[Clinical Research]

7p22.1 microdeletions involving *ACTB* associated with developmental delay, short stature, and microcephaly

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ABSTRACT

There are no published reports of patients harboring microdeletions involving the 7p22.1 region. Although 7p22.1 microdeletions are rare, some reports have shown microduplications encompassing this region. In this study, we report five patients with overlapping deletions of the 7p22.1 region. The patients exhibited clinical similarities including non-specific developmental delay, short stature, microcephaly, and other distinctive features. The shortest region of overlap within the 7p22.1 region includes five genes, *FBXL18*, *ACTB*, *FSCN1*, *RNF216*, and *ZNF815P*. Of these genes, only *ACTB* is known to be associated with an autosomal dominant trait. Dominant negative mutations in *ACTB* are responsible for Baraitser-Winter syndrome 1. We analyzed *ACTB* expression in immortalized lymphocytes derived from one of the patients and found that it was reduced to approximately half that observed in controls. This indicates that *ACTB* expression is linearly correlated with the gene copy number. We suggest that haploinsufficiency of *ACTB* may be responsible for the clinical features of patients with 7p22.1 microdeletions.

Keywords: 7p22.1 microdeletion; the beta-actin gene (*ACTB*); Baraitser-Winter syndrome 1 (BRWS1); developmental delay; short stature; microcephaly

1. Introduction

Microdeletions involving the 7p21.1 region are responsible for Saethre-Chotzen syndrome due to mutations in the twist basic helix-loop-helix transcription factor 1 gene (*TWIST1*) [Shimada et al., 2013]. Recently, microdeletions of 7p22.3, the more telomeric region of 7p, have been reported in association with tetralogy of Fallot [Richards et al., 2011]. Haploinsufficiency of the sorting nexin 8 gene (*SNX8*), located on 7p22.3, is considered a potential candidate for tetralogy of Fallot; however, this remains controversial [Rendu et al., 2014]. In comparison with both the 7p21.1 and 7p22.3 region, microdeletions involving the 7p22.1 region, located between them, are rare [Gallego et al., 2010].

Here, we undertook an international collaboration to complete a genotype-phenotype correlation study of microdeletions involving the 7p22.1 region.

2. MATERIALS AND METHODS

2.1. Materials

This study was performed in accordance with the Declaration of Helsinki principles and with approval from the ethics committee of the institutions involved. Blood samples were obtained from five patients, and their parents, after receiving written informed consent. Patients 4 and 5 were identical twins. DNA was extracted from blood samples and used for laboratory examinations. Metaphase spreads were prepared from peripheral blood lymphocytes and used for fluorescence *in situ* hybridization (FISH) analyses.

2.2. Molecular and cytogenetic analysis

Genomic copy number variations were identified using various microarray platforms. For patients 1, 4, and 5, we used the Agilent 60K Human Genome CGH Microarray platform (Agilent Technologies, Santa Clara, CA). For patient 2, we used the Bluegenome ISCA 60k design oligo array (Illumina, San Diego, CA). For patient 3, we used the 180K oligonucleotide array (Agilent Technologies).

FISH analysis was performed to confirm the microarray results observed for patient 1. Human bacterial artificial chromosomes, RP11-237F7 (7p22.1:5,391,013–5,552,776) and RP11-645N11 (7q22.1:102,564,448–102,720,289), were selected from the UCSC genome browser (<https://genome.ucsc.edu/>) for usage as probes. In this study, genomic positions were referred to GRCh37/hg19.

All data was uploaded onto the DECIPHER web-based database (<http://decipher.sanger.ac.uk/>) to allow collaboration between institutions and help identify new syndromes.

2.3. Gene expression study

Total RNAs were extracted from immortalized lymphoblasts of patient 1 and four unrelated control samples, derived from volunteers. Quantification of the beta-actin (*ACTB*) expression levels was performed using SYBR Green real-time PCR, and primers, as described previously [Filges et al., 2011]. *ACTB* expression levels were measured in three independent replicates using MX3000P (Agilent Technologies). Expression of the glyceraldehyde-3-phosphate dehydrogenase gene (*GAPDH*) was used as an internal control. Data was evaluated using the Delta Delta Ct method [Filges et al., 2011].

3. Results

3.1. Patient report

Patient 1 (DECIPHER #286782, from Japan), was a male born at 31 weeks gestation by emergency Caesarian section because of threatening premature delivery due to fetal distress. His mother was healthy during pregnancy but the infant showed intra-uterine growth retardation. Weight at birth was 946 g (<3rd centile) and Apgar score was 6 and 8 at 1 and 5 min, respectively. The proband has two healthy brothers. There was no family history of neuromuscular diseases. Due to respiratory failure, he required intubation and artificial ventilation. He was discharged from the hospital 73 days after birth (41 weeks and 1 day gestation corrected). Before discharge, brain magnetic resonance imaging was examined and no abnormalities were identified. He was breastfed and exhibited normal sucking; however, he failed to thrive. At age 2 years and 2 months (2 years corrected), his height was 74.8 cm (<3rd centile), weight was 8.7 kg (<3rd centile), and he had an occipitofrontal circumference of 44.3 cm (<3rd centile). His psychomotor development was mildly delayed with a developmental quotient of 68 on the Kyoto Scale of Psychological Development. He showed distinctive facial features with frontal bossing, sparse eyebrows, long eyelashes, hypertelorism, low-set ears, long philtrum, thin lips, right inguinal hernia, and undescended testes (Fig. 1A). Ptosis, which is characteristic of Baraitser-Winter syndrome 1 (BRWS1: MIM#243310), was not exhibited. Abdominal ultrasonographic examinations showed no visceral abnormalities and no abnormalities were observed following routine laboratory examinations. Conventional G-banding showed a normal male karyotype of 46,XY.

Patient 2 (DECIPHER #274371, from Australia) was a 19-year-old male, who showed moderate intellectual disability, short stature (10th-25th centile), obesity (95th

centile), Pierre-Robin syndrome, and gastroesophageal reflux. He exhibited distinctive features, including scaphocephaly, low posterior hairline, prominent eyes, long eyelashes, downslanting eyebrows, mid face hypoplasia, high palate, transverse right palmar crease and pectus excavatum.

Patient 3 (DECIPHER #253773, from Belgium) was a male born at 34 weeks gestation, with a birth weight of 1720g. He showed severe feeding problems with failure to thrive after birth. He also exhibited developmental delay due to axial hypotonia, short stature, and microcephaly. Bilateral radial abnormalities and inguinal hernia were noted. Distinctive features included midfacial hypoplasia and a small chin.

Patient 4 (DECIPHER #264408, from France) and patient 5 are twin sisters born at 26 weeks gestation with birth weights of 430 g and 840 g, respectively. They exhibited global developmental delay and growth delay, short stature, microcephaly, and failure to thrive. The 7p22.1 deletion was inherited from their mother, who suffered mild intellectual disability. In addition, both siblings were found to harbor an unbalanced translocation, der(14)t(14;16)(p13;q24), inherited from their father who carried a balanced translocation t(14;16). Therefore, the clinical features of both siblings result from the presence of both the 16q24 duplication and the 7p22.1 deletion.

The clinical information was briefly summarized in Table 1.

3.2. Genomic copy number aberration

The data obtained from the five patients are depicted in Fig. 2. Patient 1 was found to have a 1.5 Mb deletion in the loci 7p22.2p22.1, indicated the molecular karyotype of arr 7p22.2p22.1(4,374,018-5,864,851)×1. Subsequent FISH analysis confirmed the deletion (Fig. 1B). Neither parent showed a deletion of this region,

indicating that this deletion occurred *de novo* (data not shown). Patients 2 and 3 showed *de novo* deletions involving chr7:5,151,474-6,296,948 and chr7:5,370,746-6,781,213, respectively. Patients 4 and 5, and their mother, shared a deletion involving chr7:5,492,967-5,864,851. Patients 4 and 5 also showed a duplication of chr16:88,335,976-90,111,263 due to a paternally derived unbalanced translocation.

3.3. *ACTB* gene expression level

The *ACTB* expression ratio (patient 1 versus normal controls) was calculated for each of the three replicates and the averages are shown in Fig. 3. This result suggests that the expression level of *ACTB* in patient 1 is approximately half of that observed in controls.

4. Discussion

There are reports of patients with large 7p deletions, identified by conventional karyotyping, which include the 7p22.2p22.1 region [Schomig-Spangler et al., 1986; Speleman et al., 1989]. It is difficult to identify genotype-phenotype correlations due to the number of genes in these deleted regions. Only one report in the literature has identified the 7p22.2p22.1 microdeletion by microarray testing [Gallego et al., 2010], and this 5.5 Mb deletion expanded largely to the 7p22.2 region (Fig. 1). Here, we have successfully used the DECIPHER database to consolidate genotype-phenotype data of five patients, from four unrelated families, with overlapping 7p22.1 microdeletions (Fig. 1, Table 1). Most of the affected individuals showed non-specific developmental delay, short stature, and microcephaly. The deletion identified in patients 4 and 5 represented the shortest region of overlap (SRO). The SRO reduced the number of genes potentially

responsible for the **observed** clinical features **to five**: the F-box and leucine-rich repeat protein 18 gene (*FBLX18*), *ACTB*, the actin-bundling protein fascin homolog 1 gene (*FSCN1*), the ring finger protein 216 gene (*RNF216*), and the zinc finger protein 815 pseudogene (*ZNF815P*) (Fig. 2, Table 2).

Of the five genes in the SRO, *RNF216* and *ACTB* are implicated in human disorders and are registered in the Online Mendelian Inheritance in Man database (OMIM: <http://omim.org/>). The functional relevance of the remaining three genes is unknown. *RNF216* is implicated in Gordon Holmes syndrome (MIM#212840). Gordon Holmes syndrome is an adult-onset neurodegenerative disorder characterized by progressive cognitive decline, dementia, and variable movement disorders, such as ataxia and chorea [Margolin et al., 2013]. However, Gordon Holmes syndrome is an autosomal recessive disorder and individuals with heterozygous *RNF216* mutations show no clinical features. Whereas, heterozygous *ACTB* mutations have been reported in patients with neurological disorders, twin patients with juvenile-onset dystonia, and a patient with intellectual disability and short stature [Nunoi et al., 1999; Procaccio et al., 2006]. More recently, *ACTB* mutations are thought to be responsible for BRWS1, which is characterized by severe developmental delay, distinctive craniofacial features including hypertelorism and ptosis, and other congenital anomalies [Riviere et al., 2012]. Post-natal short stature and microcephaly, in association with brain anomalies, are also characteristic. Since the first identification of the *ACTB* mutations in patients with BRWS1 [Riviere et al., 2012], several *de novo* heterozygous *ACTB* mutations have been reported in patients with BRWS1 [Johnston et al., 2013; Di Donato et al., 2014]. All reported mutations identified in patients with BRWS1 are considered to have dominant negative effects. Loss-of-function mutations, including nonsense mutations and

truncation mutations, have not been reported in patients with BRWS1. In mice, homozygous deletions of *Actb* (*Actb*^{-/-}) are embryonically lethal and heterozygous deletions (*Actb*^{+/-}) do not show any phenotype [Shawlot et al., 1998]. Therefore, there is no direct evidence to suggest that *ACTB* haploinsufficiency is related to human disorders.

The SET binding protein 1 gene (*SETBP1*) is responsible for Schinzel-Giedion syndrome (SGS; MIM#269150). SGS is characterized by severe developmental delay, distinctive facial features, and multiple congenital malformations including skeletal abnormalities, genitourinary and renal malformations, and cardiac defects [Hoischen et al., 2010]. All *SETBP1* mutations identified in patients with SGS are considered to have a dominant-negative effect, similar to *ACTB* mutations identified in BRWS1. Previously, we reported microdeletions involving *SETBP1* in patients with non-specific language developmental delay [Filges et al., 2011]. Loss-of-function of *SETBP1*, resulting from haploinsufficiency, caused clinical manifestations similar to, but different from, SGS. It therefore follows that loss-of-function, or haploinsufficiency, of *ACTB* may have similar, but different, phenotypic consequences as dominant negative mutations.

Although there are no reports of patients with microdeletions involving the 7p22.1 region, microduplications in this region have been reported [Papadopoulou et al., 2006; Chui et al., 2011; Preiksaitiene et al., 2012; Pebrel-Richard et al., 2014; Caselli et al., 2015; Goitia et al., 2015]. Most patients with 7p22.1 microduplications show non-specific developmental delay and craniofacial abnormalities. Genotype-phenotype correlation studies of 7p22.1 microduplications have suggested *ACTB* as a strong candidate gene for craniofacial development [Preiksaitiene et al., 2012; Pebrel-Richard et al., 2014; Caselli et al., 2015; Goitia et al., 2015].

ACTB is a housekeeping gene and is often used as an internal control in gene expression studies. *ACTB* expression levels in patient 1 lymphocytes were found to be half of that observed in the controls (Fig. 3). These expression studies confirm that expression levels of *ACTB* are linearly correlated with the *ACTB* gene copy number.

In this study, we have identified 7p22.1 microdeletions in five patients presenting with developmental delay, short stature, and microcephaly. Through genotype-phenotype correlation analysis, we suggest that haploinsufficiency of *ACTB* may be responsible for the clinical features of patients with 7p22.1 microdeletions.

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Figure legends

Fig. 1. Genome map surrounding the 7p22.2p22.1 region. Previously reported chromosomal aberrations in this region and the aberrations reported in this manuscript are depicted (deletions in red and duplications in blue). The UCSC genes are shown in black rectangles. The shortest region of overlap (SRO) is constructed by patient 1 (DECIPHER #286782) and patient 4 (DECIPHER #264408).

Fig. 2. Clinical information of patient 1. (A) Patient 1 manifests some minor facial characteristics including sparse eyebrows, low-set ears, long philtrum, and thin lips. (B) Fluorescence *in-situ* hybridization (FISH) analysis confirms a 7p22.1 deletion. A single green signal labelled on RP11-237F7 (chr7:5391013-5552776) [7p22.1] indicates a deletion (a white arrow) of this region. Red signals labelled on RP11-645N11 (chr7:102,564,448-102,720,289) [7q22.1] are the marker.

Fig. 3. The result of *ACTB* expression studies. *ACTB* expression in patient 1 (P) is defined as “1.” Relative expression levels in four control individuals (C1-4) are presented. *ACTB* expression in patient 1 (P1) was less than half that observed in control individuals (C1-4).

Table 1. Summary of the patients’ clinical information in association with microdeletions/microduplications involving the 7p22.1 region

Table 2. The list of the genes included in the smallest region of overlap (SRO)

Figure 1

Figure 2

Figure 3

Table 1. Summary of the patients' clinical information in association with microdeletions/microduplications involving the 7p22.1 region

	Gender	Age	Birth weight	Developmental delay		Short stature		Microcephaly	Origin of 7p22.1 deletion/duplication	
Deletions										
Gallego <i>et al.</i> (2010)	M	7m	NA	+	-	63 cm	(10~25th cetile)	+	(<5th centile)	familial
Patient 1 (#286782)	M	1y	946 g (31WG)	+	+	61.7 cm		+	(<3rd centile)	<i>de novo</i>
Patient 2 (#274371)	M	19y	1900 g (34WG)	+	moderate		(10th cetile)	-	(90th centile)	<i>de novo</i>
Patient 3 (#253773)	M	1y	1720 g (34WG)	+			(<3rd centile)	+	(<3rd centile)	<i>de novo</i>
Patient 4 (#264408) twin sister I	F	NA	430 g (26WG)	+				+		familial
Patient 5 twin sister II	F	NA	840 g (26WG)	+				+		familial
The mother of patient 4 and 5	F	NA		+				+		familial
Duplications										
Papadopoulou <i>et al.</i> (2006)	F	9m	1700 g	+	-	66.5 cm	(25th centile)	+	(3rd centile)	<i>de novo</i>
Zahed <i>et ak.</i> (2007)	M	18m	2900 g	+	-	79 cm	(25th centile)	-	(50th centile)	<i>de novo</i>
Chui <i>et al.</i> (2011)	M	28m	3315 g	+	-	NA	(50th centile)	-	(95th centile)	<i>de novo</i>
Preiksaitiene <i>et al.</i> (2012)	F	14.5y	4200 g	+	IQ=64	172 cm	(90th centile)	-	(>97th centile)	<i>de novo</i>
Pebrel-Richard <i>et al.</i> (2014)	M	3y	3390 g	+	-	96 cm	(50th centile)	-	(50th centile)	<i>de novo</i>
Goitia <i>et al.</i> (2015)	M	29m	3528 g	+	-	NA		-		unknown
Caselli <i>et al.</i> (2015)	M	34y	3100 g	+	-	WNL		-		unknown

#, DECIPHER database ID; M, male; F, female; m, months; y, years; NA, not available; WG, weeks of gestation; WNL, within normal limit

Table 2. The list of the genes in the shortest region overlap

Gene symbol	Functions	Genomic positions*	Disease	MIM ID	Inheritance
<i>FBXL18</i>	F-box and leucine-rich repeat protein 18	5,515,428-5,553,399			
<i>ACTB</i>	actin, beta	5,566,779-5,570,232	Baraitser-Winter syndrome-1 (BRWS1)	#243310	AD
<i>FSCN1</i>	fascin homolog 1, actin-bundling protein (Strongylocentrotus purpuratus)	5,632,436-5,646,287			
<i>RNF216</i>	ring finger protein 216	5,659,672-5,821,361	Cerebellar ataxia and hypogonadotropic hypogonadism	#212840	AR
<i>ZNF815P</i>	zinc finger protein 815, pseudogene	5,862,791-5,894,066			

*, genomic positions are referred to Ghhg19; AR, autosomal recessive; AD, autosomal dominant