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Short Communication

Molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 8 or r(8)(::p11.22→q11.21::) in an 18-year-old female with short stature, obesity, attention deficit hyperactivity disorder, and intellectual disability

Chih-Ping Chen [a, b, c, d, e, f, *], Shuan-Pei Lin [b, g, h, i], Schu-Rern Chern [b], Peih-Shan Wu [j], Yen-Ni Chen [a], Shin-Wen Chen [a], Chien-Wen Yang [b], Meng-Shan Lee [a], Wayseen Wang [b, k]

[a] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
[b] Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan
[c] Department of Biotechnology, Asia University, Taichung, Taiwan
[d] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[e] Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
[f] Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[g] Department of Medicine, MacKay Medical College, New Taipei City, Taiwan
[h] Department of Pediatrics, MacKay Memorial Hospital, Taipei, Taiwan
[i] Department of Early Childhood Care, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan
[j] Gene Biodesign Co. Ltd, Taipei, Taiwan
[k] Department of Bioengineering, Tatung University, Taipei, Taiwan

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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: An 18-year-old female presented with short stature, obesity, developmental delay, speech delay, dyslexia, attention deficit hyperactivity disorder, and intellectual disability. Cytogenetic analysis of the peripheral blood revealed a karyotype of 47,XX,+mar[22]/46,XX[18]. 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: Array comparative genomic hybridization analysis of the blood revealed a result of arr 8p11.22q11.21 (39,136,065-49,725,726)×2.80 (Log2 ratio = 0.49), consistent with 70–80% mosaicism, encompassing 33 OMIM genes including *GOLGA7*, *AGPAT6*, *NKX6-3*, *KAT6A*, and *FNTA*. The sSMC(8) was r(8)(::p11.22→q11.21::). Metaphase fluorescence *in situ* hybridization analysis using the probes of RP11-754D24 (8p11.21) and RP11-769N21 (8q11.21) showed the sSMC(8) in 12/27 of cultured lymphocytes. Quantitative fluorescent polymerase chain reaction analysis excluded uniparental disomy 8.

Conclusion: Mosaic sSMC(8) derived from r(8)(::p11.22→q11.21::) can be associated with obesity, intellectual disability, and attention deficit hyperactivity disorder.

Introduction

A small supernumerary marker chromosome (sSMC) has a size equal to or smaller than that of a chromosome 20 [1]. The sSMCs account for 0.075% of prenatal cases [1–3] and have an overall 13%

* Corresponding author. Department of Obstetrics and Gynecology, MacKay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 10449, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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risk for phenotypic abnormalities [4]. 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%) [5]. Prenatally detected sSMCs derived from a nonacrocentric chromosome carry a 30% risk for phenotypic abnormalities [6].

To date, at least 68 cases of sSMC(8) with phenotypic abnormalities have been reported in the literature [7]. We previously reported two prenatal cases with sSMC(8) [8,9]. Here, we present an adult case of sSMC(8) in an 18-year-old female with short stature, obesity, attention deficit hyperactivity disorder (ADHD), and intellectual disability, which adds to the list of sSMC(8) with clinical findings.

Materials and methods

Clinical description

An 18-year-old female was referred from the metabolism department for genetic counseling and presented with short stature (147.7 cm), obesity (65.5 kg), psychomotor developmental delay, speech delay, dyslexia, ADHD, intellectual disability, and mild mental retardation. She was the first child of a 27-year-old mother and a 27-year-old father at her birth at 39 weeks of gestation with a birth weight of 3060 g. She manifested the phenotype of Turner syndrome such as small breasts, scanty pubic hair, low posterior line, and cubitus valgus. ADHD and intellectual disability had been noted since youth. Cytogenetic analysis was performed on the peripheral blood to determine the karyotype. Array comparative genomic hybridization (aCGH) and metaphase fluorescence *in situ* hybridization (FISH) analyses were performed on the peripheral blood to determine the origin and mosaicism of the sSMC, and quantitative fluorescent polymerase chain reaction (QF-PCR) on the DNA extracted from the patient's blood and parental bloods was used to exclude uniparental disomy (UPD).

aCGH

Whole-genome aCGH on the DNA extracted from peripheral blood was performed 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 patient's peripheral blood and the parents' peripheral bloods according to the standard cytogenetic protocol.

FISH

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 RP11-769N21 (8q11.21, 48,945,575-49,127,157; Texas Red, spectrum red) according to the standard FISH protocol.

QF-PCR

QF-PCR assay was performed on the DNAs extracted from the peripheral bloods of the proband and his parents. The informative

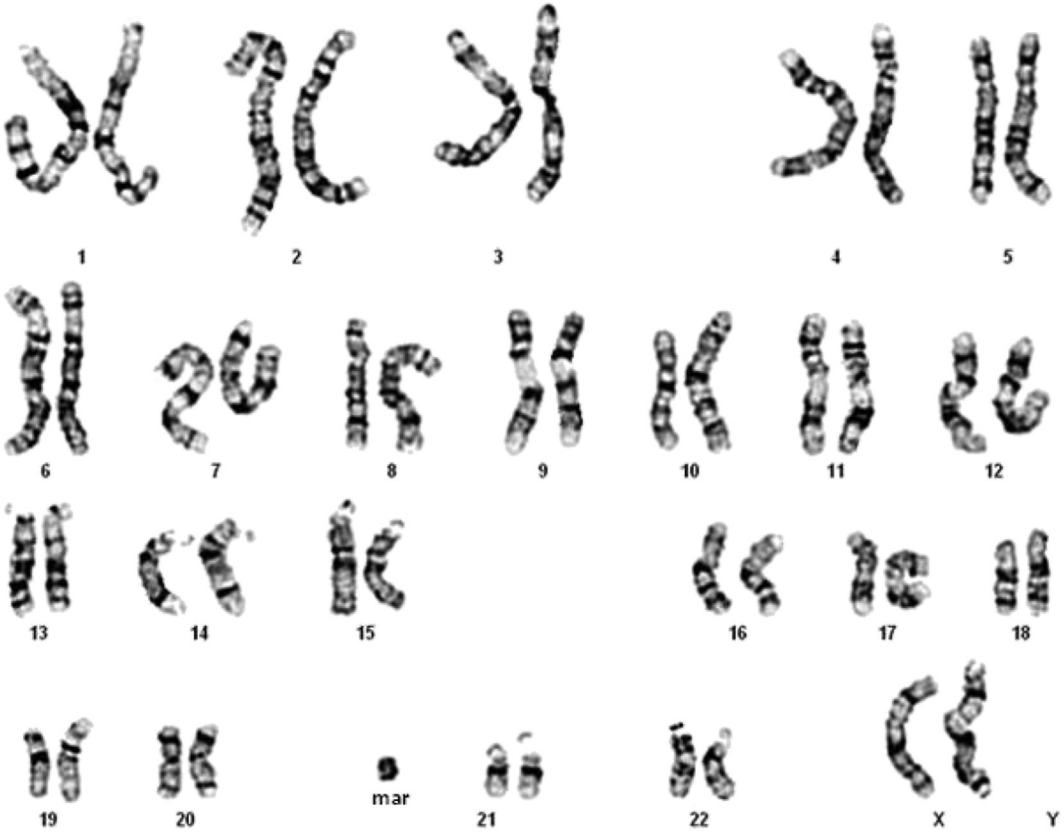

Figure 1. A karyotype of 47,XX,+mar in the patient. mar = marker chromosome.

markers of D8S587 (8q11.21) and D8S1102 (8q12.1) were applied to undertake polymorphic marker analysis to exclude UPD 8.

Results

Cytogenetic analysis of the blood revealed a karyotype of 47,XX,+mar[22]/46,XX[18] (Figure 1). The father had a karyotype of 46,XY, and the mother had a karyotype of 46,XX. aCGH analysis revealed the result of arr 8p11.22q11.21 (39,136,065-49,725,726) ×2.80 (Log2 ratio = 0.49), indicating a 10.59-Mb genomic gain in 8p11.22-q11.21 and a 70–80% mosaicism for gnomic imbalance, encompassing 33 OMIM genes including *GOLGA7*, *AGPAT6*, *NKX6-3*, *KAT6A*, and *FNTA* (Figure 2). The sSMC(8) was r(8)(::p11.22→q11.21::). Metaphase FISH identified the sSMC(8) in 12/27 of cultured lymphocytes (Figure 3). QF-PCR analysis using the informative markers of D8S587 (8q11.21) and D8S1102 (8q12.1) excluded UPD 8.

Discussion

To date, at least 16 cases of sSMC(8) involving 8p11.2→q11.21 have been reported. Four cases (4/16 = 25%) are without clinical findings, and 12 cases (12/16 = 75%) are with clinical findings. The 12 cases with clinical findings are as follows. Liehr [7] reported an 8-year-old male with 82.4% mosaicism for sSMC(8) including r(8)(::p11.2→q11.2::) in peripheral blood with autism and mental retardation. Blanchet et al [10] reported a 3-year-old female with familial inherited 9.1-Mb sSMC(8) and a karyotype of 47,XX,+mar(8)(:p11.2→q11.21:) in peripheral blood, delayed psychomotor development, intellectual disability, behavior disorder, and autistic spectrum disorder, which also appeared in her affected mother and grandmother. Sheth et al [11] reported a 6-month-old male with a karyotype of 47,XY,+min(8)(:p11.23→q11.21:)[17]/46,XY[13] and an 11.1-Mb sSMC(8) in peripheral blood, severe hypotonia, and hypospadias. Ripperger et al [12] reported a 1-year-old

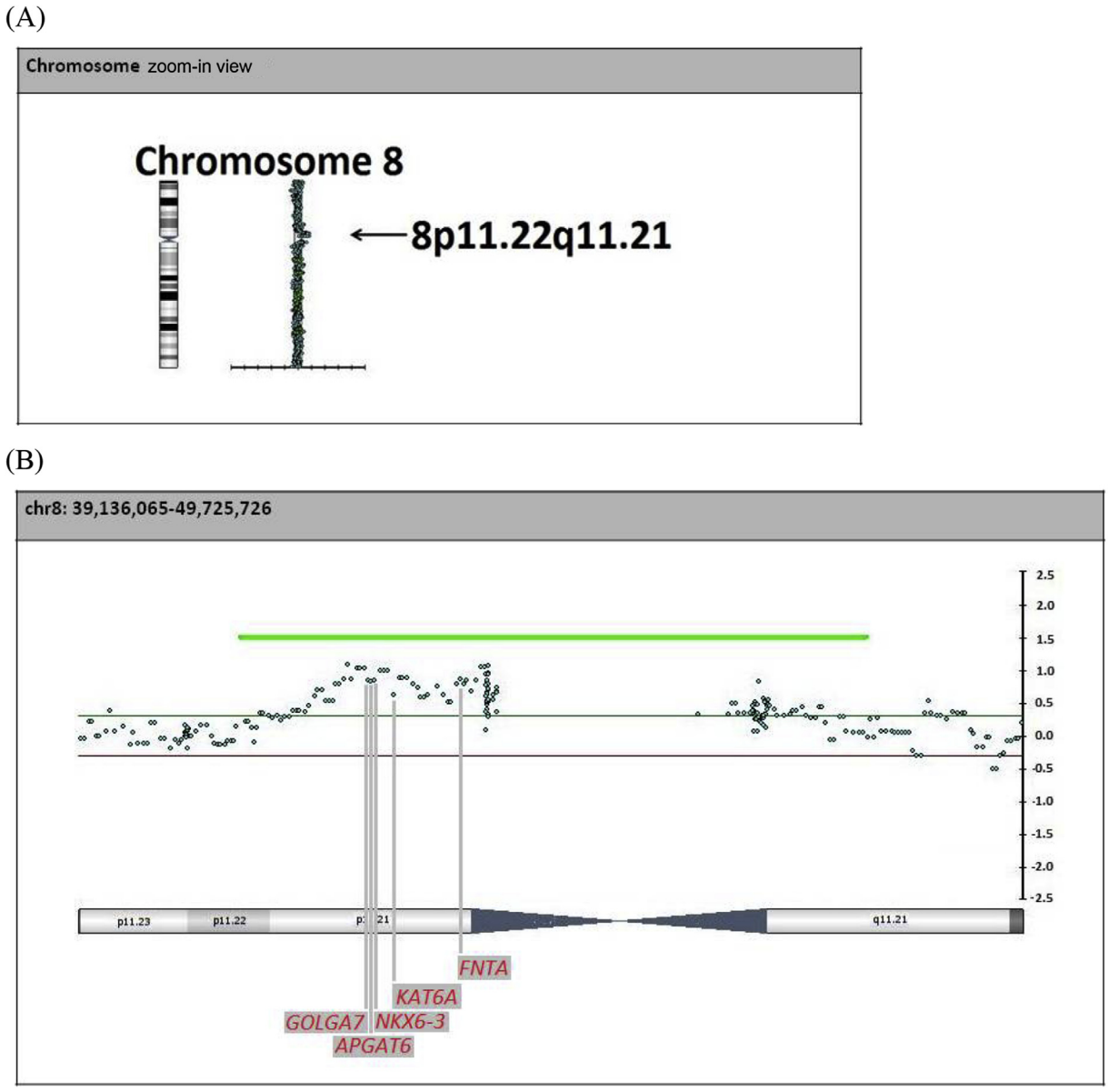

Figure 2. Array comparative genomic hybridization of peripheral blood shows a 10.59-Mb genomic gain (Log2 ratio = 0.49) in 8p11.22-q11.21 encompassing *GOLGA7*, *AGPAT6*, *NKX6-3*, *KAT6A*, and *FNTA*. (A) Chromosome zoom-in view and (B) chromosome 8. aCGH = array comparative genomic hybridization.

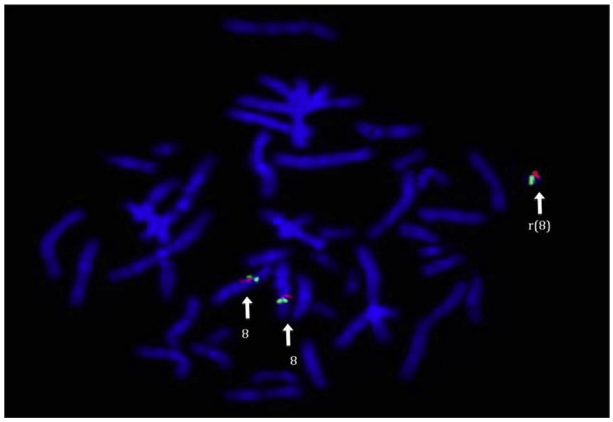

Figure 3. Metaphase fluorescence *in situ* hybridization analysis of cultured lymphocytes using the probes RP11-754D24 (8p11.21; FITC, spectrum green) and RP11-769N21 (8q11.21; Texas Red, spectrum red) shows a red signal and a green signal in the marker chromosome of r(8). FISH = fluorescence *in situ* hybridization, FITC = fluorescein isothiocyanate.

female with 38% mosaicism for a 13.5-Mb sSMC(8) or min(8)(:p11.23→q11.2:) in buccal mucosa, frontal bossing, downslanting palpebral fissures, hypertelorism, low nasal bridge, and juvenile myelomonocytic leukemia. Bettio et al [13] and Baldwin et al [14] reported a 3-year-old female with 89.7% mosaicism in amniotic fluid and 96% mosaicism in peripheral blood for sSMC(8) or r(8)(::p11.22→q11.22::), developmental delay, a supernumerary nipple, and ADHD. Liehr [7] reported a 7-year-old female with 40% mosaicism for sSMC(8) in peripheral blood including min(8)(:p11.22→q11.23:), microcephaly, and developmental delay. Spinner et al [15] reported a 7-month-old male with a karyotype of 47,XY, +min(8)(:p11.21→q11.21:)[28]/46,XY[22] in skin fibroblasts, skeletal anomalies, developmental delay, camptodactyly, ulnar deviation, growth delay, and language delay. Brecevic et al [16] reported a male with 40% mosaicism for sSMC(8) or min(8)(:p11.21→q11.21:) in peripheral blood and developmental delay. Ripperger et al [12] reported another 1-year-old female with 34% mosaicism in skin fibroblasts and 80% mosaicism in bone marrow for sSMC(8) or min(8)(:p11.21→q11.21:) and mild psychomotor developmental delay. Lopez Melchor et al [17] reported a 1-year-old female with 53% mosaicism for 2× sSMC(8) or min(8)(:p11.21→q11.21:) in peripheral blood, developmental delay, mental retardation, microcephaly, hypotonia, and dysmorphism. Liehr [7] reported prenatal diagnosis of 20% mosaicism for sSMC(8) or r(8)(::p10~11.1→q11.21::) at amniocentesis with omphalocele. Risheg et al [18] reported a male newborn with mosaicism for sSMC(8) and 2× sSMC(8) or r(8) (::p10~11.1→q11.21::), prominent forehead, plagiocephaly, hypertelorism, and low-set ears.

The four cases without clinical findings are as follows. Liehr [7] reported prenatal diagnosis of 60% (15/25) mosaicism for sSMC(8) or r(8)(::p11.21→q12.1::) at amniocentesis due to advanced maternal age, and the female neonate was normal at age 14 months. Liehr [7] reported a 35-year-old normal infertile female with 60% mosaicism for sSMC(8) or min(8)(:p11.21→q11.21:). Liehr [7] reported prenatal diagnosis of 83% mosaicism for sSMC(8) or r(8)(::p11→q11.2::) at amniocentesis, and the female neonate was normal a few months after birth. Manvelyan et al [19] reported a 44-year-old normal male with 41.2% mosaicism for sSMC(8) or min(8)(:p11.1→q11.21:) and min(8)(:p11.21→q11.1:).

The present case manifested obesity, ADHD, intellectual disability, and had gene dosage increase in *GOLGA7*, *AGPAT6*, *NKX6-3*, *KAT6A*, and *FNTA* at 8p11.21. Obesity and overgrowth have been reported in patients with sSMC(8). Liehr [7] reported an 18-year-old male with 60% mosaicism for sSMC(8) or min(8)(:p11.21→q11.1::q11.1→p11.21:) in peripheral blood, moderate mental retardation, overgrowth syndrome, deafness, facial dysmorphism, and autistic features. Baldwin et al [14] reported a case with sSMC(8), a duplication of 8p22, facial dysmorphism, learning disability and obesity. The genes of *GOLGA7*, *AGPAT6*, and *FNTA* are associated with obesity. *AGPAT6* (OMIM 608143) plays a distinct role in adipogenesis [20] and *Agpat6* deficiency causes subdermal lipodystrophy and resistance to obesity [21]. Capel et al [22] found that *FNTA* (OMIM 134635) has increased expression during moderate-fat diet. Padilla et al [23] found that *GOLGA7* (OMIM 609453) is downregulated with obesity.

Intellectual disability is common in patients with sSMC(8) involving 8p11.2→q11.2. ADHD has been previously reported in a patient with sSMC(8) or r(8)(::p11.22→q11.22::) [13,14]. *NKX6-3* (OMIM 610772) is involved in the development of the central nervous system [24]. *KAT6A* (OMIM 601408) is associated with autosomal dominant mental retardation 32 (OMIM 616268) [25,26]. Recently, Ahn et al [27] found a patient with 8q11.2 duplication and intellectual disability.

In summary, we present molecular cytogenetic characterization of mosaicism for an sSMC(8) derived from r(8)(::p11.22→q11.21::). Our presentation adds to the list of sSMC(8) with phenotypic abnormalities and shows that an sSMC(8) derived from r(8)(::p11.22→q11.21::) can be associated with obesity, intellectual disability, and ADHD.

Conflicts of interest

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

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