LOSS OF FUNCTION OF *PCDH11X* GENE IN THE PATHOGENESIS OF NEURODEVELOPMENTAL DISORDERS

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INTRODUCTION

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

The *PCDH11X* gene, predominantly expressed in the brain, plays an important role in cell–cell communication, dendritic synaptic plasticity, brain lateralization, and verbal ability. It has been proposed as a candidate gene in the aetiology of neurodevelopmental disorders, particularly autism spectrum disorder (ASD) and dyslexia.[1, 2] Although *PCDH11X* is not currently classified as a disease associated gene, emerging functional and genetic evidence suggests that loss-of-function (LoF) variants may have a moderate association with ASD, with such variants reported exclusively in males.[3, 4] Recent X-chromosome association studies have also identified significant associations between intronic and intergenic variants at this locus and autism, particularly in males.[5]

In addition, rare structural variants involving *PCDH11X*, namely deletions, have been associated with severe language impairments. Although the level of evidence remains moderate and these deletions may significantly contribute to neurodevelopmental phenotypes, especially in the domains of communication and language.[6]

Here, we report a 6-year-old male presenting with a complex neurodevelopmental phenotype, including learning difficulties, mild motor delay, speech sound disorder, and selective mutism, who carries a hemizygous 2.80 Mb interstitial deletion at Xq21.31q21.32 encompassing the *PCDH11X* gene, identified through CMA.

CASE REPORT

We report a 6-year-old male patient presenting a complex neurodevelopmental phenotype, including learning difficulties, mild motor delay, speech sound disorder, selective mutism, and global hypotonia, as well as facial dysmorphisms, such as prominent large ears, midface hypoplasia, and a high forehead.

METHODS

CMA was performed in genomic DNA extracted from peripheral blood of the patient using Thermofisher CytoScan HD® array, according to the manufacturer's recommendations. CytoScan HD array contains 740,304 polymorphic (SNP, single nucleotide polymorphism) and 1,953,249 non-polymorphic (copy number probes) markers. The results were analyzed using Chromosome Analysis Suite (ChAS) v4.5.0.34 software with NetAffx 20250601 (hg19) and the output data were interpreted with the DGV (http://projects.tcag.ca/variation/); ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/); DECIPHER (http://decipher.sanger.ac.uk) and Franklin (https://franklin.genoox.com/clinicaldb/variant/) . The functions of the genes, which were located within the region of the genomic imbalance, were retrieved from the ClinGen (http://www.clinicalgenome.org); GeneCards (http://www.genecards.org) and OMIM (http://www.ncbi.nlm.nih.gov/omim) databases.

RESULTS

Cytoscan HD SNParray analysis was performed on the patient and revealed a hemizygotic interstitial deletion with 2.80 Mb at Xq21.31q21.32 (arr[GRCh37] Xq21.31q21.32(90,594,030_93,397,746)x0), encompasses three OMIM genes: *PABPC5* (OMIM*300407), *PCDH11X* (OMIM*300246), and *NAP1L3* (OMIM*300117) (Figure 1).

Parental segregation studies were suggested in order to determine whether the CNV is inherited or *de novo.* However, they could not be performed to date.

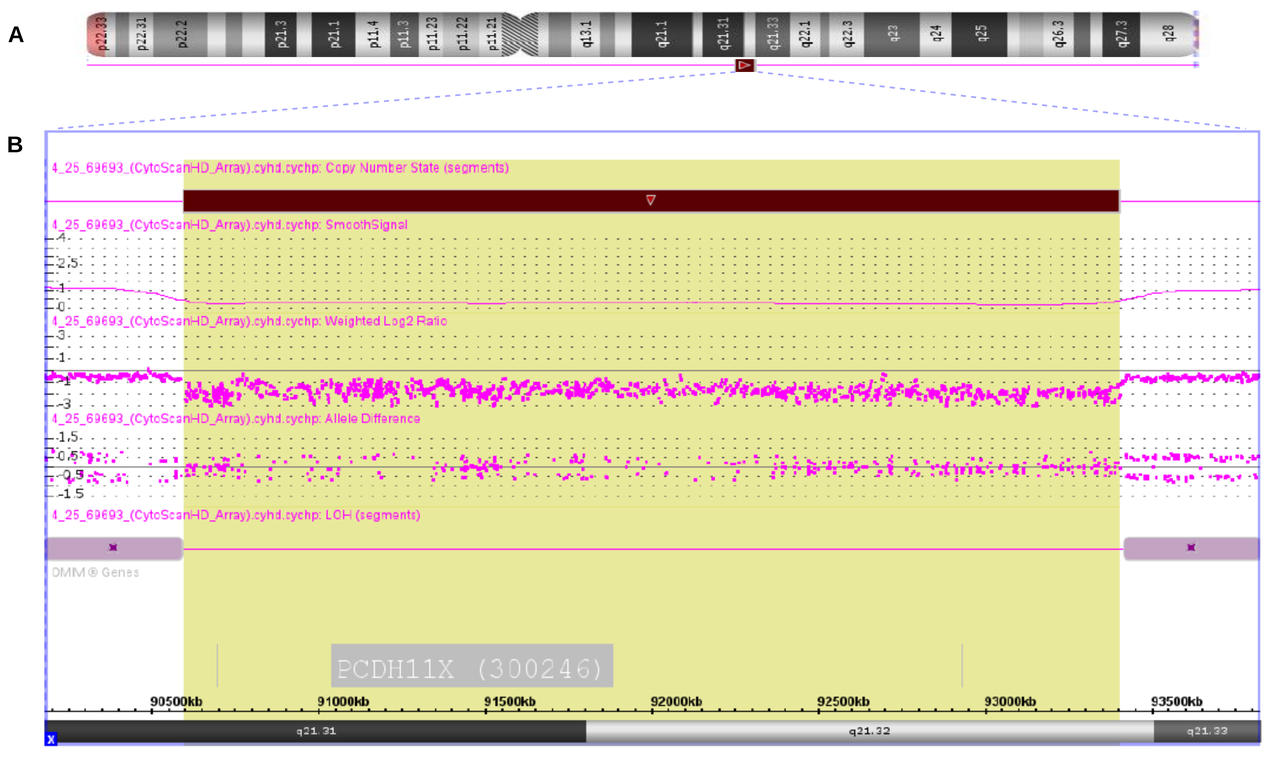

Figure 1. (A). Chromosome X ideograms showing the 2.80 Mb **loss** at Xq21.31q21.32 (**red box**); (B). SNParray profile for chromosome X with the Copy number state, Smooth signal, Copy number probe intensities (weighted log2 ratio), Allele Difference tracks indicating the deletion and OMIM Genes, being the no morbid in gray.

DISCUSSION AND CONCLUSION

The deletion of the *PCDH11X* gene has been implicated in various neurodevelopmental disorders, underscoring its relevance in brain development and function. *PCDH11X*, located on the X chromosome, forms a gene pair with *PCDH11Y* on the Y chromosome. This paralogous pair is thought to contribute to cerebral asymmetry and language development. Deletions involving *PCDH11X* have been associated with language delays and developmental dyslexia, supporting its critical role in communication and cognitive processes.[7, 8]

In the present case, the interstitial deletion encompasses three OMIM genes: *PABPC5* (OMIM**300407*), *PCDH11X* (OMIM**300246*), and *NAP1L3* (OMIM**300117*), none of which are currently classified as morbid or definitively associated with disease. However, the patient's phenotype, characterized by neurodevelopmental disorders is consistent with prior reports suggesting that alterations of *PCDH11X* may contribute to neurodevelopmental impairments.[5] Although the current level of evidence is considered moderate, this case suggests a potential role for *PCDH11X* loss of function in the pathogenesis of neurodevelopmental disorders. In particular, the overlap between the clinical features observed and the known functions of *PCDH11X*, especially those related to language and communication, reinforces the hypothesis that this gene, despite not being classified as morbid to date, may contribute causally to such phenotypes when disrupted.

While *PCDH11X* deletions have been linked to language and cognitive disorders, it is important to consider the broader genetic and environmental landscape contributing to these conditions. Interactions between *PCDH11X* and other genes located on the sex chromosomes such as *PCDH11Y* and *NLGN4Y* may modulate neurodevelopmental outcomes, as suggested in studies of autism and language impairment.[7,9] Understanding these complex interactions is crucial for establishing a genotype-phenotype correlation.

Overall, this case highlights a plausible association between *PCDH11X* deletion and neurodevelopmental disorders, adding to emerging evidence that this gene may play a meaningful role in neurodevelopment when disrupted.

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