CASE REPORT

Double Segment Chromosomal Imbalance due to Inherited Chromosomal Translocation: Detection by Cytogenetic Microarray

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Background: Balanced translocations are common with the incidence of 1 in 500. **Case characteristics**: Two cousins with intellectual disability with family history of holoprosencephaly. **Result**: Microarray showed gain on chromosome 7 and loss on chromosome 11 and *vice versa* in the other cousin. **Conclusion**: We highlight the importance of detailed family history, pedigree analysis, and utility of microarray

Keywords: *Genetic translocation, Holoprosencephaly, Intellectual disability*.

Identification of a carrier of balanced translocation is important as the risk of imbalanced gametes in the translocation carrier is significant and can lead to recurrent abortions or malformed babies [1]. Similarly, there may be some more balanced carriers in the family, who need to be detected to provide proper genetic counseling.

Traditional karyotype is the gold standard for detection of balanced chromosomal translocations [2]. In many cases, karyotype fails to detect chromosomal translocations, especially when the translocation does not change the band pattern or the length of the chromosomes. We report a unique cryptic balanced translocation in a family segregating for at least three generations leading to unbalanced offspring that could not be identified by traditional karyotype and was revealed after cytogenetic microarray (CMA) in two offspring.

Case Report

Case 1

Proband (III-3 in the pedigree, ***Fig.* 1**) was referred at 5 months of age because of congenital heart disease and facial dysmorphism. On examination, weight was 3.6 kg (-4 SD for 5 months), length was 55.5 cm (-3 SD for 5 months) and head circumference was 41 cm (50th centile for 5 months). She had bi-temporal narrowing, eversion of the right lower eye lid and thin lower lip. Both thumbs and great toes were broad. She had bilateral single palmar crease and camptodactyly in both the hands. The proband was lost to follow up and was re-evaluated at 5 years. She achieved neck holding at 6 months, sitting without support at 2 years and standing without support at 4½ years. She responded to her name and stranger anxiety was present since 3 years of age. She started saying bisyllables at 2 years. Conventional cytogenetic analysis with the G banded karyotype (at 550 band level) and magnetic resonance imaging (MRI) brain were normal. Echocardiography demonstrated atrial septal defect with patent ductus arteriosus. Cytogenetic microarray (CMA) result using Affymetrix 2.7 M array (Santa Clara, CA, USA) showed 9.4 Mb gain of 7q36.1-36.3 and 13.16 Mb loss of chromosome 11q24.1-25 [arr7q36.1q36.3(149698257-159118443) ×3, 11q24.1-25(121769912-134926021] X1.

Mother of the proband (II-1) had the history of prenatally detected congenital malformations in the previous two pregnancies. First baby (III-1 in ***Fig.*1**) was a male who had microcephaly, corpus callosal defect and some congenital anomalies of the lung. The baby expired 3 hours after birth. Second pregnancy was terminated at 18 weeks as the fetus was diagnosed to have alobar holoprosencephaly with microcephaly.

Case 2

This child (III-6) was a 4 month old female, first born child of a non consanguineous couple. Her father was the cousin of the father of case I. The child had feeding problems and was not growing well since birth. She was delivered post term with a birth weight of 2.1 kg. During the antenatal period maternal serum screening test was positive for trisomy 21. Amniocentesis was performed and karyotype at 550 band level was normal. There was a history of delayed cry and respiratory distress at birth.

On examination, the child's weight was 2.7 kg (–7 to –6 SD for 4 months), length was 50 cm (–5 SD for 4

months) and head circumference was 32 cm (–6 SD for 4 months). Facial dysmorphism included low set ears, broad nose, left eye ptosis, high arched palate and microretrognathia (***Fig.* 2B**). The nails in lower limbs were hypoplastic. There was no camptodactyly. MRI brain revealed corpus callosum agenesis and hypoplastic inferior vermis. The baby expired at 8 months. CMA analysis showed 13 Mb gain of genomic material on 11q 24.1 -25 along with 9.2 Mb loss on 7q 36.1 – 36.3 region. (arr7q36.1q36.3 (149770238-159118443) X 1, 11q24.1-25 (121769912-134926021) X 3.

Another child in the family (III-4 in ***Fig.* 1**) was also found to have some developmental disability and he was related through his father. There was a history of intellectual disability with spasticity in him. He had porencephaly on MRI brain and the cytogenetic microarray revealed normal results. In the wife of the same paternal uncle, one pregnancy was terminated after prenatal diagnosis of holoprosencephaly (III-5).

The mother of III-6 (II-6 in ***Fig.* 1**) returned in her second pregnancy for prenatal diagnosis. Chorionic villus sampling was done at 11 weeks and Multiplex ligation probe amplification revealed same genomic imbalance involving the terminal regions of chromosomes 7 and 11 (loss at 7qter and gain at 11qter) as in the proband III-6. They decided to terminate the pregnancy and the fetal autopsy did not reveal any major or minor malformation.

The unbalanced genomic rearrangements in the two cousins involving the same breakpoints suggest that the father of the proband and also of her cousin may be carriers of balanced translocation. To confirm this, we performed Fluorescent in Situ Hybridisation (FISH) analysis using centromeric probes for chromosome 7 and 11 and probes for subtelomeric region chromosome 7q36 and 11q24.1.25 in the father [II-2] of III-3. FISH confirmed the translocation between chromosomes 7 and 11.

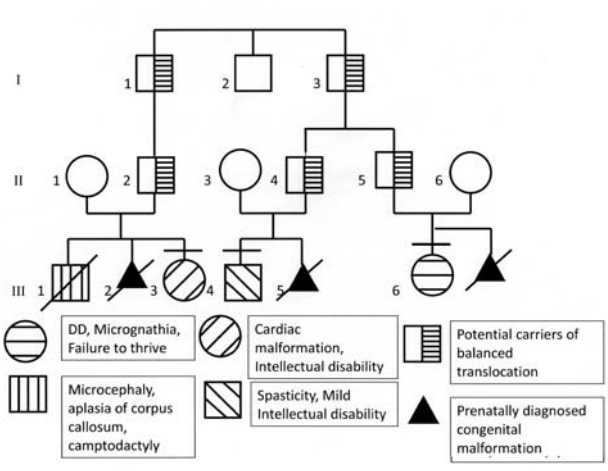

FIG. 1 *Pedigree of the family.*

DISCUSSION

In this family the possibility of balanced translocation in the fathers was confirmed by FISH in one of the possible carriers (II-2). The other possible carrier II- 5 though not confirmed by FISH, was an obligate carrier as his daughter had imbalances of the same chromosomes with the same breakpoints. II-4 is also likely to be the carrier of same translocation, as his wife's one pregnancy showed a fetus with holoprosencephaly, but CMA of the fetal sample and FISH for II 4 was not done and his son with a different phenotype did not show any genomic imbalance.

This case highlights the utility of cytogenetic microarray in cases with normal karyotype and most importantly the possibility of familial balanced translocation in cases of double segment imbalances. It is important to identify translocation carriers as they have a high risk of conceptions with genomic imbalances and can be helped by prenatal diagnosis.

There are a number of genes present in the deleted and duplicated region involving chromosome 7q36.1 and 11q24.1. The relevant genes on chromosomes 7(q36.1-36.3) and 11(q24.1-25) include two genes for holoprosencephaly (HPE), namely *SHH (Sonic Hedge hog)* at 7q36 and *CDON* (cell adhesion molecule-related downregulated by oncogenes) at 11q24 which explains the malformation in the fetuses. The penetrance of holoprosencephaly genes is 70% [3] which explains the absence of holoprosencephaly in our probands. *KIRREL* 3 gene responsible for mental retardation is present in the region ch 11q24.1-25 which explains the mental retardation in the 2 cousins.

A large study involving 5380 patients identified the chromosomal abnormalities in subtelomeric region detected by microarray [4]. There are a number of case reports related to the double segment imbalances detected by cytogenetic microarray [5,6]. This case stresses the need to suspect chromosomal abnormality in families with multiple members affected with different phenotypes of intellectual disability and dysmorphism.

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