# Cornelia de Lange Syndrome

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Cornelia de Lange syndrome is a developmental disorder that affects many parts of the body. The features of this disorder vary widely among affected individuals and range from relatively mild to severe.

Keywords: genetic conditions

## 1. Introduction

Cornelia de Lange syndrome is characterized by slow growth before and after birth leading to short stature; intellectual disability that is usually moderate to severe; and abnormalities of bones in the arms, hands, and fingers. Most people with Cornelia de Lange syndrome also have distinctive facial features, including arched eyebrows that often meet in the middle (synophrys), long eyelashes, low-set ears, small and widely spaced teeth, and a small and upturned nose. Many affected individuals also have behavior problems similar to autism, a developmental condition that affects communication and social interaction.

Additional signs and symptoms of Cornelia de Lange syndrome can include excessive body hair (hypertrichosis), an unusually small head (microcephaly), hearing loss, and problems with the digestive tract. Some people with this condition are born with an opening in the roof of the mouth called a cleft palate. Seizures, heart defects, and eye problems have also been reported in people with this condition.

## 2. Frequency

Although the exact incidence is unknown, Cornelia de Lange syndrome likely affects 1 in 10,000 to 30,000 newborns. The condition is probably underdiagnosed because affected individuals with mild or uncommon features may never be recognized as having Cornelia de Lange syndrome.

## 3. Causes

Cornelia de Lange syndrome can result from mutations in at least five genes: *NIPBL*, *SMC1A*, *HDAC8*, *RAD21*, and *SMC3*. Mutations in the *NIPBL* gene have been identified in more than half of all people with this condition; mutations in the other genes are much less common.

The proteins produced from all five genes contribute to the structure or function of the cohesin complex, a group of proteins with an important role in directing development before birth. Within cells, the cohesin complex helps regulate the structure and organization of chromosomes, stabilize cells' genetic information, and repair damaged DNA. The cohesin complex also regulates the activity of certain genes that guide the development of limbs, face, and other parts of the body.

Mutations in the *NIPBL*, *SMC1A*, *HDAC8*, *RAD21*, and *SMC3* genes cause Cornelia de Lange syndrome by impairing the function of the cohesin complex, which disrupts gene regulation during critical stages of early development.

The features of Cornelia de Lange syndrome vary widely, and the severity of the disorder can differ even in individuals with the same gene mutation. Researchers suspect that additional genetic or environmental factors may be important for determining the specific signs and symptoms in each individual. In general, *SMC1A*, *RAD21*, and *SMC3* gene mutations cause milder signs and symptoms than *NIPBL* gene mutations. Mutations in the *HDAC8* gene cause a somewhat different set of features, including delayed closure of the "soft spot" on the head (the anterior fontanelle) in infancy, widely spaced eyes, and dental abnormalities. Like affected individuals with *NIPBL* gene mutations, those with *HDAC8* gene mutations may have significant intellectual disability.

In about 30 percent of cases, the cause of Cornelia de Lange syndrome is unknown. Researchers are looking for additional changes in the five known genes, as well as mutations in other genes, that may cause this condition.

### 3.1. The Genes Associated with Cornelia de Lange Syndrome

- HDAC8
- NIPBL
- RAD21
- SMC1A
- SMC3

## 4. Inheritance

When Cornelia de Lange syndrome is caused by mutations in the *NIPBL*, *RAD21*, or *SMC3* gene, the condition is considered to have an autosomal dominant pattern of inheritance. Autosomal dominant inheritance means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases result from new gene mutations and occur in people with no history of the condition in their family.

When Cornelia de Lange syndrome is caused by mutations in the *HDAC8* or *SMC1A* gene, the condition has an X-linked dominant pattern of inheritance. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. Studies of X-linked Cornelia de Lange syndrome indicate that one copy of the altered gene in each cell may be sufficient to cause the condition. Unlike X-linked recessive conditions, in which males are more frequently affected or experience more severe symptoms than females, X-linked dominant Cornelia de Lange syndrome appears to affect males and females similarly. Most cases result from new mutations in the *HDAC8* or *SMC1A* gene and occur in people with no history of the condition in their family.

## 5. Other Names for This Condition

- BDLS
- Brachmann-de Lange syndrome
- CdLS
- de Lange syndrome
- typus degenerativus amstelodamensis

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