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Microdeletion on 17p11.2 in a Smith-Magenis syndrome patient with mental retardation and congenital heart defect: first report from China

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ABSTRACT. Smith-Magenis syndrome (SMS) is a rare syndrome with multiple congenital malformations, including development and mental retardation, behavioral problems and a distinct facial appearance. SMS is caused by haploinsufficiency of *RAI1* (deletion or mutation of *RAI1*). We describe an eight-year-old female Chinese patient with multiple malformations, congenital heart defect, mental retardation, and behavioral problems (self hugging, sleeping disturbance). High-resolution genome wide single nucleotide polymorphism array revealed a 3.7-Mb deletion in chromosome region 17p11.2. This chromosome region contains *RAI1*, a critical gene involved in SMS. To

the best of our knowledge, this is the first report of an SMS patient in mainland China.

Key words: Smith-Magenis syndrome; Congenital heart defect; High-resolution single nucleotide polymorphism; Sleeping disturbance; Mental retardation

INTRODUCTION

Smith-Magenis syndrome (SMS; OMIM#182290) is a rare kind of syndrome with multiple congenital malformations, including developmental and mental retardation (MR), behavioral problems, sleeping disturbance, and distinct facial appearance (Stratton et al., 1986). Since two unrelated patients with facial clefts and congenital heart defects (CHD) were first reported by Smith in 1982, various clinical phenotypes have been described in patients with interstitial deletion of 17p11.2 (Smith et al., 1986), and subsequently defined as a deletion syndrome in 1986 by Stratton et al. This syndrome is clinically diagnosed by the distinct facial features in combination with behavioral problems. SMS is caused by haploinsufficiency of *RAI1*, either by 17p11.2 microdeletions containing the *RAI1* gene or mutations within this gene (Greenberg et al., 1991; Slager et al., 2003). The incidence of this syndrome has been estimated to be 1:15,000~25,000 births (Greenberg et al., 1991). However, due to the insufficient sensitivity of traditional techniques, microdeletions of SMS are often underdiagnosed (Greenberg et al., 1991). Recent developments of single nucleotide polymorphism (SNP) array allow for genome-wide screening at a resolution that is undetectable (smaller than 5 Mb in size) by traditional cytogenetic methods and have facilitated the discovery of a number of novel microdeletion and microduplication syndromes (Slavotinek, 2008).

As part of a larger study on the identification of pathogenic copy number variations in children with CHD (Tan et al., 2011; Chen et al., 2012; Huang et al., 2012), high-resolution SNP array (Illumina, San Diego, CA, USA) has been performed in CHD children and their parents. Here, we present a detailed study of an 8-year-old female Chinese patient with facial dysmorphisms, behavioral problems, CHD, and MR.

MATERIAL AND METHODS

The Review Board of the Second Xiangya Hospital of the Central South University approved this research. All subjects consented to this study.

Clinical presentation

In 2010, an 8-year-old female from Central-South China was seen at our hospital for a heart murmur. She was the second child of unrelated parents and had no family history of inherited diseases. She was born at 37 weeks with a birth weight of 3.2 kg (50th) and a length of 42 cm (<3rd). At birth, she presented lip cyanosis, clubbing and heart defects (tetralogy of Fallot, atrium septum defect and patent duct artery). At 2 years old, behavior problems such as self-injury, toilet difficulties and fragmented sleep cycles with frequent nocturnal awakenings gradually appeared. At the last examination (8 years old), she had a height of 110 cm (<3rd)

with a weight of 16.5 kg (<3rd). A moderate mental retardation and a decreased ability were observed, and her IQ was 49 compared to 80 at two years old. She had hearing loss and speech problems, she only spoke some single words such as ma and pa. Additionally, she had a distinct facial appearance of a round face with depressed nasal bridge, hypertelorism, an everted upper lip with a "tented" appearance shaped like a "V", and tooth agenesis (Figure 1).

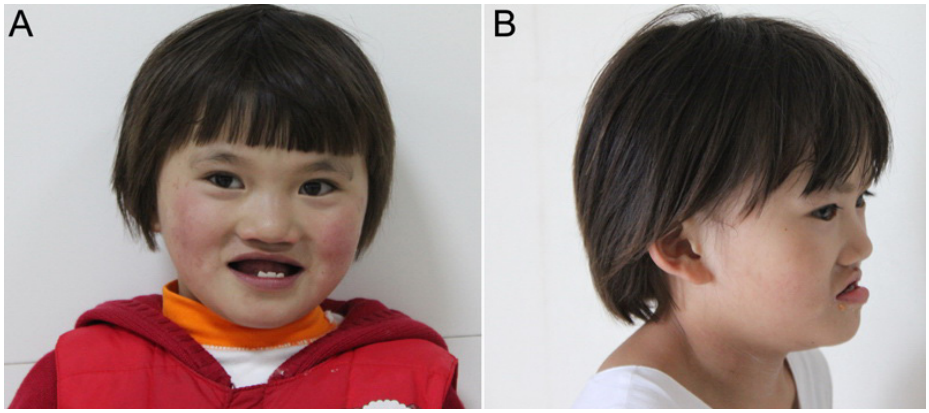

Figure 1. Distinct facial features of the proband, the patient has a round face with depressed nasal bridge, hypertelorism, an everted upper lip with a "tented" appearance like the character "V", and tooth agenesis. Frontal (**A**) and lateral (**B**) view of the patient.

Cytogenetic analysis

Chromosome analysis was performed with the patient's and her parents' peripheral blood samples by conventional G-banding techniques (550-band resolution). A sample of 2 mL peripheral blood was collected. All samples were subjected to lymphocyte culture according to standard cytogenetic protocol.

SNP array analysis

Following informed consent, peripheral venous blood was collected. Genomic DNA was isolated from peripheral blood leukocytes using a QIAamp DNA Blood Mini kit (Qiagen, Valencia, CA, USA) according to manufacturer instructions and was adjusted to a final concentration (100 ng/μL). The Human660w-Quad Chip (Illumina Inc.) and the Illumina BeadScan genotyping system (Beadstation Scanner) were employed to obtain the signal intensities of probes (SNP) as previously described (Huang et al., 2012).

RESULTS

The chromosome analysis of the patient revealed a normal female karyotype, described as 46,XX. Her parents also had a normal karyotype. Clinical examination showed a combination of phenotypes with CHD, MR, facial features, and behavior issues, raising con-

cerns about a chromosomal abnormality of microdeletion/microduplication. To explore the exact genomic lesion of this patient, we employed the SNP array system (Human660w-Quad Chip, Beadstation Scanner and BeadStudio 3.3.7 software) to analyze the whole genome copy number variations. Comparing with the Database of Genomic Variants (DGV), we identified a *de novo* 3.7-Mb deletion at chromosome 17p11.2 (Chr17: 16720137-20378904) (NCBI build 37/Hg19). This chromosome region contains about 50 annotated genes, including *RAI1*, *MYO15A*, *AKAP10*, and *ALDH3A2* (Figure 2). Her parents did not carry this genomic lesion.

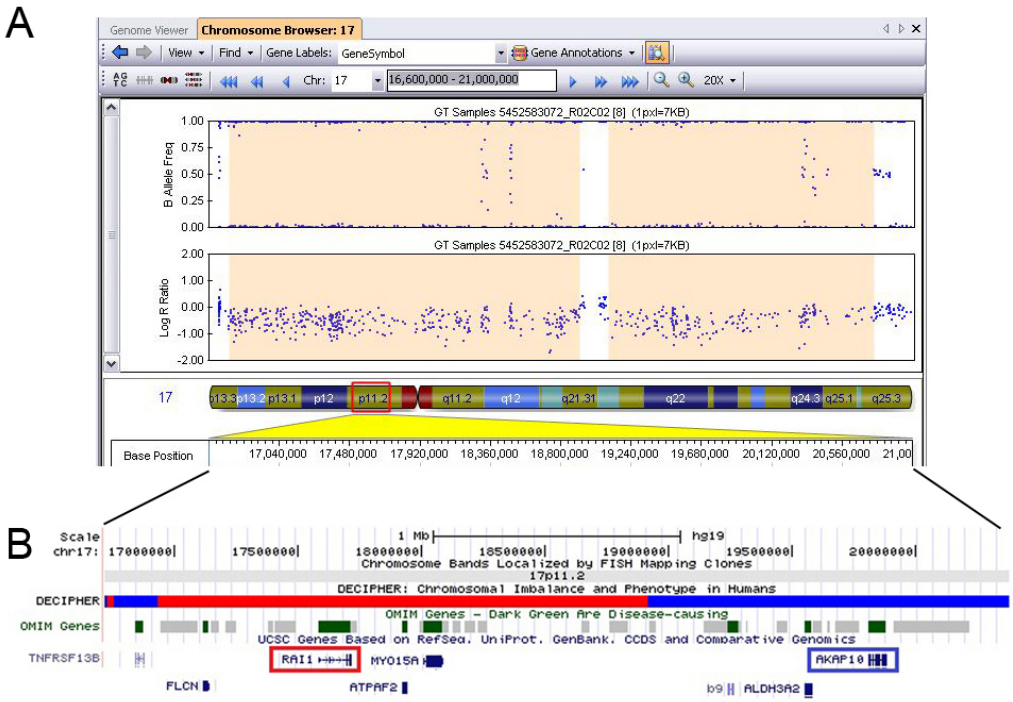

Figure 2. Human 660w-Quad SNP array result of 17p11.2 deletion in the proband. The above panel shows the region involved in cytogenetic bands 17p11.2. A *de novo* 3.7-Mb deletion on chromosome 17p11.2 (Chr17: 16720137-20378904) is identified (UCSC Genome Browser on Human GRCh37/hg19 Assembly). The lower panel shows the key annotated genes. *AKAP10* might be an interesting candidate gene for CHD.

DISCUSSION

We report here on an 8-year-old female with a *de novo* microdeletion of 3.7 Mb in 17p11.2. She had normal karyotype and presented clinical SMS-like syndrome phenotypes comprising several malformations, MR, CHD (tetralogy of Fallot), marked sleeping disturbance, and behavioral problems. By recent SNP array technology, this patient was finally diagnosed with SMS. To the best of our knowledge, she is the first reported SMS patient in China (mainland).

The phenotypes of SMS are characterized by neurological, developmental and behavioral problems (Elsea and Girirajan, 2008). While a wide phenotypic variability is observed in SMS patients, some patients show mild to moderate mental retardation, and some patients may not have typical facial features, cardiac, renal, and otolaryngologic abnormalities (Edelman et al., 2007). In developing countries, molecular approaches such as fluorescence *in situ* hybridization and microarray are limited (Gamba et al., 2011), and diagnosis is largely based on clinical recognition of the combination of these features, making accurate assessment and diagnosis of SMS difficult in children (Girirajan et al., 2006; Gropman et al., 2006). Another explanation for the difficulty in diagnosis is that SMS shares phenotypic features with other syndromes (Elsea and Girirajan, 2008). Sleep disturbance, MR, flat face, and cardiac defect are clinical suspicions in both SMS and 9q34 deletion syndrome (Kleefstra et al., 2009). Also, hearing loss, eating difficulties and MR are also frequently present in 22q11.2 deletion syndrome (Kobrynski and Sullivan, 2007). SMS also shares self-injurious, obsessive-compulsive behaviors and short stature with Prader-Willi syndrome (Cassidy and Driscoll, 2009). One additional explanation for the first report of SMS in China is that parents do not care about the molecular diagnosis of neurological diseases, especially those in the suburban and rural region of China (Shi and Jia, 2011).

Our patient showed a complex CHD (tetralogy of Fallot, atrium septum defect and patent duct artery). CHD are frequently present in the SMS patient (with an incidence of 37%) (Greenberg et al., 1996), including the first two patients reported in 1982 (Smith et al., 1982). Tetralogy of Fallot is rare and few patients have been described in previous reports (Sweeney et al., 1999; Wong et al., 2003). Other CHD such as ventricular/atrium septum defect, mitral valve prolapse/regurgitation, tricuspid valve stenosis/regurgitation, supravalvular pulmonary stenosis, and subvalvular aortic stenosis have also been reported to be associated with SMS (Greenberg et al., 1996; Myers and Challman, 2004).

The discordance between phenotypes of 17p11.2 deletion (containing the *RAI1* gene) and mutations within *RAI1* highlights the contribution of other gene(s) to some specific phenotypes of SMS (CHD, renal anomalies) (Girirajan et al., 2005; Elsea and Girirajan, 2008). Our findings also raise the question of related gene(s) for CHD in the 17p11.2 region. Fifty annotated genes, including *RAI1*, *MYO15A*, *AKAP10*, and *ALDH3A2* are found in this deletion region. AKAP10, a kinase anchor protein highly enriched in mitochondria, has been shown to modulate the sensitivity of cardiac pacemaker cells to sympathetic-vagal interactions at the sinus node in humans with cardiovascular diseases (Neumann et al., 2009). Mutations or deletions of *ALDH3A2*, which encode an enzyme that catalyzes the oxidation of fatty aldehyde to fatty acid, have been shown to cause an autosomal recessive disorder Sjogren-Larsson syndrome (Engelstad et al., 2011). *MYO15A* has been identified to be responsible for deafness (Kalay et al., 2007). However, due to the lack of molecular data and small sample size in previous studies, the precise gene(s) responsible for CHD in SMS is still unclear.

Given that SMS may not be well known to clinical cardiologists, our study will help the clinical recognition of SMS in China. Our study with high-resolution SNP array data and detailed phenotypes also provides one more piece of evidence for the identification of causative gene(s) for CHD in SMS. With the increased number of SMS cases diagnosed by recent molecular approaches, the causative gene for CHD in SMS should be uncovered in the near future, and hopefully our study may help with early diagnosis, genetic counseling and effective long-term management of SMS.

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Conflict of interest statement

The authors declare no conflict of interest.

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