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Short Communication

A new small supernumerary marker chromosome involving 14pter → q12 in a child with severe neurodevelopmental retardation: Case report and literature review

Manlong Qi [a,*], Yanyan Zhao [a,b], Yueping Wang [a], Tingting Li [a]

[a] Department of Clinical Genetics, the Affiliated Shengjing Hospital, China Medical University, Shenyang, Liaoning Province 110004, China
[b] Department of Medical Genetics, School of Basic Medicine, China Medical University, Shenyang, Liaoning Province 110001, China

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ABSTRACT

Unstable, gene-rich pericentric regions have been associated with various structural aberrations including small supernumerary marker chromosomes (sSMCs). We hereby report on a new sSMC derived from chromosome 14, generating trisomy 14pter → q12 in a child with severe neurodevelopmental delay. The patient featured facial dysmorphism, generalized hypotonia, transverse palmar creases, structural brain abnormality, and severe cognitive and motor impairment. Literature review indicated this to be a unique case of sSMC 14 which was only composed of pter → q12, and the phenotype secondary to duplications of the similar region partially overlaps with the phenotype reported in this study. The genetic analysis on our case helps to better delineate karyotype–phenotype correlations between proximal trisomy 14 and associated clinical phenomena, and we also propose that the involved chromosomal regions may contain dosage-sensitive genes which are important for the development.

1. Introduction

Around 2.7 million people in the world carry a small supernumerary marker chromosome (sSMC), among whom nearly 30% have problems with growth, development, learning and/or fertility (Liehr et al., 2006). The incidence of sSMCs ranges from 0.075% in conceptus and 0.044% in neonates to 0.288% in mentally subnormal individuals (Liehr and Weise, 2007). Most sSMCs are derived from the short arms and pericentric region of acrocentric chromosomes, while the occurrence of an additional derivative chromosome 14 is very rare.

Here, we report a new nonmosaic sSMC 14 in a 27-month-old boy with severe neurodevelopmental retardation and structural brain abnormality. Moreover, we compare our case to similar previous cases and discuss some candidate genes for the observed traits.

2. Material and methods

2.1. Clinical report

The male patient was born at 40 weeks via normal spontaneous vaginal delivery, as the only child of healthy non-consanguineous parents. His mother was 29 and his father was 31 years old at the time of the child's conception. Ultrasound indicated oligohydramnios at 24 weeks pregnant, however, the mother refused to have an amniocentesis as advised. At birth the boy weighed 2500 g (3rd centile) and had a length of 47 cm (10th centile) and head circumference of 34 cm (10th centile). At 7 months, he was hospitalized for pneumonia. Clinical evaluation confirmed general muscular hypotonia, transverse palmar creases and hypogammaglobulinemia. Facial dysmorphism was observed which included slight facial asymmetry, hypotelorism, blepharophimosis, downslanting eyes, epicanthal folds, mild ptosis, saddle-like short nose with anteverted nares, high-arched palate and low-set ears (Supplementary Fig. 1). At 27 months, his height was 80 cm (1st centile), weight was 12 kg (3rd centile), and head circumference was 48 cm (5th centile). The boy could not sit, stand or walk without support, and he was unable to say a single word. Brain MRI revealed decreased cerebellar volume and wider spaces surrounding cerebellar hemispheres (Fig. 1). Despite of normal dentition, he required assistance to eat blended foods.

Abbreviations: sSMC, small supernumerary marker chromosome; MRI, magnetic resonance imaging; CNV, copy number variation; FISH, fluorescent *in situ* hybridization; *FOXG1*, forkhead box G1; *NOVA1*, neuro-oncological ventral antigen 1; *G2E3*, G2/M-phase specific E3 ubiquitin protein ligase; *SUPT16H*, suppressor of Ty 16 homolog (*S. cerevisiae*); *CHD8*, chromodomain helicase DNA binding protein 8; *TOX4*, TOX high mobility group box family member 4; *PRKD1*, protein kinase D1; *COCH*, coagulation factor C homolog, cochlin (*Limulus polyphemus*).

* Corresponding author at: Department of Clinical Genetics, the Affiliated Shengjing Hospital, China Medical University, No 36, Sanhao Street, Heping District, Shenyang, Liaoning Province 110004, China. Tel.: +86 24 96615 13439; fax: +86 24 23892617.
E-mail address: 2005fyuan@sina.com (M. Qi).

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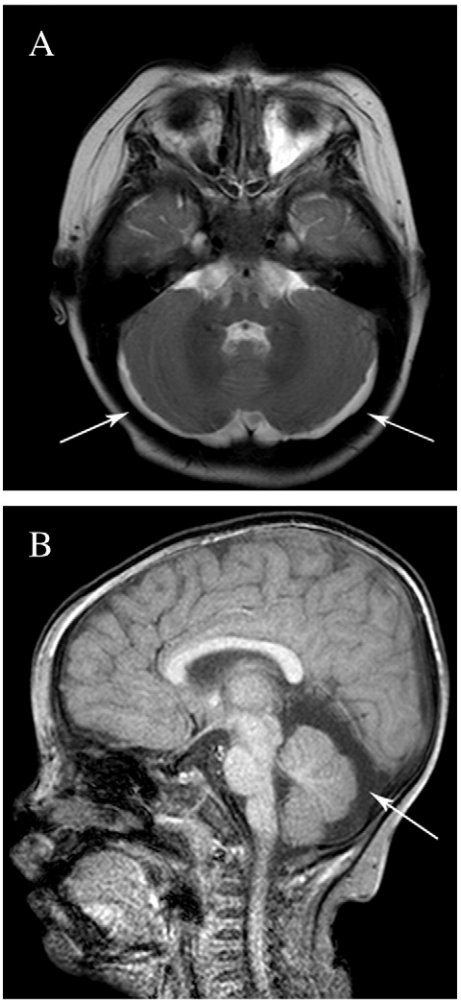

Fig. 1. Reduced cerebellar volume showed in brain MRI. A): The transverse image. B): The sagittal image.

Ophthalmologic exam confirmed strabism. Neurologic and psychomotor evaluation suggested severe developmental delay.

2.2. Conventional cytogenetics

Chromosome preparations obtained from the peripheral blood cultures of the patient and his parents were subjected to GTG-banding. To verify the results, a second round of blood sampling, cultures and karyotyping was carried out.

2.3. Molecular cytogenetics

4 ml peripheral blood (2 ml of EDTA blood for array analysis and 2 ml of heparin blood for chromosome preparation) was collected from the propositus. Oligonucleotide microarray-based copy number variation (CNV) analysis with a genome-wide human SNP array 6.0 chip (Affymetrix, Santa Clara, CA, USA) was performed by Gene Tech (Shanghai) Company Limited. The array result was further validated by fluorescent in situ hybridization (FISH) using centromere cross-hybridizing probe D14Z1/D22Z1 (Cytocell Technologies, Ltd., Cambridge, UK).

3. Results

Chromosome analysis revealed an abnormal male's karyotype 47, XY,+mar in 100% of the analyzed cells (Fig. 2A). The karyotypes of both parents were normal, suggesting that the chromosomal anomaly in the propositus occurred de novo. Array data showed the 13.43 Mb amplification at 14q11.1 → q12 (chr14: 19,002,112–32,427,778) (Fig. 2B and Table 1). The origin of sSMC was further verified by FISH using CEP14/22 (D14Z1/D22Z1) (Fig. 2C). The positive FISH signal on the marker chromosome also revealed the presence of a centromere. Based on the GTG-banding and FISH analyses, the patient's karyotype was interpreted as: 47,XY,+mar.ish der(14)(pter → q12:)(D14Z1/D22Z1+) de novo.

4. Discussion

The risk of abnormal phenotype associated with sSMC is highly variable depending on their origin and nature of genetic material (euchromatin or heterochromatin). Our case presents the first sSMC derived from 14pter → q12, suggesting that trisomy of which may play an important role in the pathogenesis of the patient's clinical features.

Literature review has found no similar sSMC report, and only one unpublished case involved sSMC 14pter → q13 in the Thomas Liehr's database (http://www.med.uni-jena.de/fish/sSMC/14.htm#Start14) is suitable for comparison with our case. Considering the trisomy of proximal 14, another four cases involving q11.2 → q12 duplication were collected (three from the reported data (Brunetti-Pierri et al., 2011) and one from DECIPHER database (http://decipher.sanger.ac.uk)). Table 2 summarizes cases with trisomy q11 → q12 which is similar to our case. The amplified region involved in our patient was almost equal in size to the largest duplication in Brunetti-Pierri's series and DECIPHER case (case 2–5), and overlapped the duplication regions with the Liehr's case 14-W-q13/3-1 (case 1) (Fig. 3). However, as shown in Table 2, only facial dysmorphism and hypotonia were described in the newborn with sSMC 14, which provides very limited information. Besides facial dysmorphism, mental retardation, psychomotor retardation and walk and speech delay were also found in our proband and in all the patients with q11.2 → q12 duplication, moreover, the growth delay was seen in four of five evaluated patients (cases 2 and 4–6), indicating that neuro/behavioral abnormalities may be common features of trisomy 14q at q11 → q12. Additionally, all the patients evaluated with brain MRI (cases 2, 3 and 6) had morphological brain changes, suggesting that trisomy 14q11 → q12 may be associated with structural brain abnormalities. Notably, decreased cerebellar volume observed in our boy has been previously seen in individuals with 22q11.2 deletion syndrome (Bish et al., 2006), Down syndrome (Moldrich et al., 2007), deletion at 7q11.23 (Axelsson, 2005) and Turner's syndrome (Reiss et al., 1993), while, it was not reported to be associated with chromosome 14. Therefore, decreased cerebellar volume, associated with delays in global development, expressive language, cognition, gross and fine motor function, is a novel malformation in trisomy 14.

A number of functional proteins have located within the 14q11 → q12 regions. Among which, *FOXG1* (*forkhead box G1*), located at 14q12, has been reported to be a dose-sensitive gene and has an important role in the developing brain (Hebert and McConnell, 2000) and postnatal neurogenesis (Shen et al., 2006), duplication of which could cause severe developmental retardation (Brunetti-Pierri et al., 2011; Yeung et al., 2009), and thus *FOXG1* may be the most important candidate to explain the abnormal neurodevelopmental phenotypes observed in our patient. Meanwhile, the role of additional genes in the large sized involved regions cannot be excluded (Fig. 3). For example, it has been proposed that *NOVA1* (*neuro-oncological ventral antigen 1*) and *G2E3* (*G2/M-phase specific E3 ubiquitin protein ligase*) in 14q12 region may have essential functions in early embryonic development. *NOVA1* homozygous mutant mice die as a result of a motor deficit associated with apoptotic death of motor neurons in the spinal cord and brainstem