

DATA REPORT

The smallest *de novo* 20q11.2 microdeletion causing intellectual disability and dysmorphic featuresHiroaki Hanafusa¹, Naoya Morisada^{2,3}, Yusuke Ishida⁴, Ryosuke Sakata⁵, Keiichi Morita⁶, Shizu Miura⁶, Ming Juan Ye³, Toshiyuki Yamamoto⁷, Nobuhiko Okamoto⁸, Kandai Nozu³ and Kazumoto Iijima³

The 20q11.2 microdeletion is a rare chromosomal aberration characterized by intellectual disability (ID), motor developmental delay, neonatal feeding problems, and facial dysmorphism. Here, a 2-year- and 6-month-old Japanese girl with a 1.2 Mb microdeletion of 20q11.2 showed ID, motor developmental delay, and distinctive facial features without feeding problems. The deleted region was identified by array-based comparative genomic hybridization and is the smallest reported for a 20q11.2 microdeletion.

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Interstitial microdeletion of the long arm of chromosome 20 (20q) is a rare condition. Indeed, to the best of our knowledge, 20q11.2 microdeletions, as confirmed by array-based comparative genomic hybridization, have only been found in a few patients.^{1–4} These patients show intellectual disability (ID), perinatal feeding problems, and facial dysmorphic features. Jedraszak *et al.*⁴ suggested the concept of ‘20q11.2 microdeletion syndrome,’ with the responsible genes being *GDF5*, *EPB41L1*, and *SAMHD1*. Here we present a patient with the smallest reported *de novo* 20q11.2 microdeletion, which does not include *GDF5*, *EPB41L1*, or *SAMHD1*.

A 2-year and 6-month-old Japanese girl was referred to our hospital, to investigate the cause of her facial dysmorphism and ID. She was the second child from unrelated parents. Her parents and elder brother were healthy. Her gestational age was 36 weeks and her Apgar score was 7 (at 1 min). She showed transient tachypnea and required temporary non-invasive respiratory support. Her birth weight was 2.460 g (50–75th percentile), height was 51.4 cm (> 97th percentile), and head circumference was 33 cm (50–75th percentile). She exhibited facial dysmorphic features, namely, bilateral epicanthus, ptosis, a depressed nasal bridge, anteverted nares, and retrognathia. She had global motor developmental delay. She could hold her head up at 7 months, roll over at 9 months, and sit on her own at 12 months but could not stand up at 2 years and 6 months. She had reduced hip abduction and significant constipation without evidence for any organic intestinal disorders such as Hirschsprung disease. She showed no apparent feeding problems and had no growth disturbance. At 2 years and 6 months old, her weight was 12.5 kg (25–50th percentile), height was 88 cm (25–50th percentile), and head circumference was 49.0 cm (50–75th percentile). Her blood tests were normal. Her karyotype, determined by chromosomal G-band testing, was 46, XX. Brain magnetic resonance imaging, electroencephalogram, electrocardiogram, and 24 h Holter electrocardiogram monitoring were all normal. Her total developmental quotient evaluated on the Kyoto Scale of Psychological Development 2001⁵ was 49 (Postural-Motor developmental quotient, 25; Cognitive-Adaptive developmental quotient, 57; and Language-Social

developmental quotient 60) at 2 years and 5 months of age. She was unable to speak any significant words at 2 years and 10 months.

To confirm her molecular diagnosis, we performed array-based comparative genomic hybridization after obtaining written informed consent from her parents. All procedures were reviewed and approved by the Institutional Review Board of Kobe University School of Medicine (86) and Hyogo Prefectural Kobe children’s hospital (28-4), and were in accordance with the ethical standards of the Declaration of Helsinki. We used the Agilent 180 K Human Genome CGH Microarray Platform (Agilent Technologies, Santa Clara, CA) according to the manufacturer’s instructions. We identified an ~1.2 Mb heterozygous deletion on chromosome 20q11.2: arr[GRCh38] 20q11.21q11.22 (32383693_33563791)x1 (Figure 1a). This region includes 21 RefSeq genes: *ASXL1*, *NOL4L*, *LOC101929698*, *LOC149950*, *C20orf203*, *COMM7*, *DNMT3B*, *MAPRE1*, *SUN5*, *BPIFB2*, *BPIFB6*, *BPIFB3*, *BPIFB4*, *BPIFA2*, *BPIFA4P*, *BPIFA3*, *BPIFA1*, *BPIFB1*, *CDK5RAP1*, *SNTA1*, and *CBFA2T2* (Figure 1b and Supplementary Table 1). The deletion was not detected in parental samples and therefore shows *de novo* occurrence.

Four patients with deleted regions confirmed by array-based comparative genomic hybridization analysis overlapped with our patient (Figure 1c). Hiraki *et al.*¹ reported a Japanese boy with a 6.5 Mb microdeletion of 20q11.2–q12. He had moderate ID and motor developmental delay, feeding problems, growth disturbance, and retinal dysplasia. Iourov *et al.*² reported a boy with mild ID and dysmorphic features, but no growth disturbance. Posmyk *et al.*³ reported a girl with a 5.7 Mb microdeletion on 20q11.21–q11.23. She had ID, motor developmental delay, growth disturbance, and dysmorphic facial features. Jedraszak *et al.*⁴ reported six patients with 20q11.2 microdeletions, with one of the patients (Patient 5) exhibiting a chromosomal deletion on 20q11.21–q11.22. Patient 5 was a 20-year-old woman with mild ID and facial dysmorphism, namely, deep-set eyes and mid-face dysplasia. Of these four patients, our patient has the smallest deletion (Table 1). An additional seven patients with 20q11.2 deletions have been reported by Callier *et al.*,⁶ Iqbal and Al-Owain,⁷ and Jedraszak

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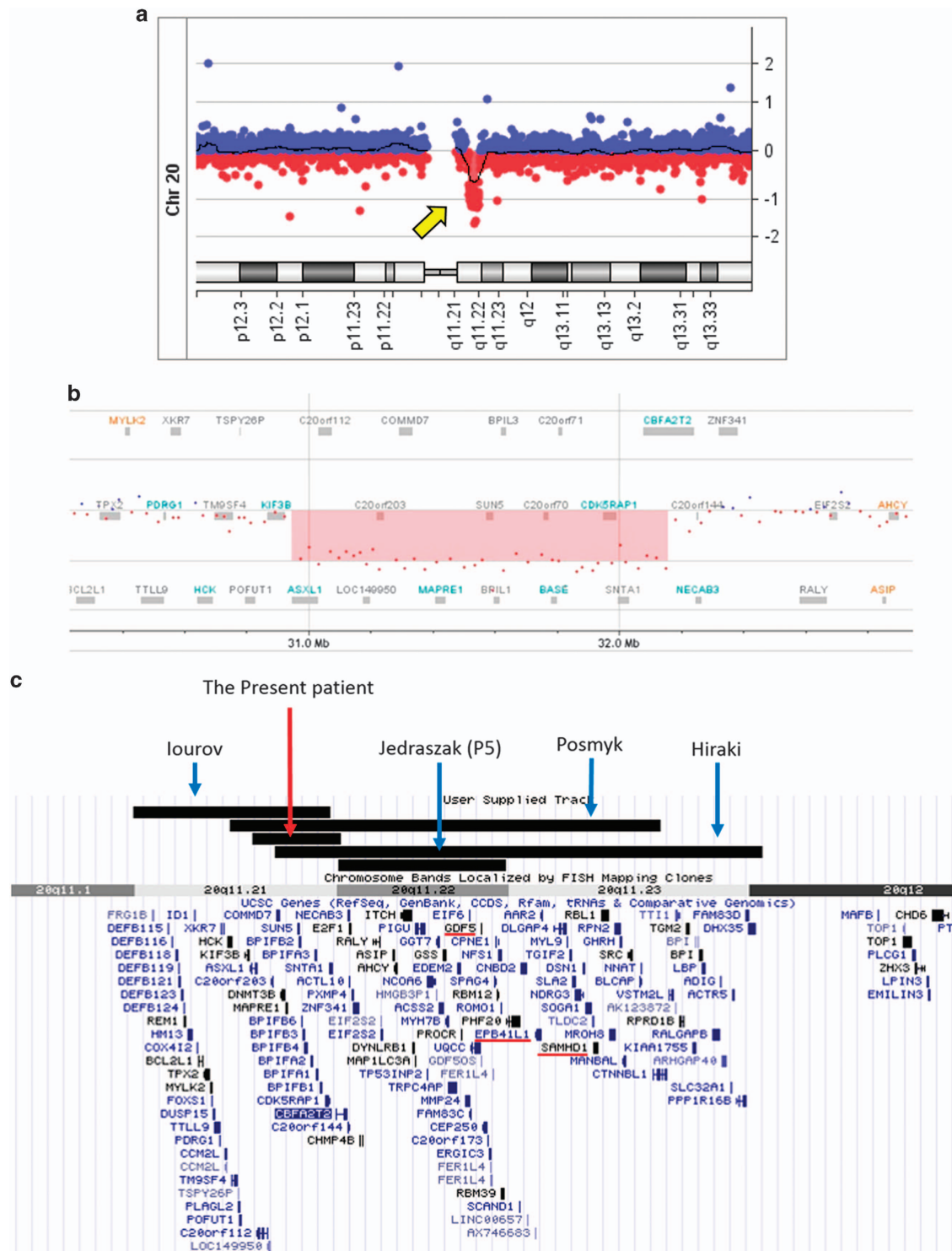


Figure 1. Chromosomal comparative genomic hybridization (CGH) microarray of the patient. An ~1.2 Mb microdeletion on the long arm of chromosome 20 was identified (a). This region includes 21 RefSeq genes (b). CytoGenomics ver. 4.0.3 (Agilent Technologies) was used to create a, b. Five patients with overlapping deleted regions were compared using the University of California, Santa Cruz (UCSC) Genome Browser (<https://genome.ucsc.edu/>). The three genes (*GDF5*, *EPB41L1*, and *SAMHD1*) underlined in red were suggested to be the critical genes of 20q11.2 microdeletion syndrome by Jedraszak *et al.*⁴ (c). P5, patient 5.

*et al.*⁴ although the deleted regions do not overlap and were more distal than the region in our patient. Most of these patients showed feeding problems and growth disturbances. Jedraszak *et al.*⁴ suggested that the facial appearance of a high forehead, frontal bossing, enophthalmos, and midface hypoplasia are typical features of 20q11.2 microdeletion syndrome, with the 1.62 Mb crucial

deleted region including *GDF5*, *EPB41L1*, and *SAMHD1*. The deleted region in our patient does not include these three genes (Figure 1c), but the clinical phenotypes are similar.

In addition, sex combs-like 1 (*ASXL1*) and syntrophin alpha-1 (*SNTA1*) are included in the deleted region of our patient as an autosomal dominant disease phenotype (Supplementary Table 1).

Table 1. Phenotypes of patients with 20q11.2 deletions overlap with the present patient

	Hiraki <i>et al.</i> ¹	Iourov <i>et al.</i> ²	Posmyk <i>et al.</i> ³	Jedraszak <i>et al.</i> ⁴ (Patient 5)	The present patient
Size	6.5 Mb	2.6 Mb	5.7 Mb	2.2 Mb	1.2 Mb
Region	arr[GRCCh38] 20q11.2q12 (32681859_39154198) x1	arr[GRCCh38] 20q11.21 (30184894_33429237) x1	arr[GRCCh38] 20q11.21q11.23 (32081803_37789383) x1	arr[GRCCh38] 20q11.21q11.22 (33530857_35773513) x1	arr[GRCCh38] 20q11.21q11.22 (32383693_33563791) x1
Age, sex	1, Male	7, Male	2, Female	20, Female	2, Female
ID	moderate	mild	+	mild	moderate
Feeding	+	+	+	not described	-
Eyes difficulty	Hypertelorism, small eyes, retinal dysplasia	Proptosis, hypertelorism, prominent eyes, upslanting palpebral fissure	Hypertelorism, epicanthus, retinal dysplasia	Ptosis, deeply set eyes, astigmatism	Ptosis, hypertelorism, epicanthus inversus, deeply set eyes
Ears	Low set ears, posterior rotated ears, hearing loss	Low set ears	Low set ears	Hearing loss	-
Nose	Wide nasal bridge, underdeveloped alae nasi	Wide nasal bridge	Wide nasal bridge, underdeveloped alae nasi	-	Anteverted nares
Other facial features	Arched eyebrows, microretrognathia, thin lips	Microretrognathia, low frontal hairline	Arched eyebrows, cleft palate, microretrognathia, thin lips, thin and sparse hair, high forehead	High forehead, midface hypoplasia,	High forehead, frontal bossing, midface hypoplasia, microretrognathia
Other features	Brain atrophy, small thorax, talipes valgus, hands and feet abnormalities	-	Hypotonia, microcephaly, preaxial polydactyly, syndactyly, heart defect	TAPVR, brachtdactyly, talipes vulgus	Constipation, acetabular dysplasia

Abbreviations: ID, intellectual disability; TAPVR, total anomalous pulmonary venous return, +, present; -, absent. Genome positions were converted in accordance with GRCh38, using LiftOver from the UCSC Genome Browser (<https://genome.ucsc.edu/cgi-bin/hg.LiftOver>).

ASXL1 is the causative gene of Bohring-Opitz syndrome (BOS, #605039), which is characterized by severe ID; prominent eyes; nevi flammei at the forehead, philtrum, or nape of neck; upslanting palpebral fissures; and severe feeding problems.⁸ BOS usually occurs in patients with *ASXL1* nonsense or frameshift variants. The deleted region in our patient includes *ASXL1* at the 3'-side marginal region. The patients reported by Iourov and Posmyk have deletions of the entire *ASXL1* gene. Iourov *et al.*² suggested that the *ASXL1* whole gene deletion may cause a milder BOS phenotype. Our patient has deep-set eyes and no growth disturbance, which is distinct from BOS. The precise reason why our patient did not show any facial features such as BOS is not clear, but the *ASXL1* truncation may have contributed to her ID and motor developmental delay. *SNTA1* encodes a gene that is responsible for long QT syndrome 12 (LQT12, 612955) in an autosomal-dominant manner. LQT12 is a rare disease and all three reported LQT12 patients have *SNTA1* missense mutations.⁹ Our patient does not show any cardiac abnormalities by echocardiogram and 24 h electrocardiogram, but more careful observation of the patient for cardiac problems should be undertaken.

Other genes included in the deleted region might affect her phenotype. *DNMT3B* (DNA methyltransferase 3 β) is the causative gene of immunodeficiency-centromeric instability-facial anomalies syndrome 1, which is an autosomal recessive disorder. Instability-facial anomalies syndrome is characterized by immunodeficiency, chromosome instability, failure to thrive, and mild facial anomalies, which include a flat face, flat nasal bridge, small upturned nose, hypertelorism, epicanthal folds, low-set ears, macroglossia, and micrognathia.¹⁰ Our patient showed facial dysmorphic features, but her face was unlike that of instability-facial anomalies syndrome. In addition, she did not show any increased vulnerability to infection and allelic losses of *DNMT3B* can be benign in some patients.² *CBFA2/RUNX1* translocation partner 2 (*CBFA2T2*) was partially deleted in our patient and Patient 5 in the study by Jedraszak *et al.*⁴ *CBFA2T2* is associated with acute myeloid leukemia and recently it has been reported that *CBFA2T2* is important for maintaining embryonic stem cell pluripotency via binding to PR domain-containing protein 14.¹¹ The high pLI score (1.00) in ExAC Browser suggests haploinsufficiency of *CBFA2T2* (<http://exac.broadinstitute.org/gene/ENSG00000078699>). The two patients were similar in facial features. The cause of this similarity remains unknown. The role of *CBFA2T2* in human germline disorders is still unclear, and further study is essential.

In conclusion, 20q11.2 microdeletion may be a recognizable disorder, but the correlation between phenotype and genotype for this disorder needs further study.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at <http://dx.doi.org/10.6084/m9.figshare.hgv.1663>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1666>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1669>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1672>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1675>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1678>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1681>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1684>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1687>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1690>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1693>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1696>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1699>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1702>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1705>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1708>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1711>, <http://dx.doi.org/10.6084/m9.figshare.hgv.1714>,

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COMPETING INTERESTS

The authors declare no conflict of interest.

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