# Neurodevelopmental Symptoms in 33 Cornelia de Lange Syndrome Patients Confirmed by Molecular Diagnosis

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## INTRODUCTION

Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder characterized by a wide clinical spectrum, ranging from mild to severe forms. Patients can present with distinctive facial dysmorphisms, intellectual disability, behavioral issues, hirsutism, growth retardation, and limb reduction anomalies, predominantly affecting the radial bones. CdLS is caused by pathogenic variants in six genes (NIPBL, SMC1A, HDAC8, SMC3, BRD4, and RAD21). This study aimed to assess the neurodevelopmental outcomes of Brazilian patients from a parental perspective.

## OBJECTIVE

Evaluation of cognitive development and independence in daily activities of patients with a molecular diagnosis of Cornelia de Lange Syndrome.

## METHODS

A questionnaire focused on cognitive and neuropsychiatric questions was sent to all families enrolled in the the Brazilian Association of Cornelia de Lange Syndrome and 160 were answered. The patients were scheduled to the Genetics Clinic and 65 patients were sent to trio Exome Sequencing, whenever possible. The answers from the questionnaire from those who had a molecular diagnosis of CdLS were reviewed.

| Characteristic | n/N | % |
|---|---|---|
| Female sex | 18/33 | 54.5 |
| Male sex | 15/33 | 45.5 |
| Mutated gene | | |
| – NIPBL | 30/33 | 90.9 |
| – SMC1A | 3/33 | 9.1 |
| Cognitive development and schooling | | |
| Attends school | 24/32 | 75.0 |
| Recognizes numbers | 12/29 | 41.4 |
| Literate | 5/31 | 16.1 |
| Independence in daily activities | | |
| Eats independently | 12/29 | 41.4 |
| Performs personal hygiene | 9/29 | 31.0 |
| Motor and communication skills | | |
| Walks independently | 29/31 | 93.5 |
| Able to speak | 22/31 | 71.0 |
| Forms complete sentences | 10/31 | 32.2 |
| Behavior and interaction | | |
| Autism signs | 7/32 | 21.9 |
| Interacts with family | 29/30 | 96.6 |
| Aggressive behavior | 16/30 | 53.3 |

**Table1:** Statistical Analysis of Participants

## RESULTS AND DISCUSSION

A total of 33 patients (18F:15M) were included at this study. The age at diagnosis ranged from birth to 9 years, with a mean of 11.4 months and a median of 4.5 years. Exome sequencing showed 30 patients presented heterozygous pathogenic ou likely pathogenic variants in the NIPBL gene and 3 in the SMC1A gene. In all cases with trio analysis the variants were de novo. All questionnaires were filled out by the mothers. 75%(24/32) of the children attended school, 41,37% (12/29) could recognize numbers, only 16,13%(5/31) were literate, 41,38% (12/29) ate independently, 31,03% (9/29) were able to perform personal hygiene, 93,5% (29/31) could walk, and 70,96% (22/31) were able to speak. 21,87%(7/32) showed signs of autism, 96,6%(29/30) interacted with family members, and 53,3% (16/30) displayed aggressive behaviors.

In the subgroup of three patients with SMC1A variants, none were able to eat independently, or perform personal hygiene. However, because one of the patients was only 2 years old at the time of the assessment, a comprehensive analysis of the group's developmental capabilities was not feasible.

## CONCLUSION

Patients in our study demonstrated significant cognitive challenges, with most showing signs of mild to moderate intellectual disability. Many require assistance with basic daily activities such as hygiene, and the majority are unable to communicate effectively; only 32.2% (10/31) are able to form full sentences.

This level of cognitive dysfunction often leads to caregiver burnout, primarily due to the high degree of dependence of the patients, which can strain both caregivers and the broader family unit.

In Brazil, where medical and social support for families with patients with rare disorders is a challenge, we must also consider strategies to provide the psychological support that parents may need, as well as public policies focused on the inclusion of people with CdLS in our society. Primarily, this can be achieved by strengthening support networks and offering multidisciplinary and psychological support for caregivers.

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