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Case Report

Prenatal diagnosis of Smith–Magenis syndrome in two fetuses with increased nuchal translucency, mild lateral ventriculomegaly, and congenital heart defects

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ABSTRACT

Objective: Smith–Magenis syndrome (SMS) is a multiple congenital anomalies/mental retardation disorder characterized by an interstitial deletion involving chromosome 17p11.2 containing the retinoic acid-induced 1 (*RAI1*) gene or due to mutation of *RAI1*. Few cases have been reported in the medical literature regarding prenatal diagnosis of SMS. We report on the prenatal diagnosis of SMS in two fetuses with increased nuchal translucency (NT), mild lateral ventriculomegaly, and congenital heart defects by whole-genome and high-resolution chromosome microarray analysis (CMA).

Case Report: The CMA result of Fetus 1, which had increased NT, mild lateral ventriculomegaly, tricuspid regurgitation, and right aortic arch with left ductus arteriosus, revealed a *de novo* 4.79-Mb deletion at 17p12p11.2. Fetus 2 had increased NT, pulmonary stenosis, and a ventricular septal defect, and showed a *de novo* 3.68-Mb deletion at 17p11.2.

Conclusion: The findings further confirm that increased NT is associated with genetic syndromes, and brain imaging is necessary for SMS fetuses. Both deletions encompass the SMS "critical region", which includes many genes including *RAI1*. However, the precise gene(s) responsible for the heart defects in SMS remain unclear; further efforts should be undertaken to understand the molecular basis of this syndrome.

Introduction

Smith–Magenis syndrome (SMS, OMIM#182290, *607642) is a multiple congenital anomalies/mental retardation disorder characterized by developmental delay, craniofacial dysmorphism, otolaryngologic abnormalities, eye abnormalities, sleep abnormalities [especially reduced rapid eye movement (REM) sleep], hearing impairment, scoliosis, brain abnormalities, cardiac abnormalities, renal abnormalities, low thyroxine levels, low immunoglobulin levels, and forearm abnormalities [1]. Cardiac abnormalities are observed in 30% of SMS individuals [2], and most of the heart defects are ventricular septal defect (VSD), atrial septal defect, and tetralogy of Fallot. A few brain abnormalities, such as ventriculomegaly, enlarged cisterna magna, enlarged foramen magnum, and dystrophic calcification of the right frontal lobe, have been described in SMS patients; ventriculomegaly is the most prevalent finding [1]. However, brain anomalies are not considered to be part of the routine clinical evaluation at this time. SMS is generally a sporadic disorder caused by an interstitial deletion involving chromosome 17p11.2 containing the retinoic acid-induced 1 (*RAI1*) gene or due to mutation of *RAI1* [3,4]. Approximately 90% of cases of SMS have a 17p11.2 deletion, whereas the remaining 10% have a mutation in the *RAI1* gene. Most patients with SMS are suspected phenotypically and then detected by karyotyping or by fluorescent *in situ* hybridization (FISH) studies postnatally. To our knowledge, only two other fetuses with prenatally diagnosed SMS due to the abnormal maternal serum screening [without nuchal translucency (NT) measurement] by karyotyping or FISH have been reported [5,6]. In our study, we report on the prenatal diagnosis of SMS in a fetus with increased NT, mild lateral ventriculomegaly, tricuspid regurgitation, and right aortic arch with left ductus arteriosus, and in another fetus with increased NT, pulmonary stenosis, and VSD by whole- genome and high- resolution chromosome microarray analysis (CMA).

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Case Report

The mother (G1P0A0) of Fetus 1 was 31 years old. First trimester NT sonography for Down's syndrome screening at 12+ weeks of gestation showed that the fetus had septated cystic hygroma, and the NT space was enlarged, extending along the entire length of the fetus; septations were clearly visible, and the measurement of NT was 7.6 mm (>3 mm). The couple was nonconsanguineous and had no significant medical, surgical or family history. They received genetic counseling on the septated cystic hygroma and underwent chorionic villus sampling at the prenatal diagnostic center. The karyotype analysis revealed a normal female (46, XX). The second trimester ultrasound at 18+ weeks of gestation showed that the width of the bilateral lateral ventricles was 10 mm and 11 mm, the thickness of the fetal nuchal fold was 9.4 mm, and the Color Doppler revealed "to-and-fro" flow between the right atrium and the right ventricle. The tricuspid valve and the right atrium were normal. To further confirm the heart abnormality, echocardiography was performed at 25+ weeks of gestation and revealed that the fetus had a right aortic arch with left ductus arteriosus (Figure 1) and tricuspid regurgitation. The brain magnetic resonance image of the fetus showed mild lateral ventriculomegaly without other obvious anomalies. CMA testing was then pursued.

The mother (G1P0A0) of Fetus 2 was 32 years old. First trimester Down's syndrome screening indicated that the fetus was at low risk, and the ultrasound showed that the measurement of NT was 3.5 mm (>3 mm) at 12+ weeks of gestation. However, the couples rejected chorionic villus sampling for genetic analysis. The second trimester ultrasound at 27+ weeks of gestation showed the presence of pulmonary stenosis and VSD. Echocardiography was performed to confirm the heart defects and revealed that the diameter of the aorta was 5.6 mm, the main pulmonary artery was 4.2 mm, and the blood flow velocities in the aorta and the main pulmonary artery were 0.9 m/s and 1.58 m/s, respectively. The width of the VSD was 3.3 mm, and the Doppler demonstrated blood flow signals between the ventricles through the defect. The brain structure was normal. The couple was nonconsanguineous and had no significant medical, surgical, or family history. They received genetic counseling on the multiple congenital heart defects and underwent cord blood sampling at the prenatal diagnostic center. The karyotype analysis showed a normal male (46, XY), and CMA testing was performed.

CytoScan 750K Array (Affymetrix Inc., Santa Clara, CA, USA) containing 750,436 25–85-mer oligonucleotide probes, including 550,000 nonpolymorphic (NP) probes and 200,436 single nucleotide polymorphic (SNP) probes, was used to analyze the two fetuses and their parents' DNA samples. Labeling, hybridization, washing, scanning, and image extraction were performed by an Affymetrix certified service laboratory according to manufacturer's instructions. The results were analyzed using Chromosome Analysis Suite (Affymetrix Inc.). The data were further aligned with the copy number variants (CNVs) listed in publically available online databases, such as Database of Chromosomal Imbalance and Phenotype in Human Using Ensembl Resources (DECIPHER, http://www.sanger.ac.uk/PostGenomics/decipher), Online Mendelian Inheritance in Man (OMIM, http://www.omim.org), Database of Genomic Variants (DGV, http://www.projects.tcag.ca/variation), University of California Santa Cruz (UCSC; http://genome.ucsc.edu/, hg19), and others. We confirmed the CNVs by real-time quantitative polymerase chain reaction (qPCR) according to the manufacturer's standard protocols. Written informed consent was obtained from the parents.

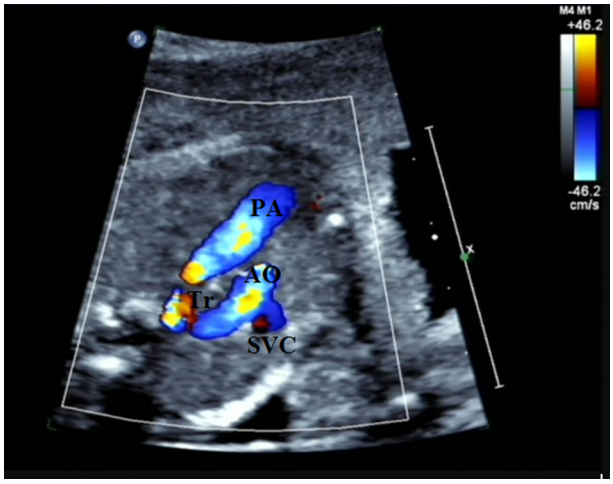
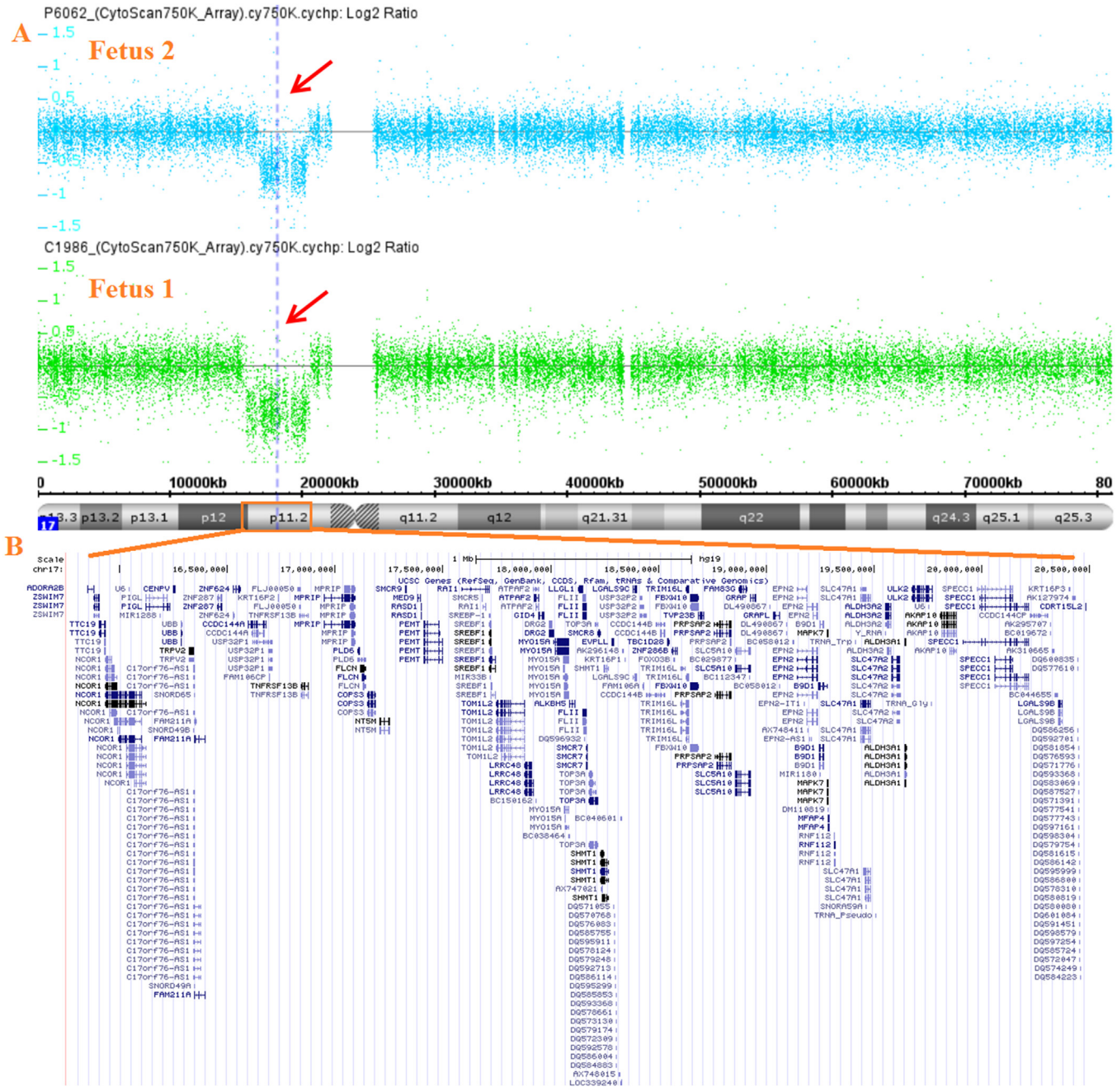


Figure 1. Fetus 1: 25+ weeks of gestation; the image shows three-vessel-trachea view of the heart with dextroaortic arch. The PA and the AO forms a "U-shape" structure and the trachea is located between the PA and the AO. AO = artery aorta; PA = pulmonary artery; SVC = superior vena cava; Tr = trachea.

The CMA result of Fetus 1 revealed a *de novo* 4.79-Mb deletion at 17p12p11.2 encompassing 42 OMIM genes (Genomic coordinates: 15759453- 20547625, UCSC hg19). Fetus 2 had a *de novo* 3.68-Mb deletion at 17p11.2 encompassing 34 OMIM genes (Genomic coordinates: 16736261-20417235, UCSC hg19). Both of the deletions encompassed the SMS "critical region", which included *RAI1*. Neither of the deletions were inherited from the parents. Figure 2 shows the deleted regions and the involved genes in the two fetuses. We offered detailed genetic counseling to the couples and informed them of the variable phenotypes of SMS. Ultimately, both couples chose to terminate the pregnancies.

Discussion

Smith–Magenis syndrome (SMS) is a clinically recognizable syndrome caused by an interstitial deletion in chromosome 17p11.2. The syndrome was first described in 1986 by Smith et al [3] in nine unrelated patients (6 males; 3 females) ranging in age from 3 months to 65 years associated with a striking similar phenotype including brachycephaly, midface hypoplasia, prognathism, hoarse voice, and speech delay with or without hearing loss, psychomotor and growth retardation, and behavior problems. Since that time, many patients with the syndrome have been described, although few have been diagnosed prenatally. To our knowledge, only two other fetuses with prenatally diagnosed SMS have been reported [5,6]. Fan et al [5] reported a fetus with a duplicated right ureter using G-banding at a resolution level of approximately 550 bands. Thomas et al [6] described a fetus at 16 weeks of gestation with multiple anomalies using high-resolution cytogenetic analysis and FISH. G-banding and FISH are the classical methods used to detect SMS deletions, whereas multiplex ligation-dependent probe amplification (MLPA) and real-time qPCR are newer, cost-effective, high-throughput technologies [7]. As CMA has been developed as a genome-wide screening strategy for detecting DNA copy number imbalances [8], it was recommended to be used as first-line test in the initial postnatal evaluation of individuals with mental retardation/developmental delay, autism, and multiple congenital anomalies [9]. Schoumans et al [10] detected a submicroscopic deletion in 17p11.2 using a 32K tiling Bacterial Artificial Chromosomes array (BAC-array) with a resolution of approximately 650 kb in a boy with the SMS phenotype. Tug et al [11] determined a 4.73-Mb interstitial deletion in 17p11.2p12 using whole-genome array comparative genomic hybridization (CGH) in a girl with a full SMS phenotype. Lee et al [12] used BAC arrays and found a 2.6-Mb sized deletion in a 2.9-yr-old boy who showed mild dysmorphic features, aggressive behavioral problems, and developmental delay. Goh et al [13] reported on a girl with a *de novo* mosaic derivative chromosome 17 involving a 7.4-Mb deletion of chromosome region



CMA = chromosome microarray analysis; UCSC = University of California Santa Cruz.

Figure 2. (A) Graphical representation of chromosome 17 and the CMA results of the two fetuses (CytoScan HD Array). The deletion regions are highlighted by arrows; and (B) overview of the deleted region according to the UCSC Genome Browser (GRCh37/hg19 assembly).

17p11.2 to 17p12 and a duplication of a 12.35 Mb region at 17q22 to 17q24 detected by array CGH (Agilent 4 × 44K). Maya et al [14] described two patients with SMS caused by a common deletion in 17p11.2 diagnosed using CMA. CMA is increasingly used in fetuses with congenital abnormalities. Our findings are the first report of the prenatal diagnosis of SMS in fetuses using the high-resolution and whole-genome Single Nucleotide Polymorphism (SNP) arrays. We present our findings on the prenatal diagnosis of a *de novo* 4.79-Mb deletion at 17p12p11.2 in a fetus with increased NT, mild lateral ventriculomegaly, tricuspid regurgitation, and right aortic arch with left ductus arteriosus and of a *de novo* 3.68-Mb deletion at 17p11.2 in a fetus with increased NT, pulmonary stenosis, and VSD.

SMS is characterized by a clinically recognizable phenotype that includes physical, developmental, neurological, and behavioral features [7]. System malformations are present in 30–40% of SMS patients, including cardiac, renal, and CNS abnormalities [2,7]. Congenital heart defects such as VSD, atrial septal defect, tricuspid stenosis, mitral stenosis, tricuspid and mitral regurgitation, aortic stenosis, pulmonary stenosis, mitral valve prolapse, tetralogy of Fallot, and total anomalous pulmonary venous return are observed in 30% of SMS individuals [2]. In our study, Fetus 1 was

Table 1
Reports of congenital heart defects in patients with Smith–Magenis syndrome.

Reference	Congenital heart disease
Smith et al [3], 1986	VSD, secundum ASD, tricuspid stenosis, mitral stenosis
Masuno et al, 1992	VSD
Fischer et al, 1993	VSD
Zori et al, 1993	ASD
Al-Qudah et al, 1994	VSD
Greenberg et al [1], 1996	VSD, ASD, mild tricuspid regurgitation, mild mitral regurgitation, subvalvular aortic stenosis, supravalvular pulmonic stenosis, pulmonic stenosis, mitral valve prolapse
Salati et al, 1996	Interatrial septal aneurysm without interatrial shunt
Behjati et al, 1997	ASD
Sweeney et al, 1999	Tetralogy of Fallot
Thomas et al [6], 2000	Tetralogy of Fallot
Wong et al, 2003	Pulmonary atresia, VSD
Myers and Challman [15], 2004	Total anomalous pulmonary venous return, tetralogy of Fallot, patent ductus arteriosus
Yamamoto et al [16], 2006	Tetralogy of Fallot, pulmonary atresia, patent ductus arteriosus
Chaudhry et al [18], 2007	VSD, ASD, dysplastic pulmonary valve
Sanford et al [19], 2011	Atrioventricular canal defect, cleft mitral valve
Huang et al [17], 2012	Tetralogy of Fallot, atrium septum defect,patent ductus arteriosus
Shen et al [20], 2012	VSD, ASD, overriding aorta and pulmonary hypertension
Li et al [21], 2015	Tetralogy of Fallot
Our report	Right aortic arch with left ductus arteriosus, tricuspid regurgitation, VSD, pulmonary stenosis

ASD = atrial septal defect; VSD = ventricular septal defect.

characterized with tricuspid regurgitation and right aortic arch with left ductus arteriosus, and Fetus 2 had pulmonary stenosis and VSD by prenatal ultrasound examination. Similar findings have been reported in previous studies, which are listed in Table 1 [15–21]. Right aortic arch is defined as an aortic arch that crosses the right bronchus instead of the left bronchus. In a case of right aortic arch, the ductus arteriosus passes either to the right or to the left of trachea to join the aortic arch. This finding is supposed to be a type of normal anatomic variance in individuals if there are no other intra/extracardiac defects, and the variance may cause tracheal compression on rare occasions. There is a high risk of right aortic arch in cases with trisomy 21 and 22q11 microdeletion [22]. However, the condition has not been previously reported in SMS, and Fetus 1 in our study is the first case to be reported in SMS.

Abnormal brain imaging has been described previously in patients with SMS. Smith et al [3] found an SMS infant characterized with microcephaly, foreshortened frontal lobes with neuronal depletion, and a small choroid plexus hemangioma in the lateral ventricle. Greenberg et al [1] reported that 13/25 (52%) of SMS cases had brain CT abnormalities including ventriculomegaly, enlarged cisterna magna, enlarged foramen magnum, dystrophic calcification of the right frontal lobe, partial absence of the cerebellar vermis and prominent cerebrospinal fluid spaces. Boddaert et al [23] performed anatomical and functional brain imaging studies in five patients and found anatomo-functional evidence consistent with the neurobehavioral features of the disease, explaining the specific severe neurobehavioral characteristics of this syndrome. Maya et al [14] described two SMS patients with subependymal periventricular gray matter heterotopia, thin corpus callosum, and thin brain stems, which had not been seen previously. In our study, Fetus 1 was found to have mild lateral ventriculomegaly; this is the most prevalent finding among imaged cases [1]. Therefore, the finding further confirms the necessity of routine brain imaging in fetuses with SMS in particular, and in fetuses with chromosomal microdeletion/microduplication syndromes in general.

Increased nuchal translucency thickness (NT) at or above the 99th percentile in the first trimester is known to be associated with chromosomal aberrations, cardiac defects, and a wide range of genetic syndromes as well as miscarriage and intrauterine death [24]. Traditional chromosomal analysis does not reveal aberrations smaller than 10-Mb on average. However, there have been reports of genetic syndromes due to chromosomal aberrations smaller than 10-Mb associated with increased NT. Grande et al [25] performed a systematic review of the literature and a meta-analysis and estimated the incremental yield of genomic microarray over karyotyping in fetuses with increased NT diagnosed by first trimester prenatal ultrasound. The review found that the use of CMA provides a 5% incremental yield in fetuses with increased NT and normal karyotype, and the most common pathogenic CNV reported were 22q11.2 deletion, 22q11.2 duplication, 10q26.12q26.3 deletion and 12q21q22 deletion. Manolakos et al [26] reported a case of 13q-syndrome presenting as increased NT diagnosed by array CGH in the first trimester of pregnancy. Law et al [27] discovered a 1.32-Mb microdeletion on chromosome 16p13.11 in a fetus with increased NT using the high-density 244K Agilent microarray. In our study, the NT of Fetus 1 was 7.6 mm and Fetus 2 was 3.5 mm, which is the first to be reported in SMS and further confirms that increased NT is associated with microdeletion/ microduplication syndromes. The results suggest CMA should be considered in fetuses with increased NT prenatally, especially in those cases with other congenital structural anomalies.

Most of the patients reported in the literature were diagnosed postnatally and had many structural congenital anomalies; however, the two fetuses in our study were only diagnosed with increased NT, mild lateral ventriculomegaly, and congenital heart defects on the ultrasound examination. As both of the families decided to terminate the pregnancies, we were not able to track whether the fetuses were characterized with craniofacial dysmorphism, small structural anomalies, speech and developmental delays, or sleep disturbance. Variability in the phenotype might be related to the impact of incomplete penetrance, the different genes in the region of deletion, and position effect, among other modifiers in the genomic background.

SMS is hypothesized to be a contiguous gene syndrome in which haploinsufficiency of one or more genes (38–70 genes) that lie within the critical interval is likely to be responsible for the SMS phenotype, although the true molecular basis of SMS is not yet known [28]. In our study, both of the fetuses had many genes affected, including *RAI1*. Approximately 90% of cases with SMS have a 17p11.2 deletion, whereas the remaining 10% have a mutation in the *RAI1* gene. Patients with an *RAI1* mutation are more likely to exhibit overeating, obesity, polyembolokoilamania, self-hugging, muscle, cramping, and dry skin, although these patients have not been reported to have short stature, cardiac, or renal anomalies [2],

suggesting a minor role for *RAI1* in these clinical features. Slager et al [4] studied three individuals with SMS and concluded that haploinsufficiency of *RAI1* is likely responsible for the behavioral, neurologic, otolaryngologic, and craniofacial aspects, but more variable features such as heart defects are probably due to hemizygosity of other genes in the 17p11.2 region. However, the precise gene(s) responsible for heart defects in SMS remain unclear; further efforts should be undertaken to understand the molecular basis of this syndrome.

We report the prenatal diagnosis of SMS in two fetuses with increased NT, mild lateral ventriculomegaly, and congenital heart defects; this was the first study to use whole-genome and high-resolution CMA to prenatally analyze fetuses with SMS. Prenatal diagnosis allows for a timely diagnosis and appropriate counseling of parents regarding pregnancy outcomes. Both of the fetuses showed increased NT in the first trimester which further confirms that increased NT is associated with genetic syndromes and CMA is the most likely option. Although relatively few SMS patients have structural brain malformations, the fetus described in our study further demonstrates the importance of performing brain imaging in fetuses with SMS. Haploinsufficiency of *RAI1* is responsible for most SMS features, but the genetic causes for the congenital heart defects remain unclear. Therefore, further studies are needed to explore the precise genes associated with congenital heart defects with SMS.

Conflicts of interest

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

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