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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.

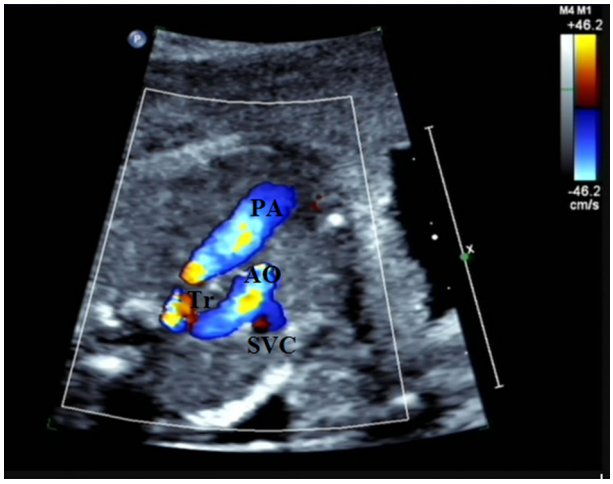

Figure 1. Fetus 1: 25+ weeks of gestation; the image shows three-vessel-trachea view of the heart with dextroaortic arch. The PA and the AO forms a "U-shape" structure and the trachea is located between the PA and the AO. AO = artery aorta; PA = pulmonary artery; SVC = superior vena cava; Tr = trachea.

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