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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- Detection of a rare balanced complex chromosomal rearrangement in a healthy female and recurrent holoprosencephaly in the fetuses

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Aims:-Complex chromosome rearrangements (CCRs) are balanced or unbalanced constitutional structural aberrations, essentially translocations, involving at least three breakpoints between two or more chromosomal segments. Individuals with CCR are extremely rare. Balanced CCR carriers are often phenotypically normal but associated with high risk of spontaneous abortion and having abnormal offspring with unbalanced karyotype. Here, we report a rare case of CCR involving chromosomes 1, 6 and 13 with two terminal breaks on a single chromosome leading to two different reciprocal translocations, furthermore there was a heterochromatic inversion on a #9.

Methods:- A young nonconsanguineous couple was referred for karyotyping and genetic counseling having a history of two miscarriages. Fetal sonography showed presence of alobar holoprosencephaly, single ventricular cavity and absence of midline flax. Enhanced nuchal translucency with septa was detected at 11 weeks of gestation. Previous pregnancy was also affected with holoprosencephaly.

Results:- Chromosomal microarray (CMA) of product of conceptus showed two CNVs. A 11.68 Mb gain at #1q43q44 and 23.74 Mb loss at #13q31.3q34. Haploinsufficiency of ZIC2 gene encompassing 13q32.3 region is known to cause holoprosencephaly in the fetus. Conventional G-banding of the father at 500 band resolution showed a normal karyotype, whereas the mother had 46,XX,der(1),der(6),der(13),inv(9)(qh). Further characterization using various FISH probes showed a CCR involving chromosome 1, 6 and 13 with two terminal breakpoints on #1 i.e. 46,XX,der(1)t(6;1;13)(p12;p3?4q34;q31.3),der(6)t(1;6)(p3?4;p12),inv(9)(p12q21.11),der(13)t(1;13)(q34;q31.1).

Conclusions:- To the best of our knowledge, no other constitutional balanced CCR involving two terminal breakpoints on chromosome 1 resulting in two different reciprocal translocations have been previously described. This case also points towards the importance of post CMA validation by parental karyotyping and comprehensive characterization by FISH to delineate the key answer to the presence of standalone der(13) in the fetus and offer precise genetic counseling then after.

Keywords:- Complex chromosomal rearrangement (CCR), reciprocal translocation ,Chromosomal microarray, FISH, holoprosencephaly, karyotyping