Schizophrenia in the Context of Neurodevelopmental Disorders in 16p12.2 Chromosomal Deletion: A Case Report

To the editor,

Research in molecular genetics proposes that a complex, polygenic model best accounts for schizophrenia. A meta-analysis of twin studies estimates the genetic and shared environmental influence on schizophrenia to be at 81% (95% CI, 73%–90%), 11% (95% CI, 3%–19%), respectively,[1] showing that genetic factors play a significant role in the etiology of schizophrenia. Genome-wide association studies (GWASs), paired with next-generation sequencing methods, have identified many susceptibility loci replicated in subsequent studies.[2] Comprehensive GWAS reveals that specific genes within distinct regions of chromosome 16 (16p11.2) are intricately linked to schizophrenia.[3] In this article, we report a patient with 16p12.2 chromosomal deletion who presented with psychosis in addition to phenotypical features previously reported in 16p12.2 deletions at various coordinates. Consent was obtained from the patient to write the report.

Case History

We present a case of a 26-year-old female second-born of a non-consanguineous parentage, born by normal vaginal delivery but found to have low birth weight (<2.5 kg), cleft palate, and mild delay in all the developmental milestones, especially in the language domain. Additionally, below-average scholastic performance, recurrent ear infections (normal hearing), and stereotypical behaviors like hand flapping, perseveration, and repetitive behaviors were reported. A family history of psychosis in a maternal uncle was noted.

She presented with persecutory delusions, delusions of control, auditory hallucinations, disorganization, aggressive behavior, and poor socio-occupational functioning since 12, with a history of worsening symptoms over the past six years. She was treated elsewhere with an adequate trial of Aripiprazole with minimal improvement. On physical examination, she was found to have dysmorphism in the form of a narrow forehead, slight facial asymmetry, hypertelorism, low-set ears, repaired cleft palate, and long and hyperextensible thumbs. Her routine blood investigations and systemic examination were unremarkable.

She was initiated on oral Risperidone up to 6 mg for her presenting complaints. Based on the presentation of psychotic symptoms, cleft palate, and intellectual disability, DiGeorge syndrome was suspected. Chromosomal microanalysis revealed a large copy number variant (CNV) of a 367.7 kb heterozygous deletion at 16p12.2 with the ISCN nomenclature—arr [GRCh37]16p12.2(21,599,125_21,966,869) x1. Because of the uncertain significance of the findings, further evaluation in the form of segregation analysis of parents and extended family members has been advised, the consent for which remains pending from the patient's family. The patient's clinical response to Risperidone is unknown and needs assessment during the follow-up visit.

Discussion

Advanced molecular studies of schizophrenia genetics have two varied approaches—while the common disease (CD)-common variant model posits that multiple common alleles have additive or multiplicative effects on the causation of schizophrenia, the CD-rare variant (CD-RV) model suggests that the etiology of schizophrenia is determined by single or multiple rare risk loci which are highly penetrant but individually rare with different families harboring different mutations. Multiple CNV studies have supported the CD-RV model.[4,5] The above-described approaches are not mutually exclusive and together could explain the genetic heterogeneity in schizophrenia.[6]

Our patient had findings phenotypically suggestive of DiGeorge syndrome but was found to have 16p12.2 deletion spanning the coordinates chr 16:21,599,125-21,966,869 encompassing eight genes, of which 2 are morbid OMIM genes OTOA(otoancorin)and UQCRC2(UBIQUINOL-CYTOCHROME c REDUCTASE CORE PROTEIN II).[7] A similar-sized deletion was noted in another case with autism spectrum disorder with epilepsy in our database. Even though there are several entries in the Database Of Genomic Variation (DGV) and Phenotype in Humans using Ensembl Resources[8] overlapping the above-mentioned region with conflicting interpretations of pathogenicity, there are several entries in the DGV[9] that overlap at least nearly completely at the region observed. Parental chromosomal analysis was unavailable to confirm the inheritance pattern, rendering the CNV a variant of uncertain significance.

Girirajan et al. have described recurrent 520-kb heterozygous microdeletion at 16p12.2 at different coordinates associated with multiple phenotypic presentations like intellectual disability, aggressive behavior, psychosis, autism, digital defects, cleft palate, and sensorineural hearing loss.[10] Another related disorder includes 16p11.2-p12.2 recurrent deletion presenting with dysmorphic features, congenital anomalies, feeding difficulties, and cognitive and developmental delays.[7,11,12] The pericentromeric region of chromosome 16 is susceptible to deletion or rearrangement due to its structurally complex arrangement of repetitive sequence elements.[11]

The finding from the above case has features of psychosis amounting to schizophrenia over and above the relatively common abnormal phenotypes described in other genomic disorders. Whether this finding is significant with respect to its association with schizophrenia will be revealed by further segregation analysis of family members, which constitutes one of the limitations of this report. The presence of features of autism in this patient can perhaps explain the etiological overlap of schizophrenia with other psychiatric diseases.

In conclusion, this case adds to the series of rare identifiable chromosomal pathologies that are associated with a presentation of schizophrenia, in turn leading to a better understanding of the genetic basis of schizophrenia.16p12.2 deletion can be a potential differential to be considered in patients presenting with intellectual disability, facial dysmorphism, congenital anomalies, and psychosis.[7]

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

CU and UMM acknowledge the support of the Department of Biotechnology (DBT) – Wellcome Trust India Alliance (IA/CRC/19/1/610005) RB acknowledges the support of the Department of Health Research(2021–1004).

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Submitted: 21 Sep. 2023
Accepted: 28 Nov. 2023
Published Online: 24 Jan. 2024

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HOW TO CITE THIS ARTICLE: Uppinkudru C, Basavaraju R, Udupi GA and Mehta UM. Schizophrenia in the Context of Neurodevelopmental Disorders in 16p12.2 Chromosomal Deletion: A Case Report. *Indian J Psychol Med*. 2024;46(3):283–284.

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Website: journals.sagepub.com/home/szj
DOI: 10.1177/02537176231222570