Multiple Non-contiguous Interstitial Deletions in 5q21q22.1, Including The *CHD1* Gene, Identified In A Boy With Developmental Delay And Severe Language Impairment

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Introduction

Intellectual disability (ID), developmental delay (DD), and behavioural disorders are complex neurodevelopmental conditions associated with multifactorial aetiologies, including genetic factors. Chromosomal microarray analysis (CMA) is a valuable diagnostic tool in identifying copy number variations (CNVs) contributing to these disorders.

Interstitial deletions of the middle region of the long arm of chromosome 5 are rare, and cases of complex chromosomal rearrangement (CCR), involving only this chromosome are even more uncommom[1,2].

A characteristic phenotype has been described in patients with 5q interstitial monosomy, including intellectual disability, failure to thrive, craniofacial dimorphism, and various structural developmental abnormalities such as cleft palate, renal, and skeletal anomalies. Furthermore, phenotypic differences appear to exist between individuals with proximal (5q15 to 5q22) and distal (5q22 to 5q31) deletions. Proximal deletions tend to be associated with milder phenotypes, including less severe intellectual disability and subtle physical anomalies. In contrast, distal deletions are generally linked to more severe manifestations, including significant intellectual impairment, failure to thrive, pronounced craniofacial dimorphism, and joint abnormalities such as dislocations or contractures[3,4,5].

The CHD1, located on 5q15q21.1, plays a crucial role in several essential molecular pathways, and its complete loss is incompatible with life. However, missense mutations and copy number variations involving this gene have been associated with autism spectrum disorder[6,7,8] and more recently to intellectual disabilities and craniofacial malformations in humans, including conditions like cleft palate and Pilarowski–Bjornsson Syndrome[9].

Here we report a 4-year-old male with DD, severe language impairment, behavioral disturbances, macrocephaly, facial dysmorphisms, and delay walking (achieved at 20 months), who carries three heterozygous interstitial deletions on 5q [2.12Mb at 5q15q21.1, encompassing the *CHD1* gene; 684Kb at 5q21.3, a gene-free region; and 3.69Mb at 5q21.3q22.1, including the *SLC25A46* gene], inherited from his mother, identified through CMA.

Case Report

We report a 4-year-old male born to nonconsanguineous couple. Family history is notable for maternal intellectual disability and paternal neonatal hypoxic-ischemic encephalopathy, resulting in hemiparesis and language impairment. Pregnancy was unmonitored, birth was at 40 weeks of gestation by caesarean section; Apgar score was 10/10 at minutes 1 and 5. At birth, weight was at 30th percentile; length at 33th percentile and head circumference at 27th percentile. He was referred to our genetics clinic due to developmental delay, walking at 20 months, severe language impairment and behavioural disturbances. At observation, he presented macrocephaly (+2.5 SD), a prominent forehead, long philtrum, and a thin upper lip.

Results

Cytoscan 750K SNParray analysis was performed on the patient and revealed three heterozygous interstitial deletions: 2.12 Mb at 5q15q21.1 (97929163-100045362), encompassing the *CHD1* gene; 684 Kb at 5q21.3 (104580978-105264711), a gene-free region; and 3.69 Mb at 5q21.3q22.1 (107047547-110727429), including the *SLC25A46* gene (Figure 1).

Parental segregation studies revealed that all three deletions were maternally inherited, who presents with learning difficulties.

Although the presence of non-contiguous losses may suggest a CCR, no further cytogenetic studies could be performed.

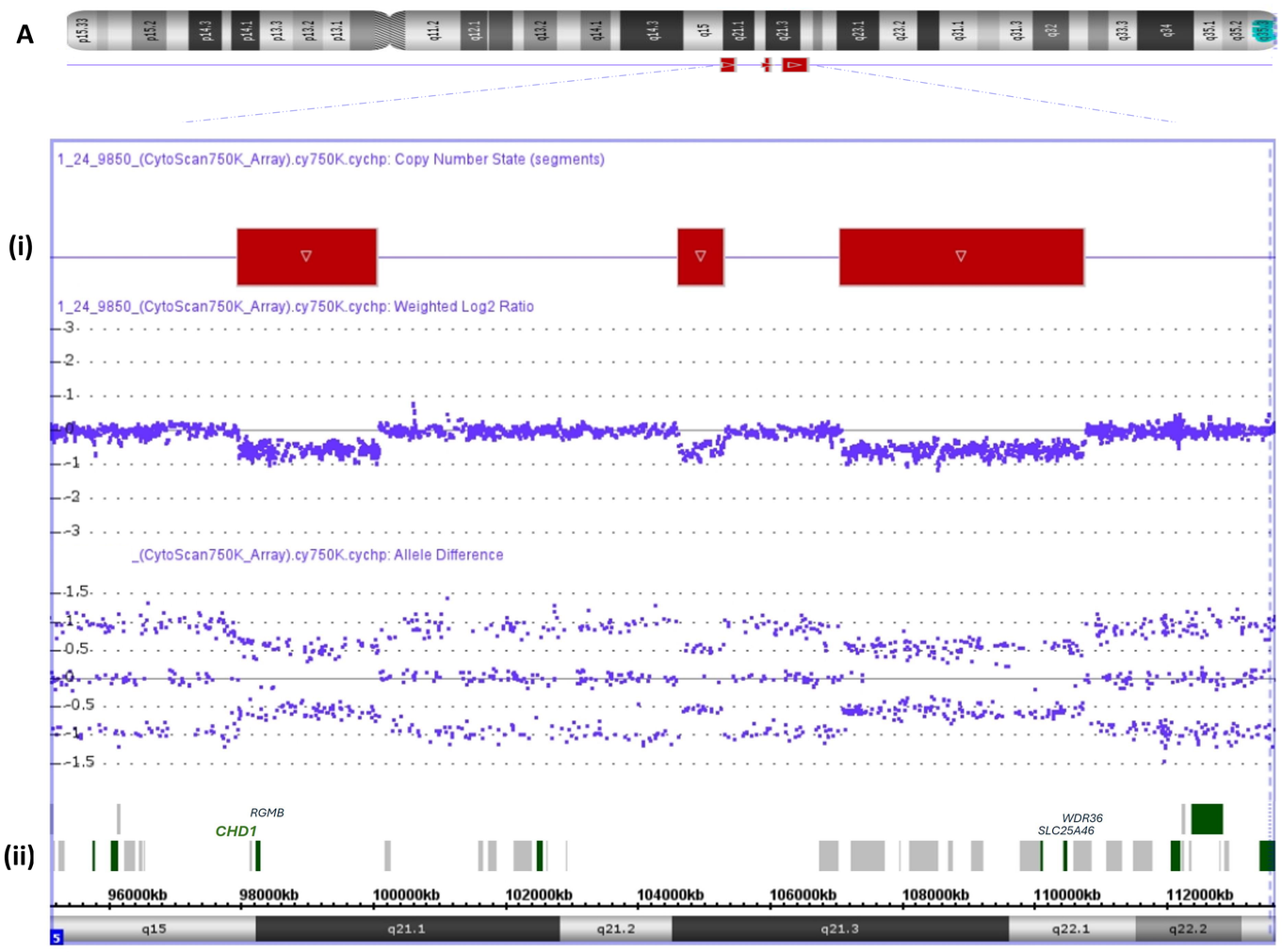

Figure 1. SNParray profile for chromosome 5 (A). Chromosome ideograms showing the deleted (red box). (i) Copy number state, smooth signal, copy number probe intensities (weighted log2 ratio) and allele peak tracks indicating the deletion. (ii) Genes deleted, being the OMIM genes in gray and morbid in dark green.

Discussion

Interstitial deletions of the middle region of the long arm of chromosome 5, encompassing the 5q15q21.2 region, are rare, and cases of CCR involving only this chromosome are even rarer.

In the present case, three heterozygous interstitial deletions on 5q, including 5q15-q21.2 region, were identified in a patient presenting facial dysmorphism, speech and motor delay. These deletions were also detected in his mother, who exhibited intellectual disability, suggesting a potential autosomal dominant inheritance pattern.

Among the genes contained within these deleted regions, *CHD1* (chromodomain helicase DNA-binding protein 1; OMIM: 602118) emerges as a strong candidate to explain the observed phenotype. Missense variants in *CHD1* have been associated with Pilarowski-Bjornsson syndrome, a neurodevelopmental disorder characterized by ID, DD, dysmorphic features, and apraxia of speech. However, deletion involving this gene are less frequently reported and may lead to speech abnormalities in the absence of ID or other major neurodevelopmental disorders. This phenotypic variability suggests that both *CHD1* deletions and missense variants may exhibit variable expressivity or incomplete penetrance[10].

Zepeda-Mendoza et al (2019), reported a familial case involving an 8.5 Mb deletion spanning 5q15q21.2 (chr5:95049966-103537589), segregating from mother to three daughters, all presenting speech delay and mild dysmorphic features with variable degrees of cognitive impairment. In our patient, the deletion identified is smaller and encompasses only two genes: *CHD1* and *RGMB* (OMIM: 612687). While *CHD1* is a candidate gene associated with neurodevelopmental disorders, *RGMB* encodes a glycosylphosphatidylinositol (GPI)-anchored member of the repulsive guidance molecule family, which plays a role in neural patterning during development, but it has not yet been linked to any human pathology.

CCRs are a rare cause of congenital malformations, yet their precise characterization is crucial for advancing to the understanding of the cellular mechanisms underlying their formation. Although chromothripsis, chromoanasynthesis, and chromoplexy can all generate CCR, these processes differ in their molecular mechanisms and exhibit distinct genomic signatures[12]. Unfortunately, the inability to perform cytogenetic studies on the proband and his mother prevented us from determining whether the observed deletions arise from a CCR, chromothripsis, or represent independent events. To address this limitation, further analyses using long-read sequencing technology (Oxford Nanopore) are currently underway.

This case highlights a possible link between CHD1 deletion and an autosomal dominant complex neurodevelopmental disorder.

Methods

DNA samples were processed according to the Thermo Fisher Scientific® manual protocol: Cytogenetics Copy Number Assay, P/N 703038 Rev. 3. Copy number variations, including gains and/or losses of genetic material, were analyzed using the CytoScan™ 750K array, which includes a total of 750,436 markers (200,436 SNPs and 550,000 non-polymorphic probes). Data analysis was performed using Genotyping Console™ v4.0 and Chromosome Analysis Suite (ChAS) v4.5.0.34, with annotation based on NetAffx™ 20250201 (UCSC hg19 reference genome). The thresholds for detection were set at a minimum of 25 altered markers within a 50 kb region for copy number gains, and at least 35 altered markers within the same window size for losses.

Conclusion

This case suggests a potential association between *CHD1* deletion and an autosomal dominant complex neurodevelopmental disorder. While CMA is typically preferred in such cases due to its higher resolution, this case highlights the continued relevance of cytogenetics in uncovering the mechanisms underlying CCRs.

Emerging molecular technologies, such as nanopore sequencing, are expanding the capabilities of genomic analysis by enabling detection of both single-nucleotide variants and larger chromosomal alterations. However, these methods have yet to achieve the robustness and reliability required for routine use in cytogenetic diagnostics.

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