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Short Communication

Prenatal diagnosis of mosaic small supernumerary marker chromosome 17 associated with ventricular septal defect, developmental delay, and speech delay

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ABSTRACT

Objective: We present molecular cytogenetic characterization of mosaic small supernumerary marker chromosome (sSMC) derived from chromosome 17.

Materials and Methods: A 43-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+mar[12]/46,XY[15]. Parental karyotypes were normal. Array comparative genomic hybridization (aCGH) and metaphase fluorescence *in situ* hybridization (FISH) were applied on cultured amniocytes. Quantitative fluorescent polymerase chain reaction (QF-PCR) was applied on the DNAs extracted from cultured amniocytes and parental bloods. The parents elected to continue the pregnancy. Conventional cytogenetic analysis on peripheral blood of the neonate was performed at age 2 months and 11 months. aCGH was performed on the peripheral blood at age 11 months.

Results: aCGH on cultured amniocytes revealed a result of arr 17q11.1q11.2 (25,372,965–27,725,134)×3.2 (Log2 ratio = 0.73) compassing *NOS2*, *POLDIP2*, *NEK8*, and *TRAF4*. Metaphase FISH analysis revealed a result of +mar .ish der(17)(D17Z1+, wcp17+)[4/5]. QF-PCR assays excluded uniparental disomy 17. The marker chromosome was the sSMC(17) of der(17)(:p11.1→q11.2:). A 3004 g male baby was delivered at 38 weeks of gestation. Ventricular septal defect, neonatal developmental delay and speech delay with language problems were noted at neonatal follow-ups. The peripheral blood at age 2 months had a karyotype of 47,XY,+mar[11]/46,XY[29]. The peripheral blood analysis at age 11 months revealed a karyotype of 47,XY,+mar[27]/46,XY[13] and the aCGH result of arr 17q11.1q11.2 (25,616,440–27,822,571) ×2.5 (Log2 ratio = 0.34).

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Conclusion: aCGH is useful in the precise measurement of the involved size of the euchromatic material and the associated genes in prenatally detected sSMC.

Introduction

A small supernumerary marker chromosome (sSMC) has a size equal to or smaller than chromosome 20 and cannot be characterized by conventional banding techniques [1]. Prenatally ascertained sSMCs account for 0.075% of prenatal cases [1–3] and have an overall risk of 13% for phenotypic abnormalities [4]. sSMCs derived from nonacrocentric chromosomes have a higher risk of phenotypic abnormalities than those derived from acrocentric chromosomes (28% vs. 7%) [5]. Liehr and Weise [6] additionally suggested that prenatally detected sSMCs derived from nonacrocentric chromosomes have a 30% risk for phenotypic abnormalities.

Prenatal diagnosis of an sSMC derived from chromosome 17 is very rare. Here, we present our experience of prenatal diagnosis of mosaic sSMC derived from chromosome 17q11.1-q11.2 associated with ventricular septal defect (VSD), neonatal developmental delay and speech delay with language problems. To our knowledge, such a case has not previously been reported. Our case adds to the literature of prenatally detected sSMC(17) with phenotypic abnormalities and emphasizes that array comparative genomic hybridization (aCGH) is useful in the precise measurement of the involved size of the euchromatic material and associated genes in prenatally detected sSMC.

Materials and methods

Clinical description

A 43-year-old, gravida 5, para 2, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 46 years of age. The couple had two healthy children, and there was no family history of congenital malformations. Amniocentesis revealed a karyotype of 47,XY,+mar[12]/46,XY[15] (Figure 1). The parental karyotypes were normal. aCGH and metaphase fluorescence *in situ* hybridization (FISH) were applied on cultured amniocytes. Quantitative fluorescent polymerase chain reaction (QF-PCR) was applied on the DNAs extracted from cultured amniocytes and parental bloods. The parents elected to continue the pregnancy. A 3004 g male baby was delivered at 38 weeks of gestation with a body length of 44.5 cm and a head circumference of 34.5 cm. VSD, neonatal developmental delay, and speech delay with language problems were noted at neonatal follow-ups. Cytogenetic analysis on postnatal peripheral blood at the age of 2 months and the age of 11 months revealed a karyotype of 47,XY,+mar[11]/46,XY[29] and a karyotype of 47,XY,+mar[27]/46,XY[13], respectively.

aCGH

Whole-genome aCGH on the DNA extracted from cultured amniocytes was performed using Roche NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). The Roche NimbleGen ISCA Plus Cytogenetic Array has 630,000 probes and a median resolution of 15–20 kb across the entire genome according to the manufacturer's instruction. aCGH on the DNA extracted from peripheral blood at the age of 11 months was performed using CytoChip ISCA Array (Illumina, San Diego, CA, USA), which 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 using G-banding techniques at 550 bands of resolution was performed on cultured amniocytes, parental peripheral bloods and neonate's peripheral blood according to the standard cytogenetic protocol.

FISH

Metaphase FISH analysis on cultured amniocytes was performed using whole chromosome 17 painting probe (WCP17) (spectrum red) (Cytocell, Adderbury, Oxfordshire, UK) and the CEP17 probe encompassing the locus D17Z1 (17p11.1-q11.1) (spectrum green, fluorescein isothiocyanate (FTIC)) (Cytocell) according to the standard FISH protocol.

QF-PCR

QF-PCR assay was performed on the DNA extracted from cultured amniocytes and parental peripheral bloods. The informative marker of D17S2180 (17q21) was applied to undertake polymorphic marker analysis to exclude uniparental disomy 17.

Results

aCGH on cultured amniocytes revealed a result of arr 17q11.1q11.2 (25,372,965–27,725,134)×3.2 (Log2 ratio = 0.73) with a 2.35 Mb genomic gain in 17q11.1-q11.2 encompassing 84 genes which contain 41 Online Mendelian Inheritance in Man (OMIM) genes including *NOS2*, *POLDIP2*, *NEK8*, and *TRAF4* (Figure 2). Metaphase FISH analysis revealed a result of +mar .ish der(17)(D17Z1+, wcp17+)[4/5] (Figure 3). The marker chromosome was the sSMC(17) of der(17)(:p11.1→q11.2:). QF-PCR assays using the informative marker of D17S2180 (17q21) excluded uniparental disomy 17. aCGH on peripheral blood at the age of 11 months revealed a result of arr 17q11.1q11.2 (25,616,440–27,822,571)×2.5 (Log2 ratio = 0.34), indicating a 2.206 Mb genomic gain in 17q11.1-q11.2 and a ~50–60% mosaicism for genomic imbalance.

Discussion

To date, at least four cases with the sSMC(17) of der(17)(:p11.1→q11.2:) or min(17) (:p11.1→q11.2:) have been reported, and 3/4 had phenotypic abnormalities [7]. Liehr [7] reported prenatal diagnosis of 47,XX,+mar[90%]/46,XX[10%] with the sSMC(17) of min(17) (:p11.1→q11.2:) (18.68-23.32 Mb) but without malformations, dysmophology, and psychomotor delay. Liehr [7] also reported a male newborn with 47,XY,+mar[13]/46,XY[17] and the sSMC(17) of min(17)(:p11.1→q11.2:) (23.086–32.75 Mb) with developmental delay. Capovia et al [8] reported a 2-year-old male with 47,XY,+mar[35]/46,XY[52] in buccal mucosa and the

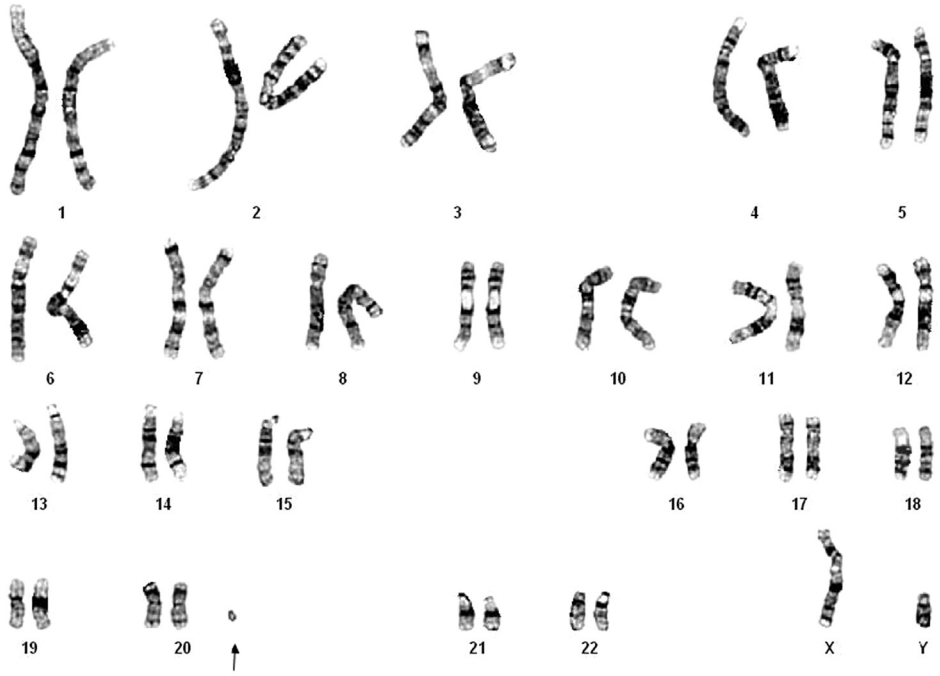

Figure 1. A karyotype of 47,XY,+mar in the fetus. The arrow indicates the marker chromosome (mar).

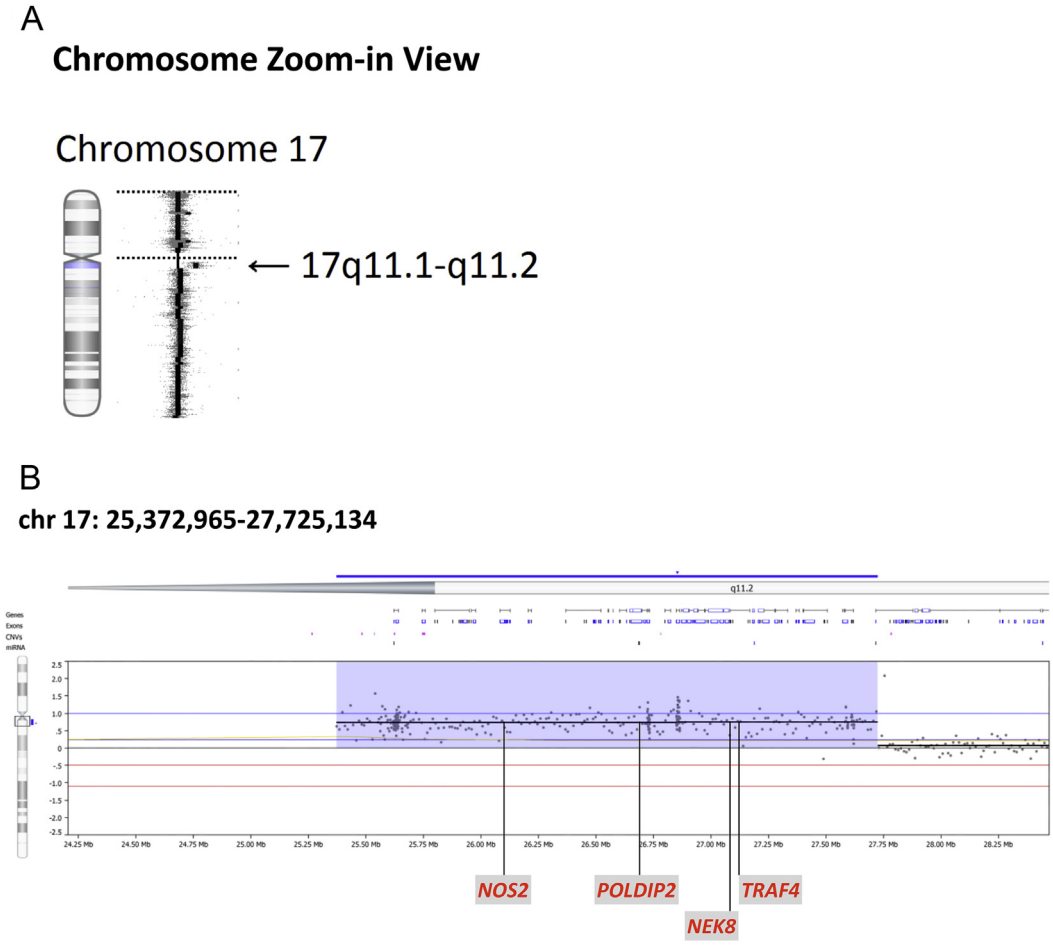

Figure 2. aCGH of cultured amniocytes shows a 2.35 Mb genomic gain in 17q11.1-q11.2 encompassing *NOS2*, *POLDIP2*, *NEK8*, and *TRAF4*. (A) Chromosome zoom-in view and (B) Chromosome 17. aCGH = Array comparative genomic hybridization analysis.

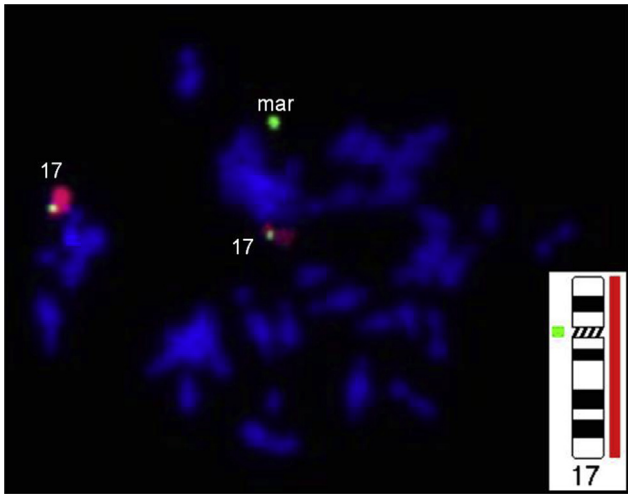

Figure 3. Metaphase FISH analysis of cultured amniocytes using whole chromosome 17 painting probe (WCP17, spectrum red) and the CEP17 probe encompassing the locus D17Z1 (17p11.1-q11.1) (spectrum green, FTIC) shows a green signal of CEP17 in the marker chromosome (arrow). FISH = fluorescence in situ hybridization; FTIC = fluorescein isothiocyanate.

sSMC(17) of min(17)(:p11.1→q11.2:) about 10 Mb in size with short stature, minor facial dysmophism, speech delay, developmental delay, and Potocki-Lupski syndrome. Hovnik et al [9] reported a 3-year-old female with 47,XX,+mar[100%] and the sSMC(17) of min(17) (:p11.1→q11.2:) (a q-arm breakpoint at 27.72 Mb) with facial abnormalities, gastroesophageal reflux, polycystic ovary, supernumerary nipples, and hypotonia. The present case manifested VSD, developmental delay, and speech delay with language problems.

The present case had a 2.35 Mb duplication of 17q11.1-q11.2 encompassing *NOS2*, *POLDIP2*, *NEK8*, and *TRAF4*. The present case manifested developmental delay and speech delay. Cornelius et al [10] reported a 22-year-old male with the phenotypic findings of Gilles de la Tourette syndrome, attention deficit hyperactivity disorder (ADHD), intellectual disability and seizures, and the sSMC(17) in 82% of the investigated cells. aCGH revealed 17p11.2q11.2 (21,200,000–27,500,000) ×2–3dn. The duplication involved *NOS2* and *TRAF4*. *NOS2* (OMIM 163730) encodes nitric oxidase synthase 2A that produces nitric oxide, a neurotransmitter. *TRAF4* (OMIM 602464) encodes TNF receptor-associated factor 4, which is required during embryogenesis for the formation of the trachea, the axial skeleton and the closure of neural tube. Cornelius et al [10] suggested that the duplication of *NOS2* plays a role in ADHD, and the duplication of *TRAF4* plays a role in ADHD, intellectual disability and movement disorder. In a review of 27 cases with the sSMC(17), Cornelius et al [10] found 70% had developmental delay or intellectual disability, and ~60% had dysmorphic features and speech delay. The present case additionally had congenital heart defect of VSD. *NEK8* (OMIM 609799) never encodes in mitosis gene A-related kinase 8, which is required for renal and cardiovascular development [11,12]. *POLDIP2* (OMIM 611519) encodes polymerase δ-interactive protein 2, which controls vascular smooth muscle cell migration by regulating focal adhesion, turnover and force polarization [13]. We speculate that the duplication of *POLDIP2* and *NEK8* may be correlated with the development of VSD in this case.

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of mosaic sSMC(17) with VSD, neonatal developmental delay and speech delay. We discuss the genotype–phenotype correlation in this case. We conclude that aCGH is useful in the precise measurement of the involved size of the euchromatic material and the associated genes in prenatally detected sSMC.

Conflict of interest

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

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