Case Report

A Child with Partial Trisomy 4 (q26 – qterminal) Resulting from Paternally Inherited Translocation (4:18) Associated with Multiple Congenital Anomalies and Death

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ABSTRACT

Parental balanced reciprocal translocations can result in partial aneuploidy in the offspring due to unbalanced meiotic segregation during gametogenesis. Herein, we report the phenotypic and cytogenetic characterization in a 9-day-old male child with partial trisomy of chromosome 4. Karyotyping of the proband and parents was performed along with multicolor fluorescence *in situ* hybridization (mFISH) of paternal chromosomes. Conventional cytogenetic analysis by karyotyping showed 47,XY,der(18),t(4;18)(q26;q22),+4 in proband, and the paternal karyotype was found as 47,XY,der(18),t(4;18)(q26;q22). mFISH analysis on paternal chromosomal preparations confirmed both region and origin of the balanced translocation. In this study, karyotyping helped us to identify both numerical and structural anomalies in the proband, and mFISH helped us to confirm our cytogenetic findings. Therefore, cytogenetic screening of both partners is recommended before pregnancy to rule out or confirm the presence of any numerical or structural anomaly in one, both, or none of the partners.

Key words: Balanced translocation, karyotyping, multicolor fluorescence *in situ* hybridization, omphalocele

Introduction

When any two different chromosomes undergo the adjacent-1 type of segregation, it leads to balanced translocations which typically present with no significant phenotypic effects unless there is involvement of an important functional gene at one or both the chromosomal breakpoint(s). Balanced translocation results in a combination of partial trisomy and/or partial monosomy in the zygote.[1] Few reports have highlighted the occurrence of partial trisomy of chromosome 4 and associated phenotypical characteristics. *de novo* translocation t(4;7)(q27;q22) in a girl aged 13 years was previously reported to have severe mental retardation, growth retardation, and hearing impairment, along with minor foot, thumb, and facial abnormalities.[2] Chen *et al.*[3] reported a case of a 23-year-old female with trisomy 4q32.3–4q35.2 and trisomy of 21q11.2–21q22.11, suffering from recurrent pregnancy losses along with mental retardation and unusual facial characteristics.[3] In this manuscript, we report the case of a male child (9 days old), diagnosed with omphalocele and facial dysmorphic features. To the best of our knowledge, the occurrence of partial trisomy of chromosome 4q26-qter due to the inheritance of paternal balanced translocation involving long arms of chromosome 4 and chromosome 18 has been reported in less than ten cases worldwide.[4] From India, translocation 4;18 associated with omphalocele along with other morphological abnormalities has not been reported yet.

Case Report

The proband was a male born to a nonconsanguineous couple, a 35-year-old father and a 25-year-old mother, with a history of one previous first-trimester abortion. Clinical

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history of the previous abortion was not available. The second pregnancy resulted in the birth of the proband, diagnosed with omphalocele along with various craniofacial anomalies, including cleft lip, wide forehead, flat nasal bridge, hypertelorism, and low set of ears [Figure 1a-d]. Blood sample from the proband was sent on the day he was born, from the Neonatal Intensive Care Unit of Kalinga Institute of Medical Sciences to our laboratory for routine genetic analysis by karyotyping, accounting to all the above-mentioned phenotypical anomalies. Conventional G-banding by trypsin and Giemsa stain (GTG banding) was performed on the metaphase chromosome spreads of the proband. The proband was viable carrying one extra copy of chromosome 4(q26-qter) which was found to be consistent with every metaphase spread scored. The proband passed away on the 9th day of his birth. We retrospectively approached the parents of the proband to know the status of their chromosomes, as it was speculated that extra copy of chromosome 4 must have come from either of the parents. They were counseled, and written consent was obtained from both parents for being active participants in this study. Family history was obtained from each of them for three generations, followed by peripheral blood collection for our further research interest. Pedigree analysis and GTG banding were performed on the metaphase chromosome spreads from both the partners.

According to the pedigree analysis [Figure 2], none of the individuals in the previous generation had any history of recurrent spontaneous abortions or any history of neonatal death; therefore, it became quite clear to us that the origin of the balanced translocation was *de novo* in nature. As per the ISCN 2016 guidelines, we report the proband karyotype as 47,XY,der(18),t(4;18)(q26-qter),+4 [Figure 3a,b]; the paternal karyotype was reported as 46,XY,der(18),t(4;18)(q26;q22) [Figures 3 and 4]; and the maternal karyotype was reported as 46, XX (data not shown). Multicolor fluorescence *in situ* hybridization was performed as described previously[5] on freshly casted slides of metaphase chromosome of the father to confirm our karyotype finding on another molecular cytogenetic platform and also to rule out the presence of any other cryptic translocations which may not have been detected by general karyotyping [Figure 3b]. Due to neonatal demise of the proband, further molecular cytogenetic studies were not performed. The male partner was found to harbor a balanced translocation involving chromosomes 4 and 18, which was inherited by the proband as an extra copy of chromosome 4(q26-qter), thus leading to partial trisomy of chromosome 4 and also resulted in neonatal demise of the proband. On the other hand, karyotype of the female partner was found to be normal.

Discussion

Balanced reciprocal translocations are known to be the most common structural chromosomal anomaly. They result from breakage and reunion of two or more chromosomes and subsequent transfer of the nucleated derivative chromosome

Figure 1: Facial dysmorphic features: Images of the proband showing wide forehead, cleft lip pallet, hypertelorism, flat nasal bridge (a), clubbed foot (b), along with omphalocele (c), and low set of ears (d)

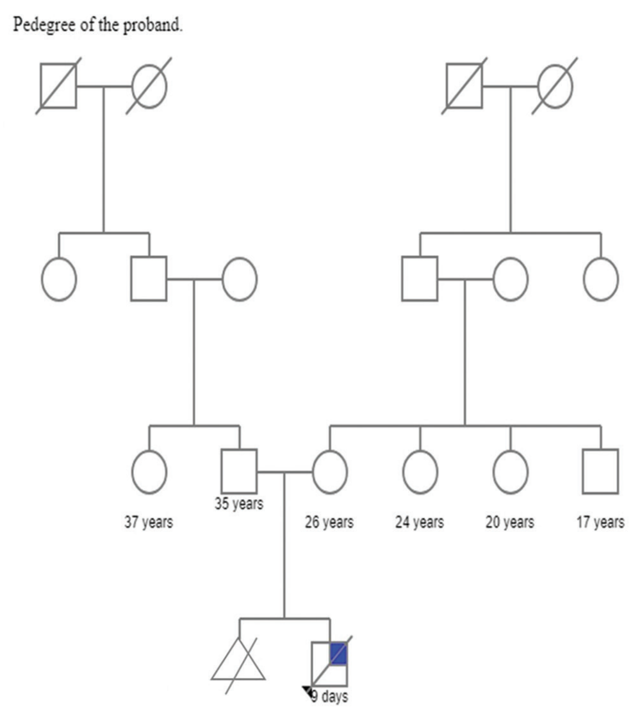

Figure 2: Pedigree analysis: Pedigree analysis of the proband up to the previous three generations. White symbol (square or circle) – a healthy person, white symbol (square or circle stroked through diagonally) – death of that individual, triangle – miscarriage, white symbol (blue colored and stroked diagonally) – proband

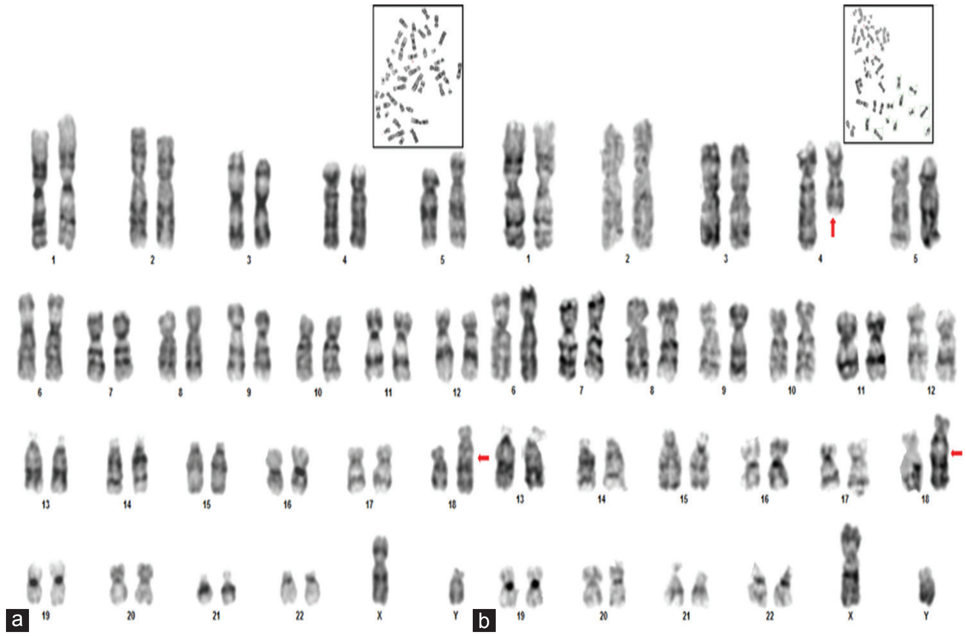

Figure 3: G-banding by trypsin and Giemsa stain banding chromosomal analysis: Both proband (a) and his father (b), karyotyping analysis reveals the presence of a balanced translocation of chromosomes 4 and 18 in the father, which has been inherited by the proband as an unbalanced partial trisomy 4(q-ter)

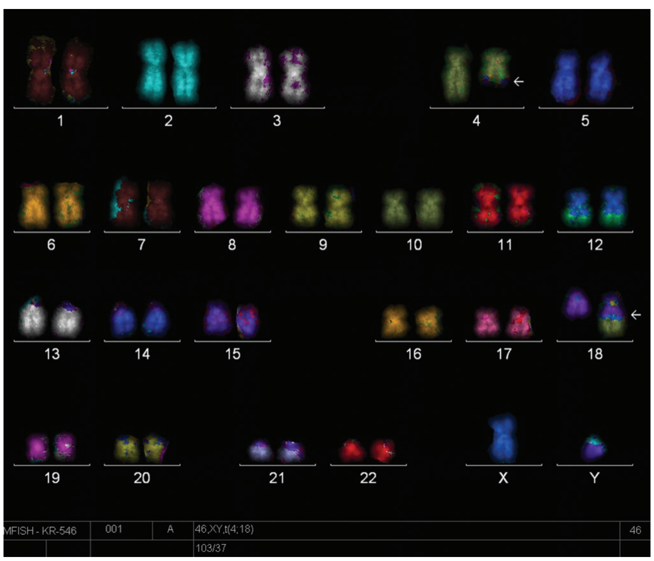

Figure 4: Multicolor fluorescence *in situ* hybridization: A stable balanced chromosomal translocation in the father of proband, detected by multicolor fluorescence *in situ* hybridization. Chromosomes involved in this translocation are indicated by arrows; a balanced chromosomal translocation is shown involving two chromosomes: 4 and 18

in following cell divisions. Carriers with balanced reciprocal chromosomal translocation are not presented with phenotypic manifestations unless the translocations result in gene disruption(s).[6] Trisomy 4q is a very rare finding. Common clinical features associated with trisomy 4q include phenotypic malformations such as low set of ears, microcephaly, psychomotor retardation, malformed limbs, hypotonia, antimongoloid slant, short neck, epicanthal folds, heart defects, simian crease, wide nasal bridge, micrognathia, malformation of the urinary system, and sloping forehead.[4] Moreover, there are reports where trisomy 4q has resulted in endocrinal abnormalities.[7] Few facial morphologic features of the proband resemble with that of *de novo* trisomy of the long arm of chromosome 4, which is also known as trisomy 4q syndrome,[2] but none of the previously reported cases presented with omphalocele followed by neonatal death. Previous reports suggested that individuals with trisomy 4q can survive for few years, but in our case, the proband deceased early probably due to cardiac failure. According to a previous literature, partial trisomy 4q presents with intellectual disability, speech delay, tall stature, seizures, and facial dysmorphism. Incidences of partial trisomy 4p are quite common as compared to 4q.[8] Inherited paternal balanced chromosomal translocation t(4;18) resulting in partial trisomy of chromosome 4(q26-ter) in offspring is a rare finding. Bands within the chromosomal location of 4q26 and 4q31 have been previously reported as the region for most constant trisomy/duplication for chromosome 4,[9-11] which was consistent in paternal karyotype in our study. Due to adjacent-1 meiotic segregation of paternal balanced chromosomal translocation, the proband was trisomic for a large segment of chromosome 4(q26-qter), with minimal loss of genetic material from chromosome 18.[12] Parental balanced reciprocal translocations can result in partial aneuploidy in the offspring due to unbalanced meiotic segregation during gametogenesis. However, the carriers are known to experience recurrent spontaneous abortion, stillbirth, infertility, nonimplantation, and developmental delay in children after birth.[13]

To the best of our knowledge, this is the first case from eastern part of India that describes a reciprocal balanced translocation of chromosomes 4 and 18 of paternal origin, resulting in a partial trisomy of chromosome 4 in the offspring. Therefore, cytogenetic screening of both partners is recommended before pregnancy to rule out or confirm the presence of any numerical or structural anomaly in one, both, or none of the partners. The cytogenetic screening will also reduce the burden of recurrent miscarriage by ruling out the inheritance of any chromosomal anomaly in the offspring.

Informed consent

All participants signed written informed consent for the publication of their clinical data. For the proband, written consent for publication was obtained by the parents/legal guardians.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that name and initials of the child will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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