International Journal of Contemporary Pediatrics
Savitha MR et al. Int J Contemp Pediatr. 2024 May;11(5):605-608
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20241045

Case Report

Cornelia de Lange syndrome type 4 with a novel heterozygous missense variant in RAD 21 gene

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Received: 07 March 2024
Revised: 03 April 2024
Accepted: 08 April 2024

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ABSTRACT

Cornelia de Lange syndrome (CdLS) is a congenital multisystemic disorder characterized by genetic heterogeneity. It presents with features such as growth and cognitive retardation, upper limb deformities, cardiac, ophthalmologic, and genitourinary anomalies, alongside distinctive facial characteristics. The CdLS phenotype represents a spectrum that includes both classic and non-classic phenotypes resulting from pathogenic variants in genes associated with cohesin functioning, including NIBPL, SMC1A, SMC3, RAD21, BRD4, HDAC8, and ANKRD11. Mutations in these genes manifest diverse clinical features, with RAD21 variants accounting for a small percentage of cohesinopathies in humans. RAD21-related cohesinopathy typically exhibits growth retardation, minor skeletal anomalies, and facial features overlapping with CdLS. However, cognitive involvement tends to be milder. Despite this, due to the limited number of reported cases with RAD21 mutations, establishing genotype-phenotype correlations remain challenging. We present the case of an 18-month-old boy exhibiting developmental delay and distinct morphological features including micro-brachycephaly, depressed nasal bridge, upturned nose, long philtrum, low-set ears, mesomelic limb dwarfism, and a complete endocardial cushion defect. Exome sequencing revealed a novel RAD21 variant in this individual.

Keywords: CdLS, RAD 21, CdLS 4

INTRODUCTION

Cornelia de Lange syndrome (CdLS), cataloged under OMIM numbers #122470, #300590, #610759, #300882, and #614701, is a multifaceted congenital disorder christened after the Dutch pediatrician Cornelia de Lange, who delineated it in two neonates in 1933.[1,2] The condition is characterized by various manifestations including growth and cognitive retardation, upper limb deformities, cardiac, ophthalmologic, and genitourinary anomalies, alongside distinctive facial features such as fine arched eyebrows, synophrys, long eyelashes, low-set posteriorly rotated ears, long philtrum, thin upper lip, and a depressed nasal bridge with anteverted nares.[3-6] The prevalence is estimated to be between 1 in 10,000 to 1 in 30,000 individuals, with most cases occurring sporadically despite familial occurrences documented.[2,6,7]

The CdLS spectrum is linked to molecular irregularities affecting genes involved in chromatin regulation, primarily those within the cohesion complex. The CdLS phenotype comprises a spectrum, encompassing the classic CdLS phenotype as well as syndromes exhibiting a similar but non-classic phenotype, all stemming from pathogenic variants in genes associated with cohesin functioning. The comprehensive CdLS phenotype can be depicted as a spectrum, incorporating both the classic CdLS presentation and syndromes exhibiting a similar yet non-classic phenotype, all resulting from pathogenic variants in genes involved in cohesin functioning.[2]

Mutations in NIPBL, a regulator of the Cohesin complex situated on chromosome 5p13, stand as the foremost and most prevalent genetic trigger for CdLS. Heterozygous mutations in Nipped B-like (NIPBL), culminating in a severe CdLS phenotype, account for approximately 60% of cases.[8-10] Furthermore, mutations in the SMC1A and SMC3 genes, responsible for encoding core cohesin complex structural components, have been observed. While SMC1A mutations contribute to about 5% of CdLS cases, they generally lead to milder phenotypes without major structural anomalies associated with classical CdLS.[11,12] HDAC8 mutations are identified in roughly 5% of individuals exhibiting typical clinical features of CdLS, but without significant limb involvement.[13] Mutations in RAD21 are responsible for a human cohesinopathy characterized by growth retardation, minor skeletal anomalies, and facial features overlapping with those found in CdLS individuals, albeit often with milder cognitive involvement.[14] Recently, mutations in BRD4, a NIPBL interactor, and ANKRD11, an inhibitor of ligand-dependent activation of transcription, have also been implicated in CdLS.

CASE REPORT

In this case report, we detail the condition of an eighteen-month-old boy born to healthy, non-consanguineous parents with no significant family medical history. Prenatal scans had initially identified complete endocardial cushion defect, and child was born at 38 weeks gestation, categorized as small for gestational age, and exhibited microcephaly without any neonatal hospitalization history.

Further investigations, including neurosonogram, abdominal, and renal ultrasounds, revealed normal findings. Confirmation of prenatal diagnosis was attained through subsequent echocardiography. Child had previously been hospitalized due to recurrent bronchopneumonia.

Physical examination unveiled short stature, micro-brachycephaly, a depressed nasal bridge, upturned nose, low-set ears, dental dysplasia characterized by the absence of incisors, and postaxial polydactyly affecting all four limbs, coupled with mesomelic limb dwarfism. Auscultation detected a grade 3/6 systolic murmur, alongside mild cognitive impairment.

Normal results were obtained from ophthalmic evaluation and BERA testing. This mutation results in a change at the protein level. The results from whole exome sequencing uncovered a heterozygous missense variant, precisely identified as c.827A>G (p.Asp276Gly), situated within the RAD21 gene. The amino acid aspartic acid (Asp), typically encoded by the codon "GAC" at position 276, is altered to glycine (Gly) due to the nucleotide substitution. This change in amino acid sequence may potentially affect structure/function of RAD21 protein.

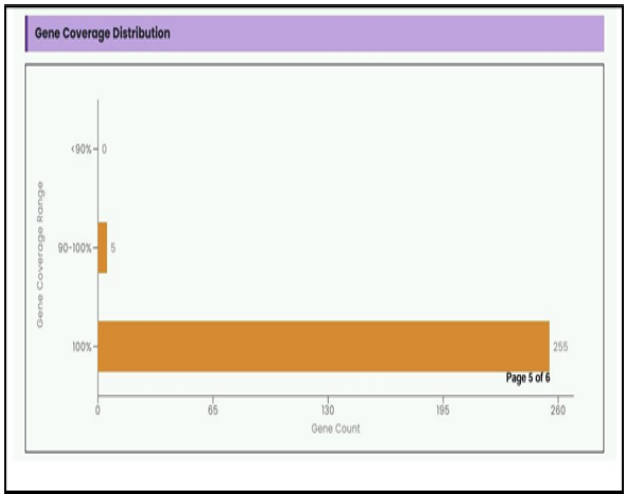

Figure 1: Gene coverage distribution.

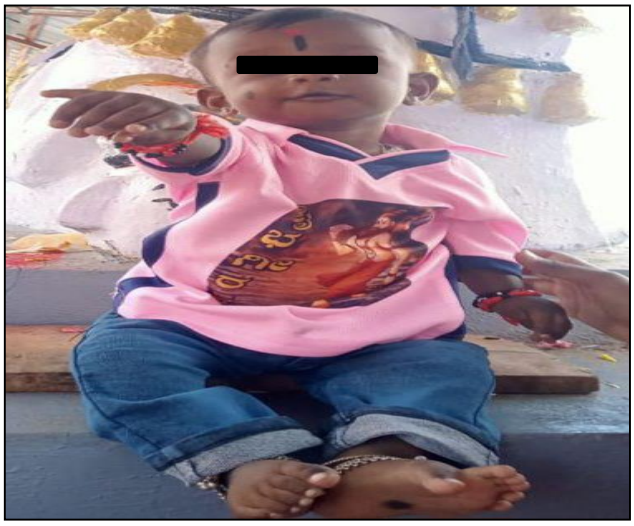

Figure 2: Depicting polydactyly of all 4 limbs with depressed nasal bridge, long philtrum and low set ears.

Figure 3: Dental dysplasia with absence of upper and lower incisors.

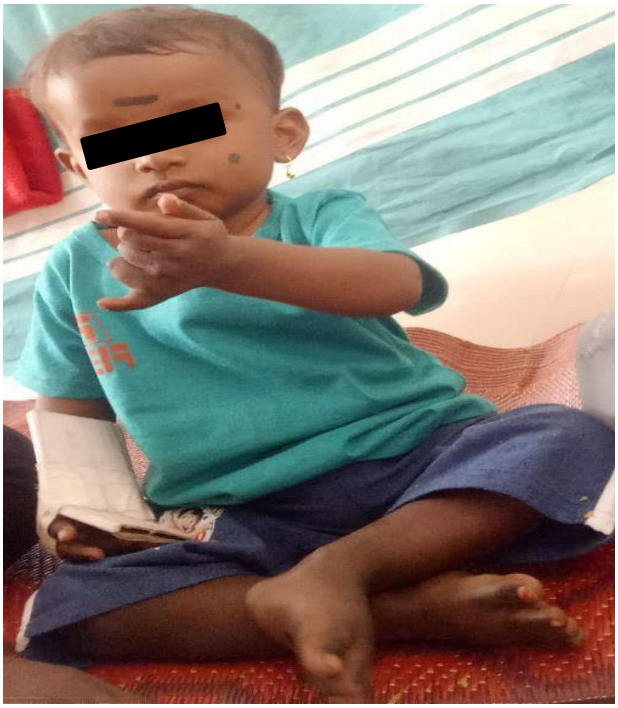

Figure 4: Micro brachycephaly with low set ears.

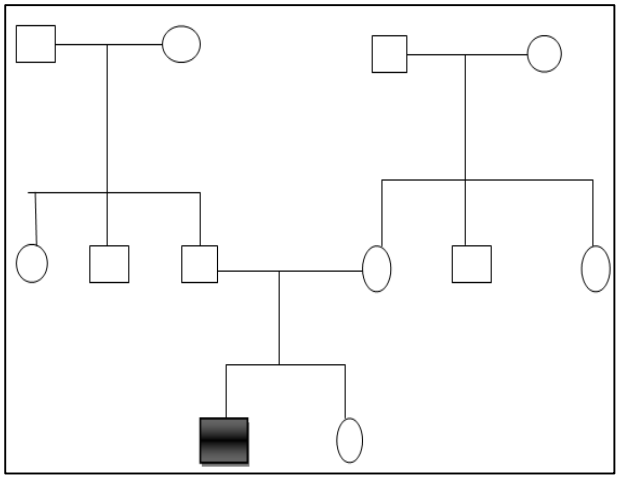

Figure 5: Three generation pedigree chart.

DISCUSSION

Classic CdLS is typically identifiable at birth due to its distinct craniofacial appearance, growth pattern, and limb malformations. However, not all individuals with CdLS display the classic phenotype, and the presentation of the disorder can vary widely, ranging from mild to severe with varying degrees of facial and limb involvement. In 2018, the International CdLS Consensus Group developed consensus criteria that classify these presentations into cardinal features, which are the most characteristic for CdLS, and suggestive features that contribute to the diagnosis. Individuals with a classic phenotype and an NIPBL variant typically score between 12 and 16, while those with a non-classic CdLS phenotype score between 9 and 11.[2] The index case in this study exhibited a clinical score of 9, indicating non-classic CdLS.

RAD21, a double-strand break repair protein, is a component of the cohesin complex. RAD21 variants represent a minority of the causes of CdLS. Initially, reports focused on missense mutations and microdeletions involving RAD21, leading to a non-classic CdLS phenotype.[14] Later findings included intragenic deletions and frameshift mutations in RAD21, observed in two patients with atypical CdLS presentations.[15] Subsequent cases involving RAD21 variants also exhibited non-classic phenotypes.[16-20]

The missense variant c.827A>G (p.Asp276Gly) within the RAD21 gene appears to be unique and hasn't been previously documented as either a pathogenic or benign variant, to the best of our knowledge. Our search through databases like gnomAD Exomes and 1000 Genomes yielded no instances of this variant in any individuals. While this variant has been submitted to the ClinVar database, unfortunately, there are no additional details available for independent evaluation.

The substitution of aspartic acid at position 276 with glycine alters the protein sequence, potentially affecting its composition and physico-chemical properties. Further research, including functional studies and clinical observations, will be necessary to fully understand the implications of this variant.

CONCLUSION

To date, only a limited number of RAD21 mutations have been uncovered in individuals with CdLS. The scarcity of reported cases impedes our ability to establish clear genotype-phenotype correlations. Further research is essential to delve into the intricate molecular mechanisms governed by RAD21, a pivotal regulator within the cohesin complex, and to comprehend how alterations in its function contribute to CdLS pathogenesis. These investigations hold promise for advancing our understanding of CdLS.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Savitha MR, Shervani MB. Cornelia de Lange syndrome type 4 with a novel heterozygous missense variant in RAD 21 gene. Int J Contemp Pediatr 2024;11:605-8.