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RESEARCH NOTE

A small supernumerary marker chromosome resulting in mosaic partial tetrasomy 4q26-q31.21 in a foetus with multiple congenital malformations

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Abstract. A parental diagnosis was performed for an unborn foetus of a healthy couple, who was due for ultrasound detection of multiple malformations and abnormal amniotic fluid karyotypes. For an accurate diagnosis, routine G-banding analysis and next-generation sequencing (NGS) were carried out. Finally, conventional cytogenetic analysis suggested that the foetus had a karyotype of 47,XX,+mar[52]/46, XN, meanwhile NGS also revealed a partial tetrasomy of 27.84 Mb from 4q26-q31.21 (117,385,735–145,225,759), and G-banding analysis excluded the couple to have carried the 4q26-q31.21 duplication. We have identified a *de novo* mosaic small supernumerary marker chromosomes (sSMC) derived from 4q26-q31.21 in a foetus with hemivertebra, polydactyly, abnormal ears, and heart and ventricular septal defect.

Keywords. hemivertebra; polydactyly; ventricular septal defect; abnormal ears.

Introduction

Small supernumerary marker chromosomes (sSMCs) are usually detected by the conventional cytogenetic analysis, but most often lack distinct banding patterns. sSMCs can originate from any chromosome and may be distinguished by molecular cytogenetic analysis. The first sSMC was described by Ilberry and coworkers in 1961 (Ilberry *et al.* 1961). The patient's karyotype was determined as 47,XY,+mar/46,XY, but the origin of sSMC was not determined (Liehr *et al.* 2008). The incidence of sSMCs has been estimated to be 0.075% among foetuses and 0.204% in the presence of abnormalities detected by ultrasonography (Liehr and Weise 2007). The presence of sSMCs may result in partial trisomy or tetrasomy. Approximately 70% of the sSMC carriers are clinically normal, while 30% are abnormal to a certain extent (Jang *et al.* 2016). The impact of sSMCs on clinical phenotype depends on their size, gene content, extent and tissue distribution of the mosaicism, and the presence of uniparental disomy. Chromosome 4 has been rarely involved in the formation of marker chromosomes. Here, we report a *de novo* nonmosaic sSMC originated from chromosome 4 detected upon prenatal diagnosis.

Investigations

The case presented here is an unborn female foetus of healthy parents (36-year-old woman and a 38-year-old man). The gravida was referred to our hospital at 25th weeks' gestation due to ultrasound detection of multiple malformations and abnormal amniotic fluid karyotypes. Foetal ultrasonography revealed a four-chamber view of foetal heart with an interruption of echo for about 2.1 mm

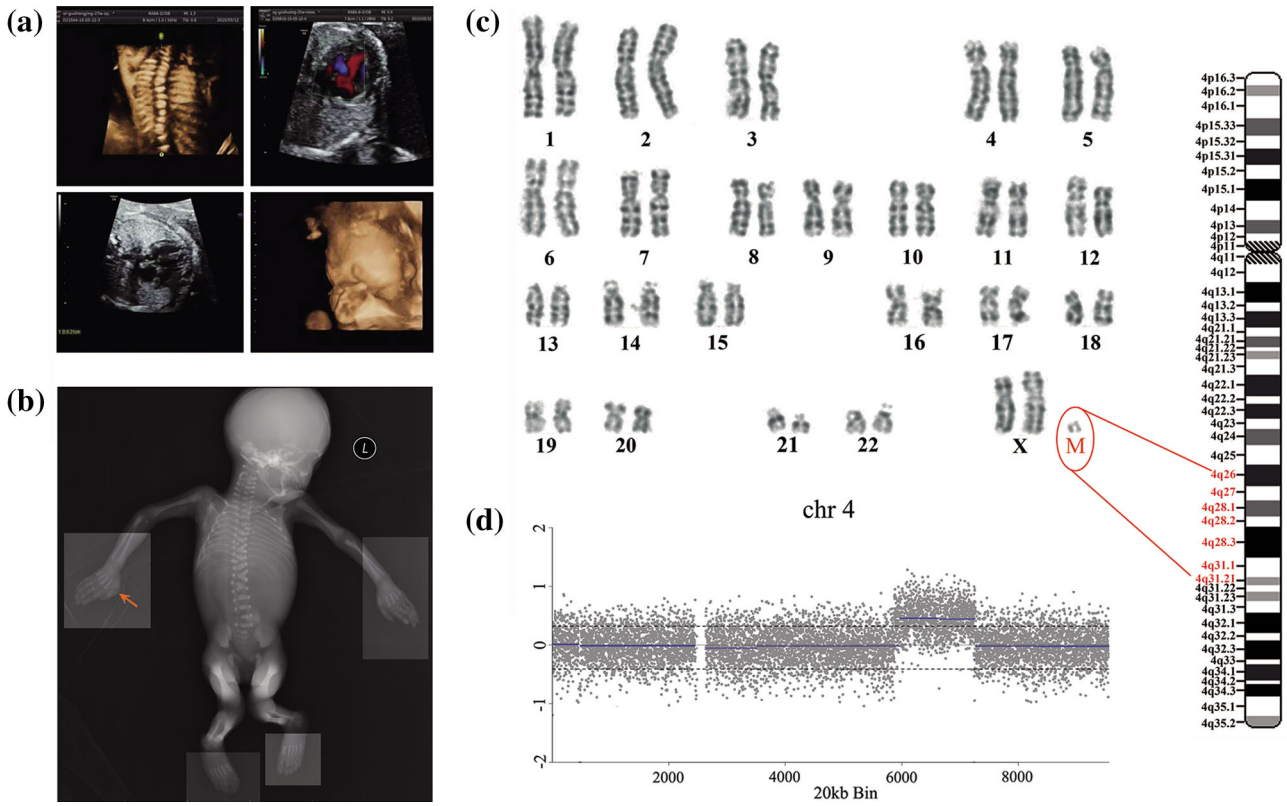

Figure 1. Clinical features and genetic analysis of the foetus. (a) Prenatal ultrasound indicated that the foetus had centrum malformations, ventricular septal defect and abnormal ears. (b) X-ray imaging indicated hemivertebra and right polydactyly (indicated by an arrow). (c) The SMC revealed by G-banding analysis (denoted by the letter 'M'). (d) NGS analysis revealed a 27.84 Mb duplication at 4q26-q31.21 (117,385,735–145,225,759).

in interventricular septum and slightly narrowed aortic arch. The centrums in thoracolumbar spine were misaligned, which suggested hemivertebra (figure 1, a&b). The foetus also had abnormal ears and polydactyly on the radial side of right hand. This was the first pregnancy and the women had denied any abnormal condition or use of drugs during her gestation. The couple also denied any family history of genetic diseases and both had apparently normal karyotypes. Following genetic counselling, the couple requested termination of pregnancy. Routine G-banding analysis (at 550-band level) was carried out on cultured cord blood lymphocytes following a standard cytogenetic protocol. After termination of the pregnancy, X-ray examination was carried out to delineate the centrum malformations and skeletal abnormalities. To verify the result of karyotyping analysis, next-generation sequencing (NGS) was conducted on an Ion Proton sequencer (Thermo Fisher, USA). The data were analysed with torrent mapping alignment program (TMAP) and DNAcopy packages using parameters recommended by the developers. Conventional cytogenetic analysis suggested that the foetus had a karyotype of 47,XX,+mar[52]/46, XN[48] (figure 1c). NGS also revealed a partial tetrasomy of 27.84 Mb from 4q26-q31.21 (117,385,735–145,225,759) (figure 1d). G-banding analysis excluded the couple to have carried the 4q26-q31.21 duplication.

Result and discussion

In this study, we have reported a 25-week unborn female foetus with a mosaic sSMC from 4q26-q31.21 and multiple congenital malformations. To the best of our knowledge, sSMCs from the middle portion of chromosomes, particularly chromosome 4, are quite rare. The karyotypes of her parents were both normal, which suggested that the foetal duplication was *de novo* and probably pathogenic. Many sSMCs were reported in prenatal diagnosis. Tetrasomy 18p has been delineated by many published case series and reports, which was accompanied by various abnormalities including congenital heart defects, micrognathia, lower extremity abnormalities, high-arched palate, microcephaly, kyphoscoliosis, myelomeningocele, hernia and renal anomalies (Balkan *et al.* 2009; Sebold *et al.* 2010; Inan *et al.* 2016). A heart defect was the most common congenital anomaly present in tetrasomy 18p population. As it was reported, of the 32 individuals who had undergone echocardiograms, 15 had some type of anomaly (Sebold *et al.* 2010).

Table 1. Reported cases carrying a 4q26-q31 duplication.

Reference	Rinaldi *et al.* (2003)	Mikelsaar *et al.* (1996)	Jeziorowska *et al.* (1993)	Fryns *et al.* (1980)	Taylor *et al.* (1977)	Vogel *et al.* (1975)	Dutrillaux *et al.* (1975)	Present study
Age in years (sex)	1 (M)	7 (F)	3 (M)	6.5 (F)	6.5 (M)	6 (F)	2.25 (F)	Unborn
Duplication region	q24-q35	q25-qter	q21.3-q31.3	q25-q31	q26-q35	q22-q34	q22-q34	q26-q31.2
Mental retardation	+	+	+	+	+	+	+	NA
Growth retardation	+	+	+	+	+	+	+	
Microcephaly	+	+	+	–	+	–	+	–
Epicanthal fold		+	+	–		+	+	
Ptosis/narrow palpebral fissures	+	+	+	+	+			
Hypertelorism or telecanthus						+		
High/broad nasal bridge	+	+	+	+	+	+	+	
Short philtrum	–	+	+	+	+	+	+	
Retromicrognathia	+	–	+	–		+	+	
Large/low set/malformed ears	+	+	+	+	+	+	+	+
Short neck		+	+	+		+	+	
Thumb anomalies	+	–	+	–	–	+	+	+
Cardiac malformations	+	–	–	–	+	–	–	+
Urogenital abnormalities	+	–	+	–	–	+	+	
Epilepsy	–	–	–	+	+	–	+	NA
Hemivertebra	–	–	–	–	–	–	–	+

NA, not applicable.

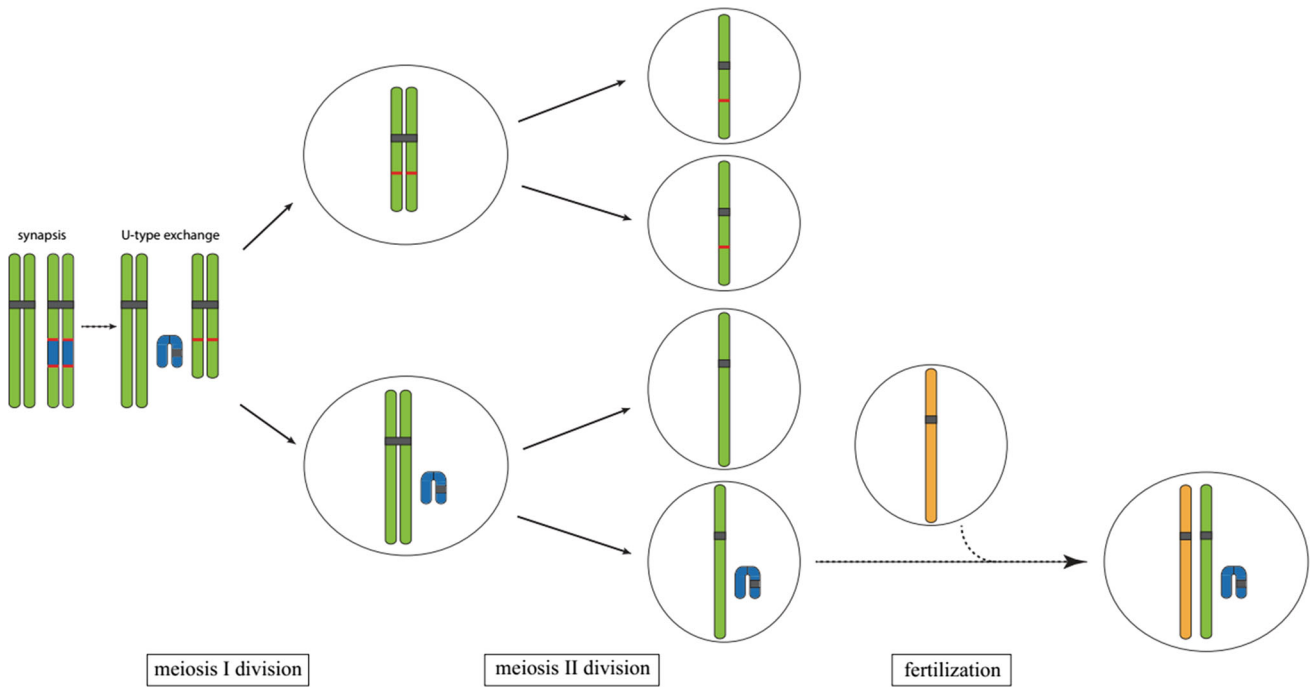

Figure 2. Possible mechanism for the sSMC derived from chromosome 4q26-q31.21.

Another review described that congenital heart disease was found in about 23% tetrasomy 18p cases (Bawazeer *et al.* 2018). The phenotypes in our case showed similarities to tetrasomy 18p cases as reported, such as heart defects, vertebral malformations and developmental anomaly.

No sSMC derived from 4q26-q31.21 has been reported so far, though there were some patients carrying duplication of 4q21-qter (Dutrillaux 1975; Vogel *et al.* 1975; Taylor *et al.* 1977; Fryns and Van Den Berghe 1980; Jeziorowska *et al.* 1993; Mikelsaar *et al.* 1996; Rinaldi *et al.* 2003), summarized in table 1. Previously reported

clinical phenotypes such as mental retardation, growth retardation and epilepsy were not reported in the case reported here, but malformations such as high/broad nasal bridge, low set malformed ears, short neck, thumb anomalies, cardiac malformations and urogenital abnormalities were found Hemivertebra has been associated with chromosome 4 mosaicism in only one case (Gentile *et al.* 2005). Our study provided new evidence for the pathogenesis of hemivertebra.

sSMC may form with diverse patterns including inverted duplication, ring, centric minute, neocentrics and complex rearrangement. Figure 2 shows the possible mechanism for the sSMC derived from chromosome 4q26-q31.21. Considering the stability of the sSMC during cell proliferation, we conjectured that there was a neocentromere in the sSMC we discovered. At anaphase and telophase of meiosis I, the homologous chromosomes were segregated, and the sSMC has entered the same daughter cell along with the unaffected homologous chromosome. After fertilization, the sSMC was removed from a proportion of cells due to foetal rescue. However, the sSMC involved many genes which are involved in various processes during embryo development, which may cause multiple congenital malformations. As shown in figure 1d, the 4q26-q31.21 segment appeared to be in full trisomy, though conventional cytogenetic analysis suggested it to be in a mosaic status. The foetus was ultimately inferred as mosaic tetrasomy 4q26-q31.21.

In summary, we have identified a *de novo* mosaic sSMC derived from 4q26-q31.21 in a foetus with polydactyly, abnormal ears and heart and vertebral malformations. The finding has broadened the clinical spectrum of sSMC derived from chromosome 4.

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