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Case Report

Tetrasomy of 11q13.4-q14.3 due to an intrachromosomal triplication associated with paternal uniparental isodisomy for 11q14.3-qter, intrauterine growth restriction, developmental delay, corpus callosum dysgenesis, microcephaly, congenital heart defects and facial dysmorphism

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ABSTRACT

Objective: We present tetrasomy of 11q13.4-q14.3 due to an intrachromosomal triplication associated with paternal isodisomy of uniparental disomy (iso-UPD) for 11q14.3-qter and multiple abnormalities.
Case report: A 30-year-old primigravid woman was found to have intrauterine growth restriction (IUGR) in the fetus since 28 weeks of gestation, and a 2056-g baby was delivered at 38 weeks of gestation with fetal distress. The baby postnatally manifested hypotonia, microcephaly, facial dysmorphism of micrognathia, retrognathia and low-set ears, ventricular septal defect, atrial septal defect, tricuspid regurgitation and corpus callosum dysgenesis. A single nucleotide polymorphism (SNP) array comparative genomic hybridization analysis on the DNA extracted from the peripheral blood revealed the result of arr 11q13.4q14.3 (71,567,724–89,547,851) × 4, arr 11q14.3q25 (89,466,484–134,942,626) hmz [GRCh37 (hg19)] with a 17.980-Mb triplication of 11q13.4-q14.3 encompassing the genes of *GRM5* and *MAP6*, and loss of heterozygosity for a 45.476-Mb region of 11q14.3-qter consistent with iso-UPD for 11q14.3-qter. Polymorphic DNA marker analysis confirmed paternal iso-UPD for 11q14.3-qter. Cytogenetic analysis of the blood revealed a karyotype of 46,XY,trp(11) (q13.4q14.3). The parental karyotypes were normal. When follow-ups at age 2 years, the neonate manifested physical and psychomotor developmental delay and intellectual disability.
Conclusion: Tetrasomy 11q13.4-q14.3 may present the phenotype of IUGR, developmental delay, corpus callosum dysgenesis, microcephaly, congenital heart defects and facial dysmorphism.

Introduction

Both the deletion and the duplication of chromosome 11q13.4-q14.3 can be associated with phenotypic abnormalities. The deletion of 11q13.4-q14.3 has been reported to be associated with microcephaly, facial dysmorphism, ptosis, developmental delay and

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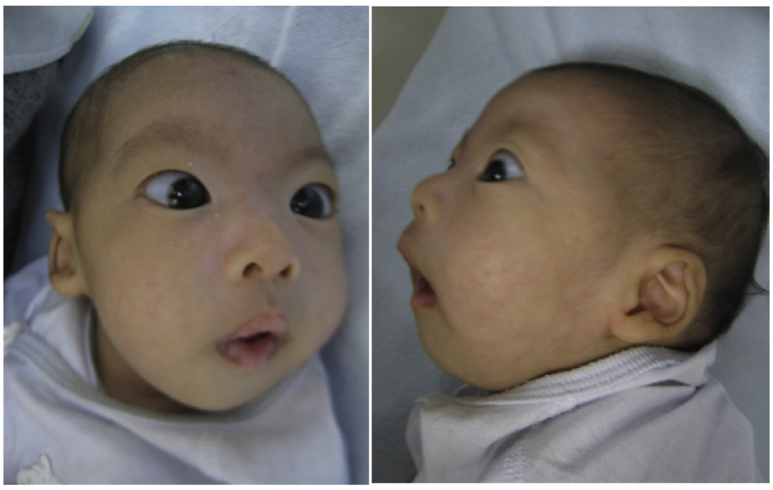

Fig. 1. Craniofacial appearance of the neonate at age one month.

behavioral disorders [1]. The duplication of 11q13.4-q14.3 have been reported to be associated with intellectual disability, microcephaly, facial dysmorphism and congenital heart defects [2–5].

Xiao et al., [6] previously reported tetrasomy of 11q13.4-q14.3 due to an intrachromosomal triplication associated with developmental delay, facial dysmorphism, microcephaly, absence of cerebellar vermis and partial absence of corpus callosum. Here, we present an additional case with perinatal phenotypic abnormalities.

Case report

A 30-year-old primigravid woman was found to have intrauterine growth restriction (IUGR) in the fetus since 28 weeks of gestation, and a 2056-g baby was delivered at 38 weeks of gestation with fetal distress. The baby postnatally manifested hypotonia, microcephaly, facial dysmorphism of micrognathia, retrognathia and low-set ears, ventricular septal defect (VSD), atrial septal defect (ASD), tricuspid regurgitation and corpus callosum dysgenesis (Fig. 1). A single nucleotide polymorphism (SNP) array comparative genomic hybridization analysis on the DNA extracted from the peripheral blood revealed the result of arr 11q13.4q14.3 (71,567,724–89,547,851) × 4, arr 11q14.3q25 (89,466,484–134,942,626) hmz [GRCh37 (hg19)] with a 17.980-Mb triplication of 11q13.4-q14.3 encompassing 92 Online Mendelian Inheritance in Man (OMIM) genes including *GRM5* and *MAP6* (Fig. 2), and loss of heterozygosity for a 45.476-Mb region of 11q14.3-qter consistent with isodisomy of uniparental disomy (iso-UPD) for 11q14.3-qter (Fig. 2). Cytogenetic analysis of the blood revealed a karyotype of 46,XY,trp(11)(q13.4q14.3) (Fig. 3). Polymorphic DNA marker analysis on the DNAs extracted from the patient's blood and parental bloods confirmed paternal iso-UPD for 11q14.3-qter (Fig. 4). The parental karyotypes were normal. When follow-ups at age 2 years, the neonate manifested physical and psychomotor developmental delay and intellectual disability. His had a body weight of 11.4 Kg (16.7 centile), a body height of 85 cm (8.3 centile), a head circumference of 41.8 cm (<3rd centile) and a body mass index (BMI) of 15.8 (44.4 centile).

Discussion

The present case provides evidence that gene dosage increase in 11q13.4-q14.3 can be associated with phenotypic abnormalities. In a review of five cases with gene dosage increase in 11q13.4-q14.3 [2–6], Xiao et al. [6] reported the clinical findings of intellectual disability (5/5), facial dysmorphism (5/5), congenital heart disease (3/5), microcephaly (3/5), hypotonia (3/5) and brain abnormalities (1/5). The present case had all the abnormalities. Ligius et al. [2] reported a 31-year-old female with

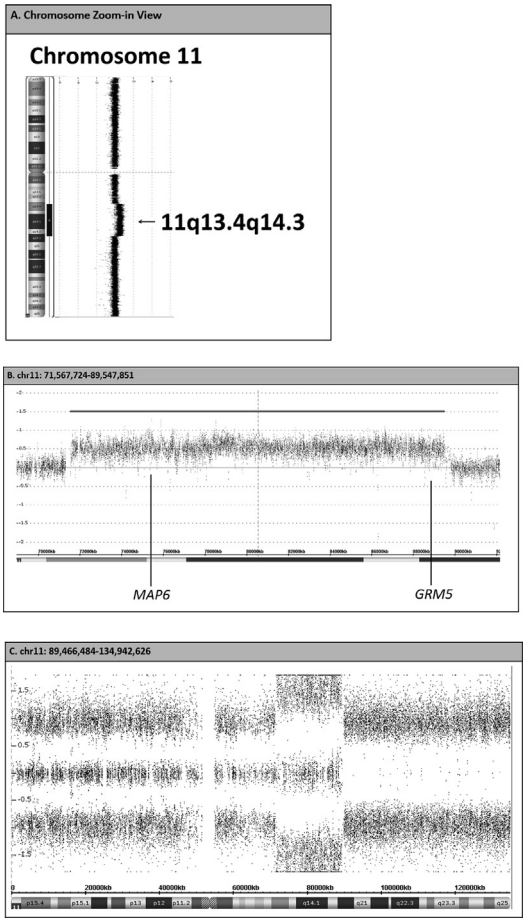

Fig. 2. Array comparative genomic hybridization analysis on the DNA extracted from the peripheral blood using CytoScan HD Array (Affymetrix, CA, USA) shows the result of arr 11q13.4q14.3 (71,567,724–89,547,851) × 4, arr 11q14.3q25 (89,466,484–134,942,626) hmz [GRCh37 (hg19)] with (A) and (B) a 17.980-Mb triplication of 11q13.4-q14.3 encompassing the genes of *GRM5 and MAP6*, and (C) loss of heterozygosity for a 45.476-Mb region of 11q14.3-qter consistent with uniparental isodisomy for 11q14.3-qter. hmz = homozygosity.

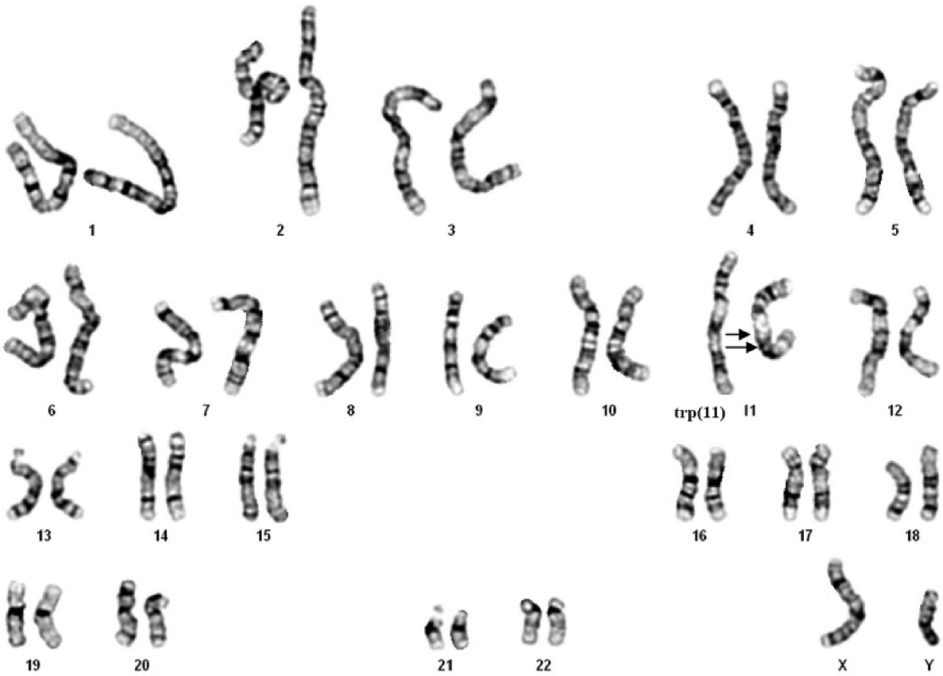

Fig. 3. A karyotype of 46,XY,trp(11)(q13.4q14.3). The arrows indicate the breakpoints of 11q13.4 and 11q14.3. trp = triplication.

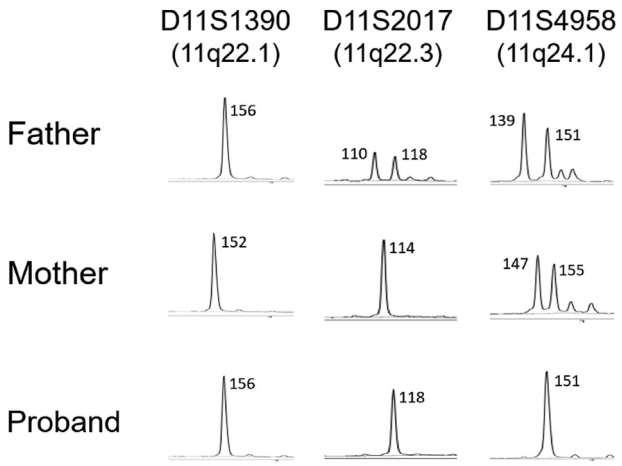

Fig. 4. Polymorphic DNA marker analysis by quantitative fluorescent polymerase chain reaction using the informative markers of D11S1390 (11q22.1), D11S2017 (11q22.3) and D11S4958 (11q24.1) shows only one paternal allele in the proband, and the result is consistent with paternal uniparental isodisomy.

de novo 46,XX,dir dup(11)(q13.3→14.2), intellectual disability, developmental delay, microcephaly, facial dysmorphy, VSD, pulmonary valvular stenosis (PVS), seizures, hypotonia, thrombocytopenia and pectus excavatum. Zhao et al. [3] reported a 5-year-old girl with 46,XX,add(11)(q25).ish dup(11)(q25q13), intellectual disability, microcephaly, facial dysmorphy, ASD, seizures, brachydactyly, malformed epiglottis and tracheomalacia. Yelavarthi and Zunich [4] reported a 2.5-year-old boy with 46,XY,dup(11) (q13.5q21).ish dup(11)(q13.5q21)(wcp11+)mat, intellectual disability, developmental delay, facial dysmorphy, hypotonia, inguinal hernia, narrow shoulder, bithoracic narrowing and mid-thoracic spinal curvature. His mother and maternal grandmother had developmental delay. Kayhan et al. [5] reported a 19-year-old girl with partial trisomy of 11q13.5→q25 or 46,X,der(X) (Xqter→Xp22.33::11q13.5→11qter), intellectual disability, developmental delay, facial dysmorphy, patent ductus arteriosus (PDA), seizures, hypoplastic labium minor, hypoplastic nails, hypotonia, hypoplastic left kidney and abnormal right clavicle. Xiao et al. [6] reported a 20-month-old girl with 18.7-Mb tetrasomy for 11q13.4-q14.3 (chr11: 71,002,347 bp-89,725,167 bp, hg19) and absence of heterozygosity for a 45-Mb stretch on 11q (chr11: 89,843,477 bp-134,930,689 bp, hg19), an 11q13.4-q14.3 triplication, paternal iso-UPD at 11q14.3→qter, intellectual disability, developmental delay, microcephaly, facial dysmorphy, absence of cerebellar vermis and partial absence of corpus callosum.

According to the DECIPHER database v10.1 [7], at least three cases with a triplication of the 11q region overlapping with the triplicated region of our case have been reported: #331609 (46,XY; 81,341,260–89,243,427) with a *de novo* 7.9-Mb triplication, intellectual disability, macrocephaly, obesity and retrognathia; #3340937 (46,XY; 79,682,422–89,547,851) with a *de novo* 9.87-Mb triplication, frontal bossing, mild intellectual disability and mild short stature; and #409197 (46,XY; 83,881,568–84,958,027) with a maternally inherited 1.08-Mb triplication and uncertain phenotype.

The present case had UPD distal to the rearrangement of intrachromosomal triplication, and the result is consistent with a postzygotic mitotic event. Carvalho et al. [8] reported complex genomic rearrangements consisting of triplication copy-number variants accompanied by extended regions of copy-number-neutral absence of heterozygosity in patients with multiple congenital anomalies. Other similar reports include trp(11)(q23.3q24.1) with UPD(11)(q24.1qter) [9], trp(5)(q33.3q34) with UPD(5)(q34qter) [10], trp(9)(q21.11q21.33) with UPD(9)(q21.33qter) [11], trp(22)(q12.1q12.2) with UPD(22)(q12.2qter) [11] and trp(11)(q13.4q14.3) with UPD(11)(q14.3qter) [6]. In contrast, a meiotic event of intrachromosomal triplication is expected to result in multiple allele dosage across SNPs in the triplicated region and lack a region of iso-UPD distal to the rearrangement [12].

The present case had a 17.980-Mb triplication of 11q13.4-q14.3 encompassing 92 OMIM genes including *GRM5* and *MAP6*. *GRM5* (OMIM 604102) encodes glutamate receptor, metabotropic, 5.

MAP6 (OMIM 601783) encodes microtubule-associated protein 6. Xiao et al. [6] suggested that *GRM5* and *MAP6* are candidate genes responsible for intellectual disability associated with tetrasomy of 11q13.4-q14.3. *GRM5* is related to rat hippocampus developmental dysregulation, Alzheimer's disease and schizophrenia [13]. *MAP6*, expressed at high levels in the central nervous system, is crucial for cognitive abilities, and *MAP6*-KO mice are associated with psychiatric disorders [14].

In summary, we present tetrasomy of 11q13.4-q14.3 due to an intrachromosomal triplication associated with paternal iso-UPD for 11q14.3-qter and multiple abnormalities. Tetrasomy 11q13.4-q14.3 may present the phenotype of IUGR, developmental delay, corpus callosum dysgenesis, microcephaly, congenital heart defects and facial dysmorphism.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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