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DEVELOPMENTAL DELAY WITH DYSMORPHISM IN A CHILD WITH RING CHROMOSOME 6

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ABSTRACT
Ring chromosome 6 is a rare sporadic genetic event that occurs mostly *de novo* with variable clinical phenotypes. It arises as an unusual circular chromosomes following the breakage and reunion of both the telomeres of the same chromosome. Ring chromosomes are unstable during chromosomal segregation and will be lost during meiosis. The proband was a 7 year old child with a history of facial dysmorphism, developmental delay and growth retardation, referred to institute for cytogenetic evaluation. Clinical examination of the child revealed low set ears, mild micrognathia, long philtrum, prominent chin, thin upper lip, flat occiput, mild webbing of neck, low hair line and clinodactyly. Chromosomal analysis revealed 46, XX, r(6) karyotype and microarray analysis revealed no significant deletions /copy number variations / loss of heterozygosity(LOH). The correlation of ring 6 phenotypes with clinical severity remains highly variable as it has multiple functions. Further, studies on molecular characterization of genes involved in ring formation helps in the establishment of accurate genotype/phenotype correlations.

KEYWORDS: Developmental delay, Dysmorphism, Karyotype, Ring chromosome.

INTRODUCTION
Cytogenetic imbalances are the most frequently identified cause of developmental delay and dysmorphic features, which affect 1–3% of children and are often seen in conjunction with growth retardation and various congenital anomalies. But only 15–40% of individuals with developmental delay and mental retardation demonstrate imbalances by conventional cytogenetic analysis, and only 3–5% of patients carry subtelomeric rearrangements. Ring chromosomes are circular chromosomes that arise from terminal breakage and reunion of the same chromosome or one telomeric break with the fusion of opposite telomere region.[1] In some cases ring chromosome is formed by the fusion of sub telomeric regions forming a complete ring with no deletions. While in other cases ring chromosome is a supernumerary ring, often very small pericentromeric material representing partial trisomies in the patients. They may also be presented in mosaic forms in the individuals where complete ring or deletion of whole ring chromosomes or monosomy 6 are seen with two to three cell lines. The clinical phenotype associated with the ring chromosomes is highly variable depending on the extent of deletion in the chromosome.[2] The clinical variability ranges from severe malformations and intellectual disability to mild dysmorphism with normal IQ. Here we report a rare case of ring 6 chromosome in a dysmorphic child for the first time from Telangana population.

MATERIALS AND METHODS
The proband was a 7 yr old female child, born to non-consanguineous couple at 40 weeks of gestation by C-section delivery with severe intra uterine growth retardation with a birth weight of 1.5kg. Present height of the proband was 102 cm and weight 17 kg with head circumference of 42cm and chest circumference of 46cm, upper segment was 49cm and lower segment 60cm. The proband was the first offspring out of three female children. There was no family history of miscarriages, birth defects or mental retardation. Clinical examination of the child revealed low set ears, mild micrognathia, long philtrum, prominent chin, thin upper lip, flat occiput, mild webbing of neck, low hair line and clinodactyly. Routine laboratory tests like complete blood picture, liver function test, serum electrolytes, glucose, urea, creatinine results were within normal range. The patient did not present with neonatal seizures or any neurological symptoms by birth. Blood samples were collected from the proband and her parents for cytogenetic analysis. A written informed consent on behalf of the child was obtained from the parents before analysis. The Study was also approved by Institutional Ethical Committee.

Chromosomal analysis was carried out by following modified method of Moorehead *et al* (1960) with 5ml of RPMI 1640 medium and 100µl of phytohaemagglutinin and 1ml of whole blood incubated for 70 hrs at 37°C. The cultures were then harvested with 60µl of colchicine at 70th hr followed by hypotonic solution (0.56% KCl) treatment and repeated fixative washes. The slides were then prepared and standard GTG banding was done.[3]

RESULTS AND DISCUSSION

A total of 25 metaphases were screened and analysed for karyotyping and more than 50 cells were scored to rule out mosaicism. Chromosomal microarray analysis (CMA) was performed using Agilent microarray, Bengaluru, which has a minimum resolution of 50KB for losses/gains and 3-10MB resolution for Loss of Heterozygosity (LOH). Chromosomal analysis indicates a female with ring chromosome 6 involving chromosomal bands 6p25 and 6q36 with 46, XX, r(6)(p25;q36) karyotype (Figure 1). Both the parents were normal with 46, XX (female) and 46, XY (male) karyotype indicating it as a *de novo* chromosomal abnormality. Microarray analysis revealed no clinically significant CNVs and regions with LOH in the patient (Figure 2).

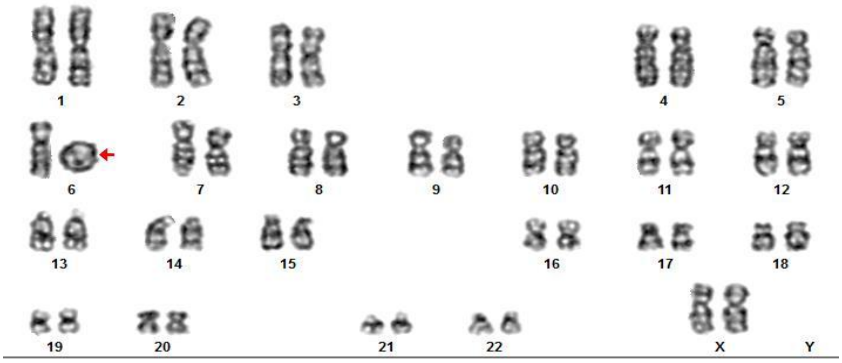

Figure 1: Karyotype of the proband with 46, XX, r(6)(p25;q36) karyotype

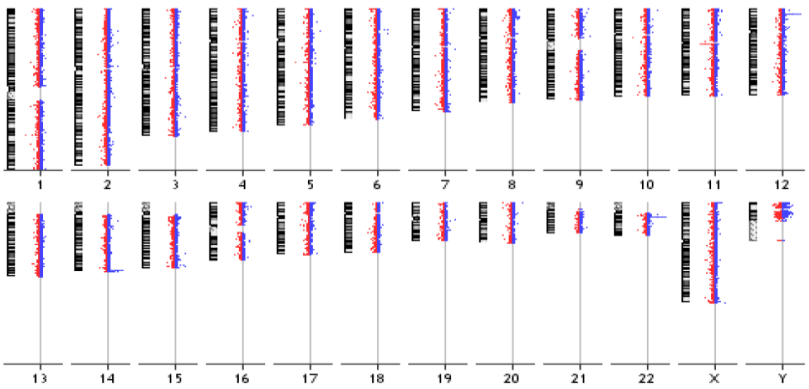

Figure 2: Microarray results showing no clinical variations.

Ring chromosomes are unusual circular chromosomes formed by the breakage and reunion of both the telomeres of the same chromosome giving rise to a circular chromosome. They are heterogeneous with uneven size and genetic content and can originate from any chromosome. Phenotypes associated are highly variable due to the deletion caused by the ring formation, and thus leads to genomic instability. Ring chromosomes are usually *de novo* as they are unstable during chromosomal segregation and thus will be always lost during meiosis or cell division. Mitotic instability of the ring chromosome 6 was stated to be responsible for the growth retardation and dysmorphic features. Most of the ring 6 cases are sterile due to chromosomal alterations and the loss of telomeres carrying functional genes. The commonly seen features in individuals with ring 6 are growth retardation, facial dysmorphism and microcephaly and with deletion of p or q arm of chromosome 6 include defects related to ocular, ear and heart malformations with telorism, intellectual disability and short neck.[4] Ring chromosome 6 was first described in 1973 by Moore *et al* in a female infant presented with dysmorphic features. Complete rings without any loss of genetic material have been reported in individuals with normal phenotype.[5] As per Ciocca *et. al*, 2013, patients with ring 6 chromosome exhibit the clinical features that include failure to thrive, congenital heart defects, intellectual disabilities, microcephaly and facial dysmorphism, vision, auditory and central nervous system disorders. However we did not find any eye, ear and heart related abnormalities in the proband which is probably due to the clinical variability seen in ring 6 chromosome.[6]

Romke et al, 1987, has mentioned that the individuals having the same breakpoints may also differ with the phenotypical outcomes.[7] The size of the deletion signifies the clinical manifestation in the individuals. The dysmorphic features and the mild developmental delay observed in the proband could be due to the disruption of chromosomal material such as microdeletions of the telomeric regions resulting in genomic imbalance located at 6p25 regions involving 13 essential genes which helps in the development of cardiac and nervous system development (like FOXC1, FOXC2 and GMDS) and few transcription factors essential for the development of T helper cells and also involved in hair, skin and eye pigmentation (IRF4).[3]

CONCLUSION

The correlation of ring 6 phenotypes with clinical severity remains highly variable as it has multiple functions. The phenotype observed in the proband could be due to the disruption of functional genes in the breakpoint regions. However, further studies on molecular characterization of genes involved in ring formation helps in the establishment of accurate genotype/phenotype correlations.

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