Clinical Vignette

A Clinical Report and Further Delineation of the Proximal 8p Deletion-Associated Phenotype

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Abstract

Chromosomal abnormalities are the most common cause of unexplained developmental delay (DD), autism, intellectual disability (ID) and multiple congenital anomalies (MCA). Proximal interstitial deletion of 8p is very rare, and only a few reports have been published till date.Here, we report a 3-years-6 months-old-boy with a *de novo* 13 Mb interstitial deletion of chromosome 8p21.1-8p22, to expand the knowledge of the phenotypic effects of this rare interstitial deletion. It was in a mosaic form and mosaicism was detected on traditional karyotyping.

Keywords: 8p interstitial deletion, mosaic

Introduction

Cytogenetic microarray (CMA) is the first-tier test in the evaluation of neurodevelopmental disorders with or without malformations. Due to cost constraints, in India, karyotyping is still used frequently. Here, we present a description of the phenotype and genotype of a child with an interstitial deletion on chromosome 8p. Cytogenetic microarray delineated the exact region and the genes in the deleted segment. Karyotype showed a low-level mosaicism of normal cell lines.

Clinical details

This 3-years-6-months-old-boy was referred to our genetic clinic with global developmental delay and recurrent seizures since 3 years of age. He was the second child of non-consanguineous parents. Both his parents and his elder brother were healthy. There was no family history of malformation or developmental delay. The child's mother had history of two first-trimester spontaneous abortions.

The proband was delivered uneventfully at 37 weeks of gestation after a normal pregnancy. At birth, the weight was 2500g (-1.9 Z score). Developmental delay was noted during infancy. He achieved neck holding at 4 months, sitting with support at 9 months, sitting without support at 15 months and walking with support at 3 years 2 months. Fine motor milestones were also delayed, and he achieved pincer grasp at 1 year 6 months. He was able to coo at 4 months and speak monosyllables at 1 year. He was not able to speak bisyllables at the time of evaluation. He achieved social smile at 6 months, could recognize his mother and reached persistently for toys. The development quotient was 36% in all domains.

His height was 87 cm (Z score of -3.33), weight was 12.6 Kg (Z score of -1.59) and head circumference was 44 cm (Z score of -3.64). He had mild pallor. Hair and eyebrows were sparse. He also had hypotelorism, deep-set eyes, low-set ears, cup-shaped pinnae, long and smooth philtrum and downturned corners of the mouth **(Figure 1a,b)**. A café au lait spot was seen on the right forearm **(Figure 1c)**.There was bilateral postaxial polydactyly in the feet **(Figure 1d)**.His tone and power were mildly decreased. There was no other abnormal systemic finding. Magnetic resonance imaging (MRI) of the brain was normal. His thyroid function tests, liver function tests, and kidney function tests were unremarkable. Hemogram revealed hemoglobin of 8.3 g/dl, suggestive of iron deficiency anaemia.

On the basis of clinical features and history of two spontaneous abortions in the mother, the possibility of a chromosomal aberration was considered. Cytogenetic analysis of G-banded metaphase chromosomes was carried out and it showed a 46,XY,del(8)(p21.3) in 41 metaphases and normal 46,XY in 9 metaphases at a resolution of 550 bands **(Figure 2)**. To delineate the exact size of deletion and breakpoints, cytogenetic microarray analysis (CMA) was performed on the patient's peripheral blood using Affymetrix CytoScan 750K Array (Affymetrix, Thermo Fisher Scientific, California, United States). This revealed an interstitial deletion of 13Mb of 8p21.1-8p22 region with the telomeric breakpoint of 8p22 located at 15,753,994 and the centromeric breakpoint of 8p21.1 located at 28,811,649 based on GRCh38 human genome assembly. No mosaicism was detected by this method. This region contains 93

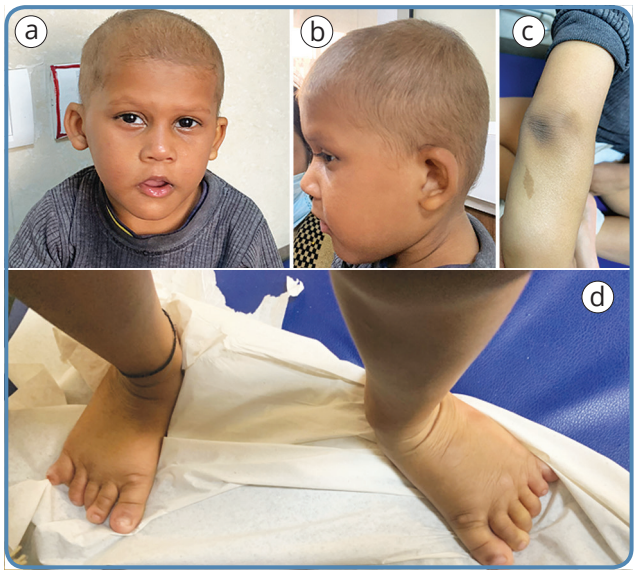
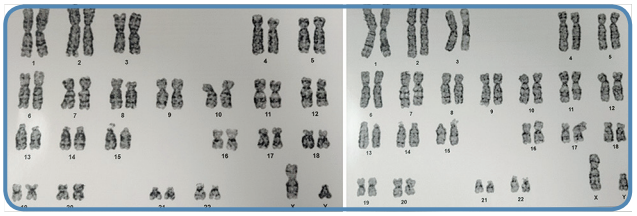


Figure 1 Facial and physical dysmorphic features of the patient at 3.5 years of age. (a) & (b) Facial image of the patient showing sparse eyebrows and hair, hypotelorism, low-set ears, cup-shaped pinnae, long and smooth philtrum and downturned corners of the mouth. (c) Image showing hyperpigmented lesion over the right forearm. (d) Image of the feet showing bilateral post-axial polydactyly in the feet.



46,XY,del(8)(p21.3)[41]/ 46,XY[9]

Figure 2 Karyotype of the patient (at 550 resolution)

OMIM genes and 96 protein-coding genes **(Figure 3)**. Microarray analysis of the parents was not performed. Karyotypes of both the parents were normal.

Similar or larger interstitial deletions of 8p21.1-8p22 region have not been reported in the Database of Genomic Variants (http://projects.tcag.ca/variation/); however, overlapping likely pathogenic or pathogenic copy number deletions have been reported in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and DECIPHER (https://decipher.sanger.ac.uk/application/) (**Table 1**). Based on the

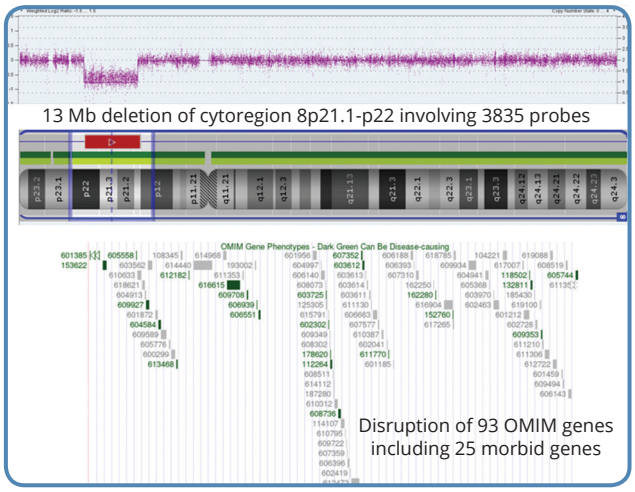


Figure 3 Deleted region of the genome. (a) SNP array scatter plot of chromosome 8 showing a 13 Mb interstitial deletion within chromosome 8p21.1-8p22. (b) UCSC Genome Browser view of the 13 Mb deleted region, showing the location of the 93 OMIM genes within this region

ACMG/AMP criteria, this deletion was classified as pathogenic (ACMG CNV score: 1.55) (Riggs et al., 2020).

Discussion

This is a report of a cytogenetically detected deletion on chromosome 8p in mosaic form. It was found to be an interstitial deletion by cytogenetic microarray. As a low level of mosaicism (18%) can be missed by cytogenetic microarray, this case emphasizes the role of classic cytogenetics in the molecular era. Mosaicism for structural chromosomal rearrangements is rare. Mosaic deletion (8p)/inversion duplication deletion (8p) were associated with both mild and severe phenotypes (Matthew et al., 2009; Soler et al., 2003; Prampero et al., 2004). The child had a café au lait spot, but patchy pigmentary regions were not seen, though there was chromosomal mosaicism.

Three entries in DECIPHER and one in ClinVar with deletions involving regions similar to this child are compared in **Table 1**. The smallest deletion in 8p is reported by Piovani et al. (Piovani et al., 2014). The individual described had mild developmental and speech delay, some facial dysmorphism and long digits. Individuals described by Izumi et al. and LaBranche et al. had deletions of 3.6 Mb and 11.49

Table 1 Phenotypes and genotypes of individuals with 8pdeletion.

Features	Our patient 13 MB CNV loss chr8: 15753993-28811649 (GRCh38)	(Izumi et al., 2011) 3.6 MB CNV loss chr8: 20850824-24473235 (GRCh38)	(Piovani at al., 2014) 1 MB CNV loss chr8: 14187850-15190363 (GRCh38)	(LaBranche et al., 2020) 11.4 MB CNV loss chr8: 5220527-16655044 (GRCh38)	ClinVar: (VCV000154449) 16.7MB CNV loss Chr8: 12383584-29033946 (GRCh38)	DECIPHER: (396045) 14.59 MB CNV loss 12798120-27386566 (GRCh38)	DECIPHER: (411603) 7. 15 MB CNV loss chr8:8: 16701235-23852321 (GRCh38)	DECIPHER: (327931) 3.95 MB CNV loss chr8: 20962469-24910423 (GRC38)
Sex	Male	Male	Male	Male	NA	Female	Male	Female
Global developmental delay	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA
Intellectual disability	Yes	Yes ADHD	Yes	Yes ADHD	Yes	Yes	Yes	Yes
Short stature	Yes	No	No	No	No	Yes	NA	NA
Microcephaly	Yes	No, Macrocephaly*	No	No	Yes	Brachycephaly	NA	NA
Dysmorphic features	Hypotelorism, upslanting palpebral fissures, deep-set eyes, low-set ears, cup-shaped pinnae, long and smooth philtrum and down-turned corners of the mouth.	Deep-set eyes, mild synophrys, horizontal eyebrows, prognathism, high palate and broad uvula	Hypertelorism, downslanting palpebral fissures, strabismus, prominent nasal bridge, small mouth, short philtrum	Deep-set eyes, mild ptosis of left eye, prominent ears, flat philtrum, thin upper lip, pointed chin	Abnormal facial shape	Hypertelorism, upslanting palpebral fissures, round face, thin upper vermilion, wide intermammillary distance, posteriorly rotated ears	Oligodontia	Upslanting palpebral fissures, prominent nasal bridge
Sparse and thin hair and eyebrows	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes

Extremities/ Joints hypermobility	Hypotonia, bilateral post-axial polydactyly in feet	Cubitus valgus	Arachnodactly, valgus knee and only one groove of the right hand with distal ligamentous laxity	Bilateral neuromuscular equinus	Generalized hypotonia	NA	NA	Hypotonia, pes cavus
Unilateral renal agenesis	NA	NA	NA	NA	NA	NA	Yes	NA
Cryptorchidism	No	NA	NA	Glandular hypospadias	Yes	NA	NA	NA
Skin pigmentary abnormalities	No	NA	NA	Yes	Yes	NA	NA	NA
Radiology (X ray/MRI brain) Imaging	Brain MRI: Normal	X ray: slipped capital femoral epiphysis and secondary avascular necrosis. Brain MRI: prominent lateral ventricles	Brain MRI: hyperintensity in the long TR sequences involving posteriorly the periventricular white matter	NA	NA	NA	NA	NA
Number of OMIM genes	93 OMIM genes	39 OMIM genes, 8 morbid genes	1 OMIM gene	53 OMIM genes, 11 morbid genes	98 OMIM genes	80 OMIM genes	58 OMIM genes	39 OMIM genes
ACMG Classification	Pathogenic ACMG CNV score: 1.55	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Likely Pathogenic	Pathogenic	Pathogenic

Mb respectively (Izumi et al., 2010; LaBranche et al., 2020) **(Table 1)**. The photographs of these individuals show deep-set eyes and characteristic nose with a prominent bridge and broadening at nostrils with pointed tip giving a triangular appearance to the nose. The characteristic facial phenotype is similar to the individual we describe. In spite of the characteristic facial phenotype, the deleted region reported by LaBranche et al. (LaBranche et al., 2020), has only 0.7Mb overlapping region with the individual we describe and no overlap with the deleted region reported by Izumi et al., 2011. Facial phenotype with cytogenetically detected deletion on chromosome 8p by Orey and Caren, is also similar (Orey and Caren, 1976). In some patients, the deletion of chromosome 8p has been found to be also associated with congenital heart malformations (Pivoni et al., 2014). Izumi et al. (Izumi et al., 2011), described the proband and his mother having a large head circumference. Polydactyly and epilepsy in the individual we describe are novel features which were not previously reported.

There are many genes in the deleted region and an inference about causative genes for neurodevelopmental disorder cannot be drawn. Tabarés Seisdedos and Rubenstein have listed the genes on chromosome 8p which are involved in neurological and psychiatric disorders (Tabarés-Seisdedos and Rubenstein, 2009). This suggests that the neurodevelopmental disability in individuals with variable deletions on chromosome 8p is likely to be due to a complex multigenic pathology.

Our report highlights the utility of systematic documentation of dysmorphic features, comparison with the published literature and clinical utility of a karyotype. We also describe polydactyly and epilepsy as novel features in 8p deletion syndrome.

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