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A 1.1 Mb deletion in distal 13q deletion syndrome region with congenital heart defect and postaxial polydactyly: Additional support for a CHD locus at distal 13q34 region

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ABSTRACT

13q deletion syndrome is a rare genetic disorder, especially for group 3 deletion (13q33–q34 deletion). Previously we described a patient with congenital heart defect and mental retardation and proposed that a distal 6 Mb region might contain the causative gene of congenital heart defect. Here we present a new patient with congenital heart defects (CHD), hand and foot anomalies and mild mental retardation. We identified a 1.1 Mb deletion at chromosome 13q34 with high resolution SNP-array BeadChips (HumanOmni1-Quad, Illumina, USA). This chromosome region contains ten annotated genes, including *GRK1*, *TFDP1*, *RASA3* and *GAS6*. To our knowledge, this represents the smallest 13q34 deletion identified to date. Our study provides additional support that distal 13q34 deletion region might contain key gene(s) responsible for cardiac development.
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1. Introduction

Congenital heart diseases (CHD) are the most common birth defects and affect appropriately seven per 1000 live births (Hoffman and Kaplan, 2002). CHD often occur as a sporadic presentation. A large proportion (about 10–15%, based on previous report and our own clinical observations) of patients present syndromic phenotypes with extracardiac malformations such as neurological disorders, cleft palate, ear malformation/hearing loss, hand and foot anomalies (Breckpot et al., 2010; Cooper et al., 2011). Previous genetic studies of CHD are largely focused on chromosomal disorders or gene mutations of Mendelian diseases. Recent advances in genome-wide microarrays, CGH-array (comparative genomic hybridization array) and SNP-array (single nucleotide polymorphism array), have significantly changed this situation (Greenway et al., 2009; Thienpont et al., 2007). Chromosomal microarrays have been suggested to be a first-tier clinical diagnostic tool for patients with multiple birth defects (Miller et al., 2010).

13q deletion syndrome is a rare genetic disorder, especially for group 3 deletion (13q33–q34 deletion) (Kirchhoff et al., 2009; Quelin et al., 2009; Walczak-Sztulpa et al., 2008). Previously we described a one-year-old female patient harboring a 12.75 Mb deletion at 13q33.1–q34 region with CHD, developmental delay and special facial features (Huang et al., 2012a). We suggested a critical region, the distal 6 Mb of 13q34, for CHD. Here we present a new case with CHD, hand and foot anomalies, and mild mental retardation. A 1.1 Mb deletion at distal 13q34 region was identified in this individual by a well-recognized SNP-array platform (BeadChips, Beadstation Scanner and GenomeStudio V2011, Illumina, San Diego, USA) (Luo et al., 2012a, 2012b).

2. Methods

The Review Board of the Second Xiangya Hospital of the Central South University has approved this research. Informed consent was obtained from parents of the affected patient.

2.1. Cytogenetic analysis

Chromosome analysis was performed on peripheral blood of the patient and his parents by conventional G-Banded techniques (550 bands resolution). 5 ml peripheral blood was collected for each individual. All samples were subjected to lymphocyte culture according to standard cytogenetic protocol.

2.2. DNA extraction

The genomic DNA was prepared from peripheral blood of the patient and the parents. Genomic DNA was prepared using a DNeasy

Abbreviations: CNV, copy number variation; CHD, congenital heart defects; SNP, single nucleotide polymorphism; CGH-array, comparative genomic hybridization array; PCR, polymerase chain reaction; IQ, Intelligence quotient; OMIM, Online Mendelian Inheritance in Man; Hg19, human genome 19; SA, single atrium; PPA, postaxial polydactyly; DGV, Database of Genomic Variants.

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Blood & Tissue Kit (Qiagen, Valencia, CA) on the QIAcube automated DNA extraction robot (Qiagen, Hiden, Germany).

2.3. SNP-array analysis

Genomic DNA samples of the patient and his parents were adjusted to a final concentration (50 ng/μl). The HumanOmni1-Quad Biochip (Illumina Inc., San Diego, USA) and the Illumina BeadScan genotyping system (Beadstation Scanner) were employed to obtain the signal intensities of SNP probes. HumanOmni1-Quad Beadchip contains over 1.1 million loci across the human genome (Pinto et al., 2011). The GenomeStudio V2011 software was used to analyze the genotypes (human genome build 37/Hg19 for analysis) and evaluate the experimental quality. The call rates of the samples are greater than 99.5%.

2.4. Quantitative PCR validation

For potentially pathogenic CNV, three primer sets were designed within the boundaries of the CNV region. Primer pairs were designed by an online PrimerQuest tool of Integrated DNA Technology (IDT) (http://www.idtdna.com/Primerquest/Home/Index). To validate variable copy numbers, real-time quantitative PCR (qPCR) were performed using the 7500 Fast Real-Time PCR systems (Applied Biosystems, Foster City, California). PCR reactions were prepared with the SYBR Premix Ex Taq II PCR reagent kit (TaKaRa Bio, Dalian, China) according to the manufacturer's protocol. Amplification levels were calculated with the $2^{-\Delta\Delta C_T}$ method.

2.5. Clinical description

The patient was the second child of healthy unrelated Chinese parents. The boy had a healthy sister. Family history of birth defects was absent. Birth weight was 3.100 kg (p50), length 45 cm (p25) with a head circumference of 33 cm (p25). Cardiac murmur and polydactyly on both hands and feet were observed. His developmental milestones were in the normal range.

At the age of 13 years, his weight was 31 kg (p25), height 1.49 m (p50). Facial features showed a high forehead with small and upslanting palpebral fissures (Fig. 1). There were multiple dispersed black-brown lentigines on the face. He had 24 digits fingers and toes, and also a pectus carinatum (Fig. 1). His IQ is 71. He had moderate intellectual disability which is predominant on the logistic side. He had normal language expression but with a very low score of mathematics test (score 4 compared to a language test score 50, with the maximum score was 100 points). He had behavior problems and was diagnosed with attention-deficit and hyperactivity disorder, and with frequent fits of anger.

He was referred to our department for cardiac surgery after a severe congenital heart defect had been observed in the fetus during a routine ultrasound examination. He was diagnosed with single atrium (SA) by two-dimensional color Doppler echocardiography. His cardiac defect was surgically repaired at our department of pediatric cardiac surgery.

3. Results

Chromosome analysis by G-banding at 550-band level showed an apparently normal karyotype (46 XY). However, SNP-array analysis revealed a distal deletion of 1.1 Mb in the 13q34 region from chr13: 113987623 to chr13: 115107157 (GRCh37/Hg19) (Fig. 2). A total of 10 Refseq genes are located in this deletion region (Table 1). Real-time Quantitative PCR (qPCR), performed on the trios (the proband and his parents) and a normal control individual, showed the deletion was de novo in the patient.

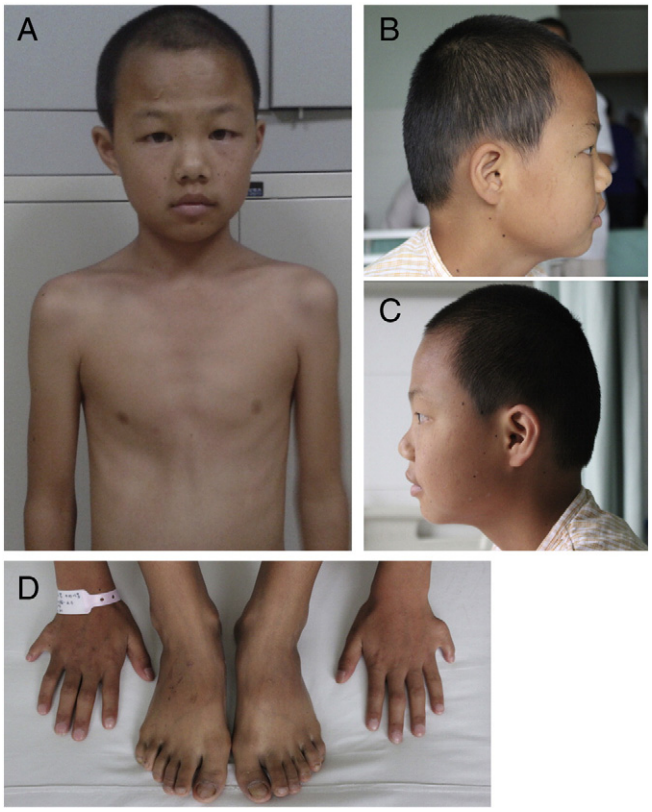

Fig. 1. Facial features of the proband (13 years old), frontal (A) and lateral (B, C) view of the patient. A: the patient has a round face, a high forehead with small and upslanting palpebral fissures, and multiple dispersed black-brown lentigines on the face. He also has a pectus carinatum. (D) polydactyly on both hands and feet (24 digits fingers and toes).

4. Discussion

This study reports the clinical and molecular findings in a patient with a pure de novo 1.1 Mb deletion in distal 13q34 region (chr13: 113987623–115107157) by SNP-array analysis. This result supports our previous suggestion that a causative gene in the distal 6 Mb region of 13q34 contributes for congenital heart defects (Huang et al., 2012a).

The de novo 1.1 Mb deletion in our proband covers a gene-rich region, and therefore is likely to be a pathogenic genomic imbalance. Ten annotated genes are located in this region, in which only one is an OMIM morbid gene that encodes the G protein-coupled receptor kinase 1(GRK1) (Table 1). GRK1 is associated with Oguchi disease type2 (OMIM: 613411), which is a rare autosomal recessive disease with stationary night blindness (Zhang et al., 2005). However, ophthalmic examination excludes the possibility of night blindness in our patient. To the best of our knowledge, no information is available in the literature regarding the pathological consequences (CHD) caused by these deleted genes.

More than 1700 genes have been estimated to play important roles in mouse cardiac development (Bentham and Bhattacharya, 2008), homologs of which might be candidate genes for CHD in humans. Through family-based linkage analyses and candidate gene approaches, a small number of these genes have been identified to carry mutations associated with CHD in humans. Most of these indentified genes encode transcription factors, contractile proteins and ligand-receptors (Wessels and Willems, 2010). Recent advances in next-generation sequencing and genomic microarrays have greatly facilitated the discovery of causative genes for cardiovascular diseases. One of the most recent examples is the identification of *TGFB2* for thoracic aortic aneurysm (Lindsay et al., 2012). Our study, together with previous reports of distal 13q deletion, will add a piece of evidence to explore the causative gene (s) for CHD.

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