International Journal of Multidisciplinary Trends

E-ISSN: 2709-9369
P-ISSN: 2709-9350
www.multisubjectjournal.com
IJMT 2025; 7(1): 96-97
Received: 05-11-2024
Accepted: 10-12-2024

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Subtle signs, significant insights: Exploring the spectrum of phenotypes in classic Cornelia de Lange syndrome

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DOI: https://doi.org/10.22271/multi.2025.v7.i1b.582

Abstract
This letter presents a case of classic Cornelia de Lange Syndrome (CdLS) that highlights the often-overlooked milder phenotypic presentations associated with *NIPBL* missense variants. Our patient, a 16-year-old girl, was diagnosed with CdLS and mild Intellectual Developmental Disorder (IDD). Despite typical facial features and growth retardation, she exhibited high autonomy and relatively preserved cognitive function. Genetic analysis revealed a likely pathogenic missense variant in the NIPBL gene, contrasting with the more severe phenotypes typically linked to frameshift and nonsense mutations. This case underscores the need for broader diagnostic criteria for CdLS, particularly in individuals with milder developmental issues and distinctive facial features. Recognizing these subtler presentations can lead to timely interventions and improved outcomes. We hope this case encourages further discussion on the expanded phenotypic spectrum of classic CdLS.

Keywords: Cornelia de Lange syndrome (CdLS), NIPBL gene, missense variants, milder phenotypic presentations

Introduction
Cornelia de Lange Syndrome (CdLS) is a rare multisystem genetic disorder characterised by a distinct spectrum of clinical presentations, ranging from severe intellectual and physical disabilities to milder forms that may be under-recognised. Central to this variability is the role of mutations in the *NIPBL* gene, particularly missense variants, which have been associated with less pronounced phenotypes. In this correspondence, we present a compelling case of a 16-year-old girl with classic CdLS features and a mild intellectual developmental disorder (IDD), whose level of autonomy and functional achievements challenge the traditional perception of this syndrome. By examining this case, we aim to broaden the understanding of CdLS phenotypic variability and underscore the importance of considering milder forms in diagnostic evaluations to ensure timely and targeted interventions.

Case Presentation
We are writing to share a noteworthy case of classic Cornelia de Lange Syndrome (CdLS) that we believe brings attention to an often-overlooked aspect of this rare disorder. Our aim is to discuss the genetic basis of CdLS, particularly relating to the *NIPBL* gene [1, 2], and to highlight the milder phenotypic presentations that may be underdiagnosed.
Our case focuses on a 16-year-old girl with classic CdLS characteristics, mild Intellectual Developmental Disorder (IDD), and a high level of autonomy. She was referred to our unit at age 11 due to generalized learning difficulties noticeable since early schooling. Born at 36 weeks to a non-consanguineous couple, she had a short length at birth but an otherwise uneventful prenatal and neonatal period. Growth retardation was observed subsequently, but developmental milestones were achieved on time without regression. By age 5, she was diagnosed with Global Developmental Delay. In first grade, at age 6, she began facing escalating learning difficulties, leading to Special Education support at ages 6-7 and therapies, including speech, sound, and occupational therapy, from ages 6 to 11. Menarche occurred at age 11. At referral, the patient exhibited weight and height below the third percentile, a triangular face, synophrys, long and thick eyelashes, a short upturned nose, a long philtrum, and a thin upper lip, alongside CdLS-like hirsutism. Notably, there were no limb anomalies. Her linguistic capabilities were marked by a mean length of utterance (MLU) exceeding 6, with minimal phonetic and phonological errors.

Despite below-average reading fluency, her comprehension was relatively intact. She faced challenges in mental calculation, although her autonomy was largely preserved. She presented symptoms of Attention Deficit Hyperactivity Disorder (ADHD) and a mild IDD, with a General Intellectual Quotient (GIQ) of 64, a Verbal IQ (VIQ) of 66, and a Performance IQ (PIQ) of 72. Next-Generation Sequencing (NGS)-based multigene panel for IDD conducted at age 15, along with parental genetic analysis, identified a likely pathogenic missense variant (c.7382G>T) in the *NIPBL* gene. All other assessments, including laboratory tests, imaging, audiometry, and initial genetic screenings, were normal. Despite her diagnosis, our patient demonstrates a high degree of functionality. She successfully completed ninth grade and she is attending a marketing professional course with a good performance. Furthermore, she manages a functional relationship with her boyfriend, contributes significantly to her family's bakery, and cares for her 14-month-old sister.

Discussion

This case highlights a critical insight: While frameshift and nonsense mutations in the *NIPBL* gene typically result in more severe CdLS phenotypes, missense variants can be associated with milder forms [3, 4].

Historically, classic CdLS has been closely associated with severe phenotypes, often characterized by significant intellectual disability and physical anomalies[1]. However, this case emphasizes the need for broader diagnostic consideration, particularly in patients with milder developmental and intellectual presentations exhibiting distinctive facial features. Recognizing and diagnosing milder forms of classic CdLS can lead to timely and appropriate therapeutic strategies, ultimately improving patient outcomes [1, 5].

We hope this case will encourage further discussion and research into the possibility that the spectrum of classic CdLS phenotypes is broader than previously recognized.

Conclusion

This case exemplifies the need for heightened awareness of the phenotypic spectrum of Cornelia de Lange Syndrome, particularly in cases involving missense mutations in the *NIPBL* gene. Our patient's successful adaptation and functional accomplishments highlight the potential for positive outcomes when milder phenotypes are appropriately identified and managed. Recognising these cases is crucial not only for accurate diagnosis but also for optimising support strategies that enhance quality of life. We hope this report will inspire further investigation into the variability of CdLS manifestations, fostering improved clinical care and a deeper understanding of this complex disorder.

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