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Prenatal Diagnosis of Fetus with Short Limbs Caused by Three Abnormal Chromosomes Inherited from Parents

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ABSTRACT A 29 year old woman with history of G2P0+1 and shortening of limbs in past pregnancy referred herself to undergo a fetal anomaly scan at 18th week of gestation. The ultrasonographic imaging of the present pregnancy admeasuring the growth of 12-13 weeks at 18th week detected hydrocephalous condition with short limbs and kyphotic spine. This report aimed at looking for chromosomal aberrations in association with the imaging results and discussed the case in light of available literature. Amniocentesis and conventional cytogenetic analysis was performed following the standard protocol of tissue culture and chromosome banding. Karyotypic analysis of 50 metaphases detected an abnormal female karyotype with 46,XX,inv(9)(p11q13),t(15;16)(q15;q22) pattern. The karyotype revealed two constitutive abnormalities involving four break-points on three different chromosomes in a female genome. Upon counseling, the parents decided to terminate the pregnancy. However, at delivery the external genitalia of the female fetus was found to be of male phenotype and ambiguous. Parental karyotyping revealed transmission of inversion from mother and the balanced translocation from father. Finally the fetal karyotype was expressed as 46,XX,inv(9)(p11q13)mat,t(15;16)(q15;q22)pat.

INTRODUCTION

Chromosomal analysis in prenatal diagnostic practice has long been considered a gold standard technique, which not only recognizes numerical alterations but also structural rearrangements to a large extent. The facility also guides for prenatal karyotyping of fetus to understand inherited or *de novo* origin and drives urgency on decision for a medical termination of pregnancy (MTP) and genetic counseling for parents, siblings and close blood-relatives. Such information on chromosomal abnormalities in adults is typically extracted retrospectively since balanced translocations and inversions do not generally express phenotypically in first generation carriers. Occurrence of chromosomal abnormalities in the general population has been shown to vary over age groups, 5-13% in adults, 2-5% in children (excluding Down syndrome), 5-10% in aborted fetus, 3-5% in live fetus, etc. (Jeong et al. 2010; Kaur and Singh 2010; WHO 2010); however, these statistics stem from referred cases only. Thus, the actual frequency in general population can be expected to be much higher and this has been reflected at least in the case of recurrent miscarriage where more than 50% fetuses are reported with major chromosomal abnormalities.

Changes in numerical alteration lead to significant phenotypic and clinical manifestation with trisomy 21 being the most common autosomal variation. Structural anomalies, if balanced, are generally not suspected in adults to express clinically. Among all such structural aberrations, pericentric inversion in 9(p11q13 or p11q12) is the most common at any age (1-2% fetuses) and is considered a polymorphic variant since it is not associated with a specific phenotypic or clinical expression. However, a number of abnormalities have been reported in carriers of inv(9) and more frequently in adults having history of primary or secondary infertility (Akbas et al. 2010; Dana and Stoian 2012; Kumar et al. 2012). Abnormalities involving other chromosomes have also been recorded in prenatal diagnosis. Whether the abnormality is numerical or structural, involvement of mostly single and rarely dual chromosomes have been reported. In prenatal diagnostic practice, generally terminations of such

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fetuses have been a choice of the couples to avoid clinical complications in future life of the children where mental retardation is a common problem.

In the present report the researchers describe a fetus with three abnormal chromosomes causing shortening of limbs and growth retardation as major abnormality detected in ultrasound imaging. Further genetic counseling has detected transmission of all aberrations from both parents and guided the family for future course of action with possible risk and recurrence of aberrations in future pregnancy. The report highlights the importance of chromosome analysis in prenatal diagnosis. The case is deemed important to the research community since the fetus is carrying three abnormal chromosomes with a unique clinical expression not directly linked to either of the involved chromosome viz. 9, 15 or 16 and their break-points and most importantly, neither parents show any phenotypic abnormality.

METHODOLOGY

Case History

Ultrasonographic imaging of the present fetus of a 29 year old woman with a history of G2P0+1 detected hydrocephalous condition with short limbs (especially shortened femurs and tibia) admeasuring the growth of 12-13 weeks at 18th week. The sonographic measurements were as follows: biparietal diameter (45 mm 19W5D), head circumference (160 mm 18W6D), abdominal circumference (136 mm 19W1D), femur length (11mm 13W2D), fetal weight (159 gm), placenta (upper anterior) and both humerus bones measured appropriate to the gestation. Gross hydrocephalus condition was noticed in lateral ventricle, trans-cerebellar diameter, Cisterna Magna Width and Nuchal thickness. Normal conditions were noticed in face, chest, abdominal wall, cord insertion, umbilical cord (3 vessels), stomach (below diaphragm) and both right and left kidneys. Four chamber view of the heart could not be obtained. Head and limbs were grossly abnormal. Kyphotic spine was also evidenced.

Following counseling, the parents decided to check the karyotype of the fetus followed by MTP. Therefore, amniocentesis was preferred for whole genome karyotyping since the gestation was appropriate for the sampling. After amniocentesis, the medical termination was performed uneventfully at 20th week. Physical examination detected a male fetus with grossly shortened limbs, bowed legs and hydrocephaly.

Two years ago, patient had experienced an intrauterine death of her first pregnancy at 28 weeks gestation. The stillborn baby had very similar features of shortened limbs as mentioned by the mother. Karyotyping was not performed.

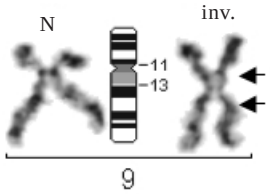
Culture of Cells and Karyotyping

Amniotic fluid sample was processed following culture of monolayer cells in complete nutrient medium in replicate sets (Barch et al. 1997). The result was obtained on 10th day following standard colchicine-hypotonic-fixative schedule and conventional G-banding technique. Peripheral blood samples of the couple were incubated in RPMI 1640 medium supplemented with fetal bovine serum and phytohaemagglutinin. Analysis of 25 cells for each individual sample following karyotypic classification was recorded with the help of IKAROS karyotyping software (MetaSystems, Germany) following ISCN nomenclature (2013).

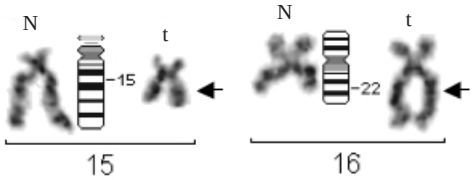
RESULTS

Fetal karyotype was detected with an abnormal female genome with 46,XX,inv(9)(p11q13),t(15;16)(q15;q22) chromosomal pattern (Fig. 1). A pericentric inversion in 9 at (p11q13) (Fig.1.a.i) and a balanced translocation between 15(q15) and 16(q22) (Fig.1.a.ii) were present in all 25 cells karyotyped. Break-points have been compared with the standard ideogram inserted on the right and the normal chromosomes are assigned on left of the partial karyograms. There were total four chromosome breaks, including two on chromosome 9 at p11 and q13, and single break on each of chromosome 15 at q15 and 16 at q22. In chromosome 9, two chromosome breaks have rejoined in inverted position resulting in an intra-chromosomal pericentric exchange of two arms (p and q). The chromosome breaks in 15 and 16 have led to rejoining of the broken segments; however, with a reciprocal exchange between the fragments of the two chromosomes. These changes of chromosomal segments at intra- and inter-chromosomal level have obvious-

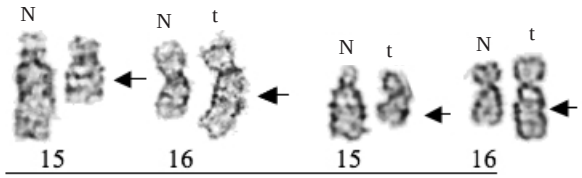
a. Partial karyotype of the fetus
i. Inversion in 9

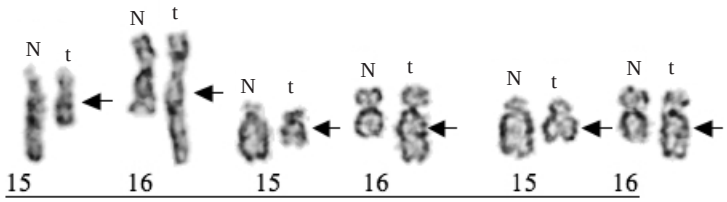


ii. Translocation between 15 and 16

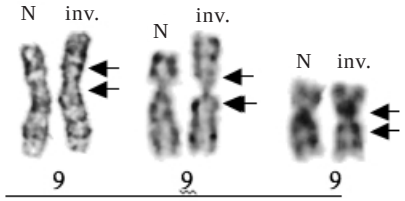


a. Partial karyotypes of the parents
i. Father with t (15:16)





ii. Mother with inv (9)



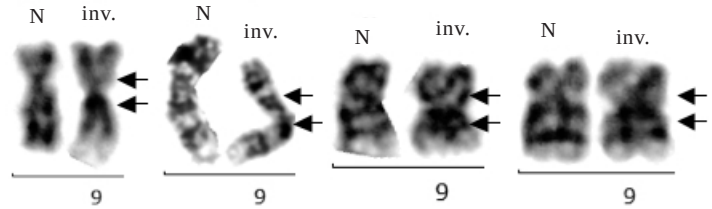


Fig. 1. Chromosome abnormalities detected in fetus and parents. a. partial karyotype of the fetus showing inv(9) (i) and balanced translocation between 15 and 16 (ii), and b. partial karyotypes of the parents (i) Father's karyotype with t(15;16) and (ii) Mother's karyotype with inv(9). In all figures, normal chromosomes are placed on the left in the pair representation.

ly altered the nucleotide sequences at all four break-points, which has resulted in chimerism of chromosome arms in all three chromosomes. The present karyotypic finding with three derivative chromosomes has raised a question on possibility of parental transmission of some of the abnormalities present in the fetus, and subsequently parental karyotyping revealed inheritance of the pericentric inversion in 9 from the mother (Fig. 1.b.i), and the balanced translocation from the father (Fig. 1.b.ii). Therefore, the fetal karyotype was revised as 46,XX,inv(9)(p11q13) mat,t(15;16)(q15;q22)pat. The cultures of the fetus and the father yielded low mitotic index with poor morphology of metaphase chromosomes.

DISCUSSION

The human genome is a highly dynamic structure that shows a wide range of genetic polymorphic variation in nature. The chromosome 9 is structurally highly polymorphic with 145 Megabases in approximately 1,149 genes and 426 pseudogenes and represents 4 - 4.5 percent of the total DNA in a diploid cell. Apart from genes responsible for male-to-female sex reversal, cancer and neurodegenerative disease, this chromosome contains the largest interferon gene cluster of a human genome (Humphray et al. 2004). It also contains the largest autosomal block of heterochromatin, which is heteromorphic in 6-8% of humans, whereas pericentric inversions occur only in 1-1.6% of the population. A pericentric inversion is an intrachromosomal rearrangement involving centromere and occurs when a single chromosome undergoes breakage on both p and q arms and rejoining within itself.

The most common familial inversion seen in humans is on chromosome 9, at (p11q13). In the present case, the mother had a pericentric inversion in 9 with an apparently normal phenotype and no major clinical expression except reproductive failure. However, in individuals who are heterozygous for an inversion, there is an increased production of abnormal chromatids through crossing-over within the span of the inversion (Ganguly et al. 2000). Inversion heteromorphisms may promote reshuffling of tandem arrays of DNA repeat sequences, thereby giving rise to new heteromorphic domains. Alternatively, the repetitive nature of the sequences lends to the structural variations observed within chromosomes (or any other abnormal chromosome that is the result of recombination between, or breakage within, repetitive DNA). This leads to lowered fertility due to production of unbalanced gametes.

Despite being categorized as a minor and balanced chromosomal rearrangement, many reports in the literature presented conflicting views regarding its association with subfertility and recurrent abortions (30% of affected couples), abnormal clinical conditions, as well as chromosomal abnormalities arising as a result of having this inversion. Till date a number of cases have been reported with this inversion in different age groups with divergent clinical expression, more frequently primary or secondary infertility (Ganguly 2006). A number of cases have also been reported with early onset of hematologic malignancies where this inversion could be a predisposing factor (Ganguly and Agarwal 2005). Marked signs and symptoms of psychomotor retardation, developmental delay, kidney anomalies, mental retardation, genital abnormalities, vertebral abnormalities, craniofacial anomalies, microcephaly, narrow eye slits, protruding tongue, impaired intelligence, learning disability, behavioral problems were reported in a child with inv(9) (Akbas et al. 2010). Schizophrenia has also been reported in a case with the mother carrying a pericentric inversion of chromosome 9, which indicates the possibility of a candidate gene located in chromosome 9 (Lee et al. 1998). The present fetus had shortened limbs, hydrocephaly, kyphotic spine and ambiguous genitalia. Many other dysmorphic features could have been manifested during childhood; however, the current pregnancy was terminated with an anticipation of IUFD as experienced in the first pregnancy. Association of inv(9) and abnormal ultrasound findings including hydramnios, anhydramnios, hydroureter, hydronephrosis, encephalocele and prune belly syndrome, occurring singly or in combination was reported by Salihu et al. (2001). The present pregnancy was observed to have oligohydramnios in ultrasound imaging. Inv(9) was also observed to cause oculo-auriculo-vertebral (OAV) spectrum or Goldenhar syndrome associated with axial skeleton anomalies, eventration of the right hemi-diaphragm, accessory spleen, unlobulated right lung, agenesis of right kidney, right ovary and right uterine horn, and partial agenesis of corpus callosum in a premature newborn delivered

with low birth weight and microcephaly after 36 weeks of gestation (Stanojeviæ et al. 2000). Chromosome 9p11 and 9q13 holds *FGF7*-like genes which are responsible for the development of ovarian cancer. Overexpression of *FGF7* gene has been detected in surgical specimens of 4 of 9 stage I or II cases and in 10 of 11 stage III or IV cases (Yasuhara et al. 2005).

In addition to inv(9), the present fetus had a balanced translocation between chromosomes 15 and 16 of paternal origin. The father with 46,XY,t(15;16)(q15;q22) had no phenotypic characteristics; however, the fetus had gross anomalies detected in USG. Chromosome 15 has crucial involvement in Prader Willi syndrome and Angelman syndrome, particularly 15q11-q13. However, in the present case, the break occurred at (15q22). In the present fetus, the clinical manifestation could be due to rearrangement of 16q22 at 15q15 and 15q15 at 16q22 and eventual rearrangement of genes located on the two chromosomal segments.

Thrombospondin1 *(THBS1)* gene was mapped on chromosome 15q15 (Jaffe et al. 1990). This homotrimeric glycoprotein with disulfide-linked subunits binds heparin, collagen V, fibrinogen, plasminogen etc. The limb-girdle muscular dystrophy, which usually occurs in childhood, (*LGMD*) locus was assigned proximal to 15q15-q22 by demonstration of linkage to D15S25 (Beckmann et al. 1991). Pignatelli and Bodmer (1988) hypothesized that the gene for controlling an arg-gly-asp-thr-directed collagen receptor is also located on chromosome 15. In the present fetus, rearrangement at 15q15 could be a possible underlying mechanism for skeletal dysplasia. The chromosome band 16q22 is linked to an autosomal dominant familial leukemia where *CBFB* (a core-binding factor) gene maps. A genome-wide scan mapped *HCHOLA4,* a hypercholesteromia gene, at 16q22.1. Chromosome 16 has fragile sites at 16p13.11 (*FRA16A*) (folate sensitive) and at 16q22 (*FRA16B*) (distamycin A-inducible). Haptoglobin gene is located in the vicinity of *FRA16B* (Mulley et al. 1989). Hap 2-2 is associated with myocardial infarction. Chen et al (1991) mapped calbindin (*CALB2*), brain calcium binding protein and carbonic anhydrase (CA4) to distal portion of 16q22.1. Chromosome 16q22-q23 contains the proto-oncogene *MAF* as reported by Yoshida et al. (1991). The deduced amino acid sequence of the *V-MAF* gene product contains a leucine zipper motif similar to that found in a number of DNA binding proteins, including gene products of *FOS, JUN and MYC* oncogenes. Chromosome 16q22.1 holds *UVO* (uvomorulin) gene distal to *LCAT* (lecithin: cholesterol acyltransferase deficiency) and proximal to *HP* and *TAT* loci (Chen et al. 1991). Uvomorulin is a specific calcium ion-dependent cell adhesion molecule. *LCAT* is assigned to 16q22 with 6 exons spanning about 4200 basepairs. Lack of *LCAT* activity leads to accumulation of free cholesterol in the tissues and causes Norim disease, Fish-eye disease, etc. Natt et al. (1987) narrowed the assignment of *TAT* (tyrosine transaminase) gene to 16q22.1-q22.3. *TAT* deficiency or tyrosine aminotransferase deficiency causes herpetiform corneal ulcer, palmoplanter keratosis and mental retardation and elevation of hydroxyphenylpyruvic acid in the urine. Collier et al. (1991) demonstrated that type IV collaginase (*CLG4A* and *CLG 4B*) are situated on chromosome 16. The present fetus had rearrangement at 16q22 with 15q15, which could have led to clinical expression with some of the abovementioned alteration during childhood. 16q22 harbors *CDH11* gene that regulates cell-cell adhesion molecule and mediates adhesion by Ca2+-dependent interactions. *CDH11* works in maintaining tissue architecture and cell polarity through alpha and beta-catenin of actin cytoskeleton, and also induces apoptosis, and regulates epithelial-mesenchymal transition (Li et al. 2011).

Shortening of limbs can lead to achondroplasia or dwarfism without cartilage formation or its ossification. The genetic cause of achondroplasia is translated as autosomal dominant inheritance. In the present family, both parents were normal with apparently normal height and weight. There was no similar history in both maternal and paternal families. Therefore, it can be speculated that rearrangement of multiple genes located on the three chromosomes have contributed in shortening of limbs and kyphotic spine.

The parents of the present case did not have any significant phenotypic or clinical expression except consecutive reproductive failure with similar clinical expressions (although cytogenetic investigation was not performed for first pregnancy). The rearrangement in the mother was of an intra-chromosomal nature whereas that in the father was of an inter-chromosomal one, bal-

anced and heritable. It has been reported that balanced rearrangement does apparently not cause loss of nucleotides and clinical manifestation in first generation carriers. In the present case, karyotyping could not be done for the grandparents due to their apprehension; however, the sibling of the mother had normal reproductive outcome. The meiotic cell division of one individual with balanced chromosomal rearrangement leads to recombination during crossing over. Therefore, the sequence of nucleotides of a balanced rearrangement in parents is expected to be changed in gametes. Hence there is likelihood of phenotypic expression in offspring carrying the inherited balanced recombinant rearrangement. Molecular analysis of the breakpoints could have deciphered the recombination of nucleotides in fetus carrying balanced chromosomal alterations transmitted by the parents and could have identified the candidate gene(s) responsible for shortening of limbs in the two fetuses.

There is a great deal of phenotypic overlap and genetic heterogeneity among patients with skeletal dysplasia which is characterized by abnormalities in the development of bone and cartilage tissues. Wieczorek et al. (2002) reported normal male karyotype and normal high-resolution CGH result in a 5-year-old boy with skeletal defects, genital hypoplasia, and mental retardation, whereas, aCGH had identified an approximately 8-Mb *de novo* deletion on the paternal chromosome 11 in a region containing about 72 genes. And sequence analysis of *ZBTB16* gene on the maternal allele revealed a missense mutation. The mother being a heterozygous carrier of the mutation had no hand or forearm abnormalities on X-ray imaging. On the contrary, no mutations were found in the *ZBTB16* gene in 41 patients who had clinical overlap with this patient, including patients with thrombocytopenia-absent radius syndrome, a tentative diagnosis of Holt-Oram syndrome, or severe radial defects. In the present study, all chromosomal alterations were apparently balanced; however, balanced translocations may host cryptic chromosomal rearrangements. Thus the possibility of deletions and molecular recombination of genes due to breakage and reunion cannot be ruled out.

The genes *TBX3* (12q24.1) and *CHST3* (10q22.1) have been reported to contribute for limb and skeleton development in human, and mutations in these genes have affected limb, genital and skeleton development in children (Bamshad et al. 1997). However, in the present case, chromosomes 10 and 12 appeared normal. Rearrangement in chromosome 15 at 16q22 could be the possible cause of abnormality in limb development in the present case. The U.S. National Library of Medicine (2014) has reported that mutation in *CAPN3* (calpain 3) which is located at 15q15.1 is responsible for limb-girdle muscular dystrophy, also called calpainopathy. More than 300 mutations in the *CAPN3* gene have been identified, which account for approximately 30 percent of limb-girdle muscular dystrophy. More than 30 mutations in *CDAN1* gene (15q15.2) are responsible for congenital dyserythropoietic anemia (CDA) by reducing the function of codanin-1 protein. In such cases, shortage of healthy red blood cells leads to anemia and other clinical complications including hepatosplenomegaly and an abnormal buildup of iron that can damage the body's organs. And the mutations in *CATSPER2* gene, located at 15q15.3, causes sensorineural deafness and male infertility. People with a homozygous deletion in 15q15 cannot produce CATSPER2 protein, which is an essential element for sperm motility and fertilization. Ortolan et al. (2003) have observed rocker-bottom feet in cases with duplication of 16q22. Therefore, in the present case, balanced t(15;16) and its molecular recombination during paternal gametogenesis has possibly resulted in rearrangement in some of the abovementioned genes and affected limb development in the fetus.

Therefore, it is true that identification of disease-genes would improve patient care through genetic diagnosis as well as improving understanding of the diseases and molecular mechanism of skeletal tissue formation. Molecular studies by employing aCGH or exome sequencing of skeletal dysplasia in the present fetus would also have helped to identify disease-genes affecting limb-cartilage and characterize molecular changes at nucleotide level of single or multiple genes located on the three chromosomes. Thus, in the present case clinical information was limited to chromosomal changes in all three individuals.

In the present couple, 50% of female gametes will carry normal 9, whereas the balanced translocation in the male partner will produce four different male gametes with normal (25%), and balanced (25%) and unbalanced (50%) rearrangements. The unbalanced translocations will carry partial monosomy of one and partial trisomy of the other chromosome. Participation of gametes with unbalanced translocations in fer-

tilization will have significant clinical and phenotypic effects, which could further be aggravated by involvement of a female gamete carrying inv(9). Union of gametes with inv(9) and reciprocally rearranged 15 and 16 has likely resulted in shortening of limbs in the present case. The chance of fertilization of two normal gametes lies around 12% in the present family. Therefore, this mother, though biologically fertile, may opt to conceive through IVF technique with male donor's gametes followed by pre-implantation genetic testing (PGD) for selection of embryonic clone with normal 9, and prenatal diagnosis (PND) for chromosome analysis at whole genome level.

CONCLUSION

Shortening of limbs appears to be caused by three balanced chromosomal rearrangements. Further molecular characterization could reveal the translocation or deletion of gene sequences at the breakpoints and/or perturbation of gene-expression caused by three chromosomal rearrangements. This is the first prenatal case to report shortening of limbs indicatively caused by three abnormal chromosomes inherited from both parents.

RECOMMENDATIONS

The present report has indicated that normal phenotype does not always guarantee a normal genotype. Therefore, antenatal counseling and fetal karyotyping not only establish the chromosomal fingerprint of the child long before birth but also prevents the global burden of genetic impairment, and societal and familial stress. Hence, this report strongly suggests prenatal karyotyping of all pregnancies of any age and duration, and mandatorily before cord blood stem cell banking.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in carrying out the investigation. The couple's consent was obtained upon counseling.

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