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Short Communication

A unique combination of 17pter trisomy and 21qter monosomy in a boy with developmental delay, severe intellectual disability, growth retardation and dysmorphisms

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ABSTRACT

Background: Microduplication at 17p13.3 and microdeletion at 21q22 are both rare chromosomal aberrations. The presence of both genomic imbalances in one patient has not been previously reported in literature. In this study, we performed a molecular diagnostic testing with a whole genome microarray on a 3-year-old boy with developmental delay, mental retardation and multiple malformations.
Methods: A routine G-banding karyotype analysis was performed using peripheral lymphocytes. Chromosome microarray analysis (CMA) was done using Affymetrix CytoScan™ HD array. Genomic imbalances were further confirmed by multiple ligation-dependent probe amplification (MLPA).
Results: The result of karyotyping was normal but CMA detected a 9.8 Mb microduplication at 17p13.3–13.1 (chr17: 1–9,875,545) and a 2.8 Mb microdeletion involving 21q22.3–qter (chr21: 45,239,077–48,097,372). The imbalances were due to a balanced translocation present in patient's mother. The patient was characterized with short stature, profound developmental delay, non-verbal, intellectual disability as well as craniofacial dysmorphism, subtle brain structural anomaly and sparse scalp hair.
Conclusions: This is the first patient reported with a combination of a microduplication at 17p13.3–13.1 and a microdeletion at 21q22.3–qter. Both genomic imbalances were undetected by conventional karyotyping but were delineated with CMA test. Synergistic effect from the two rare genomic imbalances is likely responsible for the severe clinical phenotypes observed in this patient.

1. Introduction

While a deletion of a full chromosome 21 typically results in prenatal death (Joosten et al., 1997; Mori et al., 2004), partial monosomy 21 has been reported as rare genomic imbalances in patients with variable clinical presentations depending on the size and location of the deletions (Béri-Dexheimer et al., 2008; Chettouh et al., 1995; Hoyer et al., 2007; Huret et al., 1995; Lindstrand et al., 2010; Matsumoto et al., 1997; Shinawi et al., 2008; Theodoropoulos et al., 1995; Tuschl et al., 2007; Weise et al., 2003; Yamamoto et al., 2011).

Several genomic disorders have been identified on chromosome 17 and dosage sensitive genes such as *PMP22*, *PAFAH1B1*, *YWHAE*, *RAI1*, and *NF1* have been implicated as key genes responsible for the main clinical phenotypes of the genomic disorders (Lupski, 1998, 2009; Lupski & Stankiewicz, 2005; She et al., 2004). Recently defined chromosome 17p13.3 duplication is the third microduplication syndrome described involving chromosome 17 (Avela et al., 2011; Bi et al., 2009; Faletra et al., 2011; Hyon et al., 2011; Roos et al., 2009). It is reciprocal to the microdeletion encompassing *PAFAH1B1* resulting in Miller–Dieker syndrome (MDS, OMIM #247200).

17pter trisomy and 21qter monosomy are both rare genomic aberrations, and to the best of our knowledge, a combination of both imbalances in one patient has not been previously reported in literature. In this study, we report such a unique combination in a boy with developmental delay, mental retardation and multiple malformations.

Abbreviations: MLPA, multiplex ligation-dependent probe amplification; DS, Down syndrome; MDS, Miller–Dieker syndrome; CT, computed tomography; CNV, copy number variation; MR, mental retardation; DD, developmental delay; CMA, chromosomal microarray; ID, intellectual disability; ASD, autism spectrum disorders; MCA, multiple congenital anomalies; MDSR, MDS critical region; Mb, megabase; DSCR, DS critical region.

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2. Materials and methods

2.1. Patient data

The 3-years old male patient was the first child of non-consanguineous parents. He was born in 28+ weeks without specified cause for premature birth. The birth weight was 2000 g and the delivery was normal. The patient was on oxygen for several hours after the delivery. The neonatal period was otherwise uneventful. The patient had pneumonia at 4 months of age and his growth essentially stopped after pneumonia. The patient had intermittent (every 1 to 3 days) vomiting since 8 or 9 months of age. Vomiting often co-occurred with fever and the content of vomit was of dark color. At 3-years old when he was last examined, he was vomiting once a month and the vomit was of gastric content. The patient was globally delayed, hypotonia, incapable of speaking or walk and had bowel incontinence. On examination, the patient was alert and had a height of 43.5 cm (<3rd), a weight of 7000 g (<3rd). His craniofacial dysmorphisms include a triangular face with micrognathia, a prominent forehead/frontal bossing, prominent ears, a bulbous nasal tip of a small nose, a small mouth and abnormal teeth. He also had high palate, sparse scalp hair and simian crease. The physical examination revealed a normal respiratory, cardiovascular, and gastrointestinal system. Bilateral reducible inguinal hernias were noticed. An enlarged cisterna magna and a bilateral mastoid effusion were also detected by brain CT imaging. The parents were unrelated, and the family history was unremarkable on both sides. Parental karyotyping detected an apparent balanced translocation (46,XX,t(17;21)(p13;q22.3)) in the mother and a normal male in the father.

2.2. CMA

With informed consent, genomic DNA samples were extracted with GentraPuregene Kit (Qiagen, Germany) from peripheral blood collected from the patient and his parents. A genomic hybridization was performed with CytoScan™ HD array (Affymetrix, USA) in accordance with the manufacturer's instruction. The array is characterized with >2,600,000 CNV markers including 750,000 genotype-able SNP probes and >1,900,000 non-polymorphism probes. All data was visualized and analyzed with Chromosome Analysis Suite (ChAS) software Package (Affymetrix, USA).

2.3. MLPA analysis

Two MLPA analyses were performed on the patient and his parents with P064-B3 Mental Retardation-1 kit and P365-A1 Human

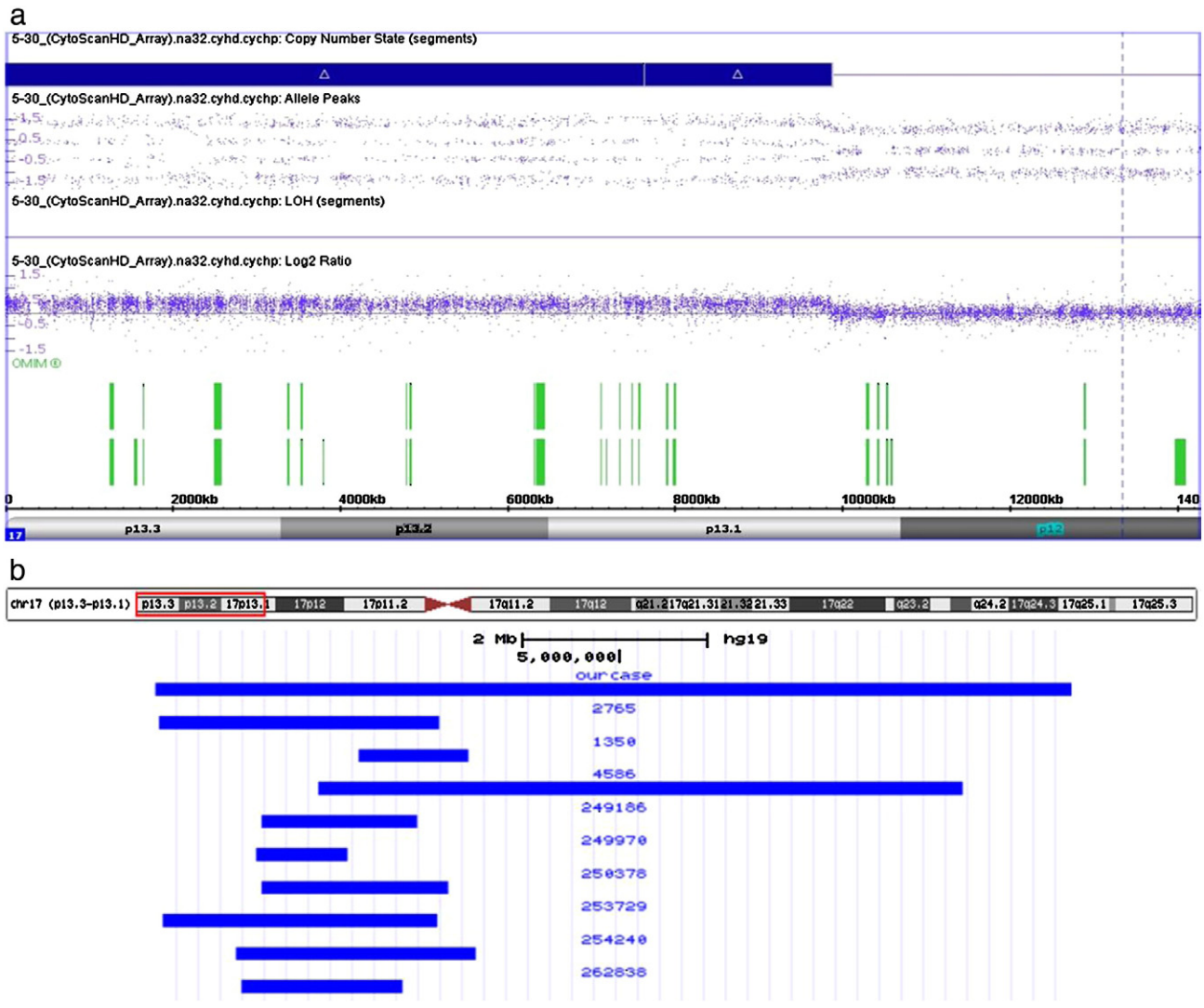

Fig. 1. 17p13 microduplications. The chromosome microarray profile of the (17)(p13.3p13.1) microduplication in our patient (a) and custom tracks generated from the data of genomic aberrations involving 17p13 duplications in our patient and patients from Decipher database (b).