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CASE REPORT

Non-disjunction Event in A Reciprocal Translocation Carrier Causing Pure Partial Trisomy 9p and 3q

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Abstract

Partial trisomy is a common chromosomal abnormality finding in cases with dysmorphisms and intellectual disabilities, which can involve a small or large chromosome region, as long as it involves the critical region. Here we report a 6 month-old baby girl with dysmorphisms who was found to have an extra chromosome, a derivative chromosome 9, which has been inherited via non-disjunction event from her mother who is a carrier of a balanced chromosome translocation between chromosome 9 and 3. This is the first reported case involving partial trisomy 9pter until 9q13 and 3q27 until 3qter. The phenotypes of our case resemble more of partial trisomy 9p features, but the developmental milestones could not be fully assessed at the time of presentation.

Keywords: non-disjunction; partial; trisomy; 9p; 3q

Introduction

A non-disjunction (NDJ) event is a well-known mechanism that leads to aneuploidy. Trisomy is an aneuploidy resulting from non-disjunction event during cell division resulting in an extra chromosome in the karyotype. Common examples are Down syndrome (trisomy 21), Patau syndrome (trisomy 13) and Edwards syndrome (trisomy 18). Meanwhile, the term partial trisomy is used to describe the presence of an extra chromosome region rather than one complete chromosome. Usually partial trisomy is as a result of structural abnormality of a chromosome. It can be inherited or occur de novo.

We are reporting a special case of partial trisomy 9p and 3q in a baby who inherited a derivative chromosome, as a result of non-disjunction event, from a healthy parent who is a carrier of a reciprocal chromosome translocation.

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Clinical History

The patient is a 6-month old baby girl who was noted to have dysmorphism. She has microcephaly, low set ears, flat nasal bridge, skin tag on the sternum and overlapping of toes on her right foot. Patient was born at term via normal vaginal delivery. The parents were both 33 years old, healthy and unrelated. The patient is their first child. The mother had gestational diabetes and hypertension during pregnancy but the pregnancy was otherwise uneventful. There was no family history of dysmorphism or intellectual disability in both of the parents' family members.

Methodology

Conventional cytogenetic analysis by GTG banding was performed on the patient's peripheral blood sample. Due to an abnormal karyotype result, the parents' peripheral blood sample were requested for further investigation.

The mother's sample revealed an abnormal karyotype, thus subsequently the patient's sample was analysed with fluorescence in situ hybridisation (FISH) technique using Whole Chromosome Painting Probe 3 (WCP 3) and Whole Chromosome Painting Probe 9 (WCP 9) for confirmation.

Result

Conventional cytogenetic analysis by GTG banding of the patient's sample revealed a female karyotype with an extra unidentified (marker) chromosome (Figure A). Samples from the parents' showed normal karyotype for the father; but the mother's karyotype turned out to be 46,XX,t(3;9)(q27;q13) (Figure B). The analysis revealed that the mother is actually a carrier of a reciprocal chromosome translocation between chromosome segment 3q27 and 9q13. FISH performed using WCP 3 and WCP 9 of the patient's sample confirmed the composition of the marker chromosome to be from chromosome 3 and 9 (Figure C). Thus, the patient's final karyotype is reported as 47,XX,+der(9)t(3;9)(q27;q13)mat (Figure D).

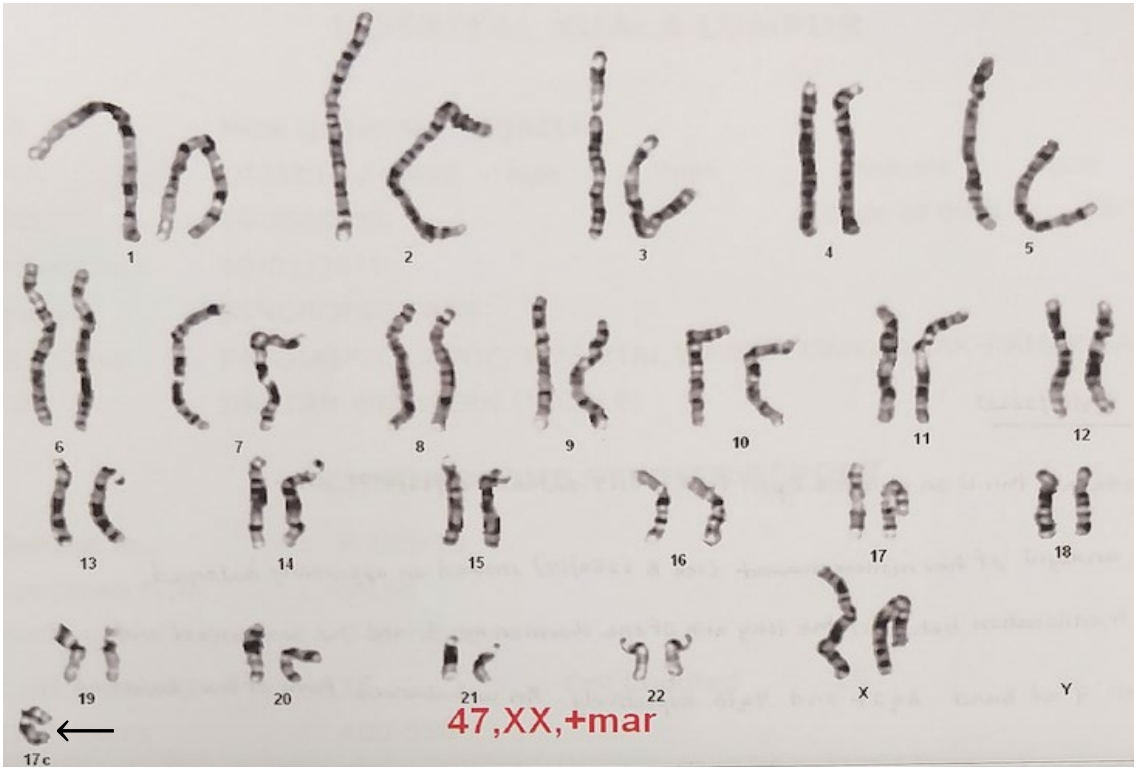

Figure A. Karyotype of the patient revealed 47,XX,+mar karyotype. The (⟵) arrow is showing the marker chromosome

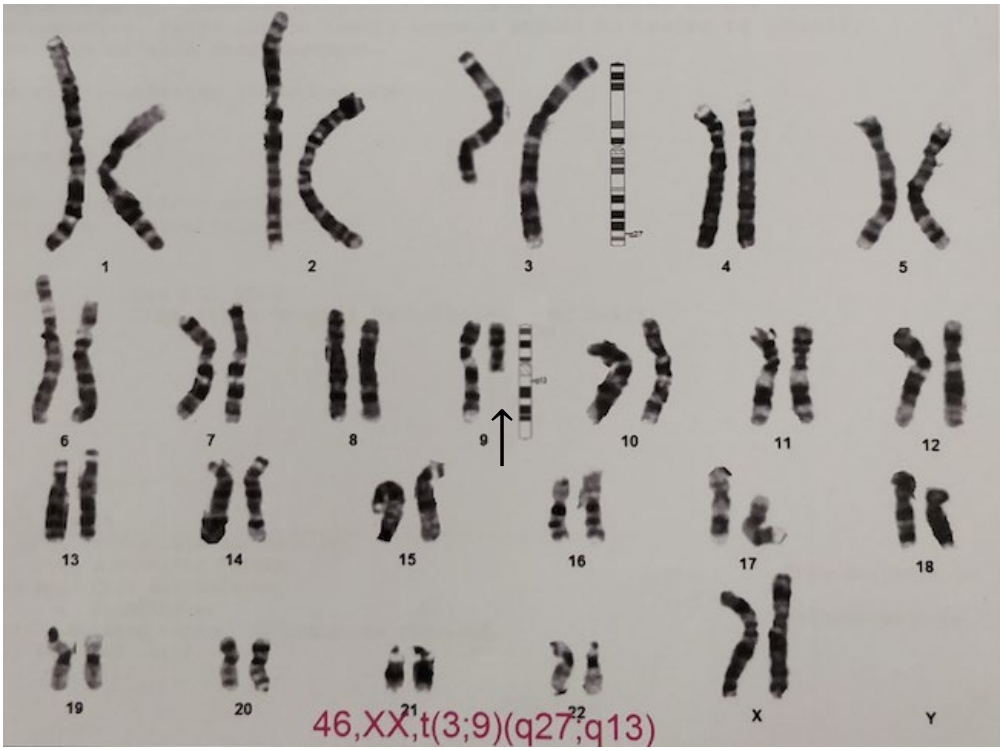

Figure B. Karyotype of the mother revealed a reciprocal chromosome translocation between chromosome segment 3q27 and 9q13. Inheritance of this derivative chromosome 9 through non-disjunction (↑black arrow) that occurred in her daughter.

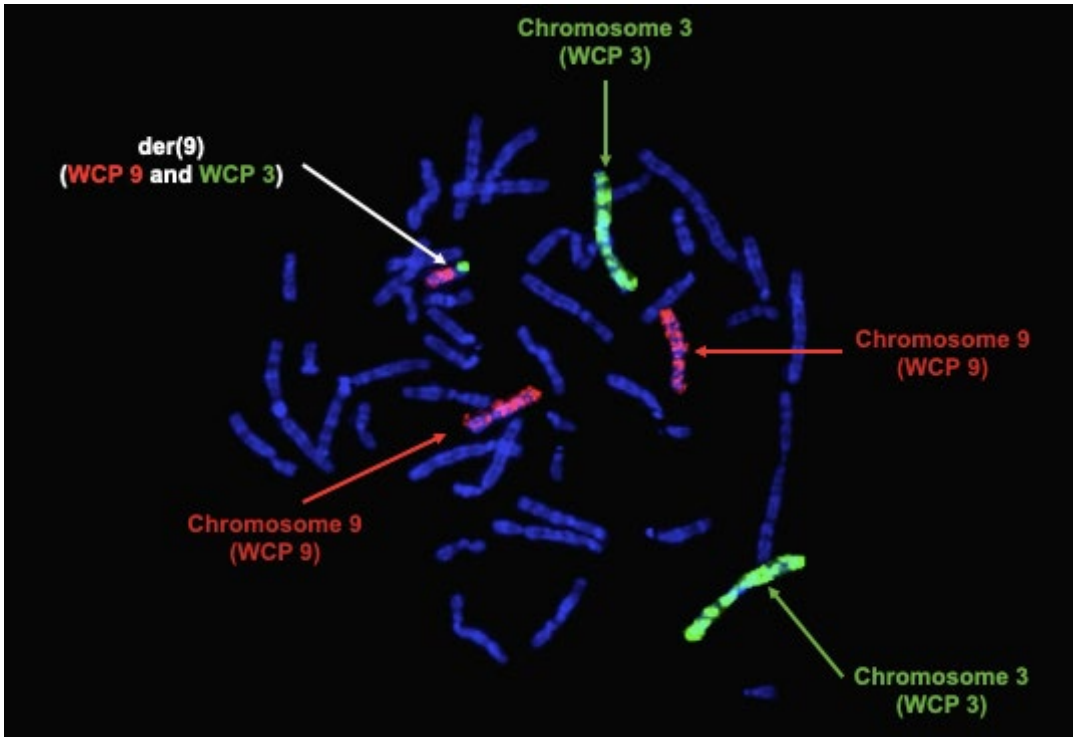

Figure C. FISH analysis of the patient's sample showing both chromosome 3 painted green by WCP 3 and both chromosome 9 painted red by WCP 9. The marker chromosome is confirmed to be a derivative chromosome composed of chromosome 3 and chromosome 9.

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Figure D. The patient's final karyotype is reported as 47,XX,+der(9)t(3;9)(q27;q13)mat.

Discussion

Pathogenesis

The importance of normal meiosis cannot be underestimated. This intricate process involves distributing equal amount of genetic material in a form of chromosomes into each daughter cells (gametes). Disordered steps in the process could produce chromosomally abnormal gametes which will result in abnormal conceptus. The unique timing of meiosis in human female suggests as risk factors for the development of abnormal chromosome segregation. In a female fetus, meiosis I starts at 3 months of intrauterine life. This process arrests at prophase I when pairing, synapsis and recombination had taken place. Prophase I stays arrested until just prior to ovulation where it continues to complete meiosis I. It progresses further until it reaches metaphase II where it stays arrested again until it is being fertilised and the meiotic process completes. This prolonged process of gametogenesis is hypothesised as the main cause of maternal non-disjunction (Turnpenny et al., 2017)

Non-disjunction (NDJ) is a process where there is failure of separation between 2 homologous chromosomes during meiosis I or separation failure of sister chromatids during meiosis II. It results in one daughter cell receiving 2 copies of the same chromosome and the other daughter cell receives none. After fertilisation with a normal gamete with the daughter cell that has 2 copies of the same chromosome, it results in fetus with trisomic dosage of the non-disjunctioned chromosome. It is the leading cause of pregnancy loss, intellectual disability and birth defects. Down, Edwards and Patau syndromes are the common examples of syndromes caused by non-disjunction event.

Partial trisomy on the other hand is a state where a segment of a chromosome present in 3 copies in an individual. This state causes a trisomic dosage effect of the said segment. The ways that partial trisomy can be caused are by duplication; or the inheritance of a derivative chromosome from a parent who is a carrier of a reciprocal chromosome translocation. Reciprocal chromosome translocation is an exchange of segments when a break occurs in each of two chromosomes with the

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segments being exchanged, forming two new chromosomes; which are called derivative chromosomes. Inheritance of either one of the derivative chromosome in a normal 2:2 segregation will result in a fetus with partial trisomy of a segment and monosomy of the counter-part of the derivative chromosome segment. On the other hand, inheritance of a derivative chromosome from a non-disjunction event (3:1 segregation) leads to a pure partial trisomy of all the chromosomes segments components of the derivative chromosome (Turnpenny et al., 2017; Gardner et al., 2012).

This NDJ event is demonstrated in our case. The mother is a carrier of a balanced chromosome translocation with the karyotype being 46,XX,t(3;9)(q27;q13) (Figure E). As mentioned earlier, the mother of the patient is of normal phenotype and has an unremarkable family history. There is actually 1 in 500 individuals in the population who is a carrier of a balanced chromosome translocation (Ogilvie and Scriven, 2002). The origin of a reciprocal translocation is said to be due to inheritance, de novo nonhomologous chromosome rearrangements or exposure to chemicals and radiation (Tucker et al., 2008). The risk of having de novo translocation is higher than inherited with the incidence of 6% to 9%. Often, these carriers are normal phenotypically as there is no loss of genetic material and the breaks occur in the non-coding region. Only rarely it causes abnormal phenotype, that is when the breaks occur within a gene or within the controlling elements of a gene (Trump et al., 2010). Even though carriers are phenotypically normal, they are at higher risk of infertility (Gardner et al, 2012), recurrent miscarriages 3% (Dorothy Trump, 2010) and 1% to 10% risk of having an abnormal child if the conceptus is viable (Turnpenny et al, 2017).

The important thing in regards to a reciprocal translocation carrier is the behaviour of the derivative chromosomes during meiosis. The derivative chromosomes form a quadrivalent at pachytene to maintain homologous pairing, instead of a normal bivalent before they segregate. 2:2 segregation can be in 3 different patterns. One is alternate segregation which results in a normal carrier child. The others are Adjacent-1 or Adjacent-2 patterns which result in chromosomally unbalanced gametes. If a non-disjunction event occurred, this results in 3:1 segregation pattern. This event can cause the production of an unbalanced, trisomic zygote after fertilisation, in a form of tertiary trisomy or interchange trisomy. Tertiary trisomy is when there is the derivative chromosome together with the 2 normal chromosomes. Meanwhile interchange trisomy is when there are 2 derivative chromosomes together with either one of the normal chromosome. The 3:1 event that had occurred in the mother of our patient is tertiary trisomy where she passed one of the derivative chromosomes (derivative chromosome 9 [der(9)]) and normal chromosome 3 and 9. This diagram for the mechanism of segregation is shown in Figure F. The der(9) consists of 9pter until 9q13 region and 3q27 until 3qter region. This resulted in the patient having trisomic dosage of 9p until 9q13 and 3q27 until 3qter region (Figure G).

The pathogenesis of NDJ has been widely studied in trisomy 21 and increasing maternal age is found to be the most significant risk factor followed by altered recombination which is age-independent. With increasing age, there is loss of proper chromosome segregation due to degradation of meiotic proteins that serves to promote proper segregation (Steuerwald et al, 2001). But in our case, the mother is still young at 33 years old. According to the literature, altered recombination pattern during meiosis; which are no chromosomal exchange and telomeric exchange in meiosis I or pericentrometric exchange in meiosis II, contributed to the highest proportion of NDJ mechanisms in young mothers (Kong et al., 2004; Lamb et al., 2005; Oliver et. al., 2008). These altered recombination states cause failure of chiasmata formation that is important to stabilise the paired chromosomes until separation occurs. This failure allows the chromosome pairs to separate prematurely and segregate randomly to daughter cells (Turnpenny et al., 2017; Oliver et al., 2008). Thus in our case, altered recombination may have contributed to the NDJ event in the mother. The reason why these events happen is still under study.

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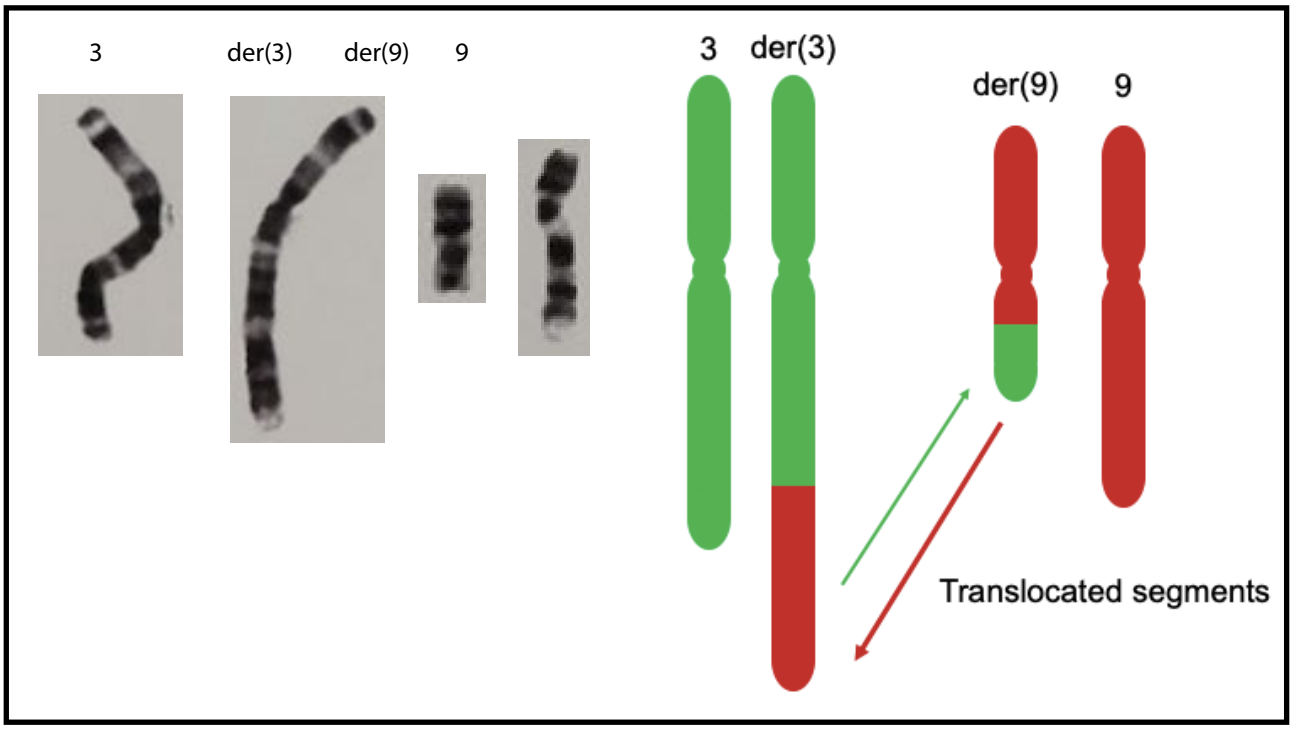

Figure E. The mother's karyotype with balanced translocation between chromosome 3 [der(3)] and chromosome 9 [der(9)]. The balanced translocation between these chromosomes result in normal phenotype in the mother as this karyotype contains normal chromosome dosage.

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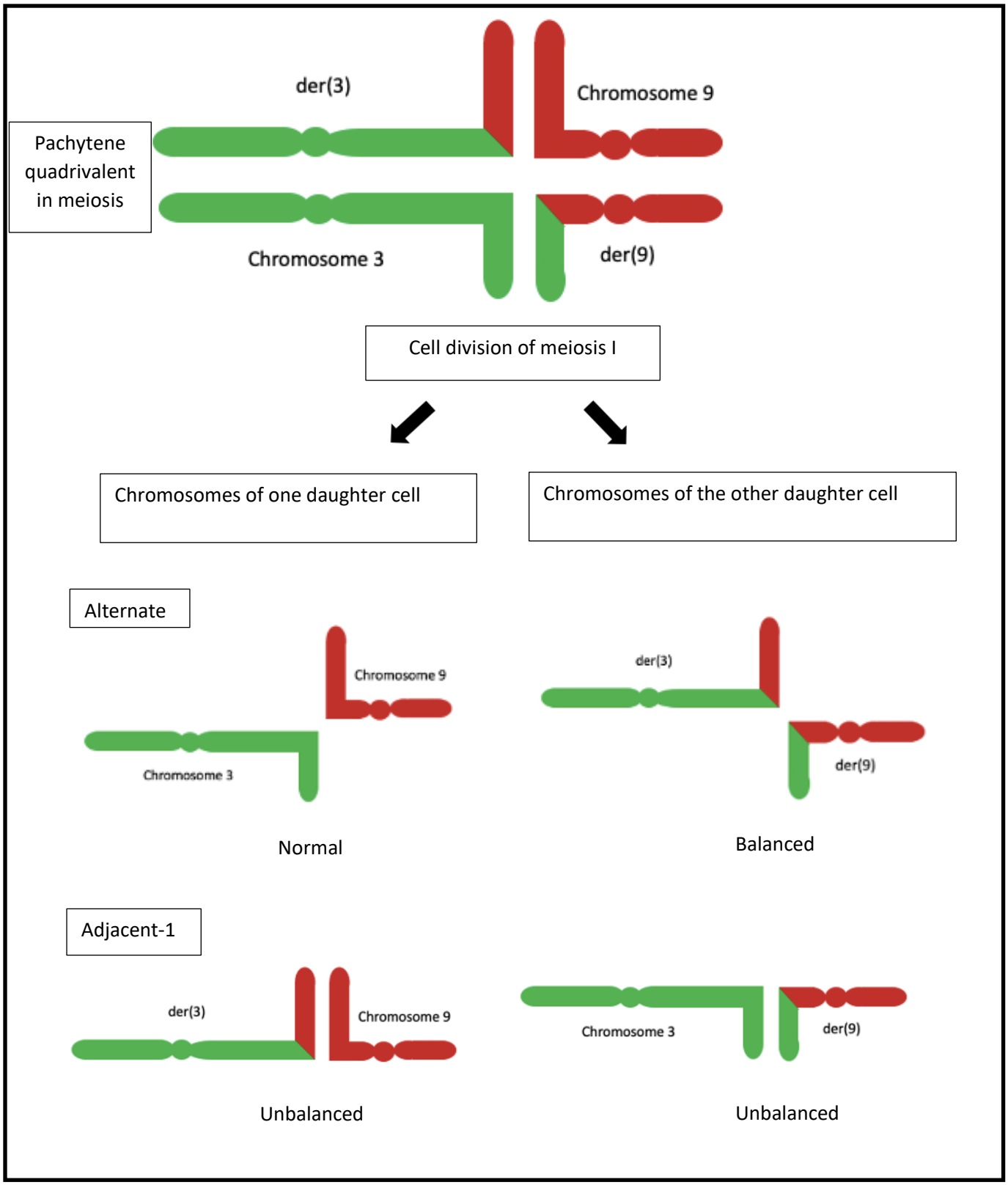
Pachytene quadrivalent in meiosis
der(3)
Chromosome 9
Chromosome 3
der(9)
Cell division of meiosis I
Chromosomes of one daughter cell
Chromosomes of the other daughter cell
Alternate
Chromosome 9
Chromosome 3
der(3)
der(9)
Normal
Balanced
Adjacent-1
der(3)
Chromosome 9
Chromosome 3
der(9)
Unbalanced
Unbalanced

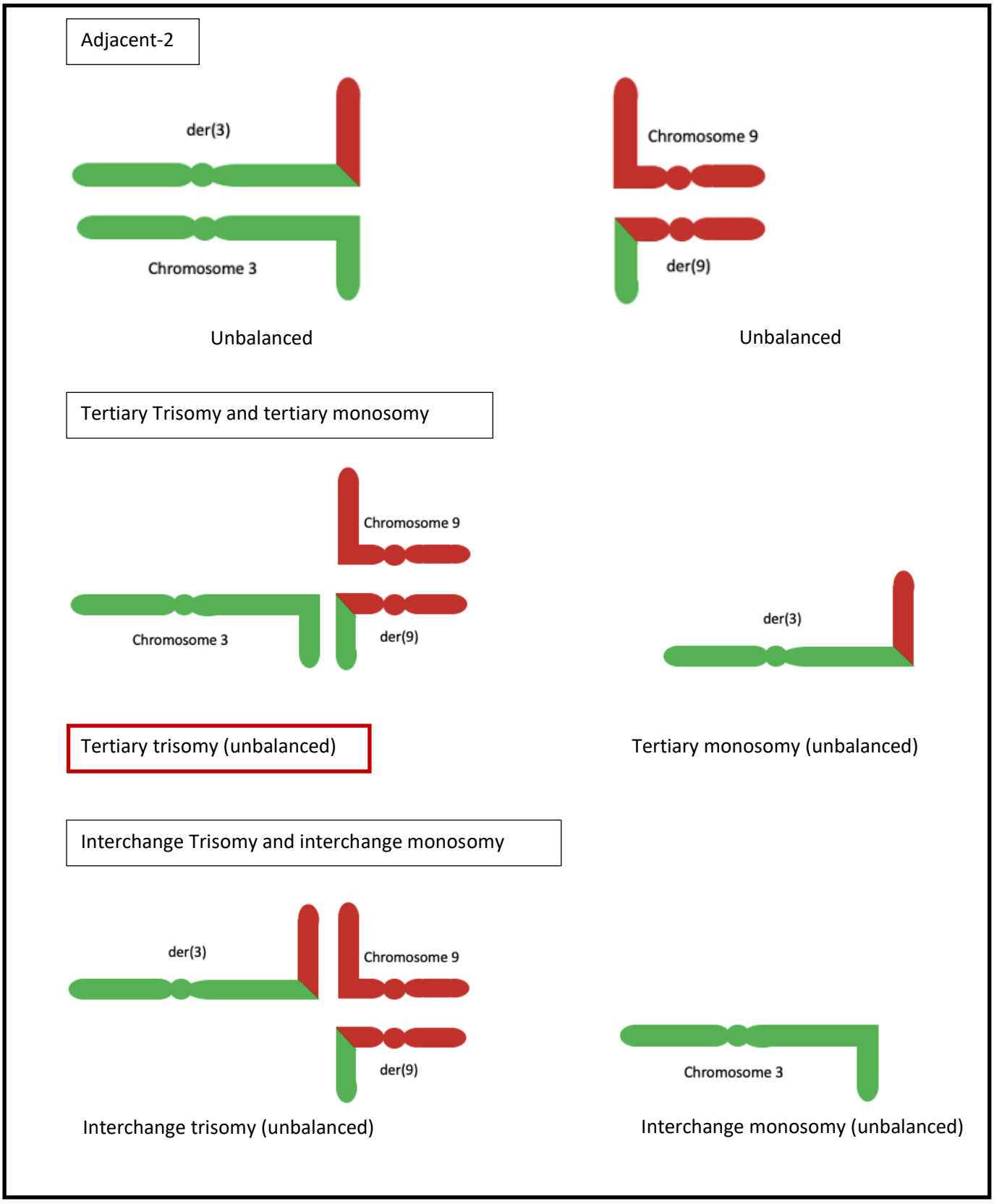

Figure F. The possible mode of segregations in a carrier with reciprocal chromosome translocation. The red box ( ) indicates the segregation mode that occurred in the patient's mother during meiosis which caused the patient to have an extra chromosome (derivative chromosome 9) after fertilisation with a normal gamete.

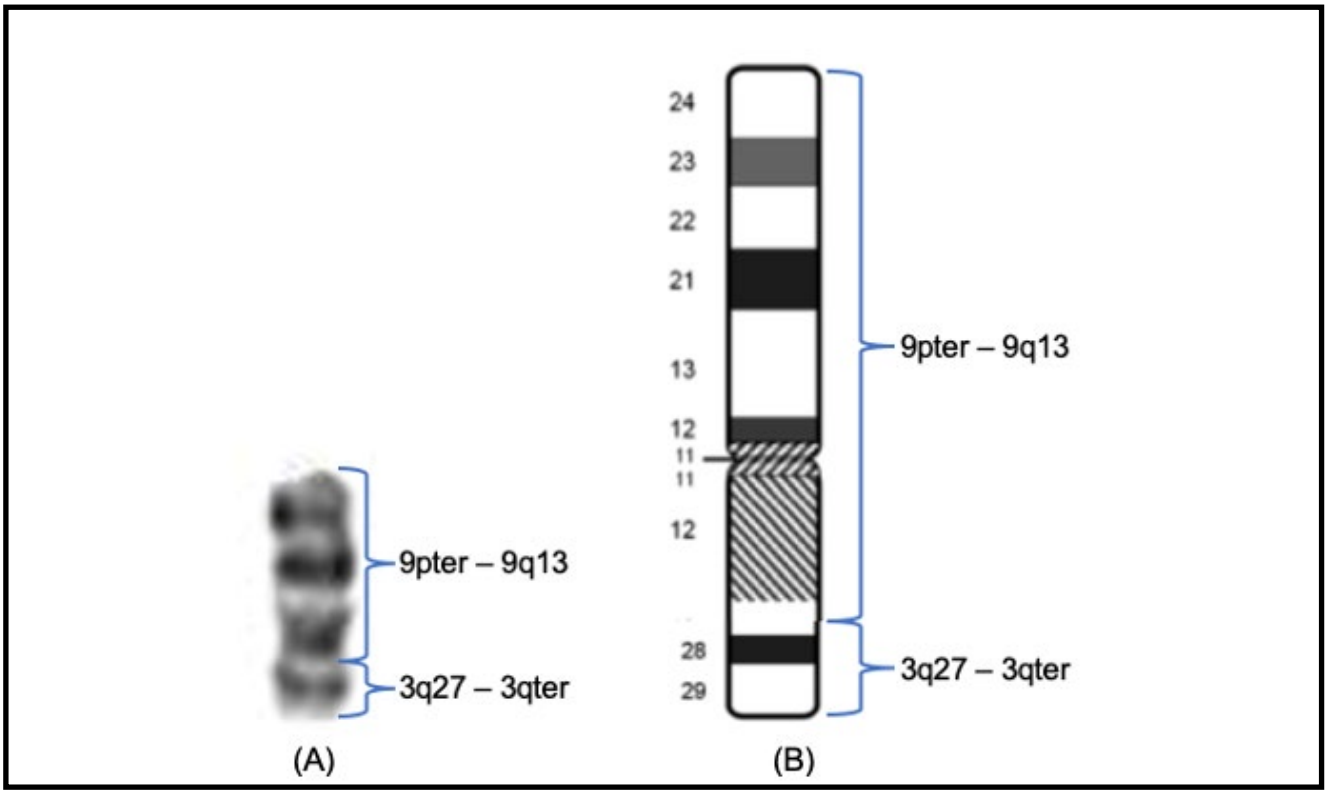

Figure G. (A) The derivative chromosome 9 identified in the carrier mother (B) Schematic representation of the marker derivative chromosome 9. The inheritance of this chromosome resulted in the patient having partial or duplicated region of chromosome segment 9pter – 9q13 and 3q27 – 3qter. [Edited from International System for Human Cytogenetic Nomenclature (ISCN), 2016].

Clinical features

We searched for features of partial trisomy 9p (de Pater et al., 2002; de Ravel et al., 2004; Temtamy et al., 2007; Cammarata-Scasili, 2019) and 3q (Ireland et al., 1995; Rizzu et al., 1997; Grossman et al., 2009; Pasinka, 2019) in the literature and compared to the patient's phenotypes as presented in Table 1.

Table 1. Comparison of phenotypes between reported cases of partial trisomy 9p and 3q with the patient

Phenotypes	**Trisomy**		**Patient**
	9p	3q(x)	
Low birth weight	+	-	-
Growth retardation	+	+	-
Delayed developmental milestones	+	+	-
Intellectual disability	+	+	N/A
Head and Facial Features			
Microcephaly	+	+	+
Low set ears	+	+	+
Flat nasal bridge	+	+	+
Micrognathia	+	-	+
Down slanting palpebral fissures	+	+	-
Hypertelorism	+	+	-
Prominent or bulbous nose	+	+	-
Downturned corner of mouth	+	+	-
Hypertrichosis	-	+	-
Low frontal hairline	-	+	-
Prominent philtrum	-	+	-
Synophrys	-	+	-

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Cleft palate	-	+	-
Upslanting palpebral fissures	-	+	-
Limbs			
Overlapping toes	+	-	+
Hypotonia	-	+	-
Clinodactyly	-	+	-
Dermoglyphics abnormalities	+	-	-

Sign present (+); sign absent (-); N/A not assessed

To our knowledge, there has been more than 200 reported cases of partial trisomy 9p making it the fourth common trisomy reported in the literature after trisomy 21, 13 and 18 (Cammarata-Scasili, 2019; Fan et al., 2020). As a result, the features for partial trisomy 9p have been well delineated. They are frequently reported to have intellectual disability, growth retardation, hypertelorism, malformed ears, prominent or bulbous nose, downturned corners of the mouth, hand-foot anomalies, hypotonia and dermatoglyphics abnormalities (Temtamy et al., 2007). de Ravel et. Al proposed that the critical region for trisomy 9p phenotype is between chromosome segment 9p22.1 until 9p22.2 (de Ravel et al., 2004). This region is present in our patient and she does possess most of the facial dysmorphisms related to partial trisomy 9p. Unfortunately, her developmental milestones could not be fully assessed during her current presentation. Our patient's der(9) chromosome also includes the region 9q10 until 9q13. But according to the literature, this region is believed to be of little significance on the phenotype (Temtamy et al., 2007) as cases with trisomy 9q phenotypes usually involves region 9q2 and beyond (Tiong et al., 2010).

On the contrary, partial trisomy 3q are rare with only 50 reported cases (Anonymous). The phenotypes that have been frequently described with trisomy 3q are the features of Cornelia de Lange syndrome such as normal birth weight but poor weight gain post natally, hypertrichosis, synophrys, low set ears, up-slanting palpebral fissures and wide nasal bridge (Grossman et al., 2009; Pasinka, 2019). The critical region that has been proposed to cause these phenotypes is located between 3q26.3 until 3q27 (Rizzu et al., 1997). The patients who are trisomic for regions proximal or distal to this region do not show resemblance with Cornelia de Lange syndrome phenotypes (Grossman et al., 2009). Furthermore, it has been reported that the regions distal to 3q27 causes less severe effects both on physical formations and intellectual development (Yatsenko et al., 2003; Grossman et al., 2009). This is likely the reason why our patient does not have the features of partial trisomy 3q syndrome.

Conclusion

To our knowledge, this is the first reported case of supernumerary marker chromosome involving der(9)t(3;9)(q27;q13) resulting in pure partial trisomic dosage of chromosome 9p and 3q as a result of inheritance of a derivative chromosome 9 from a mother who is carrier of a reciprocal translocation via non-disjunction event. The features of our patient are more in concordance with partial trisomy 9p features. This may be caused by the presence of larger amount of trisomic genetic material from chromosome region 9p as compared to 3q and the presence of the critical region 9p22.1 until 9p22.1. But our current phenotypic data of the patient is still limited thus the patient needs to be observed for a longer period of time in order to accumulate more data on her phenotype. For further management of the parents, before embarking on their next pregnancy, they should be offered genetic counselling and preimplantation genetic testing.

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