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[Total word counts: 3589]

【Original Article】

Genotype-phenotype correlation in six patients with interstitial deletions spanning 13q31

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Abstract

Objective: Since the gene responsible for neurodevelopmental delay observed in patients with chromosomal microdeletions involving the 13q31 region has never been identified, we aimed to narrow the candidate genes.

Methods: Analysis of genomic copy number variations was performed as a part of the diagnostic workflow for six patients with neurodevelopmental disorders. Detailed clinical information was collected for each patient carrying a 13q31 deletion. Then, genotype-phenotype correlation analysis was carried out.

Results: Genotype-phenotypic correlation analysis excluded regions that were not considered disease-related and focused on the shortest region overlapped between three patients (chr13:75691448_83625667). Among the genes included in this region, *MYCBP2* showed a pLI score of "1", suggesting haploinsufficiency intolerance, and was therefore considered as one of the possible candidate genes for neurodevelopmental delay.

Conclusions: There is little information on chromosomal microdeletions involving the 13q31 region, and more information should be accumulated to better understand the genomic contribution of this region.

Keywords: chromosomal microarray testing, genomic copy number variation, Hirschsprung disease, loss-of-function intolerant

Introduction

Some parts of chromosome 13 display characteristic features. In 1993, Brown et al. reported a clinical case series of patients with 13q microdeletions, and proposed the classification of 13q microdeletions into three groups [1, 2]. Group 1: patients with proximal deletions not extending into q32, associated with mild or moderate delays in development, with no major anomalies. Group 2: patients with distal deletions, including q32, associated with severe delays in development and major malformations. Group 3: patients with subtelomeric deletions in 13q, associated with severe delays in development, but no major anomalies. The Zic family member 2 gene (*ZIC2*) located on 13q32.3 was later confirmed to be the gene responsible for the main clinical features of group 2, in association with holoprosencephaly [3, 4]. Apart from these classifications, deletions in the 13q14 region are associated with retinoblastoma, because the retinoblastoma 1 gene (*RB1*) responsible for this phenotype is located in this region, and *RB1* haploinsufficiency is causative of retinoblastoma [5, 6].

Among these subgroups, patients with deletions classified as Groups 1 are rare, and the clinical features are not yet well established [7-10]. In this study, we aimed to clarify the clinical features of patients with microdeletions involving the 13q31 region, and narrow the possible candidate genes for neurodevelopmental delay observed in patients with deletions involving the 13q31 region.

I Materials and methods

Analysis of genomic copy number variations (CNVs) was performed as a part of the diagnostic workflow for patients with neurodevelopmental disorders. This study was performed in accordance with the Declaration of Helsinki, and was approved by the

79 ethics committee of this institution. After receiving written informed consent from
80 patients and their families, we obtained blood samples from the patients, and from their
81 parents when necessary. In this study, genomic copy number analyses were first
82 performed for patients with neurodevelopmental abnormalities of unknown etiology, in
83 accordance with a previously described study [11]. Patients with chromosomal
84 microdeletions involving the 13q31 region were included in this analysis. Detailed
85 clinical information was collected for each patient carrying a 13q31 deletion. Then,
86 genotype-phenotype correlation analysis was carried out.
87 Genomic positions of CNVs are reported according to the GRCh37/hg19 genome
88 build.
89
90 **II Results**
91 **1. Chromosomal deletions**
92 We identified six deletions that included the 13q31 region (Figure 1). Genomic
93 positions of the deletions are summarized in Table 1. Because the parents of patient 3
94 showed no deletion, the deletion identified in patient 3 was confirmed to be de novo.
95 The deletion identified in patient 6 was inherited from his healthy father, indicating that
96 this deletion was not pathogenic, as reported previously [11]. The parents of the other
97 patients declined to be genotyped.
98 **2. Clinical features of patients with microdeletions involving 13q31 region**
99 Clinical information on the patients with microdeletions in the 13q31 region is
100 summarized in Table 1. The details are described below.
101 A 3-month-old girl (patient 1) was born at term. At birth, the patient was unable to
102 cry. Because vocal cord paralysis was detected by fiberscope, respiratory management

103 was performed after intubation. Although no clinical findings were suggestive of
104 Hirschsprung disease, weak pigmentation was noted in her iris. She required tube
105 feeding and showed early developmental delay. After tracheostomy, the patient was
106 discharged from the hospital.

107 A 4 -year-old boy (patient 2) was born at term with normal delivery. At 4 years of
108 age, the patient was examined due to deficient growth, with a height of 88.3 cm (-3.6
109 SD), a weight of 11.1 kg (-2.6 SD), and an occipitofrontal circumference (OFC) of 47.2
110 cm (-1.9 SD). However, his growth hormone levels were within normal limits. His
111 development was moderately delayed. He could speak words, but no sentences. He had
112 low-set ears, and micrognathia. No findings were suggestive of Hirschsprung disease or
113 Waardenburg syndrome.

114 An 11-month-old boy (patient 3) was born at term by normal delivery. Mild right
115 ear deafness (40 dB) and moderate left ear deafness (70 dB) were detected soon after
116 birth, although there was no family history of deafness. The patient showed abnormal
117 pigmentation in his iris, with gray, radial, and sparse pigmentation. A slightly large
118 auricle, wide nasal ala, and decreased muscle tonus (hyperactivity, positive heel-ear
119 sign) were noted. His psychomotor development level was diagnosed as borderline,
120 because he could not move with crawling. At the time of his last hospital visit, his
121 height was 66.0 cm (-1.9 SD), his weight was 7.2 kg (-1.4 SD), and his OFC was 42.0
122 cm (-2.1 SD), indicating microcephaly.

123 An 11-year-11-month-old girl (patient 4) was born at 39 weeks of gestation by
124 normal delivery. Her birth weight was 2,284 g (-1.8 SD). Congenital hip dysplasia was
125 noted during infancy. She showed a mild delay in psychomotor development. At the age
126 of 11 years, her height was 136.0 cm (-2.1 SD), her weight was 40.7 kg (standard), and

her OFC was 51.7 cm (-0.8 SD), indicating growth deficiency. Her intelligence quotient was evaluated as 60 using the Wechsler Intelligence Scale for Children™-IV. She underwent precocious puberty, and experienced overactive bladder. Distinctive features were not observed.

An 18-month-old girl (patient 5) was born at 39 weeks and 2 days of gestation, with a birth weight of 2,114 g (-2.4 SD), a birth length of 44.5 cm (-2.2 SD), and an OFC of 33.5 cm (mean). Her mother had no history of miscarriage (she was the first child). Lateral ventricular enlargement was observed by fetal ultrasonography. Brain MRI revealed middle interhemispheric variant of holoprosencephaly [12]. Distinctive features included narrow palpebral fissures, low-set ears, and a flattened back of the nose. At her last visit, she could roll over but could not sit. She could not speak meaningful words. Her length was 74.3 cm (-1.9 SD), her weight was 8.4 kg (-1.5 SD), and her OFC was 40 cm (-4.3 SD), indicating microcephaly.

A 9-year-old boy (patient 6) was born at 38 weeks of gestation by cesarean section due to fetal head position and pelvic imbalance. Birth weight was 2,556 g (-0.8 SD), birth length was 49 cm (+0.5 SD), and OFC at birth was 33 cm (mean). At present, his height is 112.1 cm (-4.0 SD), his weight is 19.4 kg (-1.8 SD), and his OFC is 51.0 cm (-1.3 SD), indicating growth delay. Owing to hypothyroidism, he has been prescribed thyroxine. His motor development was delayed, with head control achieved at 6 months of age, sitting at 14 months, and walking at 30 months. He forms no meaningful words, and displays the most severe intellectual disability. Owing to poor eye contact, autistic traits were also diagnosed. He can walk, but with an ataxic gait. He demonstrates distinctive features, including a constant happy and smiling face, strabismus, a high forehead, a high and broad nasal bridge, and a protruding tongue. Owing to intractable

epilepsy, he has been prescribed anti-epileptic drugs. He requires support for his daily life. Comprehensive genomic analysis detected a nonsense variant in the lysine (K)-specific demethylase 5C gene (*KDM5C*) located on the X-chromosome, which was inherited from his carrier mother. Details of this variant have been reported previously [13].

Ⅲ Discussion

The six chromosomal deletions including 13q31 band identified in this study were initially classified as "group 1" according to the classification scheme proposed by Brown et al. [1]. Patient 3 showed congenital deafness and abnormal iris pigmentation. Because the deletion identified in patient 3 included the endothelin receptor type B gene (*EDNRB*), he was considered to have clinical features of Waardenburg syndrome type 4A (MIM # 277580) [14]. The deletions identified in patients 1 and 2 also had microdeletions that included *EDNRB*. Patient 1 showed weak pigmentation of the iris, while patient 3 did not. These findings can be explained by variable expressions or incomplete penetrance of the clinical features [15]. Although patients with Waardenburg syndrome often also have Hirschsprung disease, patients 1-3 whose deletions included *EDRNB* displayed no clinical features of Hirschsprung disease. Puffenberger et al. suggested that the chance of developing Hirschsprung disease was 74% in homozygotes and 21% in heterozygotes [16]. Because *EDRNB* does not correlate with developmental delay, we considered that other candidate gene(s) would exist in this region.

Regarding genotype-phenotype correlation in other patients, only the deletion identified in patient 5 extended to the 13q32.3 region, involving *ZIC2* within the deletion region. This is why patient 5 showed holoprosencephaly and severe

developmental delay. Thus, this deletion may be classified as "group 2" rather than "group 1." Patient 6 had a small deletion in 13q31, which was inherited from his healthy father, indicating that the deletion identified in patient 6 was not responsible for his clinical features. Rather, patient 6 had a *KDM5C* mutation inherited from his mother, which could explain his clinical features. This finding gave us the important insight that haploinsufficiency of the genes included in the deletion identified in patient 6 would not underly clinical features such as neurodevelopmental delay. Jia et al. reported a similar small deletion in a healthy mother and child [17]. Thus, this region should also be excluded from the possible critical region for neurodevelopmental delay (Figure 1).

Valdes-Miranda et al. reported a microdeletion involving 13q31.3-q32.1, identified in an individual with normal intelligence [18]. This entire deletion was included in the deletion in patient 4, narrowing the critical region for developmental delay to the distal region of patient 4's deletion. This region includes six genes (*PGC5*, *GPC6*, *DCT*, *TGDC*, *GPR180*, and *SOX21*), but none of them display a clear association with the neurodevelopmental delay observed in patient 4.

Previously, Poreau et al. reported a fetus with a 13q31 deletion. Because the fetus was aborted, it is unknown whether this deletion was associated to neurodevelopmental delay [19]. As an alternative strategy, they analyzed the data included in DECIPHER database (https://www.deciphergenomics.org/). DECIPHER #256224 (chr13:79728762-79945691) showed language delay, but the identified microdeletion was inherited from the healthy parent. This small deletion encompasses only the RNA binding motif protein 26 gene (*RBM26*), suggesting that haploinsufficiency of *RBM26* is likely benign and not responsible for neurodevelopmental delay. DECIPHER #268351 (chr13:79568105-80247708) showed language delay, and the identified microdeletion was inherited from

199 a parent with a similar phenotype. Thus, a contribution of this deletion region to the
200 clinical phenotype cannot be ruled out.
201 The result of the above discussion for genomic regions for neurodevelopmental
202 delay narrowed the shortest region of overlapped (SRO) among patients 1-3 into
203 (chr13:75691448_83625667) (Figure 1). Table 2 lists the genes included in the SRO and
204 describes their relationships to their functions and phenotypes. Among them, the F-box
205 and leucine-rich repeat protein 3 gene (*FBXL3*) is the only gene related to intellectual
206 development, and mutations are associated with short stature, facial anomalies, and
207 speech defects (MIM #606220). However, this condition displays autosomal recessive
208 inheritance [20]. Thus, haploinsufficiency of *FBXL3* would not be related to
209 neurodevelopmental delay observed in patients with microdeletions in this region.
210 In the genes included in the SRO, only *MYCBP2* and *RBM26* show the probability
211 of loss-of-function intolerance (pLI) score of "1" according to the gnomAD browser
212 (https://gnomad.broadinstitute.org/). This indicates that loss-of-function of these genes
213 may not be tolerated. The function of the RNA binding motif protein 26 (*RBM26*) is
214 unknown but the MYC binding protein 2 E3 ubiquitin protein ligase gene (*MYCBP2*)
215 may be related to neurodevelopmental delay, because *MYCBP2* regulates neuronal
216 functions [21]. Thus, *MYCBP2* haploinsufficiency may correlate with
217 neurodevelopmental delay observed in patients 1-3.
218 In conclusion, we identified six microdeletions that include 13q31. Some regions
219 were excluded from possible candidacy for neurodevelopmental delay. Because three
220 patients (patients 1-3) with microdeletions including the proximal 13q31 region showed
221 mild to moderate delay, some of the genes included in this deletion region are likely
222 related to neurodevelopment. Distinctive features commonly observed in reported

patients were not detected.

We appreciate the cooperation of the patients and their families for this study. This work was supported by JSPS KAKENHI JP18K07803, a grant from Health, Labour and Welfare Sciences Research from MHLW Japan, and Initiative on Rare and Undiagnosed Diseases (grant number 20ek0109301) from the Japan Agency for Medical Research and Development (AMED).

Conflict of interest

All authors have no conflict of interest.

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Figure legends

Table 1: Clinical features of the patients in this study

m, months; y, years; NT, not tested; w, weeks; d, days; NA, not available

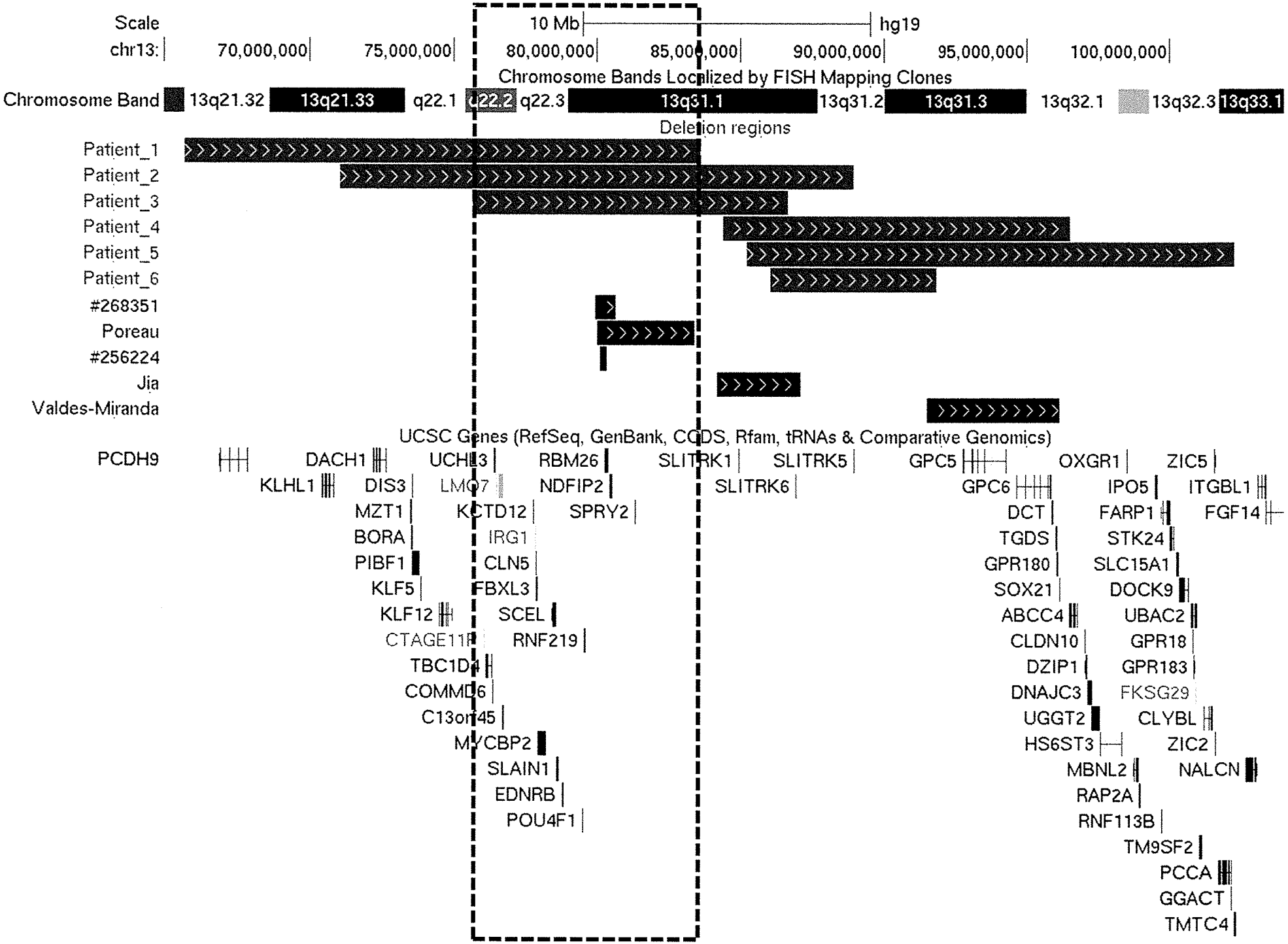
Table 2: List of the genes located on the possible candidate region

pLI, probability of loss-of-function intolerance; MIM, mendelian inheritance in man; AR, autosomal recessive; AD, autosomal dominant

Figure 1: Genome map of the region surrounding 13q31

Identified microdeletions are depicted on the genome map created by the UCSC genome browser (https://www.genome.ucsc.edu/) using a custom track in accordance with GRCh37/hg19. Grey and black bars with white arrow heads inside indicate deletions identified in this study and the previously reported deletion (DECIPHER data are also included), respectively. A translucent box shown by a black dotted line indicates the shortest region overlapped discussed in the text.

図


Scale
10 Mb
hg19
chr13:
70,000,000
75,000,000
80,000,000
85,000,000
90,000,000
95,000,000
100,000,000
Chromosome Bands Localized by FISH Mapping Clones
Chromosome Band
13q21.32
13q21.33
q22.1
q22.2
q22.3
13q31.1
13q31.2
13q31.3
13q32.1
13q32.3
13q33.1
Deletion regions
Patient_1
Patient_2
Patient_3
Patient_4
Patient_5
Patient_6
#268351
Poreau
#256224
Jia
Valdes-Miranda
UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)
PCDH9
DACH1
UCHL3
RBM26
SLITRK1
SLITRK5
GPC5
OXGR1
ZIC5
KLHL1
DIS3
LMO7
NDFIP2
SLITRK6
GPC6
IPO5
ITGBL1
MZT1
KCTD12
SPRY2
DCT
FARP1
FGF14
BORA
IRG1
TGDS
STK24
PIBF1
CLN5
GPR180
SLC15A1
KLF5
FBXL3
SOX21
DOCK9
KLF12
SCEL
ABCC4
UBAC2
CTAGE11P
RNF219
CLDN10
GPR18
TBC1D4
DZIP1
GPR183
COMMD6
DNAJC3
FKSG29
C13orf45
UGGT2
CLYBL
MYCBP2
HS6ST3
ZIC2
SLAIN1
MBNL2
NALCN
EDNRB
RAP2A
POU4F1
RNF113B
TM9SF2
PCCA
GGACT
TMTC4

表

Table 1. Clinical features of the patients in this study

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	3m	4y5m	8m	11y11m	18m	9y
Sex	Female	Male	Male	Female	Female	Male
Microarray kit	44K	60K	60K	60K	60K	60K
Chromosome band	q21.32q31.1	q21.33q31.2	q22.2q31.1	q31.1q32.1	q31.1q33.1	q31.1q31.3
Start(bp)	65732480	71028436	75691448	84431421	85236169	86046386
End(bp)	83625667	88958577	86658563	96530663	102244722	91816350
Deletion Size [Mb]	17.9	17.9	11.0	12.1	17.0	5.8
Origin	NT	NT	de novo	NT	NT	Inherited from father
Gestational age	39w6d	40w6d	38w1d	39w	39w2d	38w
Birth weight	2676	2555	3210	2284	2114	2556
Birth length	47.4	43.9	49.2	NA	44.5	49.0
Birth OFC	30.3	29.8	33.0	NA	33.5	33.0
Developmental delay	+	Moderate	Border	Mild	Severe	Moderate
Growth deficiency	+	+	Mild	+	+	+
Microcephaly	NA	-	+	-	+	-
Pigmentary changes of the	+	-	+	-	-	-
Hirschsprung disease	-	-	-	-	-	-
Deafness	-	-	+	-	-	-
Neurological findings	-	-	Hypotonia	-	-	Hypotonia
Distinctive facia features						
Low-set-ears	-	+	-	-	+	-
Epicanthus	-	-	+	-	-	-
Blepharophimosis	-	-	-	-	+	-
Micrognathia	-	+	-	-	-	-
Flat nasal bridge	-	-	-	-	+	-
Large auricle	-	-	+	-	-	-
Wide ala nasi	-	-	+	-	-	-
Other findings	Vocal cord paralysis			Precocious puberty, congenital dysplasia of the hip	Holoprosencephaly	Hypothyroidism

m, months; y, years; NT, not tested; w, weeks; d, days; NA, not available

表

Table 2. List of the genes located on the shortest region of overlapping (chr13:75691448_83625667)

Gene name	Symbol	Start	End	pLI	Gene/Locus MIM number	Phenotype	Phenotype MIM number	Inheritance
CTAGE family, member 11, pseudogene	*CTAGE11P*	75811889	75814517					
TBC1 domain family, member 4	*TBC1D4*	75858809	76056250	0	612465	Diabetes mellitus, noninsulin-dependent, 5	616087	
COMM domain containing 6	*COMMD6*	76099350	76111991	0.17	612377			
carboxyl-terminal esterase L3 (ubiquitin thiolesterase)	*UCHL3*	76123886	76180156	0	603090			
LIM domain 7	*LMO7*	76210459	76434006	0	604362			
chromosome 13 open reading frame 45	*C13orf45*	76445174	76457948	0				
potassium channel tetramerisation domain containing 12	*KCTD12*	77454304	77460540	0.06	610521			
immunoresponsive 1 homolog (mouse)	*IRG1*	77526624	77532776	0	615275			
ceroid-lipofuscinosis, neuronal 5	*CLN5*	77566059	77576652	0	608102	Ceroid lipofuscinosis, neuronal, 5	256731	AR
F-box and leucine-rich repeat protein 3	*FBXL3*	77579389	77601331	0.98	605653	Intellectual developmental disorder with short stature, facial anomalies, and speech defects	606220	AR
MYC binding protein 2, E3 ubiquitin protein ligase	*MYCBP2*	77618792	77901177	1	610392			
sciellin	*SCEL*	78109809	78219398	0	604112			
SLAIN motif family, member 1	*SLAIN1*	78271989	78338377	0.9	610491			
endothelin receptor type B	*EDNRB*	78469616	78493903	0.01	131244	Hirschsprung disease, susceptibility to, 2	600155	AD
						ABCD syndrome	600501	AR
						Waardenburg syndrome, type 4A	277580	AD, AR
POU class 4 homeobox 1	*POU4F1*	79173230	79177695	0.89	601632			
ring finger protein 219	*RNF219*	79188421	79233314	0	615906			
RNA binding motif protein 26	*RBM26*	79894100	79979923	1				
Nedd4 family interacting protein 2	*NDFIP2*	80055259	80130212	0.53	610041			
sprouty homolog 2	*SPRY2*	80910112	80915086	0.97	602466	IgA nephropathy, susceptibility to, 3	616818	AD

pLI, probability of loss-of-function intolerance; MIM, mendelian inheritance in man; AR, autosomal recessive; AD, autosomal dominant