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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	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)
Atrial 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)

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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.

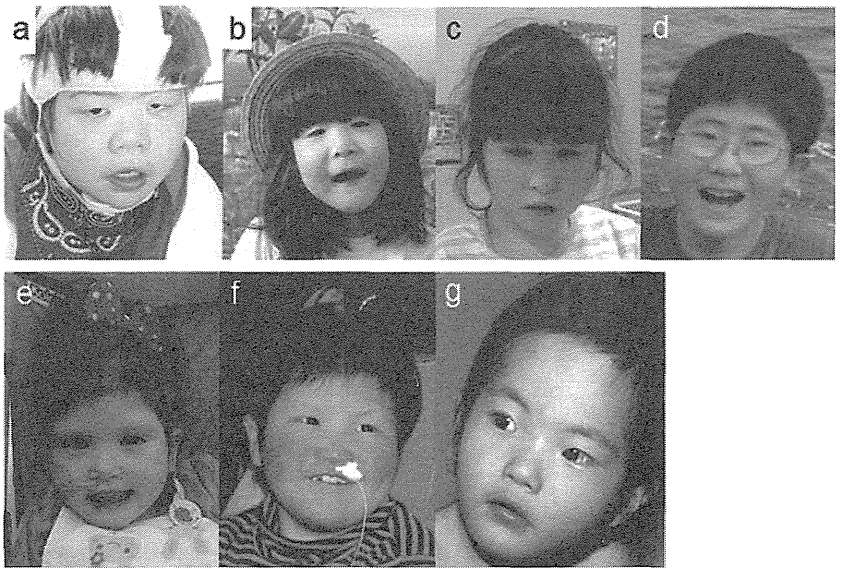

Fig. 1. Facial features of the patients with variably sized 1p36 deletions. Pt 1 (a; at 14 years of age) shows edematous eyelids rather than deep-set eyes. Pt 3 (b; 6 years), 6 (c; 5 years), and 14 (d; 15 years) share characteristic features, including deep-set eyes, hypotelorism, and pointed chins. 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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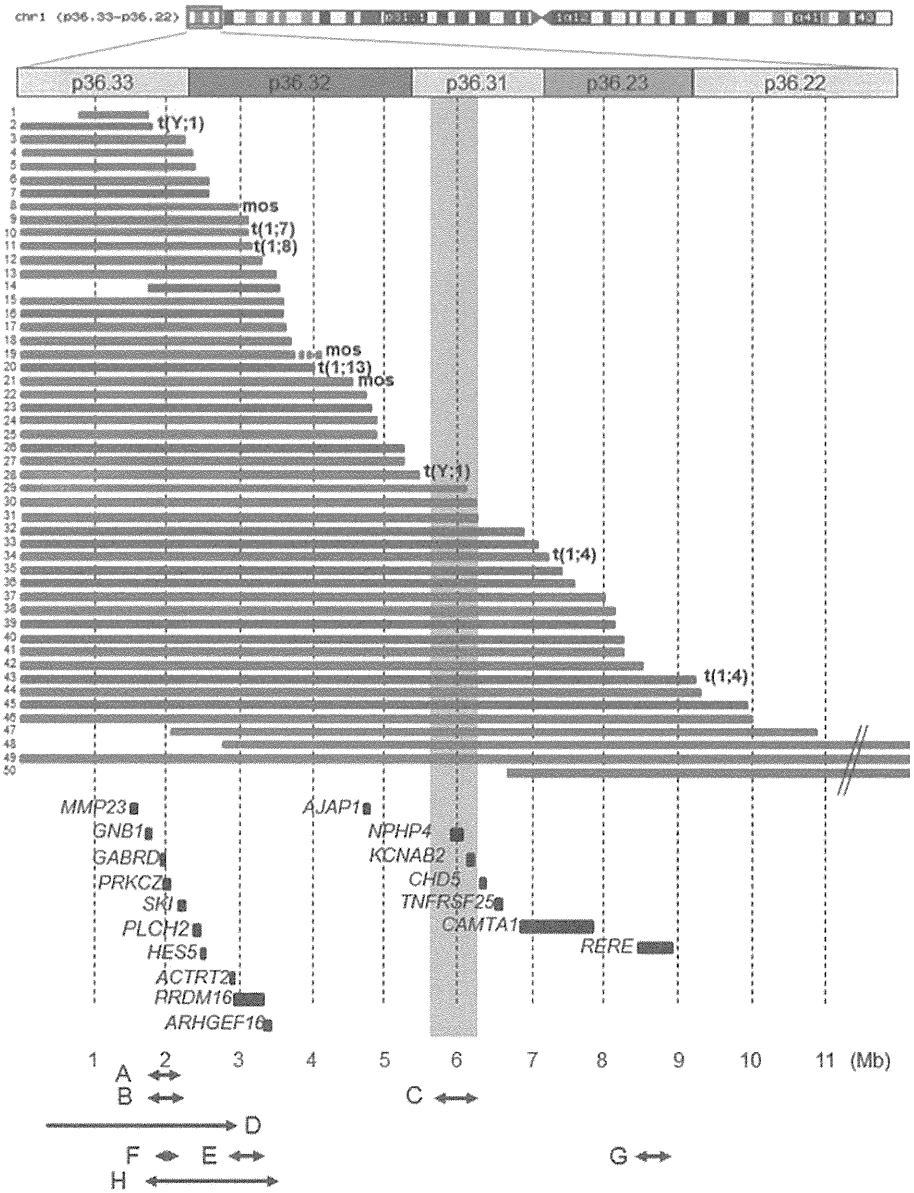

Fig. 2. Result of chromosomal microarray testing depicted in a genome map of the 1p36 region. The scheme of chromosome 1 (top) is downloaded from the UCSC genome browser. Red and blue bars indicate the deletion regions identified in female and male patients, respectively. Black bars indicate the locations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

[1] Shapira SK, McCaskill C, Northrup H, Spikes AS, Elder FFB, Sutton VR, et al. Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome. Am J Hum Genet 1997;61:642–50.
[2] Gajecka M, Yu W, Ballif BC, Glotzbach CD, Bailey KA, Shaw CA, et al. Delineation of mechanisms and regions of dosage imbalance in complex rearrangements of 1p36 leads to a putative gene for regulation of cranial suture closure. Eur J Hum Genet 2005;13:139–49.
[3] Heilstedt HA, Ballif BC, Howard LA, Lewis RA, Stal S, Kashork CD, et al. Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. Am J Hum Genet 2003;72:1200–12.
[4] Shao L, Shaw CA, Lu XY, Sahoo T, Bacino CA, Lalani SR, et al. Identification of chromosome abnormalities in subtelomeric regions by microarray analysis: a study of 5,380 cases. Am J Med Genet A 2008;146A:2242–51.
[5] Heilstedt HA, Ballif BC, Howard LA, Kashork CD, Shaffer LG. Population data suggest that deletions of 1p36 are a relatively common chromosome abnormality. Clin Genet 2003;64:310–6.
[6] Slavotinek A, Shaffer LG, Shapira SK. Monosomy 1p36. J Med Genet 1999;36:657–63.
[7] Battaglia A, Hoyme HE, Dallapiccola B, Zackai E, Hudgins L, McDonald-McGinn D, et al. Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics 2008;121:404–10.
[8] Battaglia A. Del 1p36 syndrome: a newly emerging clinical entity. Brain Dev 2005;27:358–61.
[9] Zenker M, Rittinger O, Grosse KP, Speicher MR, Kraus J, Rauch A, et al. Monosomy 1p36-a recently delineated, clinically recognizable syndrome. Clin Dysmorphol 2002;11:43–8.
[10] Kurosawa K, Kawame H, Okamoto N, Ochiai Y, Akatsuka A, Kobayashi M, et al. Epilepsy and neurological findings in 11 individuals with 1p36 deletion syndrome. Brain Dev 2005;27:378–82.
[11] Buck A, du Souich C, Boerkoel CF. Minimal genotype–phenotype correlation for small deletions within distal 1p36. Am J Med Genet A 2011;155A:3164–9.
[12] Rosenfeld JA, Crolla JA, Tomkins S, Bader P, Morrow B, Gorski J, et al. Refinement of causative genes in monosomy 1p36 through clinical and molecular cytogenetic characterization of small interstitial deletions. Am J Med Genet A 2010;152A:1951–9.
[13] D'Angelo CS, Da Paz JA, Kim CA, Bertola DR, Castro CIE, Varela MC, et al. Prader–Willi-like phenotype: investigation of 1p36 deletion in 41 patients with delayed psychomotor development, hypotonia, obesity and/or hyperphagia, learning disabilities and behavioral problems. Eur J Med Genet 2006;49:451–60.
[14] Okamoto N, Toribe Y, Nakajima T, Okinaga T, Kurosawa K, Nonaka I, et al. A girl with 1p36 deletion syndrome and congenital fiber type disproportion myopathy. J Hum Genet 2002;47:556–9.
[15] Hiraki Y, Fujita H, Yamamori S, Ohashi H, Eguchi M, Harada N, et al. Mild craniosynostosis with 1p36.3 trisomy and 1p36.3 deletion syndrome caused by familial translocation t(Y;1). Am J Med Genet A 2006;140A:1773–7.
[16] Saito Y, Kubota M, Kurosawa K, Ichihashi I, Kaneko Y, Hattori A, et al. Polymicrogyria and infantile spasms in a patient with 1p36 deletion syndrome. Brain Dev 2011;33:437–41.
[17] Shimada S, Maegaki Y, Osawa M, Yamamoto T. Mild developmental delay and obesity in two patients with mosaic 1p36 deletion syndrome. Am J Med Genet A 2014;164A:415–20.
[18] Shimada S, Okamoto N, Hirasawa K, Yoshii K, Tani Y, Sugawara M, et al. Clinical manifestations of Xq28 functional

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disomy involving MECP2 in one female and two male patients. Am J Med Genet A 2013;161A:1779–85.
[19] Shimada S, Okamoto N, Ito M, Arai Y, Momosaki K, Togawa M, et al. MECP2 duplication syndrome in both genders. Brain Dev 2013;35:411–9.
[20] Kang SH, Scheffer A, Ou Z, Li J, Scaglia F, Belmont J, et al. Identification of proximal 1p36 deletions using array-CGH: a possible new syndrome. Clin Genet 2007;72:329–38.
[21] Shimojima K, Paez MT, Kurosawa K, Yamamoto T. Proximal interstitial 1p36 deletion syndrome: the most proximal 3.5-Mb microdeletion identified on a dysmorphic and mentally retarded patient with inv(3)(p14.1q26.2). Brain Dev 2009;31:629–33.
[22] Benzing T, Schermer B. Clinical spectrum and pathogenesis of nephronophthisis. Curr Opin Nephrol Hypertens 2012;21:272–8.
[23] Otto EA, Ramaswami G, Janssen S, Chaki M, Allen SJ, Zhou W, et al. Mutation analysis of 18 nephronophthisis associated ciliopathy disease genes using a DNA pooling and next generation sequencing strategy. J Med Genet 2011;48:105–16.
[24] Gajecka M, Mackay KL, Shaffer LG. Monosomy 1p36 deletion syndrome. Am J Med Genet C 2007;145C:346–56.
[25] Wu YQ, Heilstedt HA, Bedell JA, May KM, Starkey DE, McPherson JD, et al. Molecular refinement of the 1p36 deletion syndrome reveals size diversity and a preponderance of maternally derived deletions. Hum Mol Genet 1999;8:313–21.
[26] Colmenares C, Heilstedt HA, Shaffer LG, Schwartz S, Berk M, Murray JC, et al. Loss of the SKI proto-oncogene in individuals affected with 1p36 deletion syndrome is predicted by strain-dependent defects in $Ski^{-/-}$ mice. Nat Genet 2002;30:106–9.
[27] Heilstedt HA, Burgess DL, Anderson AE, Chedrawi A, Tharp B, Lee O, et al. Loss of the potassium channel beta-subunit gene, *KCNAB2*, is associated with epilepsy in patients with 1p36 deletion syndrome. Epilepsia 2001;42:1103–11.
[28] Arndt AK, Schafer S, Drenckhahn JD, Sabeh MK, Plovie ER, Caliebe A, et al. Fine mapping of the 1p36 deletion syndrome identifies mutation of *PRDM16* as a cause of cardiomyopathy. Am J Hum Genet 2013;93:67–77.
[29] Potts RC, Zhang P, Wurster AL, Precht P, Mughal MR, Wood III WH, et al. CHD5, a brain-specific paralog of Mi2 chromatin remodeling enzymes, regulates expression of neuronal genes. PLoS One 2011;6:e24515.
[30] Neal J, Apse K, Sahin M, Walsh CA, Sheen VL. Deletion of chromosome 1p36 is associated with periventricular nodular heterotopia. Am J Med Genet A 2006;140:1692–5.
[31] Saito S, Kawamura R, Kosho T, Shimizu T, Aoyama K, Koike K, et al. Bilateral perisylvian polymicrogyria, periventricular nodular heterotopia, and left ventricular noncompaction in a girl with 10.5–11.1 Mb terminal deletion of 1p36. Am J Med Genet A 2008;146A:2891–7.
[32] Descartes M, Mikhail FM, Franklin JC, McGrath TM, Bebin M. Monosomy1p36.3 and trisomy 19p13.3 in a child with periventricular nodular heterotopia. Pediatr Neurol 2011;45:274–8.
[33] Dobyns WB, Mirzaa G, Christian SL, Petras K, Roseberry J, Clark GD, et al. Consistent chromosome abnormalities identify novel polymicrogyria loci in 1p36.3, 2p16.1-p23.1, 4q21.21-q22.1, 6q26-q27, and 21q2. Am J Med Genet A 2008;146A:1637–54.
[34] Thienpont B, Mertens L, Buyse G, Vermeesch JR, Devriendt K. Left-ventricular non-compaction in a patient with monosomy 1p36. Eur J Med Genet 2007;50:233–6.
[35] Cremer K, Ludecke HJ, Ruhr F, Wieczorek D. Left-ventricular non-compaction (LVNC): a clinical feature more often observed in terminal deletion 1p36 than previously expected. Eur J Med Genet 2008;51:685–8.
[36] Gajecka M, Saitta SC, Gentles AJ, Campbell L, Ciprero K, Geiger E, et al. Recurrent interstitial 1p36 deletions: evidence for germline mosaicism and complex rearrangement breakpoints. Am J Med Genet A 2010;152A:3074–83.
[37] Faivre L, Morichon-Delvallez N, Viot G, Martinovic J, Pinson MP, Aubry JP, et al. Prenatal detection of a 1p36 deletion in a fetus with multiple malformations and a review of the literature. Prenat Diagn 1999;19:49–53.
[38] Riegel M, Castellan C, Balmer D, Brecevic L, Schinzel A. Terminal deletion, del(1)(p36.3), detected through screening for terminal deletions in patients with unclassified malformation syndromes. Am J Med Genet 1999;82:249–53.
[39] Redon R, Rio M, Gregory SG, Cooper RA, Fiegler H, Sanlaville D, et al. Tiling path resolution mapping of constitutional 1p36 deletions by array-CGH: contiguous gene deletion or "deletion with positional effect" syndrome? J Med Genet 2005;42:166–71.
[40] Digilio MC, Bernardini L, Lepri F, Giuffrida MG, Guida V, Baban A, et al. Ebstein anomaly: genetic heterogeneity and association with microdeletions 1p36 and 8p23.1. Am J Med Genet A 2011;155A:2196–202.
[41] Sinkovec M, Kozelj M, Podnar T. Familial biventricular myocardial noncompaction associated with Ebstein's malformation. Int J Cardiol 2005;102:297–302.
[42] Sentex E, Wang X, Liu X, Lukas A, Dhalla NS. Expression of protein kinase C isoforms in cardiac hypertrophy and heart failure due to volume overload. Can J Physiol Pharmacol 2006;84:227–38.
[43] Wu SC, Solaro RJ. Protein kinase C zeta. A novel regulator of both phosphorylation and de-phosphorylation of cardiac sarcomeric proteins. J Biol Chem 2007;282:30691–8.
[44] Kim BJ, Zaveri HP, Shchelochkov OA, Yu Z, Hernandez-Garcia A, Seymour ML, et al. An allelic series of mice reveals a role for RERE in the development of multiple organs affected in chromosome 1p36 deletions. PLoS One 2013;8:e57460.
[45] Barron DJ, Kilby MD, Davies B, Wright JG, Jones TJ, Brawn WJ. Hypoplastic left heart syndrome. Lancet 2009;374:551–64.
[46] Grossfeld PD. The genetics of hypoplastic left heart syndrome. Cardiol Young 1999;9:627–32.
[47] Sanchez-Valle A, Pierpont ME, Potocki L. The severe end of the spectrum: hypoplastic left heart in Potocki–Lupski syndrome. Am J Med Genet A 2011;155A:363–6.
[48] Chen CP, Chern SR, Hsu CY, Lee CC, Lee MS, Wang W. Prenatal diagnosis of de novo partial trisomy 13q (13q22 → qter) and partial monosomy 8p (8p23.3 → pter) associated with holoprosencephaly, premaxillary agenesis, hexadactyly, and a hypoplastic left heart. Prenat Diagn 2005;25:334–6.
[49] Tsuyusaki Y, Yoshihashi H, Furuya N, Adachi M, Osaka H, Yamamoto K, et al. 1p36 deletion syndrome associated with Prader–Willi-like phenotype. Pediatr Int 2010;52:547–50.

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Clinical research

Overlapping microdeletions involving 15q22.2 narrow the critical region for intellectual disability to *NARG2* and *RORA*

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ABSTRACT

Microdeletions in the 15q22 region have not been well documented. We collected genotype and phenotype data from five patients with microdeletions involving 15q22.2, which were between 0.7 Mb and 6.5 Mb in size; two were of *de novo* origin and one was of familial origin. Intellectual disability and epilepsy are frequently observed in patients with 15q22.2 deletions. Genotype-phenotype correlation analysis narrowed the critical region for such neurologic symptoms to a genomic region of 654 Kb including the NMDA receptor-regulated 2 gene (*NARG2*) and the PAR-related orphan receptor A gene (*RORA*), either of which may be responsible for neurological symptoms commonly observed in patients with deletions in this region. The neighboring regions, including the forkhead box B1 gene (*FOXB1*), may also be related to the additional neurological features observed in the patients with larger deletions.
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1. Introduction

Chromosome 15 is one of the acrocentric chromosomes and has only the long arm. In this 15q region, many recurrent interstitial deletions are known to cause congenital anomaly syndromes. Prader–Willi/Angelman syndrome is the most established syndrome because of the recurrent 15q11.2 microdeletion, which is caused by non-allelic homologous recombination (NAHR) derived from the existence of low-copy repeats (LCRs) in the narrow region [Chai et al., 2003]. In the telomeric region of the Prader–Willi/Angelman critical region, there is a cluster of LCRs that contributes to the occurrence of the newly identified microdeletion syndromes by NAHR mechanism, which were identified because of the widespread use of chromosomal microarray testing and recognized as 15q13.3 microdeletion syndrome [Sharp et al., 2008]. The 15q24 microdeletion, which is more telomeric, is also known to be the consequence of LCRs-mediated interstitial deletion commonly observed in patients with intellectual disability (ID) [Sharp et al., 2007].

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Compared to that, random microdeletions involving the intermediate region of 15q are not well established as clinical entities. Fryns et al. [1982] and Yip et al. [1987] reported patients with deletions in the 15q21 region who showed developmental delay, growth retardation, hypotonia, and distinctive features with beaked nose, small alae nasi, thin upper lip, truncal obesity, and small hands and feet [Fryns et al., 1982; Yip et al., 1987]. This entity was later reported as the 15q21 deletion syndrome by others [Lalani et al., 2006; Liehr et al., 2003; Martin et al., 1990; Pramparo et al., 2005]. Tempesta et al. [2008] reported a patient with a *de novo* interstitial deletion of 15q21.2q22.1; however, this patient only showed mild ID [Tempesta et al., 2008]. Thus, they excluded the critical region for 15q21 deletion syndrome from the identified deletion region in the patient [Tempesta et al., 2008]. As a result, the 2.8 Mb-region (from 46.2 Mb to 49.0 Mb) is now considered as the critical region for the 15q21 deletion syndrome.

In this study, we collected data of five patients with microdeletions involving 15q22.2. Genotype-phenotype correlation analysis narrowed the critical region for ID.

2. Materials and methods

2.1. Materials

Patients' blood samples were collected after obtaining written informed consent based upon approval of the ethical committee of each institution. Genomic DNA was extracted from blood samples and used for subsequent evaluation.

2.2. Molecular and cytogenetic analysis

Genomic copy numbers were analyzed by chromosomal microarray testing. The Agilent CGH array 60K was used for patients 1 and 4, and the Agilent CGH array 44K was used for patients 3 and 5 (Agilent Technologies, Santa Clara, CA), according to the method described elsewhere [Yamamoto et al., 2011]. For patient 2, the GeneChip Human Mapping 205K Nsp Array (Affymetrix Inc., Santa Clara, CA) was used. Metaphase spreads prepared using the blood sample from patient 1 was used for fluorescence *in situ* hybridization (FISH) analysis. The bacterial artificial clones (BAC), RP11-48A4 (chr15:101,616,306–101,769,799) and RP11-358M11 (chr15:57,495,409–57,751,414), were selected from the UCSC genome browser (http://www.gwenome.ucsc.edu; GRCh37/hg19, February 2009) for use as probes. Both parental samples were also obtained and analyzed by FISH to confirm whether the aberration identified on patient 1 was *de novo*. For patients 4 and 5, both parents were tested by microarray.

The obtained data were up-loaded to the web-based database, DECIPHER (http://decipher.sanger.ac.uk/), in accordance with the policy to collaborate in order to establish a new syndrome of chromosomal abnormality, as described previously [Shimojima et al., 2011].

3. Results

3.1. Genomic copy number aberrations

We identified genomic copy number aberrations in the 15q22.2 region. After the results had been uploaded to DECIPHER database, some overlapping aberrations were identified. Then, a collaborative effort was made to study genotype–phenotype correlations. Consequently, we successfully collected data of five patients from four institutions. Genotype data are summarized in Table 1 and depicted in the genome map (Fig. 1). The genes included in the deletion region of the patients are summarized in Supplemental Table S1. All genotype data including that reported by Tempesta et al. [2008] were transferred and presented in accordance with build19. The five microdeletions involving 15q22.2 were between 0.7 Mb and 6.5 Mb in size; two had *de novo* origin and one was familial origin (Table 1). Parental origins were not examined in two patients. Patients 3 and 4 showed additional aberrations that were not on chromosome 15, i.e., at 9p24.1 and 16p12.2, respectively, associated with genomic copy number gains. The duplication of 16p12.2 was considered as a benign copy number variation (CNV) due to the inheritance from a normal parent; however, because the duplication of 9p24.1 could not be tested in parental DNA, the significance of this duplication was not evaluated.

Subsequent FISH analyses confirmed the presence of a simple interstitial deletion in metaphase spreads in patient 1 (Fig. 2). Because the same deletions were absent in the patient's parents, it was determined to be of *de novo* origin.

3.2. Clinical description

Clinical features of patients 1, 3, 4, and 5 are summarized in Table 2.

3.2.1. Patient 1

A 3-year-old girl (DECIPHER #271644) was born with a birth weight of 2712 g (50–90th centile) and occipitofrontal circumference (OFC) of 30.0 cm (<10th centile) at 37 weeks and 5 days gestation. There were no complications during pregnancy; however, the baby was delivered by cesarean section because of breech presentation. Although she showed motor developmental delay from her early infancy, i.e., head control at 4 months, rolling over at 12 months, sitting unsupported at 12 month, and walking at 31 months, the first meaningful word was spoken when she was 11 months old. Because of the developmental delay, she was examined at a hospital and generalized hypotonia and distinctive facial features were noted. Her developmental quotient (DQ) was

Table 1
Genotype data of the patients.

	DECIPHER number	Chromosomal band	Start[a]	End[a]	Size	Attribute	Inheritance
Patient 1	#271644	15q21.3–q22.2	55,951,100	62,484,416	6.5 Mb	Loss	*de novo*
Patient 2	#250973	15q21.3–q22.2	57,690,644	60,250,100	2.6 Mb	Loss	NT
Patient 3	#253216	15q21.3–q22.2	57,842,670	63,354,210	5.5 Mb	Loss	NT
		9p24.1	5,420,412	7,029,245	1.6 Mb	Gain	NT
Patient 4	#270602	15q21.3–q22.2	58,961,099	61,516,024	2.6 Mb	Loss	*de novo*
		16p12.2	21,951,379	22,380,197	429 Kb	Gain	Inherited
Patient 5	#250670	15q22.2	60,653,222	61,306,920	654 Kb	Loss	Inherited

NT; not tested.
[a] Genomic position referring to build 19.

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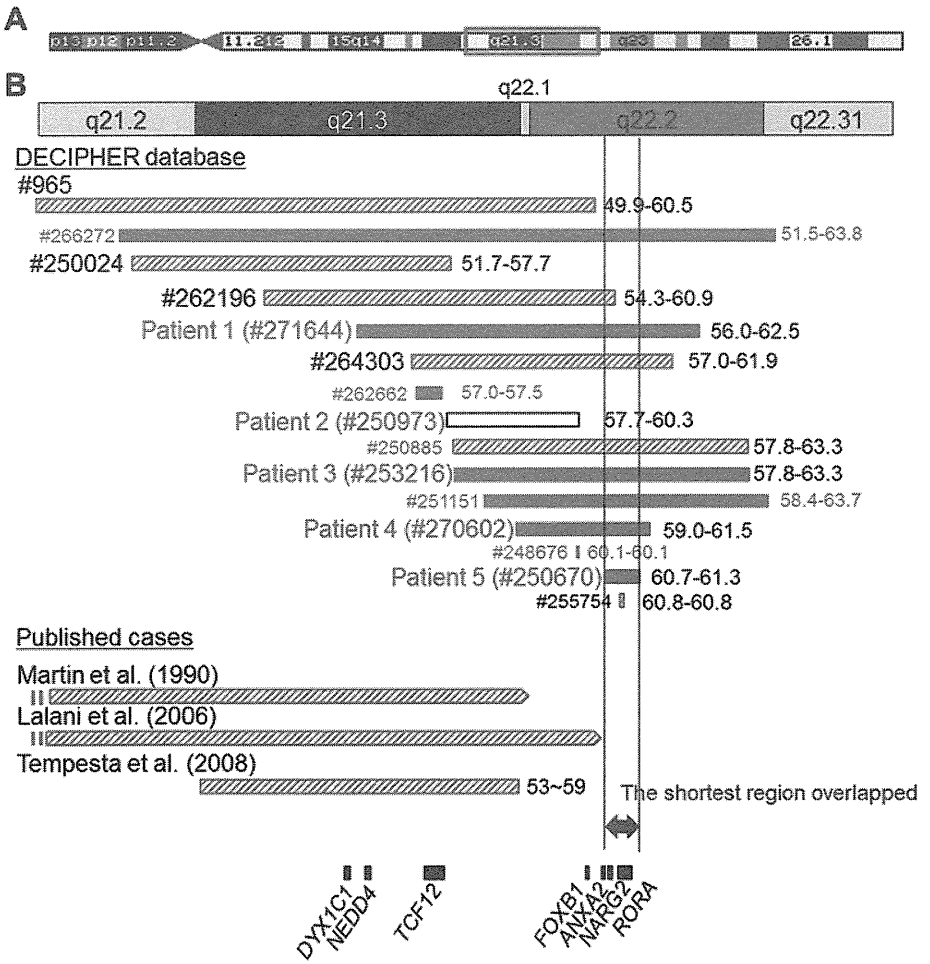

Fig. 1. Chromosomal microarray testing and genome map around 15q21.2-q22.31. (A) Schematic representation of chromosome 15 downloaded from the UCSC genome browser. The 15q21.2–q22.31 region (expanded below) is highlighted with a red rectangle. (B) Genome map in which the reported deletions are depicted. Registered deletions are extracted from the DECIPHER database and marked by rectangles. Red filled rectangles indicate the deletion regions of the patients in this study. A white rectangle indicates the deletion in the patient in this study but not associated with intellectual disability (ID). Red diagonally lined rectangles indicate the deletions in patients from the DECIPHER database and published reports associated with ID. Three deletions from the literature reported by Martin et al. [1990], Lalani et al. [2006], and Tempesta et al. [2008] are also included. Because the deletion regions reported by Martin et al. [1990] and Lalani et al. [2006] are at the chromosomal levels, they are indicated by arrows and dots. Gray bars indicate those of patients without any clinical information. The locations of potential candidate genes are indicated by black rectangles. The proposed responsible region is indicated by a blue bar with arrows in both sides. The deletion range of each patient is shown on the right side. Gene symbols are shown in italic.

determined to be 67, indicating mild developmental delay. Cranial computed tomography showed no abnormality. For further examination, she was referred to our institution.

At present, her height is 80.0 cm (−1.8 standard deviation [SD]), weight is 12.3 kg (+0.3 SD), and OFC is 50.8 cm (+2.1 SD), indicating macrocephaly. Her distinctive features are frontal bossing, short palpebral fissures, hypertelorism, telecanthus, flat nasal bridge, anteverted nares, thin lips, open mouth, a pointed chin, and right simian crease (Fig. 3). Strabismus of the left eye is noted. She can understand some simple oral suggestions and can speak some meaningful words, including "dangerous" and "sweet", but she cannot speak more than two words. She can use a spoon to eat food and can drink from cups. She shows self-injury behavior, e.g., head banking when she is scolded. She often shows a startle response when she suddenly hears a loud sound. She does not have sleep disturbance.

3.2.2. Patient 2

A 20-year-old male patient (DECIPHER # 250973) is not mentally retarded and has no congenital malformations. Genetic studies were initiated because he and his mother both have had terminal kidney failure at a young age, necessitating kidney transplantation. The X-linked form of Alport syndrome was excluded because there was no hematuria. In spite of no clear evidence of a histological diagnosis, chromosomal microarray testing was performed to confirm the absence or presence of the nephronophthisis 1 (juvenile) gene (*NPHP1*) deletion, which is associated with nephronophthisis; however, this deletion was not detected. Instead, the 15q deletion was identified. The cause of renal failures in mother and son has not been identified.

3.2.3. Patient 3

A 13-year-old girl (DECIPHER #253216) was born with a birth weight of 3210 g (50–75th centile), length of 50 cm (90–97th centile), and OFC of 34.4 cm (75–90th centile) at 41 weeks of gestation. Pregnancy and delivery were unremarkable, without any complication. At 20 months of age, she experienced spasm associated with syncope and convulsive motion. At that time, she showed growth delay: i.e., her weight was 10.5 kg (−2.0 SD), height was 80 cm (−1.0 SD), and OFC was 45 cm (−2.0 SD). She showed prominent forehead, short philtrum, upslanting palpebral fissures, thin and long fingers, and slight clinodactyly of both index fingers (Fig. 3B). Although

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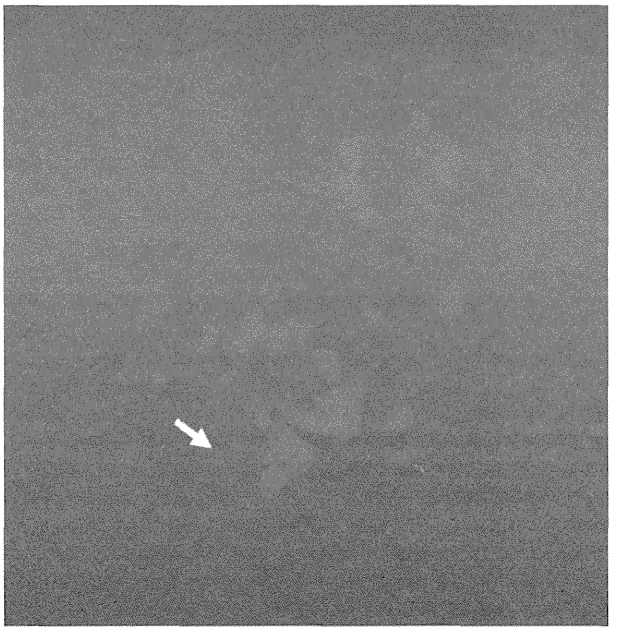

Fig. 2. Fluorescence *in situ* hybridization analysis for patient 1. Two red signals labeled on RP11-48A4 are the markers of 15q26.3. One of the targeted signals for 15q21.3, RP11-358M11 labeled by a green signal, is absent (arrow), indicating the deletion of this region.

anti-epileptic drugs were prescribed, she showed status epilepticus at the age of 4 years. Neurological examination revealed dysmetria, apraxia, ataxia and intention tremor. A sleep electroencephalogram (EEG) showed abnormal activities in the brain's left hemisphere. Brain magnetic resonance imaging (MRI) showed partial agenesis of the vermis. At 13 years of age, her weight was 42 kg (+1.0 SD), length was 141.5 cm (−2.0 SD), and the OFC was 53 cm (mean [M]), indicating she was overweight. Because this patient had not acquired reading and writing skills, which indicated severe ID with poor language skills, we could not assess her intelligence quotient (IQ). She still showed intractable complex partial epilepsy.

3.2.4. Patient 4

A 14-year-old boy (DECIPHER #270602) was born at 41 weeks of gestation, with a weight of 3,400 g (M), length of 52 cm (+2.0 SD), and OFC of 35 cm (M). The pregnancy was unremarkable. At 3 months of age, the patient started to show seizure attacks associated with drooling, which were intractable to antiepileptic treatment. At the age of 4 months, he showed head control and followed things with his eyes. Although he started to walk at the age of 24 months, he showed a significant delay in language development. At the age of 9 years, an ophthalmological surgery was performed to correct his strabismus. At the age of 11 years, he could speak about 50 meaningful words. At present, he shows autistic symptoms associated with moderate-mild ID with an estimated developmental quotient (DQ) of 50. He does not complain of sleep disturbance and does not show abnormal eating behavior. Puberty has not started. He shows minor morphological abnormalities such as brachycephaly, downturned corners of the mouth, deep-set eyes, prominent ears, short hands, and pes cavus (Fig. 3C).

3.2.5. Patient 5

A 13-year-old boy (DECIPHER #250670) was born at 40 weeks of gestation after an uneventful pregnancy. His birth weight was 3240 g (M). He started to walk unsupported at 16 months of age, and he was able to say the first meaningful word at 36 months of age. At the age of 3.5 years, he had an epileptic convulsion without fever. Brain MRI revealed slight ventricular asymmetry, and EEG showed paroxysmal activity in the frontal cerebral hemispheres. At the age of 9 years, he had a second seizure attack with aphasia, ataxia, and drowsiness; he had several epileptic episodes later. A subsequent EEG showed slow paroxysmal activities in the posterior-parietal-occipital areas of the right hemisphere. The patient is now under sodium valproate therapy. The Wechsler Intelligence Scale for Children-Revised test (WISC-R; performed at 13 years) revealed an IQ of 65, indicating mild ID. At our first examination his growth parameters were in the normal range (height 147 cm [10–25th centile], weight 47 kg [50–75th centile], and OFC 55 cm [50–75th centile]) (Fig. 3D, Table 2). His father, a 37-year-old man, stutters since childhood. The Wechsler Adult Intelligence Scale later revised test (WAIS-R) revealed an IQ of 59, indicating mild ID.

4. Discussion

In this study, we successfully collected genotype and phenotype data of five patients with microdeletions involving the 15q22.2 region. The deletion regions of these five patients were depicted on the genome map (Fig. 1) together with other data included in DECIPHER database; however, detailed clinical information of them was not available. The deletion regions of the previously reported patients, who had deletions in this region, are also depicted in Fig. 1. According to the genotype data, the deletion regions of three patient in this study (patient 1–3) overlapped with that reported by Tempesta et al. [2008] but did not overlap with the critical region of the 15q21 deletion syndrome [Tempesta et al., 2008]. This was expected because these three patients did not show any phenotypic characteristics resembling those of the 15q21 deletion syndrome (e.g., beaked nose). Rather, the deletion region extended toward the telomere (Fig. 1).

Although patient 2 had a microdeletion in this region, this patient did not show any neurological symptoms, but had a hereditary kidney disease of unknown origin. Therefore, this unexpectedly identified deletion was considered a benign CNV, and this region can be excluded from the candidate region for ID. The other four patients of the present study showed ID associated with some dysmorphic features, and three of them (patient 3, 4, and 5) also showed epilepsy. Because the shortest region of overlap (SRO)

Table 2
Summary of the clinical characteristics of the patients.

	Patient 1	Patient 3	Patient 4	Patient 5
Neurological symptoms				
Epilepsy	−	+	+	+
Intellectual disability (ID)	+	+	+	+
Strabismus	+	−	+	+
Dysmorphism				
Macrocephaly	+	−	−	−
Square face	+	+	+	+
Prominent fore head	+	+	+	−
Short palpebral fissures	+	−	−	−
Up-slanting palpebral fissures	+	+	−	−
Down-slanting palpebral fissures	−	−	−	+
Hypertelorism	+	−	−	−
Telecanthus	+	−	−	−
Flat nasal bridge	+	−	−	−
High nasal bridge	−	−	−	+
Anteverted nares	+	−	−	+
Short philtrum	+	+	+	−
Thin lips	+	+	−	+
Open mouth	+	−	−	−
Downturned corners of the mouth	−	−	+	+
Pointed chin	+	+	+	−

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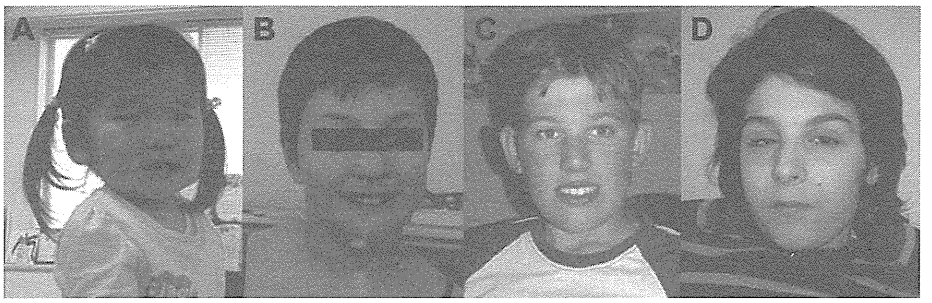

Fig. 3. Portraits of the presented patients. Patients 1 (A), 3 (B), 4 (C), and 5 (D). Prominent forehead and square face are commonly seen in all four patients. Upslanting palpebral fissures can be seen in patient 1 (A) and patient 3 (B).

could be narrowed down to the 654 Kb deletion region of patient 5 (chr15:60,653,222–61,306,920), genes included in this region are likely to be related to the phenotype.

Only three genes were included in this SRO, i.e., the annexin A2 gene (*ANXA2*), the NMDA receptor-regulated 2 gene (*NARG2*), and the RAR-related orphan receptor A gene (*RORA*) (Supplemental Table S1). Although some functional relevance to the phenotype has been reported, *ANXA2* has not been shown to have any neurological function [Cockrell et al., 2008]. On the other hand, *NARG2* is regulated by the NMDA receptor and is expressed at high levels in the neonatal brain in regions of neuronal proliferation and migration [Sugiura et al., 2001, 2004]. It is well known that NMDA receptor signaling is important for synaptic function [Hardingham and Bading, 2010]. Thus, *NARG2* can be considered as possible candidate gene for ID observed in the patients described in this study. The third gene, *RORA*, has been reported to be reduced in autistic brains [Nguyen et al., 2010]. Therefore, *RORA* can also be considered as a possible candidate gene for ID. Although the DECIPHER #255754 case was not included in this collaboration study, this male patient showed a *de novo* small interstitial deletion of 27 kb in size, which included only some of the exons of *RORA* in the SRO (Fig. 1). Clinical manifestations of this patient were delayed speech/language development and ID (web information from DECIPHER), indicating that *RORA* could be responsible for ID.

Patient 5 in this study showed mild ID; the identified deletion was inherited from his father who also showed mild ID and several epileptic episodes. Compared to this patient, neurological features of patients 3 and 4 were more severe. This difference may be attributed to the expanded deletion region and genes included in the additionally deleted region in patients 3 and 4. The forkhead box B1 gene (*FOXB1*) is located proximal to the deletion region in patient 5. *FOXB1* is a member of the forkhead box (FOX) gene family, which is known to be involved in the regulation of embryonic development [Takebayashi-Suzuki et al., 2011]. Expression of mouse *Foxb1* was detected in posterior regions of the early embryo; at later stages, it was localized to specific regions such as the midbrain, spinal cord and hypothalamus [Takebayashi-Suzuki et al., 2011]. Mice deficient in *Foxb1* have complex phenotypes, including reduced posterior tissue formation, severe open neural tube defects and impaired hypothalamus [Takebayashi-Suzuki et al., 2011]. Because *FOXB1* is not included in the deletion region identified in patient 2 (who showed no neurological features), this gene is still likely to be related to the phenotype.

Regarding genes with some functional relevance for the neurological symptoms, some genes in the neighboring region were identified by analysis of in-silico libraries. The dyslexia susceptibility 1 candidate 1 gene (*DYX1C1*) is known to be related to dyslexia; however, this gene was not included in the deletion region in the present patients. The neural precursor cell expressed developmentally down-regulated 4 gene (*NEDD4*) encodes an ubiquitin ligase and has been identified by a screening for genes related to brain development; however, detailed functions have not been identified yet [Donovan and Poronnik, 2013]. In 2013, the transcription factor 12 gene (*TCF12*; chr15:57,210,833–57,580,714) was identified as a gene responsible for coronal craniosynostosis [Sharma et al., 2013]. A loss-of-function mechanism was suggested in accordance with the existence of chromosomal deletions [Fukushima et al., 1990; Hiraki et al., 2008]; however, the penetrance of the phenotype is incomplete. Indeed, patient 1 whose deletion included *TCF12* did not show any coronal craniosynostosis.

In conclusion, thanks to a collaborative effort between four international centers, trough the DECIPHER database, we were able to collect genotype and phenotype data of five patients bearing microdeletions involving 15q22.2 and successfully narrowed the candidate genes for ID to *NARG2* and *RORA*.

Disclosure

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2014.02.001.

References

Chai JH, Locke DP, Greally JM, Knoll JH, Ohta T, Dunai J, et al. Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader–Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet 2003;73:898–925.

Cockrell E, Espinola RG, McCrae KR. Annexin A2: biology and relevance to the antiphospholipid syndrome. Lupus 2008;17:943–51.

Donovan P, Poronnik P. Nedd4 and Nedd4–2: ubiquitin ligases at work in the neuron. Int J Biochem Cell Biol 2013;45:706–10.

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Fryns JP, de Muelenaere A, van den Berghe H. Interstitial deletion of the long arm of chromosome 15. Ann Genet 1982;25:59–60.
Fukushima Y, Wakui K, Nishida T, Nishimoto H. Craniosynostosis in an infant with an interstitial deletion of 15q [46,XY,del(15)(q15q22.1)]. Am J Med Genet 1990;36:209–13.
Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nat Rev Neurosci 2010;11:682–96.
Hiraki Y, Moriuchi M, Okamoto N, Ishikawa N, Sugimoto Y, Eguchi K, et al. Craniosynostosis in a patient with a de novo 15q15-q22 deletion. Am J Med Genet A 2008;146A:1462–5.
Lalani SR, Sahoo T, Sanders ME, Peters SU, Bejjani BA. Coarctation of the aorta and mild to moderate developmental delay in a child with a de novo deletion of chromosome 15(q21.1q22.2). BMC Med Genet 2006;7:8.
Liehr T, Starke H, Heller A, Weise A, Beensen V, Senger G, et al. Evidence for a new microdeletion syndrome in 15q21. Int J Mol Med 2003;11:575–7.
Martin F, Platt J, Tawn EJ, Burn J. A de novo interstitial deletion of 15(q21.2q22.1) in a moderately retarded adult male. J Med Genet 1990;27:637–9.
Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. FASEB J 2010;24:3036–51.
Pramparo T, Mattina T, Gimelli S, Liehr T, Zuffardi O. Narrowing the deleted region associated with the 15q21 syndrome. Eur J Med Genet 2005;48:346–52.
Sharma VP, Fenwick AL, Brockop MS, McGowan SJ, Goos JA, Hoogeboom AJ, et al. Mutations in TCF12, encoding a basic helix-loop-helix partner of TWIST1, are a frequent cause of coronal craniosynostosis. Nat Genet 2013;45:304–7.
Sharp AJ, Mefford HC, Li K, Baker C, Skinner C, Stevenson RE, et al. A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. Nat Genet 2008;40:322–8.
Sharp AJ, Selzer RR, Veltman JA, Gimelli S, Gimelli G, Striano P, et al. Characterization of a recurrent 15q24 microdeletion syndrome. Hum Mol Genet 2007;16:567–72.
Shimojima K, Isidor B, Le Caignec C, Kondo A, Sakata S, Ohno K, et al. A new microdeletion syndrome of 5q31.3 characterized by severe developmental delays, distinctive facial features, and delayed myelination. Am J Med Genet A 2011;155A:732–6.
Sugiura N, Dadashev V, Corriveau RA. NARG2 encodes a novel nuclear protein with (S/T)PXX motifs that is expressed during development. Eur J Biochem 2004;271:4629–37.
Sugiura N, Patel RG, Corriveau RA. N-methyl-D-aspartate receptors regulate a group of transiently expressed genes in the developing brain. J Biol Chem 2001;276:14257–63.
Takebayashi-Suzuki K, Kitayama A, Terasaka-Iioka C, Ueno N, Suzuki A. The forkhead transcription factor FoxB1 regulates the dorsal–ventral and anterior–posterior patterning of the ectoderm during early Xenopus embryogenesis. Dev Biol 2011;360:11–29.
Tempesta S, Sollima D, Ghezzo S, Politi V, Sinigaglia B, Balducci F, et al. Mild mental retardation in a child with a de novo interstitial deletion of 15q21.2q22.1: a comparison with previously described cases. Eur J Med Genet 2008;51:639–45.
Yamamoto T, Shimojima K, Nishizawa T, Matsuo M, Ito M, Imai K, et al. Clinical manifestations of the deletion of Down syndrome critical region including DYRK1A and KCNJ6. Am J Med Genet A 2011;155A:113–9.
Yip MY, Selikowitz M, Don N, Kovacic A, Purvis-Smith S, Lam-Po-Tang PR, et al. Deletion 15q21.1–q22.1 resulting from a paternal insertion into chromosome 5. J Med Genet 1987;24:709–12.