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Short Communication

Molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 8 or r(8)(::p12→q13.1::) associated with phenotypic abnormalities

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ABSTRACT

Objective: We present molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome (sSMC) derived from chromosome 8.

Materials and Methods: A 35-year-old woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+mar[20]/46,XY[39]. However, array comparative genomic hybridization analysis on the subcultured amniocytes revealed no genomic imbalance. Prenatal ultrasound showed bilateral ventriculomegaly, intrauterine growth restriction, and an enlarged right atrium. At 36 weeks of gestation, a 2380-g baby was delivered with mild facial dysmorphism. The baby postnatally manifested right hydronephrosis, vesicoureteral reflux, hypospadias, hypotonia, strabismus, developmental delay and mild mental retardation. Array comparative genomic hybridization and metaphase fluorescence *in situ* hybridization analyses were performed on the peripheral blood to determine the origin and mosaicism of the sSMC, and quantitative fluorescent polymerase chain reaction was used to exclude uniparental disomy.

Results: The blood had a karyotype of 47,XY,+mar[17]/46,XY[23]. Array comparative genomic hybridization revealed arr 8p12q13.1 (33,476,753–67,428,722) × 2.40 (Log2 ratio = 0.24) encompassing 98 Online Mendelian Inheritance in Man (OMIM) genes including *CHD7*, consistent with 30–40% mosaicism for r(8)(::p12→q13.1::). Metaphase fluorescence *in situ* hybridization identified the sSMC(8) in 21/33 of cultured lymphocytes. Quantitative fluorescent polymerase chain reaction excluded uniparental disomy 8.

Conclusion: Mosaic sSMC(8) derived from r(8)(::p12→q13.1::) can present phenotypic abnormalities. Chromosome 8q12 duplication syndrome should be included in differential diagnosis when an sSMC(8) contains 8q12.2 and *CHD7*.

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Introduction

A small supernumerary marker chromosome (sSMC) is a structurally abnormal chromosome that cannot be identified or characterized by conventional cytogenetics, and its size is equal to or smaller than that of chromosome 20 [1]. Prenatally ascertained sSMCs occur in 0.075% of prenatal cases [1–3] and have an overall 13% risk for phenotypic abnormalities [4]. Crolla et al [5] suggested that an sSMC derived from a nonacrocentric chromosome has a higher risk for phenotypic abnormalities than an sSMC derived from an acrocentric chromosome (28% vs. 7%). Liehr and Weise [6] additionally suggested that a prenatally detected sSMC derived from a nonacrocentric chromosome has a 30% risk for phenotypic abnormalities.

Prenatal diagnosis of an sSMC derived from chromosome 8, or sSMC(8), is very rare [7,8]. To date, at least 68 cases of sSMC(8) with clinical findings have been reported [9]. Here, we present an additional case of sSMC(8) derived from r(8)(::p12→q13.1::) with phenotypic abnormalities.

Materials and methods

Clinical description

A 35-year-old, gravida 2, para 0, woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+mar[20]/46,XY[39]. The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis on the subcultured amniocytes 4 weeks after amniocentesis using an oligonucleotide array CytoChip Oligo (BlueGnome, Cambridge, UK) detected no genomic imbalance. Prenatal ultrasound findings at 30 weeks of gestation showed bilateral ventriculomegaly, intrauterine growth restriction, and an enlarged right atrium. The parents elected to continue the pregnancy. At 36 weeks of gestation, a 2380-g male baby was delivered with mild facial dysmorphism of large ears, full cheeks with medial flaring of eyebrows, epicanthic folds, brachycephaly, a broad nasal bridge, and a small mouth. At the age of 1½ years, he had a body weight of 7.9 kg (<3rd centile), a body length of 77 cm (<3rd centile), and a head circumference of 44 cm (<3rd centile). He had a small right kidney with right hydronephrosis. He underwent a surgery of bilateral reimplantation of ureters to treat bilateral vesicoureteral reflux at the age of 6 months. He underwent a surgery of urethral reconstruction to treat hypospadias at the age of 10 months. He had normal vision and normal hearing function, but could not follow the orders. He presented with strabismus, hypotonia, developmental delay, and mild mental retardation. The brain ultrasound showed an arachnoid cyst. At the age of 22 months, aCGH, metaphase fluorescence *in situ* hybridization (FISH), and conventional cytogenetic analysis were performed on the peripheral blood to determine the mosaicism and origin of the sSMC, and quantitative fluorescent polymerase chain reaction assay was used to exclude uniparental disomy 8.

Array comparative genomic hybridization

Whole-genome aCGH was performed on the DNA extracted from the peripheral blood using CytoChip ISCA (Illumina, San Diego, CA, USA). The array has 60,000 probes and a median resolution of 51 kb across the entire genome according to the manufacturer's instruction.

Conventional cytogenetic analysis

Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed on the neonate's peripheral blood according to the standard cytogenetic protocol.

Fluorescence in situ hybridization

Metaphase FISH analysis on cultured lymphocytes was performed using bacterial artificial chromosome probes of RP11-754D24 [8p11.21, 40,098,705–40,275,557; fluorescein isothiocyanate, spectrum green] and RP11-1005P2 (8q12.1, 60,341,410–60,534,153; Texas Red, spectrum red) according to the standard FISH protocol.

Quantitative fluorescent polymerase chain reaction

Quantitative fluorescent polymerase chain reaction assay was performed on the DNAs extracted from the peripheral blood of the proband and his parents. The informative markers of D8S589 (8q11.21) and D8S593 (8q12.1) were applied to undertake polymorphic marker analysis to exclude uniparental disomy 8.

Results

Cytogenetic analysis of the blood revealed a karyotype of 47,XY,+mar[17]/46,XY[23] (Figure 1). An aCGH analysis revealed the result of arr 8p12q13.1 (33,476,753–67,428,722) × 2.40 (Log2 ratio = 0.24), indicating a 33.95-Mb genomic gain in 8p12-q13.1 encompassing 98 Online Mendelian Inheritance in Man (OMIM) genes including *CHD7* and a 30–40% mosaicism for gnomic imbalance (Figure 2). The sSMC(8) was r(8)(::p12→q13.1::). Metaphase FISH identified the sSMC(8) in 21/33 of cultured lymphocytes (Figure 3). Quantitative fluorescent polymerase chain reaction assay using the informative markers of D8S589 (8q11.21) and D8S593 (8q12.1) excluded uniparental disomy 8.

Discussion

The present case had a 33.95-Mb gene dosage increase in 8p12-q13.1 encompassing *CHD7* and manifested some of the features of 8q12 microduplication syndrome, which is characterized by neonatal hypotonia, developmental delay, facial features, heart defects, and Duane anomaly [10–14]. *CHD7* (OMIM 608892) is located at 8q12.2 and encodes chromodomain helicase DNA-binding protein 7, which is a transcriptional regulator that binds to enhancer elements in the nucleoplasm. *CHD7* deletion or loss-of-function mutation will cause coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies (CHARGE) syndrome (OMIM 214800) and hypogonadotropic hypogonadism 5 (OMIM 612370), whereas *CHD7* duplication and gain of dosage will cause 8q12 microduplication syndrome.

To date, at least five cases with an sSMC(8) encompassing the 8q12.2 critical region have been reported, and all were associated with phenotypic abnormalities [9,15–17]. Blennow et al [15] and Anderlid et al [16] reported a female with a karyotype of 47,XX,+r(8)(::p10→q21.1::)/46,XX with 40% mosaicism in the peripheral blood and 72% mosaicism in fibroblasts. When examined at the age of 8 years, she manifested delayed motor development, hearing loss, difficulty in social communication, facial dysmorphism, and intelligence of 1 year below normal. Eyüpoğlu et al [17] reported a 2-year-old male with a karyotype of 47,XY,+r(8)(::p11.21→q21.13::)[47]/46,XY[36] in the peripheral blood with a marker size of 43.92 Mb and the clinical features of multiple congenital abnormalities, thoracolumbar scoliosis, mild pulmonary stenosis, laryngomalacia, hypospadias, and atypical facial appearance. Liehr [9] reported a 29-year-old male with a karyotype of 47,XY,+r(8) (::p11.2→q13~21.1::) in the peripheral blood with phenotypic abnormalities. Liehr [9] reported a 4-year-old male with a karyotype of 47,XY,+min(8)(:p11.1→q21.?3:)[5]/46,XY[15] in the peripheral blood with developmental delay, hip dysplasia, cardiomyopathy, partial right ptosis, congenital stridor,