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Original article

Microarray analysis of 50 patients reveals the critical chromosomal regions responsible for 1p36 deletion syndrome-related complications

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Abstract

Objective: Monosomy 1p36 syndrome is the most commonly observed subtelomeric deletion syndrome. Patients with this syndrome typically have common clinical features, such as intellectual disability, epilepsy, and characteristic craniofacial features.

Method: In cooperation with academic societies, we analyzed the genomic copy number aberrations using chromosomal microarray testing. Finally, the genotype–phenotype correlation among them was examined.

Results: We obtained clinical information of 86 patients who had been diagnosed with chromosomal deletions in the 1p36 region. Among them, blood samples were obtained from 50 patients (15 males and 35 females). The precise deletion regions were successfully genotyped. There were variable deletion patterns: pure terminal deletions in 38 patients (76%), including three cases of mosaicism; unbalanced translocations in seven (14%); and interstitial deletions in five (10%). Craniofacial/skeletal features, neurodevelopmental impairments, and cardiac anomalies were commonly observed in patients, with correlation to deletion sizes.

Conclusion: The genotype–phenotype correlation analysis narrowed the region responsible for distinctive craniofacial features and intellectual disability into 1.8–2.1 and 1.8–2.2 Mb region, respectively. Patients with deletions larger than 6.2 Mb showed no ambulation, indicating that severe neurodevelopmental prognosis may be modified by haploinsufficiencies of *KCNAB2* and *CHD5*, located at 6.2 Mb away from the telomere. Although the genotype–phenotype correlation for the cardiac abnormalities is unclear, *PRDM16*, *PRKCZ*, and *RERE* may be related to this complication. Our study also revealed that female patients who acquired ambulatory ability were likely to be at risk for obesity.

Keywords: 1p36 deletion syndrome; Chromosomal deletion; Genotype–phenotype correlation; Intellectual disability; Ambulation; Epilepsy; Distinctive features

1. Introduction

Monosomy 1p36 syndrome is a congenital malformation syndrome caused by the subtelomeric deletion of the short arm of chromosome 1 [1–3]. This syndrome is the most commonly observed subtelomere deletion syndrome, with an estimated incidence of 1:5000–1:10,000 [4,5]. Patients with this syndrome exhibit common clinical features, including intellectual disability (ID) and characteristic craniofacial features; such as straight eyebrows, deep-set eyes, epicanthus, and a pointed chin [6–9]. Although the levels of ID vary among patients, craniofacial features are commonly seen [10]. The patients with the 1p36 deletion syndrome also show many other complications, including hypotonia, seizures, hearing loss, structural heart defects, cardiomyopathy, ophthalmological abnormalities, and behavior abnormalities [7]. Recent advances in microarray-based chromosomal testing have helped us to identify small chromosomal rearrangements that are invisible by conventional G-banded chromosomal tests/karyotyping [11,12]. Using this method, the precise locations of the aberrations can be revealed at the molecular level. These advances have also allowed the study of more in-depth genotype–phenotype correlations for this syndrome, as well as the identification of some of the regions responsible for individual complications [12,13].

In this study, we performed a nation-wide survey for the 1p36 deletion syndrome in Japan. The aim of this study was to identify the chromosomal regions responsible for individual complications in patients with 1p36 deletions. We analyzed the affected genomic regions in 50 patients with 1p36 deletions, and performed correlational analyses of the genotype data with the clinical information.

2. Materials and methods

2.1. Patients and samples

We performed a nation-wide survey for the 1p36 deletion syndrome with the cooperation of two academic societies; the Japanese Society of Child Neurology and the Japan Society of Pediatric Genetics. The study subjects were Japanese patients who had already been diagnosed using various diagnostic methods, including conventional karyotyping, subtelomere fluorescence *in situ* hybridization (FISH) analysis, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray testing. Five patients

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(patient [Pt] 8, 9, 21, 28, and 43), whose clinical features have been previously reported [14–17], were also included in this study. With the questionnaire survey for attending physicians, we accumulated the patients' clinical information, including craniofacial/skeletal features, neurodevelopmental features, brain structural abnormalities, cardiac abnormalities, sensory-organs abnormalities, urogenital abnormalities, endocrinological and nutritional findings among others. This study was approved by the ethics committee in Tokyo Women's Medical University.

On receipt of written informed consents from the families of the patients, we obtained the patients' blood samples to determine genomic copy number losses in the patients. Genomic DNA was extracted from the blood samples using the QIA quick DNA Extraction Kit (QIAGEN, Hamburg, Germany). Metaphase spreads were also prepared from blood samples and used for FISH analyses. In cases, if we could obtain written informed consent, parental samples were also analyzed.

2.2. Molecular and cytogenetic analyses

Chromosomal microarray testing was performed using any of the Agilent Oligo Microarray Kits 44, 60, 105, 180, and 244 K (Agilent Technologies, Santa Clara, CA), as described previously [18,19]. Genomic copy number aberrations were visualized using Agilent Genomic Workbench version 6.5 (Agilent Technologies). For cases in which variations of unknown significance were identified or suspected, parental samples were also analyzed. In cases of complex chromosomal rearrangements or mosaicism, metaphase spreads prepared using the patients' samples were used for FISH analyses for confirmation. The bacterial artificial clones were selected from the UCSC genome browser (http://genome.ucsc.edu/) for use as probes. For the target probes, RP11-425E15 (1p36.33: 949,400–1,132,489), RP11-82D16 (1p36.33: 2,046,751–2,208,312), RP11-70N12 (1p36.32: 2,740,703–2,922,551), CTD-3209F18 (1p36.32: 3,530,092–3,769,006), and RP11-933B18 (1p36.31: 5,988,719–6,177,261) were selected, while CTB-167K11 (1q44: 249,250,621–249,250,621) was used as a marker of chromosome 1. All of the genomic regions are described according to the February 2009 human reference sequence (GRCh37/hg19) in this study.

3. Results

3.1. Molecular-cytogenetic findings

We obtained clinical information from 86 patients with chromosomal deletions involving 1p36 regions. Among them, 50 patients (15 males and 35 females) were successfully genotyped. All of the genotypes were summarized in Tables 1 and 2, and 1p36 deletions identified in the patients were depicted in the genome map (Fig. 2). The minimum and maximum deletion sizes was 0.9 and 12.9 Mb, respectively. Pure terminal deletions were identified in 38 patients (76%). Among them, three patients (Pt 8, 19, and 21) exhibited mosaicism. Pt 8 was first diagnosed with mosaic 1p36 deletion by chromosomal microarray testing, and Pt 21 had been diagnosed with 1p36 deletion using subtelomere FISH analysis; however, mosaicism was not reported at that time [17]. Although the mosaic deletion of 1p36 in Pt 19 had been firstly confirmed by FISH, we could not detect the breakpoint by chromosomal microarray testing due to low frequency (28% mosaic ratio). As the breakpoint was determined to be between two FISH probes (CTD-3209F18 and RP11-933B18), the proximal end of CTD-3209F18 was used as the minimum deletion region in this patient.

Additional aberrations with the sizes over 0.5 Mb were identified in eight patients (Pt 2, 10, 11, 15, 20, 28, 34, and 43) involving chromosomes 4, 7, 8, 13, and Y (Table 2), including a possible benign copy number aberration in Pt 15, which was also observed in the healthy mother. The other seven patients were confirmed to have unbalanced translocations by cytogenetic evaluation (14%), using either G-banding or FISH analysis. Two translocations were diagnosed as de novo, and the others were designated as unknown because of the lack of availability of parental information.

Five patients (Pt 1, 14, 47, 48, and 50) had interstitial deletions (10%) with a deletion size between 0.9 and 10.3 Mb.

3.2. Clinical findings

Clinical information of the 50 patients successfully genotyped is summarized in Table 3. Estimated frequencies of each complication are also included in Table 3. Pt 26 and 49 suddenly died at 24 and 10 months old of age, respectively. Pt 49 probably died due to heart failure but Pt 26 died of an unknown cause (detailed information unavailable).

3.2.1. Craniofacial features

Most of the patients showed craniofacial features, including straight eyebrows (84%), deep-set eyes (93%), broad nasal bridge (97%), low set ears (88%), and a pointed chin (89%). Constellations of these findings make distinctive facial impressions for 1p36 deletion syndrome, observed in Pt 3, 6, and 14 (Fig. 1b–d). This observation suggests that hypotelorism is rather characteristic among these patients. On the other hand, Pt 1 did not show deep-set eyes (Fig. 1a). The craniofacial features of three patients (Pt 47, 48, and 50) did not exhibit hypotelorism (Fig. 2e–g). From the genotypic point of view, these three patients (Pt 47, 48, and 50) would be diagnosed as having the proximal 1p36 deletion syndrome [20,21].

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Table 1
The ranges of 1p36 deletions analyzed by chromosomal microarray testing.

Patient number	Age (year)	Gender	Platform (k)	Start[a]	End[a]	Additional aberration	FISH probe	Mosaic ratio[b] (%)	References
1	14	F	180	834,101	1,770,669	Interstitial	RP11–425E15		
2	9	M	44	1	1,820,584	der(1)t(Y;1), idic(Y)			
3	6	F	180	1	2,186,829				
4	1	F	60	1	2,239,497				
5	3	F	44	1	2,281,699				
6	5	F	60	1	2,553,982				
7	2	M	60	1	2,553,982				
8	5	F	44	1	3,044,953	Mosaicism	RP11–82D16	70	Shimada et al. [17]
9	13	F	44	1	3,102,718				Okamoto et al. [14]
10	18	F	44	1	3,102,718	der(1)t(1;7)			
11	17	F	60	1	3,138,565	der(1)t(1;8)			
12	8	F	60	1	3,265,702				
13	11	F	244	1	3,408,152				
14	5	M	60	1,786,789	3,472,907	Interstitial			
15	2	F	180	1	3,564,328				
16	13	M	60	1	3,582,084				
17	4	F	44	1	3,607,275				
18	2	F	60	1	3,660,110				
19	3	F	60	1	3,769,006	Mosaicism	CTD-3209F18	28	
20	3	M	44	1	4,070,842	der(1)t(1;13)			
21	17	F	44	1	4,481,324	Mosaicism	RP11–82D16	77	Shimada et al. [17]
22	2	F	180	1	4,703,581				
23	6	M	60	1	4,779,157				
24	3	F	60	1	4,843,370				
25	6	F	44	1	4,843,718				
26	2	M	60	1	5,252,985				
27	0	F	44	1	5,252,985				
28	25	F	44	1	5,411,803	der(1)t(Y;1)			Hiraki et al. [15]
29	3	F	44	1	6,128,223				
30	3	F	60	1	6,282,562				
31	1	F	60	1	6,282,562				
32	3	M	60	1	6,882,431				
33	7	M	60	1	7,035,075				
34	1	F	60	1	7,187,535	der(1)t(1;4)			
35	10	M	60	1	7,392,688				
36	8	M	60	1	7,581,058				
37	3	F	44	1	8,077,959				
38	2	F	60	1	8,104,671				
39	3	M	44	1	8,104,671				
40	4	M	44	1	8,181,042				
41	5	F	44	1	8,181,042				
42	1	F	60	1	8,427,633				
43	3	M	60	1	9,180,975	der(1)(1;4)			Saito et al. [16]
44	5	F	60	1	9,251,936				
45	4	M	60	1	9,953,030				

46	2	F	44	1	10,001,011	
47	4	F	44	2,080,309	10,869,155	Interstitial
48	8	F	60	2,785,042	12,743,178	Interstitial
49	0	F	44	1	12,917,483	
50	22	F	180	6,614,950	16,890,814	Interstitial

[a] The genomic position reffering build19.
[b] The mosaic ratio was confirmed by FISH; F, female; M, male.

3.2.2. Neurological features

Almost all patients showed ID (98%) but a patient (Pt 2) having a deletion in the far distal region of 1p36 showed borderline ID, with an intelligence quotient (IQ) of 80. Therefore, this region could be eliminated from the responsible region for ID (Fig. 2). The smallest deletion, an interstitial deletion between genomic positions 0.8 and 1.8 Mb, was identified in Pt 1 (Fig. 2). In spite of having this smallest deletion, Pt 1 had severe ID, i.e., she was locomotive but aphasic and required support for all activities in her daily life. This was probably a consequence of intractable epilepsy associated with tonic seizures, caused by factors other than the interstitial deletion of this region. The proximal and distal ends of the breakpoints in Pt 3 and 14 defined the shortest region of overlap for ID, spanning the 1.8–2.2 Mb region (Fig. 2; region B). Axial hypotonia (92%) and poor sucking (70%) were also commonly observed. Epilepsy, one of the major complications in 1p36 deletion syndrome, was observed in 70% of the patients. Infantile spasms were observed in 16% of the patients.

In this study, many types of structural brain abnormalities were identified; not only in the cerebral cortex but also in the white matter (Table 3), indicating that there is no major pattern. The most frequently observed abnormality was a nonspecific finding with enlargement of lateral ventricles.

3.2.3. Cardiac abnormality

Cardiac abnormality is one of the most frequently observed complications in patients with 1p36 deletions. In this study, congenital heart defects and functional abnormalities were observed in 69% (34/49) and 22% (11/49) of the patients, respectively. The most frequently observed patterns were patent ductus arteriosus (PDA; 37% [18/49]) and ventricular septal defects (VSD; 37% [18/49]).

3.2.4. Other complications

Many kinds of complications were observed in many organs. Cryptorchidism was the most frequently observed complication in male patients (64% [9/14]). As Pt 14, with a small interstitial deletion spanning from 1.8 to 3.5 Mb, had cryptorchidism, the deleted region was likely involved in abnormalities of the external genitalia (Fig. 2; region H). Hearing problems (39% [19/49]) and strabismus (33% [15/46]) were relatively common among the patients. Obesity was observed in 5 patients (11% [5/46]).

Renal abnormalities were rare and identified only in three patients. Among them, Pt 26, who had a 5.3 Mb deletion, was diagnosed with the autosomal recessive cystic kidney disease of nephronophthisis (this patient died at 2 years of age) [22]. One of the genes responsible for this condition, the nephronophthisis 4 gene

Table 2
Additional aberrations identified in the patients.

Patient number	Chr	Start[a]	End[a]	Remark	Attribute	Origin
2	Y	1	59,373,566	der(1)t(Y;1)(p36.3;q12), idic(Y)(q12)	dup	NA
10	7	1	6,870,943	der(1)t(1;7)(p36.32;p22.1)	dup	NA
11	8	1	3,909,039	der(1)t(1;8)(p36.22;p23.2)	dup	NA
15	1	146,324,068	149,192,104	del(1)(q21.1;q21.2)	del	Common with mother
20	13	100,462,233	115,169,878	der(1)t(1;13)(p26.32;q32.3)	dup	De novo
28	Y	26,435,039	59,373,566	der(1)t(Y;1)(q12;p36.32)[#]	dup	NA
34	4	1	13,396,747	der(1)t(1;4)(p36.31;p15.33)	dup	De novo
43	4	189,012,426	191,154,276	der(1)t(1;4)(p36.31;q35.2)	dup	NA

[*] The genomic position reffering build19; dup, duplication; del, deletion; NA, not available.
[#] This case was previously reported by Hiraki et al. [15].

(*NPHP4*), is located on 1p36 (chr1: 5,946,555–5,965,543) [23], proximal to the deletion region of three patients with renal abnormalities (Pt 26, 33, and 35). It is unclear whether there is a correlation between *NPHP4* and the renal abnormalities observed in this study.

4. Discussion

4.1. Previous genetic studies on the 1p36 deletion syndrome

Many cohort studies have been performed to delineate the phenotypic features of patients with 1p36 deletion syndrome and to evaluate the frequency of complications [1,6,7]. It has been reported that there is no correlation between the deletion size and the number of observed clinical features [24], while the critical region responsible for core phenotypic features, including clefting, hypothyroidism, cardiomyopathy, hearing loss, large fontanel, and hypotonia, has been narrowed down to a region 2.2 Mb from the telomere [3]. Compared to such core phenotypic features, other complications tend to vary with the size of the deletion, and study subjects with larger deletions tend to have more phenotypic features [25], suggesting that the various phenotypic features are dependent on genes involved in the deletion regions. Thus, precise knowledge of the genotype–phenotype correlations could potentially lead to more personalized treatments for individuals with 1p36 deletions and might identify mutations for single gene disorders [3]. The potassium voltage-gated channel, shaker-related subfamily, beta member 2 gene (*KCNAB2*) and the v-ski sarcoma viral oncogene homolog gene (*SKI*) were identified as candidate genes for the epilepsy phenotype and clefting abnormalities, respectively [26,27]. More recently, the PR domain containing 16 gene (*PRDM16*) was identified as a possible candidate gene for cardiomyopathy, as *PRDM16* was included in a minimal deletion among patients with 1p36 deletions associated with cardiomyopathy, while in patients with pure cardiomyopathy, single nucleotide variants of *PRDM16* were identified as the cause of cardiomyopathy [28]. This was one of the most successful studies of genotype–phenotype correlation in patients with 1p36 deletions [28].

4.2. Craniofacial features

As mentioned above, a region 2.2 Mb from the telomere has been reported to be responsible for core phenotypic features of 1p36 deletion syndrome [3]. Compared to this, we observed atypical facial features in four patients (Pt 1, 47, 48, and 50) whose deletions did not include the 1.8–2.1 Mb region, in this study. Thus, the region responsible for typical facial features is narrowed into this region (Fig. 2; region A). Because hypotelorism has never been listed in the clinical delineations of 1p36 deletion syndrome reported from Western countries, we did not include this finding in the questionnaire survey and the frequency of this finding in Japanese patients could not be calculated. However, it is commonly observed in Japanese patients with typical 1p36 deletion syndrome. Therefore, hypotelorism may be a characteristic finding among Asian patients.

4.3. Neurological features

Although more severe ID was reported to be associated with larger 1p36 deletions [10], the genomic region responsible for severe ID has never been identified. In this study, a patient (Pt 28) having a 5.4 Mb deletion acquired independent gait, while patients with >6.1 Mb deletions had not yet acquired independent gait, and exhibited severe ID. Thus, the region between 5.4 and 6.1 Mb would appear to be the borderline for independent gait (Fig. 2; region C), and the modifier genes for prognosis of development may be located in the region proximal to this borderline. *KCNAB2*, mentioned above, may be one of the modifier genes responsible for severe ID. Chromodomain helicase DNA-binding protein 5 (*CHD5*; chr1: 6,161,847–6,240,194), which encodes a neuron-specific protein, is

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Table 3
Summary of clinical features of the patients with 1p36 deletions.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	Frequencies
1. Craniofacial and skeletal features																																																		
Characteristic craniofacial features																																																		
Microcephaly	NA	+	NA	+	+	NA	NA	–	+	NA	+	NA	NA	+	NA	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	+	+	+	NA	–	–	+	NA	NA	NA	+	NA	+	NA	+	NA	–	NA	+	NA	+	+	+	+	83% (20/24)
Brachycephaly	+	NA	–	+	+	NA	NA	–	+	NA	+	NA	NA	–	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	+	NA	NA	NA	NA	NA	NA	–	NA	NA	+	NA	NA	NA	NA	+	+	+	65% (11/17)
Straight eyebrow	–	+	+	+	+	+	+	+	+	+	+	–	+	+	NA	+	+	+	NA	+	+	+	+	+	+	NA	NA	+	+	NA	+	–	+	+	NA	NA	NA	NA	+	+	+	NA	+	+	NA	NA	–	–	+	–	84% (32/38)
Deep-set eyes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	NA	NA	+	+	+	+	+	+	+	+	+	NA	NA	+	+	+	+	+	+	+	+	NA	+	NA	+	+	NA	+	NA	+	+	NA	+	–	+	–	93% (37/40)
Epicanthus	+	NA	+	+	+	+	+	+	+	NA	+	+	+	–	NA	NA	+	+	NA	+	–	+	+	+	NA	NA	NA	+	+	+	–	–	NA	+	NA	NA	+	NA	+	+	+	NA	+	+	NA	+	–	+	+	86% (30/35)
Broad nasal root/bridge	+	NA	+	+	NA	+	+	+	+	NA	+	+	+	–	NA	NA	+	+	+	+	+	NA	+	NA	NA	NA	NA	+	+	+	+	+	+	+	+	NA	NA	+	NA	NA	NA	+	NA	+	+	NA	+	+	+	97% (32/33)
Long philtrum	+	+	+	–	NA	–	–	+	+	+	+	–	–	–	NA	NA	+	+	+	+	+	+	+	NA	NA	NA	NA	+	–	NA	–	–	+	+	NA	NA	+	NA	NA	–	NA	NA	+	NA	+	+	–	+	–	63% (22/35)
Low set ears	–	–	+	–	NA	–	+	NA	+	NA	+	+	NA	+	NA	NA	NA	NA	NA	+	+	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	+	+	NA	NA	+	NA	NA	+	+	NA	NA	+	+	+	88% (29/33)
Pointed chin	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	NA	NA	+	+	NA	+	+	+	+	+	NA	+	NA	+	+	+	+	+	+	+	+	+	NA	NA	NA	NA	+	+	NA	+	+	–	+	–	89% (34/38)
Late closure of the anterior fontanel	–	NA	+	–	–	–	NA	NA	+	NA	NA	NA	NA	NA	+	NA	+	NA	+	+	+	–	–	NA	NA	–	+	+	–	+	+	+	+	+	–	+	NA	NA	–	+	–	–	–	+	NA	+	NA	–	NA	NA	56% (18/32)
Cleft palate problem																																																	
High palate	–	–	–	–	–	–	+	–	+	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	NA	–	–	+	+	–	+	–	+	–	–	+	–	+	–	+	+	–	–	+	+	29% (14/49)
Cleft palate	–	–	+	–	–	–	–	–	–	–	–	+	–	+	–	–	+	–	–	–	+	–	–	–	–	–	–	+	–	NA	–	–	–	–	+	–	+	–	–	+	–	+	–	+	–	–	–	–	–	22% (11/49)
Cleft lip	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	+	–	–	NA	–	–	–	–	+	–	+	–	+	–	–	+	–	+	–	–	–	–	–	16% 8/49)
Cleft jaw	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	2% (1/50)
Limb abnormalities																																																	
Finger abnormalities	–	–	NA	–	–	–	–	–	–	–	–	NA	–	+	–	+	–	+	–	–	–	–	+	–	–	+	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15% (7/48)
Limb deformity	–	–	NA	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	4% (2/48)
Other skeletal abnormalities																																																
Rib abnormalities such as 11 ribs	–	–	NA	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	4% (2/48)
Scoliosis	–	–	NA	–	–	–	+	–	–	NA	–	–	–	+	–	–	–	+	–	–	–	–	–	+	–	–	+	–	+	–	–	–	–	+	–	+	–	+	–	–	–	–	–	+	+	–	+	25% (12/48)
Congenital dislocated hip	–	–	NA	–	–	–	–	–	+	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	4% (2/48)
Developmental dysplasia of the hip	–	–	NA	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	2% (1/48)
2. Neurological features (clinical)																																																
Axial hypotonia	+	+	NA	–	+	+	+	+	+	+	+	+	+	NA	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92% (44/48)
Poor sucking	–	–	NA	–	–	–	+	–	+	–	+	NA	+	NA	+	NA	+	+	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70% (32/46)
Difficulty of swallowing	–	–	+	–	–	–	+	–	+	–	+	NA	–	NA	+	+	+	+	–	+	+	–	–	–	–	+	–	–	+	–	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	56% (27/48)
Developmental delay																																																
Intellectual disability	S	B	S	S	M	S	S	M	S	S	S	S	S	M	S	S	M	S	S	S	M	S	M	M	S	S	NA	S	M	S	S	S	S	S	S	S	S	NA	S	S	S	S	S	S	S	S	NA	S	S	98% (49/50)
Acquire independent gait	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	+	–	+	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	32% (16/50)
Expressive language																																																
Sentence	–	+	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6% (3/50)
Only words	–	–	–	–	+	+	–	+	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	16% (8/50)
Dysarthria	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8% (4/50)
Gestures	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	+	+	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10% (5/50)
Behavior disorders																																																
Self–injury	–	+	+	–	–	NA	+	–	NA	–	+	NA	+	NA	–	NA	–	NA	+	–	–	NA	–	NA	–	–	NA	+	+	+	–	–	NA	–	–	–	NA	–	–	+	+	–	–	NA	–	–	–	NA	–	30% (11/37)
Temper tantrum	+	–	–	–	–	NA	+	+	NA	+	+	NA	+	NA	–	NA	–	NA	–	+	NA	+	NA	–	–	NA	+	–	–	–	–	–	NA	–	–	–	NA	–	–	–	–	+	+	NA	–	–	–	NA	–	30% (11/37)
Poor social interaction	+	–	+	+	–	NA	–	+	NA	–	+	NA	+	NA	–	NA	–	NA	–	+	–	NA	–	NA	–	–	NA	+	–	–	–	+	NA	–	–	–	NA	–	–	–	–	–	–	NA	+	–	–	NA	–	27% (10/37)
Epilepsy																																																
History of epilepsy	+	–	+	+	–	–	+	–	–	+	+	+	–	+	+	+	–	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–	+	+	+	70% (35/50)
Infantile spasms	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	+	–	+	–	–	–	+	–	+	–	–	–	–	16% (8/50)
3. Neurological features (radiological)																																																
Cerebral cortex																																																
Periventricular nodular heterotopia (PVNH)	–	–	NA	–	–	–	–	+	–	NA	–	–	+	–	NA	NA	+	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	NA	–	–	+	–	–	–	–	–	–	–	–	–	NA	–	10% (4/42)
Polymicrogyria	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	–	–	–	–	–	–	–	+	NA	–	–	NA	–	–	NA	–	–	–	–	+	–	–	–	+	–	–	–	–	NA	–	7% (3/42)
Cortical dysplasia	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	+	NA	–	–	–	–	–	–	–	+	–	–	–	–	NA	–	5% (2/42)
Cortical hypoplasia	–	–	NA	–	–	–	–	–	–	NA	–	+	–	–	NA	NA	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	+	–	+	–	–	NA	–	7% (3/42)
Cerebral white matter																																																
Enlargement of lateral ventricles	–	–	NA	+	–	–	–	–	–	NA	–	–	+	+	NA	NA	–	–	–	+	–	–	–	–	–	–	NA	–	+	NA	–	+	NA	+	+	–	+	–	+	–	–	+	–	+	+	+	+	NA	–	36% (15/42)
Delay in myelination	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	+	+	–	–	–	–	–	–	–	+	NA	–	–	NA	+	+	NA	–	+	–	+	–	–	–	–	–	–	+	–	–	NA	–	21% (9/42)
Hypoplasia of corpus callosum	–	–	NA	+	–	–	–	–	–	NA	–	–	–	+	NA	NA	–	–	–	+	–	–	–	–	–	+	NA	–	+	NA	–	–	NA	–	–	–	+	–	–	+	–	+	–	+	–	–	NA	–	24% (10/42)
Cerebellum																																																
Chiari type II malformation	–	–	NA		–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	NA	+	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	2% (1/42)
Others																																																
Cavum septum pellucidum	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	+	–	–	–	–	–	–	+	–	–	NA	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	5% (2/42)
Choroid plexus cyst	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	+	–	–	–	–	–	–	–	NA	–	–	NA	–	–	NA	+	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	5% (2/42)
Arrested hydrocephalus	–	–	NA	–	–	–	–	–	–	NA	–	–	–	+	NA	NA	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	2% (1/42)
Enlargement of subdural space	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	–	–	–	–	–	–	+	–	NA	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	2% (1/42)
Arachnoid cyst	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	–	–	–	–	–	–	–	+	NA	–	–	NA	–	–	NA	–	–	+	–	–	–	–	–	–	–	–	–	–	NA	–	5% (2/42)
4. Cardiac abnormalities																																																
Congenital heart defects																																																
Patent ductus arteriosus (PDA)	–	–	–	–	–	–	–	–	–	+	+	+	–	–	NA	–	–	–	–	+	–	–	+	+	–	–	+	–	+	+	–	+	–	+	–	+	+	–	+	–	–	+	–	+	–	–	+	–	+	37% (18/49)
Ventricular septal defects (VSD)	–	–	–	–	–	+	–	+	–	–	–	+	–	–	NA	+	–	–	–	+	–	+	–	–	–	–	+	–	–	+	+	+	–	–	–	+	+	+	–	–	+	–	–	+	+	+	–	–	37% (18/49)
Artial septal defects (ASD)	–	–	–	–	–	–	–	+	–	–	–	–	–	–	NA	–	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	–	+	+	–	–	–	+	–	+	–	–	–	–	+	–	–	–	16% (8/49)
Aortic stenosis (AS)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	4% (2/49)
Pulmonary stenosis (PS)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	4% (2/49)
Aortic valve prolapse	–	–	–	–	–	–	–	–	–	–	–	+	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/49)
Ebstein anomaly	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	6% (3/49)
Double outlet right ventricle (DORV)	–	–	–	–	–	+	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	6% (3/49)
Hypoplasia of the left ventricle (HLHS)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/49)
Patent foramen ovale (PFO)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/49)
Partial anomalous pulmonary venous connection (PAPVC)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/49)

Pulmonary atresia (PA)	–	–	–	–	–	+	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/49)
Positional anomaly of valsalva sinus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	2% (1/49)
Functional abnormalities																																																			
Pulmonary hypertension (PH)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	8% (4/49)
Left ventricular noncompaction (LVNC)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	+	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	10% (5/49)
Dilated cardiomyopathy	–	–	–	–	–	–	–	–	+	–	+	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4% (2/49)
5. Sensory organs																																																			
Ears																																																			
Hearing problems	–	+	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	+	+	–	–	+	–	–	–	+	+	–	–	+	–	–	NA	+	–	+	+	+	–	–	+	+	+	+	+	–	–	–	+	–	39% (19/49)
Eyes																																																			
Strabismus	–	–	+	–	–	–	+	NA	–	–	+	–	+	–	–	–	+	+	–	–	+	–	–	+	–	–	–	–	+	NA	–	–	NA	+	–	–	+	–	–	+	+	–	NA	–	–	+	–	–	–	+	33% (15/46)
Ametropia	–	–	+	–	–	–	–	NA	–	–	+	–	–	+	–	–	+	+	+	–	+	–	+	–	+	–	–	–	–	NA	–	–	NA	–	–	–	–	–	–	+	–	–	NA	–	–	+	–	+	–	–	26% (12/46)
Nystagmus	–	–	–	–	–	–	–	NA	+	–	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	NA	–	–	NA	+	–	–	–	–	–	+	–	–	NA	+	+	–	+	–	–	–	20% (9/46)
Oculomotor disturbance	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	–	NA	–	–	+	–	–	–	–	2% (1/46)
Coloboma	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	–	+	–	–	–	–	–	NA	–	–	–	–	–	–	–	2% (1/46)
Congenital microphthalmia	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	+	–	2% (1/46)
Retinitis pigmentosa	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	NA	–	–	NA	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	2% (1/46)
6. Urogenital abnormalities																																																			
Renal abnormalities																																																			
Renal hypoplasia	–	–	NA	–	–	–	NA	NA	–	+	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	NA	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/43)
Hydronephrosis	–	–	NA	–	–	–	NA	NA	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	+	–	NA	–	–	–	NA	–	NA	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5% (2/43)
Pyelectasis	–	–	NA	–	–	–	NA	NA	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	NA	+	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/43)
Nephronophthisis	–	–	NA	–	–	–	NA	NA	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	+	–	NA	–	–	–	NA	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/43)
Extragenital abnormalities																																																			
Ectopic kidney	–	–	NA		–	–	NA	NA	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	+	–	NA	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2% (1/44)
Ambiguous external genitalia	–	–	NA	–	–	–	NA	NA	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	NA	+	–	–	–	–	–	–	–	–	+	+	–	–	NA	–	–	7% (3/43)
Cryptorchidism	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	–	NA	NA	NA	+	NA	NA	+	NA	NA	+	NA	NA	NA	NA	NA	+	–	NA	–	+	NA	NA	+	+	NA	NA	–	NA	+	NA	NA	NA	NA	NA	64% (9/14)
Scrotal hypoplasia	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	NA	–	NA	NA	NA	–	NA	NA	–	NA	NA	–	NA	NA	NA	NA	NA	–	–	NA	+	–	NA	NA	–	–	NA	NA	–	NA	+	NA	NA	NA	NA	NA	14% (2/14)
7. Endocrinology and nutrition																																																			
Hypothyroidism	–	–	NA	–	–	–	NA	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	NA	+	–	–	+	+	NA	–	–	–	+	–	–	–	NA	–	–	16% (7/45)
Obesity	–	–	NA	–	NA	–	–	+	–	+	+	–	+	–	–	–	–	–	–	NA	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	11% (5/46)
8. Other complications																																																			
Respiratory tract related																																																			
Stenosis of nasal cavity	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	
Laryngomalacia and/or tracheomalacia	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Adenoidal hypertrophy and/or enlarged tonsil	NA	+	NA	–	NA	NA	NA	+	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Obstructive sleep apnea	NA	NA	NA	–	NA	NA	NA	+	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Allergy related																																																			
Atopic dermatitis	NA	NA	NA	–	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	+	NA	NA	–	–	NA	+	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Food allergy	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Bronchial asthma	NA	+	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Related to secondary																																																			
Precocious puberty	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Breast enlargement	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Others																																																			
Atresia of external acoustic foramen	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	
Dental abnormalities	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	
Non alcoholic steatohepatitis (NASH)	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Constipation	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	–	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	

NA, not available; S, severe; B, borderline; M, moderate.

Fig. 1. Facial features of the patients with variably sized 1p36 deletions. Pt 1 (a; at 14 years of age) shows edematous eyelids rather than deep-set eyes. Pt 3 (b; 6 years), 6 (c; 5 years), and 14 (d; 15 years) share characteristic features, including deep-set eyes, hypotelorism, and pointed chins. Pt 47 (e; 4 years) and 48 (f; 8 years) do not exhibit such characteristic features, with round faces rather than hypotelorism and pointed chins. Pt 50 (g; 3 years) exhibits distinctive features with arched eyebrows and hypertelorism. Written informed consent to publish patient photos was obtained from all the patient families.

involved in chromatin remodeling and gene transcription, regulating the expression of neuronal genes [29]. Thus, *CHD5* also may be a modifier gene for severe ID.

It has been suggested that two genes, gamma-aminobutyric acid (GABA) A receptor delta (*GABRD*; chr1: 1,950,768–1,962,192), and *KCNAB2* (chr1: 6,105,981–6,161,253), are associated with the manifestations of epilepsy [27]. This is also been suggested by our present study, as there was no history of epilepsy in a patient (Pt 2) with a 1.8 Mb terminal deletion and a patient (Pt 50) with a 10.0 Mb interstitial deletion; both of the deletions includes neither *GABRD* nor *KCNAB2* (Fig. 2). The incidence of epilepsy was higher in the patients with severe ID (30/38; 79%) than in the patients with moderate ID (4/8; 50%). Thus, the severity of ID was associated with the incidence of epilepsy and the same gene/set of genes may be involved in both of these neurological manifestations.

Several case reports have suggested an association between periventricular nodular heterotopia (PVNH) and 1p36 deletion [16,30–32], and the candidate region for polymicrogyria has been mapped to the distal 4.8 Mb region [33]. As the smallest deletion among the patients with abnormal neuronal migration was 3.0 Mb (Pt 8), the gene(s) responsible for this phenotype may be narrowed down to the distal 3.0 Mb region (Fig. 2; region D). Chiari malformation type II was identified only in Pt 34, who showed an unbalanced translocation with chromosome 4. Thus, this rare feature may be attributable to the partial trisomy of chromosome 4.

4.4. Cardiac abnormality

Previously, the genetic region responsible for left ventricular noncompaction (LVNC) was assigned to the 1.9–3.4 Mb region [34–36]. On the other hand, there are many reports which show an association between Ebstein anomaly and 1p36 deletion [7,37–40]. The genomic region responsible for Ebstein anomaly was assigned to the 2.9–3.8 Mb region [39,40]. In 2005, Sinkovec et al. reported two patients with LVNC associated with Ebstein anomaly [41]. In this study, we identified a patient (Pt 24) who showed both LVNC and Ebstein anomalies. Given this perspective, it might be reasonable to conclude that the critical regions involved in LVNC and Ebstein anomaly are relatively close. As mentioned above *PRDM16* located on chr1: 2,985,742–3,355,185 was reported as a gene responsible for cardiomyopathy and LVNC [28]. This is in agreement with our study, as the smallest deletion identified in a patient (Pt 9) with DCM was 3.1 Mb in size. It is possible that *PRDM16* may also be related not only to LVNC but also to the Ebstein anomaly.

Although double-outlet right ventricle (DORV) has never been reported in individuals with 1p36 deletions, we found DORV in two patients. We found a relatively small deletion (2.5 Mb) in a patient (Pt 6) with DORV (Fig. 2; region D). There is a possibility that the protein kinase C zeta gene (*PRKCZ*; chr1 chr1: 1,981,909–2,116,834) is related to cardiac abnormalities, because this gene had been implicated in a variety of process including cardiac muscle function [42,43]. The positional

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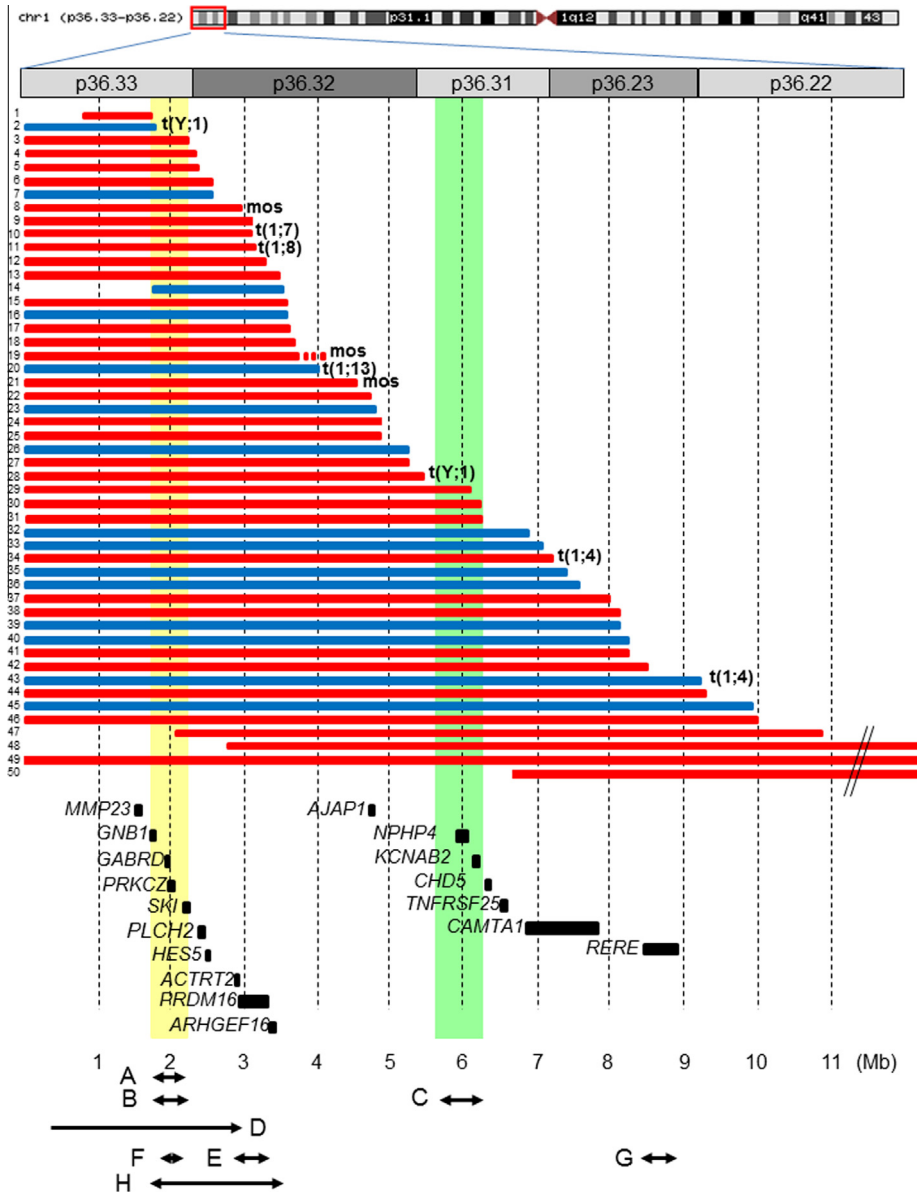

Fig. 2. Result of chromosomal microarray testing depicted in a genome map of the 1p36 region. The scheme of chromosome 1 (top) is downloaded from the UCSC genome browser. Red and blue bars indicate the deletion regions identified in female and male patients, respectively. Black bars indicate the locations of the genes, discussed in the text. The numbers depicted on the left side of each bar indicate patients' numbering. "t" and "mos" indicate unbalanced translocations and mosaicism, respectively. Yellow and green translucent vertical lines emphasize the proposed responsible regions for ID. Proposed responsible regions for each phenotype; A, distinctive craniofacial findings; B, ID; C, modifier effect for ID; D, LVNC and Ebstein anomaly; E, DORV; F, cardiac anomalies; G, cryptochidisms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

effects for *PRDM16* may be another possibility in this case.

The arginine-glutamic acid dipeptide (RE) repeats gene (*RERE*; chr1: 8,412,464–8,877,699) has been reported to play a critical role in early cardiovascular development [44]. In this study, all patients with deletions larger than 8.4 Mb, which involve *RERE*, showed cardiac anomalies. Thus, *RERE* may be involved in the pathogenesis of congenital heart defects (Fig. 2; region G).

Only Pt 20, with an unbalanced translocation between 13q32.3, showed hypoplasia of the left ventricle (HLHS) in this study. HLHS accounts for 2–3% of all congenital heart defects, and a minority of HLHS cases have been associated with congenital anomaly syndromes, e.g., the Jacobsen, Turner, and Potocki–Lupski syndromes, respectively [45–47]. As 13q duplication has been reported to be associated with this manifestation, the findings of HLHS found in Pt 20 may be due to a partial trisomy of 13q [48].

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4.5. Other complications

In patients with 1p36 monosomy, a Prader–Willi syndrome (PWS)-like phenotype has been described [6,13,49]. The clinical features that overlap between the 1p36 deletion syndrome and PWS are ID, neonatal hypotonia, obesity, craniofacial anomalies, hyperphagia, short stature, and behavior problems. D'Angelo et al. described a patient with a 2.5 Mb deletion within the chromosome region 1p36.33–1p36.32 [13]. Tsuyusaki et al. hypothesized that the critical region for the PWS-like phenotype was within 4 Mb from 1pter [49]. Rosenfeld et al. suggested a critical region for the PWS-like phenotype in the 1.7–2.3 Mb region [12]. In this study, all five patients with obesity (Pt 8, 10, 11, 13, and 21) were female, and acquired ambulatory ability within the ages of 2–8 years. Two of the patients (Pt 8 and 21) showed mosaic deletions [17]. From these perspectives, we speculate that female patients who showed 1p36 deletions involving the critical region and who acquired ambulatory ability are likely to be at risk for obesity.

5. Conclusion

In this study, we successfully accumulated the genotype–phenotype data of 50 patients with the deletions of 1p36 regions. As hypotelorism was commonly observed in patients, it may be characteristic of Asian patients. The genotype–phenotype correlation analysis narrowed down the regions responsible for distinctive craniofacial features and ID to the 1.8–2.1 and 1.8–2.2 Mb regions, respectively. Patients with deletions larger than 6.2 Mb showed no ambulation, indicating that severe neurodevelopmental prognosis may be modified by haploinsufficiencies of *KCNAB2* and/or *CHD5*, located 6.2 Mb away from the telomere. Although the genotype–phenotype correlation for the cardiac abnormalities is unclear, *PRDM16*, *PRKCZ*, and *RERE* may be related to this complication. One more finding revealed by this study for the first time, is that female patients who acquired ambulatory ability are likely to be at a risk for obesity.

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