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Research paper

A rare occurrence of two large *de novo* duplications on 1q42-q44 and 9q21.12-q21.33

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ABSTRACT

De novo partial distal 1q trisomy is uncommon and mostly occurs in combination with monosomy of another chromosome due to a parental translocation. Distal 1q trisomy co-occurring with another *de novo* duplication on a separate chromosome is extremely rare. Here, we reported a patient carrying two large *de novo* interstitial duplications including a 20 Mb duplication at 1q42-q44 and a 14.2 Mb duplication at 9q21.12-q21.33. The patient presented with features of pre- and postnatal growth retardation, low birth weight, failure to thrive, developmental delay and frequent infection. Her dysmorphic features included macrocephaly, prominent forehead, triangular face, wide fontanelle, hypertelorism, flat nasal bridge, tented mouth, micrognathia, protruding and low-set ears, slender limbs with toe-walking appearance. In addition, she presented with subdural hematoma. The clinical presentations of this patient are mostly consistent with those of distal 1q trisomy syndrome or 9q interstitial duplication. The interstitial 1q trisomy may have contributed to the macrocephaly, prominent forehead and limb abnormalities of our patient. Either or both *de novo* duplications could have contributed to the features of growth retardation, developmental delay and dysmorphic features including hypertelorism, low-set ears and abnormal nose/nasal bridge.

1. Introduction

Trisomy of chromosome 1 long arm (trisomy 1q syndrome) is a rare condition, which is often combined with another chromosomal anomaly. The duplicated material can be a result of either an inherited rearrangement of parental balanced translocation or a *de novo* duplication or insertion. There are breakpoint hot spots on 1q25, 1q32 and 1q42 (Gfatter et al., 1998). Thirteen cases with "pure" distal duplications involving 1q41 or 1q42 to 1qter had been previously reported (Chia et al., 1988; Verschuuren-Bemelmans et al., 1995; Villa et al., 2000; De Brasi et al., 2001; Polityko et al., 2005; Cocce et al., 2007; Percesepe et al., 2007; Kulikowski et al., 2008; Morris et al., 2016; Watanabe et al., 2016). The most common clinical manifestations of patients with trisomy 1q41 or 1q42-qter are developmental delay, pre- and postnatal growth retardation, abnormalities involving craniofacial, limb and central nervous system (Cocce et al., 2007; Cervantes et al., 2014). Patients with 9q trisomy had also been reported before (Deng et al., 2014), but only five individuals had been reported carrying duplications of comparable size that overlaps with 9q21.12-q21.33 (Kajii et al., 1987; Lindgren et al., 1994; Travan et al., 2015), Their clinical features included low birth weight, prenatal or postnatal growth retardation, developmental delay and behavioral/psychiatric abnormality, and craniofacial abnormalities. So far, no case has been reported to carry a distal trisomy 1q co-occurring with a *de novo* duplication on 9q. Here, we reported a patient carrying two large *de novo* interstitial duplications including a 20 Mb trisomy 1q42-q44 and a 14.2 Mb 9q21.12-q21.33 duplication.

2. Materials and methods

2.1. Clinical report

The index patient was a girl born at 37 weeks and 2 day gestation to a G1P0 healthy woman. The mother and father were not related and

Abbreviations: CMA, chromosome microarray analysis; SD, standard deviation; SNP, single nucleotide polymorphisms; βHCG, β-human chorionic gonadotrophin; PAPPA, pregnancy-associated plasma protein-A; NT, nuchal translucency; IUGR, intrauterine growth retardation; IVH, intraventricular hemorrhage.

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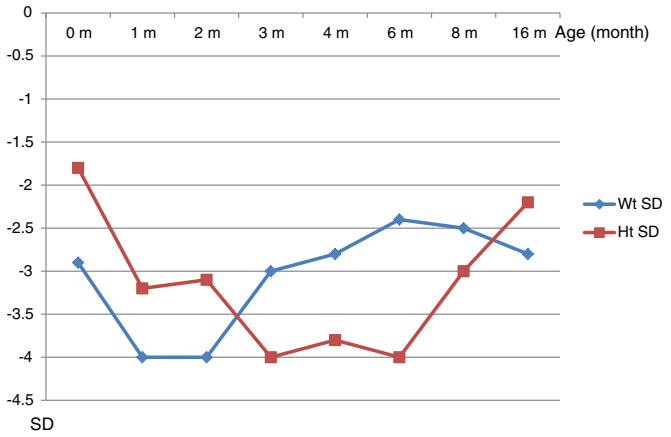

Fig. 1. Postnatal growth of the patient: standard deviations (SD) of weight and height were calculated based on the Chinese children growth standardized values and curves (Li, 2009).

were 23 and 24 years old respectively. The mom had mild gestational diabetes mellitus. The pregnancy was at high risk for Edwards syndrome (trisomy 18) and other aneuploidies when screened at 12 weeks of gestation by measuring serum free β-human chorionic gonadotrophin (βHCG) and pregnancy-associated plasma protein-A (PAPPA). The measurement of fetal nuchal translucency (NT) by ultrasound was normal, but intrauterine growth retardation (IUGR) was noticed. Invasive diagnostic test was not followed. The baby had intraventricular hemorrhage (IVH) without experiencing asphyxia or trauma. She had moderate anemia and was hospitalized due to severe pneumonia at 42 days after birth and at 7 months of age again. The brain MRI showed left frontal and temporal chronic subdural hematoma, mild hydrocephalus at 7 months of age.

This girl had noticeable growth retardation and developmental delay. She could raise her head at 6 months of age, could sit and turn over at 9 months, but could not stand and walk at 16 months of age. The girl's mental development status was evaluated at the age of 10 months and 14 months using Gesell Developmental Scale revised by Beijing Mental Development Cooperative Group. She was shown to have mild to moderate development delay. She had language delay but showed some social responsiveness including a friendly behavior, a happiness demeanor and a positive emotional reaction at 16 months of age. She experienced feeding difficulty and exhibited failure to thrive. Her growth parameters in Fig. 1 were determined following the Chinese children's growth standardized values and curves (Li, 2009). Her birth weight was 2.3 kg (−2.9 SD), birth length was 48 cm (−1.8 SD). At 16 months of age, her weight was 7.8 kg (−2.8 SD) and her height was 73.5 cm (−2.2 SD).

The girl was recently evaluated at the age of 16 months and was noticed to have craniofacial abnormalities including macrocephaly (47 cm, +2 SD), triangular face, prominent forehead, wide fontanelle, protruding ears, hypertelorism, flat nasal bridge, tented mouth, micrognathia, hairless, nystagmus. She also had ventricular septal defect which was closed spontaneously. She appeared to have slender limbs with snubby and posteriorly positioned big toes. She stood on her toes with help (Fig. 2).

2.2. Chromosomal microarray (CMA) analyses

DNA samples were extracted from peripheral blood using Lab-Aid DNA kit (Zeesan Biotech Co., Ltd., China). Genomic profiling was performed using the Illumina HumanSNPcyto-12 v2.1 BeadChip array

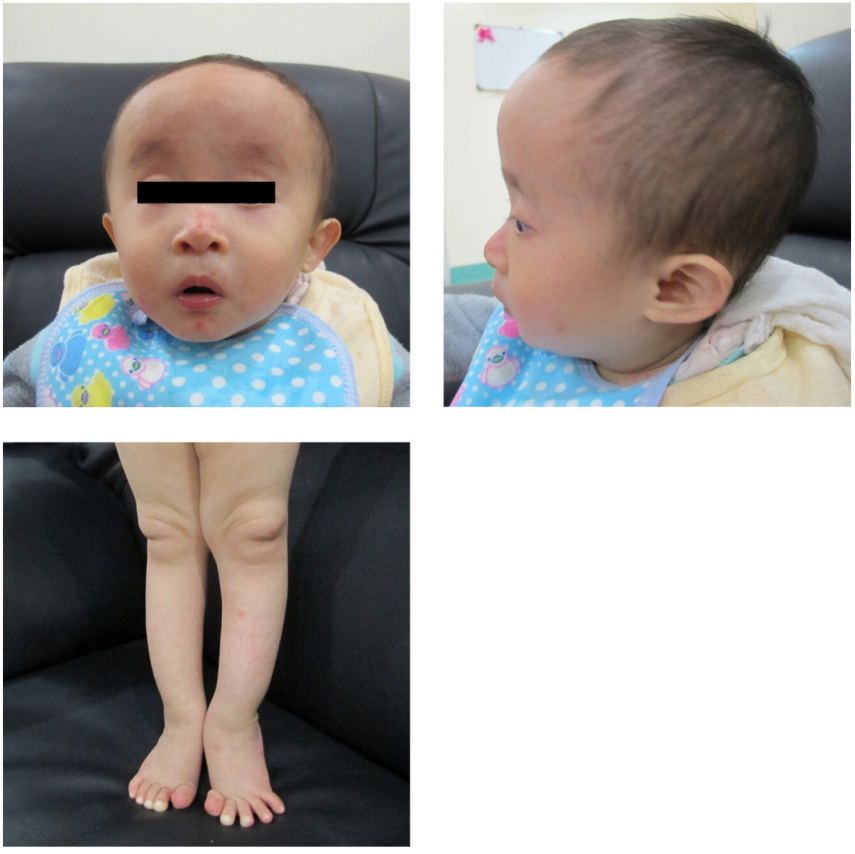

Fig. 2. Patient's craniofacial features including macrocephaly, prominent forehead, triangular face, hypertelorism, flat nasal bridge, micrognathia, protruding and low-set ears, tented mouth, slender limbs posteriorly located big toes, standing on toes.