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

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Table 2
Additional aberrations identified in the patients.

Patient number	Chr	Start*	End*	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	+	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	+	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	+	+	+	+	+	+	+	+	88% (29/33)
Pointed chin	+	+	+	+	NA	+	+	+	+	+	+	+	+	+	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	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	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	10% (4/42)
Polymicrogyria	–	–	NA	–	–	–	–	–	–	NA	–	–	–	–	NA	NA	–	–	–	–	–	–	–	–	+	NA	–	–	–	NA	–	–	NA	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	7% (3/42)
Cortical dysplasia	–	–	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.

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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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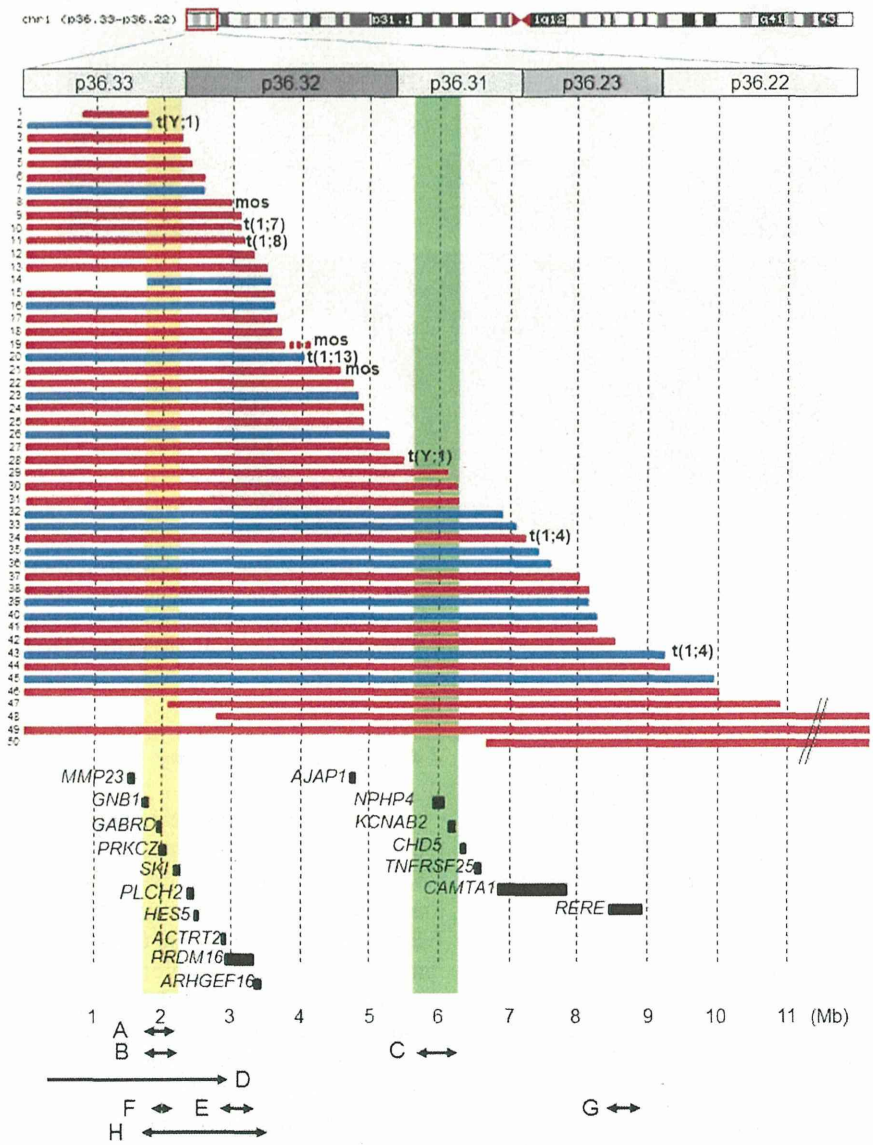

Fig. 2. Result of chromosomal microarray testing depicted in a genome map of the 1p36 region. The scheme of chromosome 1 (top) is downloaded from the UCSC genome browser. Red and blue bars indicate the deletion regions identified in female and male patients, respectively. Black bars indicate the locations 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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Original article

Clinical and genetic features of acute encephalopathy in children taking theophylline

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Abstract

Background: Theophylline has recently been suspected as a risk factor of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), although there has been no systematic study on the relationship between acute encephalopathy in children taking theophylline (AET) and AESD.

Methods: We recruited 16 Japanese patients (11 male and 5 female, median age of 2 years and 7 months) with AET from 2008 to 2013. We evaluated their clinical features, such as the duration of first seizure, biphasic clinical course and cranial CT/MRI imaging and compared them with those of AESD. We analyzed the polymorphisms or mutations of genes which are associated with AESD.

Results: Clinically, 12 patients had neurological and/or radiological features of AESD. Only one patient died, whereas all 15 surviving patients were left with motor and/or intellectual deficits. Genetically, 14 patients had at least one of the following polymorphisms or mutations associated with AESD: thermolabile variation of the carnitine palmitoyltransferase 2 (*CPT2*) gene, polymorphism causing high expression of the adenosine receptor A2A (*ADORA2A*) gene, and heterozygous missense mutation of the voltage gated sodium channel 1A (*SCN1A*) and 2A (*SCN2A*) gene.

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Conclusions: Our results demonstrate that AET overlaps with AESD, and that AET is a multifactorial disorder sharing a genetic background with AESD.

Keywords: Theophylline; Adenosine receptors; Acute encephalopathy; Status epilepticus

1. Introduction

Theophylline is a methylxanthine that exerts multiple pharmacologic effects by inhibiting phosphodiesterases. Until recently, it has been commonly used in clinical practice for the treatment of bronchial asthma and acute bronchitis, especially in Japan. However, theophylline may trigger seizures in patients with or without epilepsy, even when the concentration is within the therapeutic range [1,2]. The pro-convulsive effects of theophylline are explained by its activity as a non-selective, competitive antagonist of adenosine. In the central nervous system (CNS), adenosine plays a role as an endogenous anticonvulsant [3,4], since the effects of anti-excitatory A1 receptor (ADORA1) predominate over those of pro-excitatory A2A receptor (ADORA2A). Theophylline-associated seizures (TASs) are most prevalent among children under 6 years of age and usually occur during a febrile infectious disease [5]. TASs often persist and resist first-line anticonvulsants, leading to refractory status epilepticus and a poor neurologic outcome [6,7].

When a post-ictal coma lasts for more than 24 h, the condition should be regarded as acute encephalopathy rather than a mere seizure [8]. Acute encephalopathy with inflammation-mediated status epilepticus includes multiple syndromes [9], such as fever-induced refractory epileptic encephalopathy in school-aged children (FIRES) (or its eponym, acute encephalitis with refractory, repetitive partial seizures (AERRPS)), and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [10] (or its eponym, acute encephalopathy with febrile convulsive status epilepticus (AEFCSE)) [11]. In a case series in a referral hospital in Japan, many children taking theophylline reportedly had clinical and radiological features of AESD or AEFCSE [12]. Thus, theophylline has recently been suspected as a risk factor of AESD [8], although there has been no systematic study on the relationship between acute encephalopathy in children taking theophylline (AET) and AESD.

In this paper, we recruited Japanese patients with AET by means of a nationwide, multi-institutional study supported by the Japanese Society of Child Neurology. We reviewed their clinical data and examined whether the findings meet the diagnostic criteria of AESD. We also conducted genetic analysis of these patients, focusing on genes that were shown to be associated with AESD in our previous studies: carnitine palmitoyltransferase 2 (*CPT2*), *ADORA2A*, and voltage-gated sodium channel subunit 1A (*SCN1A*) and 2A (*SCN2A*) [12–15]. The aim of this study was to elucidate the relationship between AET and AESD from both clinical and genetic viewpoints.

2. Methods

2.1. Patients

We defined acute encephalopathy based on the following criteria [16,17]: (1) acute onset of severe and sustained impairment of consciousness after a preceding infection, and (2) exclusion of CNS inflammation. We defined AET as acute encephalopathy with the onset with status epilepticus within several hours after administration of oral theophylline or intravenous aminophylline, and recruited patients with AET from hospitals in Japan during 2008–2012 in a retrospective manner. Sixteen Japanese patients (11 male and 5 female) aged from 6 months to 4 years and 4 months (median, 2 years and 7 months), participated in this study. One case (Case 2) had been reported previously [14]. Their clinical characteristics including the family and past history, preceding infection, serum concentration of theophylline, duration of status epilepticus, presence or absence of biphasic seizures, cranial CT and/or MRI findings, therapy and outcome, were evaluated. The diagnosis of AESD was based on the criteria described previously [16]. It was regarded as 'definite' when both the characteristic clinical course (biphasic seizures) and CT/MRI findings (delayed appearance of cerebral cortical edema, distribution of lesions showing lobar or hemispheric involvement and peri-Rolandic sparing, and restricted diffusion of the subcortical white matter (so-called bright tree appearance) were present [8,10], 'probable' when either clinical or CT/MRI features were present, and 'possible' when prolonged febrile seizures were followed by non-specific CT/MRI findings (diffuse cortical damage) and other diagnostic possibilities were unlikely. In some patients whose CT/MRI findings in the acute/subacute period were either unavailable or insufficient, distribution of lesions was inferred on the basis of those in the convalescence. Other conditions that occasionally show bright tree appearance, such as hemorrhagic shock and encephalopathy syndrome, head

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