



Short Communication

576 kb deletion in 1p36.33–p36.32 containing *SKI* is associated with limb malformation, congenital heart disease and epilepsyXin Zhu^a, Yi Zhang^a, Jian Wang^{b,c}, Jin-Fu Yang^{b,c}, Yi-Feng Yang^{b,c}, Zhi-Ping Tan^{b,c,*}^a Department of Gynecology and Obstetrics, Xiangya Hospital of Central South University, China^b Department of Cardiothoracic Surgery, the Second Xiangya Hospital of Central South University, China^c Clinical Center for Gene Diagnosis and Therapy of State Key Laboratory of Medical Genetics, the Second Xiangya Hospital of Central South University, Changsha, Hunan Province 410011, China

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ABSTRACT

1p36 deletion (monosomy 1p36) is one of the most common terminal deletions observed in humans, characterized by special facial features, mental retardation, heart defects, development delay and epilepsy. Previously, we reported molecular findings in patients with limb, congenital heart disease (CHD) and other malformations with SNP-array. In a syndromic patient of the same cohort, we detected a small deletion of 1p36.33–p36.32 containing *SKI* (Sloan–Kettering Institute protooncogene). Recently, dominant mutations in *SKI* were identified to be correlated with Shprintzen–Goldberg syndrome. Retrospective examination revealed this patient with limb malformations, CHD, epilepsy and mild development delay. Together with previous reports, our study suggests that the 1p36.33–1p36.32 deletion encompassing *SKI* may represents a previous undescribed microdeletion disorder.

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1. Introduction

1p36 deletion syndrome (monosomy 1p36) is the most common terminal deletion syndrome seen in humans. The main clinical findings of 1p36 deletion are typical craniofacial dysmorphism, developmental delay and mental retardation. Central nervous system malformations (88%), heart defects (71–75%), seizures (44–79%), skeletal anomalies (41%) and other features (e.g. vision problems, hearing loss) are also frequently observed in patients with 1p36 deletion syndrome (Battaglia et al., 2008; Bursztejn et al., 2009; Gajeccka et al., 2007; Heilstedt et al., 2003; Zenker et al., 2002). Because of variability in phenotypes, diversity in the sizes and positions of the deletion (Heilstedt et al., 2003), little genotype–phenotype correlations have been found among 1p36 deletion syndrome (Buck et al., 2011). This has led to the hypothesis that the 1p36 deletion syndrome may be constituted by different types of microdeletion disorders (terminal, interstitial or others) with variable causative gene(s) for specific phenotypic features (Heilstedt et al., 2003; Rosenfeld et al., 2010).

Malformations in limb and ear are clinically important because they facilitate the diagnosis of patients with multiple malformations

(Biesecker, 2011). In our clinical gene diagnosis center, we have genotyped a cohort of 206 patients with an Illumina SNP-array platform in CHD patients with limb, ear and other malformations (Chen et al., 2012; Luo et al., 2012). In a patient from the same cohort, we identified a small deletion of the 1p36.33–p36.32 region containing *SKI*, *PRKCZ* and *PEX10*. Because no information is available in the literature regarding the pathological consequences caused by these genes, we defined this genomic lesion as copy number variation (CNV) with unknown clinical importance. Recently, *SKI* (Sloan–Kettering Institute protooncogene) was identified as causative gene for Shprintzen–Goldberg syndrome (SGS, MIM 182212) (Carmignac et al., 2012; Doyle et al., 2012). Retrospective examination identified this patient with limb malformations, CHD, epilepsy and mild development delay.

We describe here a two-year old boy with multiple malformations and a 576 kb deletion in 1p36.33–p36.32 containing *SKI*. Clinical and genetic findings in all four patients (including this patient) with small 1p36.33–1p36.32 deletions were summarized.

2. Clinical report

The patient was first seen in the Department of Gynecology and Obstetrics of Xiangya Hospital. The baby boy was born to a normal and non-consanguineous Chinese parent. Family history of birth defects was absent. Vaginal bleeding occurred during the first 3 months of pregnancy and medical treatment was required. The patient was born by cesarean section at 40th week of gestation weighing 3,000 g (25th centile) and measuring 45 cm (25th centile) with a head circumference of 33 cm (25 centile). After birth, the patient was observed to have

Abbreviations: CNV, copy number variation; CHD, congenital heart defects; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; CT, computed tomography; OMIM, Online Mendelian Inheritance in Man; Hg19, human genome 19; ASD, atrial septal defect; DGV, Database of Genomic Variants; SGS, Shprintzen–Goldberg syndrome.

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cardiac murmurs and a hypoplastic thumb of left hand. Psychomotor milestones were mildly delayed, sitting without support at 10 months and walking independently at 18 months. Other related information was not remarkable.

At 2 years old, the patient was referred to our in-patient department for surgical treatment of cardiac defects. The boy was diagnosed with secundum atrial septal defect (ASD) by two-dimensional color Doppler echocardiography. The ASD was subsequently surgically repaired. Physical examination showed short stature with a height of 80 cm (3rd centile) and a weight of 12 kg (3rd centile). He had facial features including upslanting palpebral fissures, broad nasal tip, elongated philtrum, a pointed chin and a small mouth (Fig. 1.A). A hypoplastic thumb of left hand (with less function) and bilateral fifth finger clinodactyly were also observed. (Fig. 1.B). Epileptic seizures occurred in early childhood and he has been seizure-free for 6 months. A CT scan revealed slightly enlarged cerebral ventricles.

3. Methods

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

3.1. Cytogenetic analysis

Chromosome analysis was performed with the peripheral blood samples of the patient by conventional G-Banded techniques at the level of 550 bands. Five milliliters of peripheral blood was collected and subjected to lymphocyte culture according to standard cytogenetic protocol.

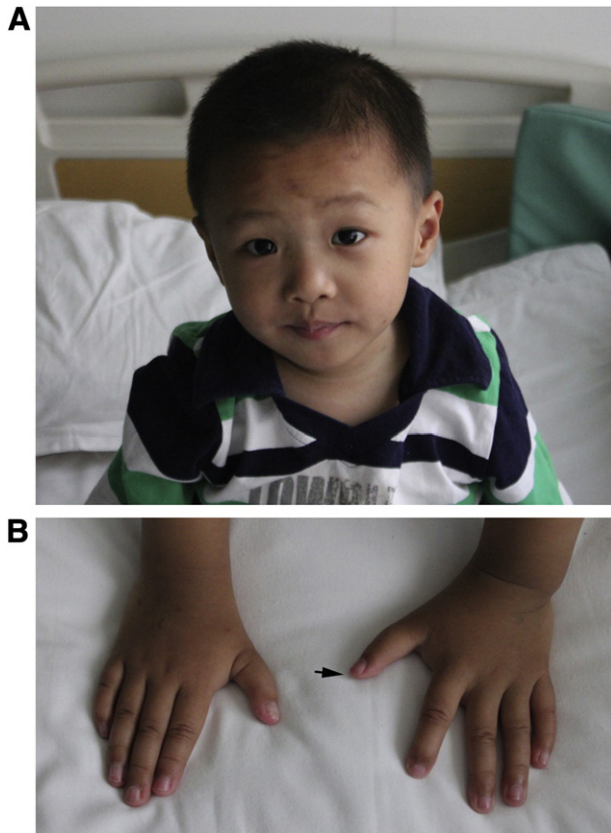


Fig. 1. Clinical features of the proband. (A) Upslanting palpebral fissures, broad nasal tip, elongated philtrum, a pointed chin and a small mouth. (B) A hypoplastic thumb of left hand with less function (arrow) and bilateral fifth finger clinodactyly.

3.2. DNA extraction

The parents of the patient gave written informed consent and genomic DNA was prepared from peripheral blood of the patient and his parents. Genomic DNA was prepared using a DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA) on the QIAcube automated DNA extraction robot (Qiagen, Hilden, Germany).

3.3. SNP array analysis

The Human660W-Quad Chip (Illumina Inc, San Diego, USA) and the Illumina BeadScan genotyping system (Beadstation Scanner) were employed to obtain the signal intensities of probes (SNP) following the manufacturer's instructions. The Illumina GenomeStudio V2011 and Illumina cnvPartition (V2.3.4) softwares were used to analyze the genotypes (human genome build 37/Hg19) and evaluate the experimental quality. The call rates of the samples are greater than 99.5%. We performed a family-based CNV validation with the PennCNV algorithm to obtain authentic CNVs.

3.4. Quantitative PCR validation

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). For potentially pathogenic CNV, two primer sets were designed within the boundaries of the CNV region. Primer pairs were designed by an online tool (PrimerQuest, IDT) (<http://www.idtdna.com/Primerquest/Home/Index>). 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 efficiencies were identical and the relative copy number was calculated with the $2^{-\Delta\Delta Ct}$ method (Livak and Schmittgen, 2001).

4. Results

Karyotype analysis of the patient was apparently normal. We hypothesized that copy number variations may contribute to the multiple birth defects of this boy and employed SNP-array analysis to identify such a change (Human660W-Quad Chip, Beadstation Scanner and GenomeStudio V2011 software). We identified a 576 kb deletion of 1p36.33–1p36.32 (chr1:2,045,453–2,622,423/Hg19), which includes *SKI*, *PRKCZ*, *PEX10* and *PLCH2* (Fig. 2). Real-time quantitative PCR (qPCR) with genomic DNA of the trios (the proband and his parents) confirmed this *de novo* deletion. We compared the clinical and genetic features of this patient with those patients carrying small deletions (<1 Mb) of 1p36.33–1p36.32 containing *SKI* (Table 1).

5. Discussion

Shprintzen–Goldberg syndrome (SGS, OMIM# 182212) is a rare autosomal-dominant disorder with a marfanoid habitus and neurological, cardiovascular and skeleton anomalies. SGS has been previously suspected to be associated with aberrant TGF- β signaling. In consistent with this suggestion, mutations in *FBN1* and *TGFBR2* have been detected in patients with phenotypes of SGS (Kosaki et al., 2006; Sood et al., 1996). Therefore, it is likely that SGS, Marfan syndrome and Loays–Dietz syndrome (LDS) share a similar pathogenesis. Recently, *SKI* (Sloan–Kettering Institute protooncogene) was found to underlie SGS by two independent groups with exome sequencing (Carmignac et al., 2012; Doyle et al., 2012).

SKI is a conserved protein and functions as a negative regulator of the TGF- β signaling (Luo, 2004). *SKI* locates at chromosome 1p36 and has been proposed to contribute for the phenotypes such as cleft lip/palate in 1p36 deletion syndrome (Colmenares et al., 2002). This hypothesis is also supported by the study of *ski* homozygous mutant

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