. Other reported findings included increased nuchal thickness (51%), diaphragmatic hernia (28%), and heart defects (15%).When considering prenatal testing, it is essential to discuss the benefits, limitations, and ethical considerations with prospective parents to ensure that investigations align with their preferences and the available technical, medical, and legal options.

Prenatal molecular testing can be performed using samples from chorionic villus sampling (CVS), amniocentesis, or embryonic cells obtained via in vitro fertilization. Most commonly, single-gene sequencing, with or without deletion/duplication analysis, is used. In some countries, gene panels allow simultaneous testing of all known CdLS-related genes in one analysis. Non-invasive cell-free fetal DNA testing is also emerging and can detect de novo variants in families without a previous CdLS case, but this approach currently has limitations. Comparison with parental DNA is crucial to interpret variants accurately, and many variants remain of uncertain significance, limiting the test's routine use.

Because of these challenges—including the difficulty of interpreting novel variants and the possibility of mosaicism—prenatal testing for CdLS outside of families with a known pathogenic variant remains complex. Parents should receive careful counseling on the accuracy, limitations, and potential ethical implications of test results before making decisions about prenatal sampling or pregnancy management.(18)

Establishing the Diagnosis of Cornelia de Lange Syndrome (CdLS)

CdLS is diagnosed in an individual based on characteristic clinical features and/or through molecular genetic testing. A confirmed diagnosis can be made if a heterozygous pathogenic (or likely pathogenic) variant is found in NIPBL, RAD21, SMC3, or BRD4, or a hemizygous pathogenic (or likely pathogenic) variant in HDAC8 or SMC1A.

Option 1: Gene-Targeted Testing

When a patient exhibits features strongly suggestive of CdLS, gene-targeted testing is preferred. This typically involves:Multigene panels: Panels including NIPBL, SMC1A, HDAC8, SMC3, RAD21, BRD4, and other genes associated with similar syndromes (like AFF4, ANKRD11, CREBBP, EP300) are highly effective. Panels using next-generationsequencing (NGS) can detect mosaicism, ideally using fibroblasts, though buccal or bladder epithelial cells can also be used.

This method focuses on identifying the genetic cause while limiting the detection of unrelated variants or VUS. Panel composition and sensitivity can vary between laboratories and may change over time. Some labs offer custom panels or phenotype-focused exome analysis. For CdLS, panels should include both sequence analysis and deletion/duplication testing.Serial single-gene testing: In cases with strongly indicative features or when panels are unavailable, genes can be tested sequentially:Start with NIPBL sequence analysis, followed by deletion/duplication testing if needed.If NIPBL is negative and features are mild, test SMC1A next.If both NIPBL and SMC1A are negative but CdLS is still suspected, test BRD4, SMC3, RAD21, and HDAC8.

Option 2: Comprehensive Genomic Testing

For individuals with atypical or unclear features, where CdLS is not strongly suspected, comprehensive genomic testing is recommended. This includes exome sequencing (most common) or genome sequencing, which can identify causal variants without prior assumptions about which genes might be involved.

Treatment of Cornelia de Lange Syndrome (CdLS)

Treatment for CdLS is tailored to each child's individual needs, since the condition can affect multiple parts of the

body. Management usually involves a team of healthcare professionals working together.

Feeding Support:High-calorie formulas or, in some cases, a feeding tube (gastrostomy) may be needed to help with growth and nutrition.A nutritionist can provide guidance to address feeding challenges.

Surgical Interventions:Surgery may be necessary to correct certain physical issues, including:

1. Skeletal abnormalities
2. Gastrointestinal problems
3. Heart defects
4. Cleft palate
5. Undescended testicles

Medications:

Anticonvulsants to control seizures

Antidepressants for managing self-injury or aggressive behaviors

Antibiotics for respiratory infections

Some medications may also help treat gastrointestinal or heart-related issues

Therapies:

Ongoing therapies play a vital role in supporting growth, learning, and behavior:

1. Physical therapy to improve movement and strength.
2. Occupational therapy for daily living skills.
3. Speech therapy to aid communication.
4. Psychotherapy to support emotional and behavioral development.(19)

CONCLUSION

Cornelia de Lange Syndrome (CdLS) is a rare and complex genetic condition that affects multiple body systems and highlights the vital role of cohesin-related genes in human growth and development. Since its first description nearly a century ago, major advances in genetics have deepened our understanding of the disorder's origins, linking mutations in genes such as NIPBL, SMC1A, SMC3, RAD21, and HDAC8 to the wide range of clinical features seen in patients. CdLS presents along a broad spectrum, from severe, classic forms with noticeable facial and limb abnormalities to milder variants with more subtle traits.

Although significant improvements have been made in genetic testing, diagnosis, and patient care, several challenges persist—particularly in detecting mosaicism and addressing the variability in symptoms among individuals. Early identification, continuous medical supervision, and coordinated care from a team of specialists can greatly enhance developmental outcomes and quality of life. As ongoing research continues to reveal new genetic pathways and mechanisms, it paves the way for more accurate diagnostic techniques, personalized treatments, and better long-term management. In the broader sense, studying CdLS not only improves care for those affected but also deepens our understanding of how genes regulate human development and health.

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REFERENCES

1. Cascella M. CdLS is a genetic disorder that affects many organs, leading to various clinical presentations. Typical features of this rare disease include restricted growth. 2023. Cited by: 17.
2. Kline AD, Moss JF, Selicorni A, Bisgaard AM, Deardorff MA, Gillett PM, Ishman SL, Kerr LM, Levin AV, Mulder PA, Ramos FJ. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nature Reviews Genetics. 2018 Oct;19(10):649-66.
3. Brachmann WR. Ein Fall von angeborenen Anomalien der Gliedmaßen und Gesichtspartie. Deutsche Medizinische Wochenschrift. 1916;42:1989–1991.
4. de Lange CC. Sur un type nouveau de dégénérescence anthropoïde du développement. Ned Tijdschr Geneeskd. 1933;77:195–210.
5. Opitz JM. Brachmann-de Lange syndrome: Historical, clinical, and genetic perspectives. *Am J Med Genet.* 1985;21:793–799.
6. Weiss FD, Katsman-Katz S, Zamir A, Ben-David E, Lubling Y, Orenstein Y, et al. Neuronal genes deregulated in Cornelia de Lange syndrome respond to removal and re-expression of cohesin. Nat Commun. 2021;12:2919.
7. García-Gutiérrez P, García-Domínguez M. BETting on a transcriptional deficit as the main cause for Cornelia de Lange syndrome. Front Mol Biosci. 2021;8:709232.
8. Deardorff MA. Cornelia de Lange syndrome (CdLS) encompasses a spectrum of findings from mild to severe. 2020. Cited by: 171.
9. Mehta D, Kline AD, Deardorff MA, Jackson LG, Krantz ID, Selicorni A, et al. Characterization of limb differences in children with Cornelia de Lange syndrome. Am J Med Genet A. 2016;170(6):1524–1530.
10. Muto A, Kuroda M, Yamamoto T, Kawauchi T, Kuriyama S, Kuriyama M, et al. Multifactorial origins of heart and gut defects in Nipbl+/- mice. PLoS Biol. 2011;9(5):e1001181.
11. Grados MA, Jackson LG, Clark D, Kaur M, Deardorff MA, Krantz ID, et al. Behavioral and psychiatric manifestations in Cornelia de Lange syndrome. *Am J Med Genet A.* 2017;173(6):1586–1592.
12. Shi A, McGowan JM, Deardorff MA, et al. Ophthalmologic findings in Cornelia de Lange syndrome. Ophthalmic Genet. 2019;40(5):441-449.
13. Olley G, Ansari M, Bengani H, et al. BRD4 interacts with NIPBL and BRD4 is mutated in a Cornelia de Lange-like syndrome. Nat Genet. 2018;50(3):329-332.
14. Huisman SA, Redeker EJ, Maas SM, et al. Mosaicism in NIPBL: implications for diagnosis of Cornelia de Lange syndrome. J Med Genet. 2013;50(2):80–87.
15. Liu J, Krantz ID. Cornelia de Lange syndrome, cohesin, and beyond. Clinical genetics. 2009 Oct;76(4):303-14.
16. Sarogni P, Krawczynska N, Ansari M, et al. Cornelia de Lange syndrome: from molecular diagnosis to clinical management. J Med Genet. 2020;57(5):289-297.
17. Mehta L, Kline AD, Deardorff MA, et al. Tissue-specific pathogenic NIPBL variant causing Cornelia de Lange syndrome. GIM Open. 2024;3(1):e284.
18. Clark DM, McGillivray BC, McPherson E, et al. Prenatal profile of Cornelia de Lange syndrome. Am J Med Genet A. 2012;158A(3):535-541.
19. Krawczynska N, Houge G, Borsheim EI, et al. Mosaicism in Cornelia de Lange syndrome: detection using DNA from buccal swabs. Clin Genet. 2019;95(4):452-460.


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