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CASE REPORT

Mild prominence of the Sylvian fissure in a Bainbridge-Ropers syndrome patient with a novel frameshift variant in *ASXL3*

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Key Clinical Message

A Japanese boy aged 7 years with Bainbridge-Ropers syndrome (BRPS) had a prominent domed forehead without metric ridge, mild prominence of the Sylvian fissure with bitemporal hollowing, and a heterozygous de novo novel variant "p.P1010Lfs*14" in *ASXL3* gene in addition to typical findings of BRPS.

Keywords

ASXL3, Bainbridge-Ropers syndrome, Sylvian fissure.

Introduction

Bainbridge–Ropers syndrome (BRPS; MIM 615485) was first described in 2013 and is characterized by failure to thrive, feeding problems, severe developmental delay, hypotonia, autism, delays in language acquisition, postnatal growth retardation, and abnormal facial features with arched eyebrows and anteverted nares. BRPS is caused by de novo dominant truncating variants in the Transcriptional Regulator gene Additional Sex Combs Like 3 (*ASXL3*), while missense variants in *ASXL3* have been identified in individuals with autism spectrum disorder (ASD) [1, 3, 5, 14]. ASXL family members are assumed to be epigenetic regulators that are involved in hereditary neurological disorders as well as malignancies [1, 2, 6, 8].

We describe a boy aged 7 years with a novel frameshift variant in *ASXL3*, identified by whole-exome and Sanger sequencing. The patient had characteristic BRPS features as well as additional findings of mild prominence of the Sylvian fissure with bitemporal hollowing, stereotypic movements such as whispering face and hand-wringing, deep palmar creases, abnormal facial features, and severe developmental delay with speech delay with only a few meaningful words.

Clinical Report

The patient was a boy, the first born child to a healthy, nonconsanguineous couple. At the time of his birth, both of parents were 35 years of age. Two other elder children were healthy. There was no family history of BRPS. Both of pregnancy and delivery at 39 weeks of gestation were uneventful. At birth, weight was 3658 g (+1.6 SD), length 47.4 cm (−0.7 SD), and occipitofrontal circumference (OFC) 37.5 cm (+2.8 SD). Hearing impairment was suspected in audiometry of the newborn screening at the age of 5 days. In addition to that, he was referred to our clinic for failure to thrive. At the age of 1 month, his weight was 4380 g (−1.6 SD), length 54.8 cm (−1.2 SD), and OFC 38.0 cm (−0.5 SD). He had a prominent forehead, arched eyebrows, edematous periorbital region, hypertelorism, short nose, anteverted nostrils, long

philtrum, thin upper lip, full cheeks, bitemporal hollowing, and deep palmar creases without camptodactyly (Fig. 1A,C,H,I). He had mild hypotonia and bilateral mild sensorineural deafness (40–50 dB). Ophthalmological findings showed hyperopia and astigmatism. He had been repeatedly admitted to hospital for asthmatic bronchitis up to the age of 4 years. His developmental milestones were delayed – head control at the age of 6 months, rollover at 8 months, sitting unaided at 2 years and 4 months, walking with support at 2 years and 7 months. At the age of 7 years, he had a few meaningful words. He had stereotypic movements such as whispering face (Fig. 1B) and hand-wringing. At the age of 4 years, his length was 88.0 cm (−3.0 SD), weight 11.5 kg (−2.1 SD),

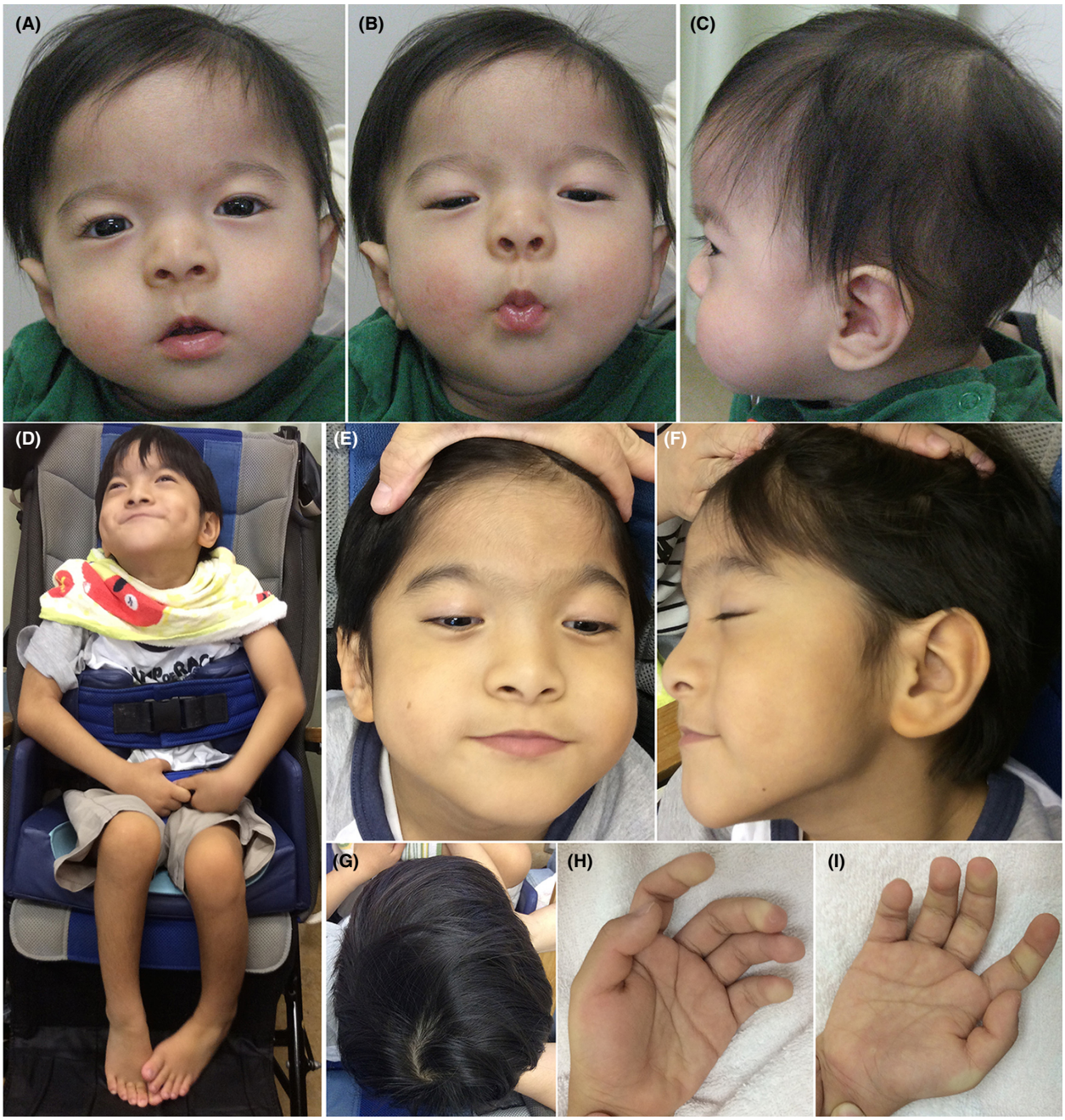

Figure 1. Patient's appearance: at age 1 year and 2 months (A–C) and 7 years and 6 months (D–I). Face (front; A, B, E, lateral; C, F), full-length body (D), head (G), hand (left; H, right; I). Reproduction of the pictures was kindly permitted by his parents.

and OFC 48.5 cm (−1.1 SD). At the age of 7 years and 10 months, he was evaluated to have profound mental retardation (DQ = 10) and short stature (105.0 cm; −3.7 SD) as well as poor weight gain (16.2 kg; −1.9 SD). Auditory brain stem response (ABR) revealed normal hearing ability at age 7 years. Radiological examination at the age of 3 years revealed scoliosis at Th12-L1 (Fig. 2L). Magnetic resonance imaging (MRI) showed a hypoplastic body of the corpus callosum (Fig. 2A), mild bilateral prominence of the Sylvian fissure (Fig. 2B–D,F–H), mild atrophy of the cerebellar vermis (Fig. 2E), and mild white matter loss of the left frontal lobe with normal myelination (Fig. 2D,H). The intrafissural venous plexus of the right parietal area (Fig. 2I) was reduced at the age of 3 years and 7 months compared with the finding at 9 months. No malformation of the carotid artery was detected by magnetic resonance angiography. Three-dimensional CT imaging showed prominent domed forehead without the ridge of the metopic suture and also shallow hollowing of the backward region of the frontoparietal suture without craniosynostosis (Fig. 2J,K), consistent with the region where mild prominence of the Sylvian fissure was found. Levels of plasma amino acids, urinary organic acids, lactate and pyruvic acid, and blood gas analysis were all normal. A chromosomal analysis showed a normal karyotype. We searched the original

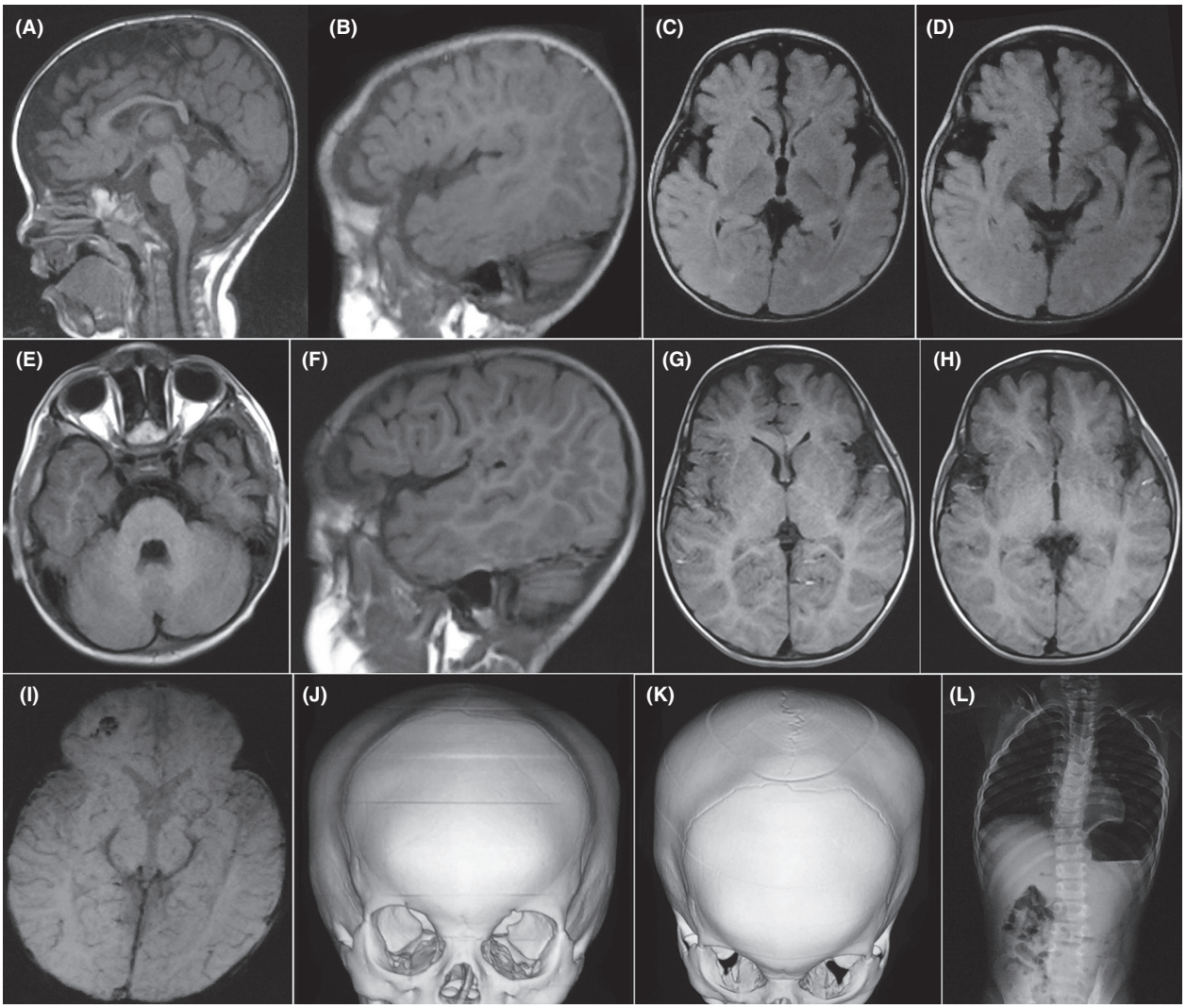

Figure 2. Imaging study taken at the age of 9 months (A–D, I), 2 years and 7 months (E–H), 3 years and 7 months (J, K), and 7 years and 5 months (L). T1 MRI imaging of the brain; sagittal plane: median (A), left side (B, F), and cross section (C–E, G, H). Cross-sectional SW1 MRI imaging (I). Frontal view of the brain by three-dimensional CT imaging (J, K) and of the spine by radiography (L). MRI, magnetic resonance imaging; CT, computerized tomography.

computerized database for possible malformation syndromes: UR-DBMS (University of the Ryukyus-Database for Malformation Syndromes: http://becomerich.lab.u-ryukyu.ac.jp) edited by Naritomi [12]. Although Char syndrome (MIM 169100), Miller–Dieker lissencephaly syndrome (MIM 247200), Pallister–Killian syndrome (MIM 601803), 10q26 deletion, 2q3 trisomy, 7q3 monosomy were suggested as candidates matching all nine signs, no syndromes were considered to be appropriate. An array-based comparative genomic hybridization analysis revealed no pathogenic copy number variations in the patient. Whole-exome sequencing using the SureSelect Human All Exon V6 kit (Agilent Technologies, Santa Clara, CA) and HiSeq2500 (illumina, San Diego, CA) was performed. To identify disease-causative mutations, we excluded all known variants found in the 1000 Genomes database (http://www.internationalgenome.org/), Japanese Genomes database [11], dbSNP (http://www.ncbi.nlm.gov/SNP), the genome Aggregation Database (gnomAD; http://gnomad.broadinstitute.org/), and the Human Genetic Variation Database (HGVD; http://www.genome.med.kyoto-u.ac.jp/SnpDB/). By focusing on nonsynonymous SNVs, insertions and deletions, and splice site variants, we narrowed down to 10 variants including four autosomal dominant inherited types and six autosomal recessive inherited types (Table S1). A heterozygous mutation in the *ASXL3* gene (NM_030632) is causative for BRPS, which was considered highly similar to our patient. We identified a heterozygous single nucleotide deletion (c.3028delC) in exon 11 of *ASXL3* gene, which

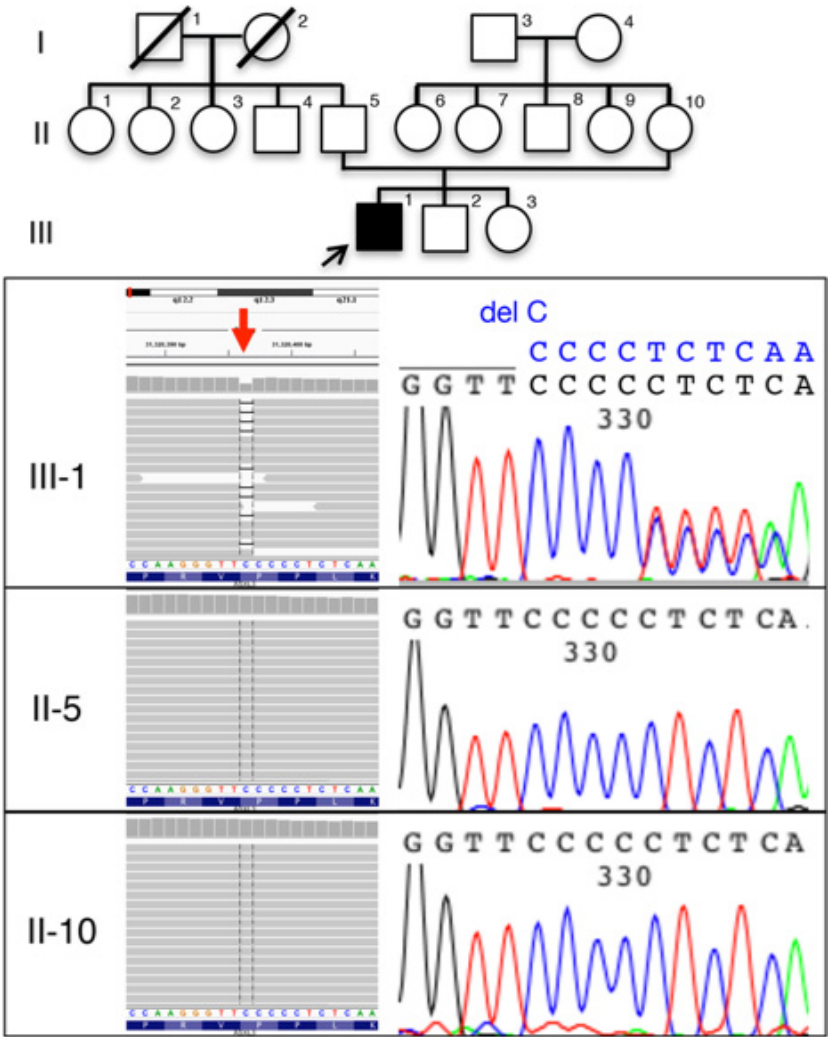

Figure 3. Sequencing profiles of the *ASXL3* gene in the patient and his parents. Integrative genomics viewer images of next-generation sequencing data of the ASXL3 gene at exon 13 and Sanger sequencing diagram for the patient (III-1), father (II-5), and mother (II-10). An arrow indicates the deletion of cytosine nucleotide.

resulted in a frameshift (p.P1010L*fs**14) and a truncated protein. The p.P1010L*fs**14 variant was not detected in his parents, suggesting that the variant was de novo. This finding was confirmed by Sanger sequencing (Fig. 3). The p.P1010L*fs**14 variant was not previously described and predicted by Mutation Taster (http://www.mutationtaster.org) as a disease-causing variant.

The study was performed in accordance with the standards of the Ethics Committee of the Ryukyus Graduate School of Medicine (Okinawa, Japan). Informed consent for his parents was obtained by Dr. Yasutsugu Chinen.

Discussion

BRPS is a unique disorder that has phenotypic overlap with Bohring–Opitz syndrome (BOS) (also known as C-like syndrome: MIM 605039), which is caused by heterozygous variant in the *ASXL1* gene (MIM 612990) on chromosome 20q11, Shashi-Pena syndrome (SHAPNS) (MIM 617190), which is caused by heterozygous variant in the *ASXL2* gene (MIM 612991) on chromosome 2p23, and C syndrome (Opitz trigonocephaly syndrome: MIM 211750), which is caused by heterozygous variant in the *CD96* gene on chromosome 3q13 [1, 5, 7, 14]. The features of C syndrome are, however, milder than those of BOS.

Unlike BOS, SHAPNS, and C syndrome, in BRPS, trigonocephaly, prominent metopic suture, exophthalmos, nevus flammeus of the face, upslanting palpebral fissures, redundant skin, hirsutism, and "BOS posture" of elbow and wrist flexion are mild or absent [1, 5, 7, 14]. The phenotype of the propositus is concordant with those of previous reports of BRPS – severe/profound mental retardation, hypotonia, delays in language acquisition, short stature of postnatal onset, craniofacial dysmorphism (prominent forehead, arched eyebrows, edematous periorbital region, short nose, anteverted nostrils, long philtrum, thin upper lip, full cheeks), and central nervous system abnormalities (hypoplastic body of the corpus callosum, mild atrophy of the cerebellar vermis, mild white matter loss of the frontal lobe). Prominent domed forehead with bitemporal hollowing and without metopic ridge might be one of the hallmarks in BRPS. Unlike previous reports, the patient had additional findings, that is, stereotypic movements (whispering face and hand-wringing), deep palmar creases, mild prominence of the Sylvian fissure with bitemporal hollowing, intrafissural venous plexus in the right parietal area, and scoliosis. Deep palmar creases were reported in SHAPNS by Shashi et al. [14]. Our listed variations other than the *ASXL3* gene and the *DISC1* gene (Table S1) had not yet been established gene–phenotype relationships. DISC1 may confer susceptibility to psychiatric illnesses such as schizophrenia, schizoaffective disorder, and bipolar disorder [10, 13, 15]. We should consider whether a degree of clinical findings might be affected by those variations with unestablished gene–phenotype relationships, but we could not disclose such an influence in the present study.

In previous reports of BRPS, all of the disease-causing variants in *ASXL3* were truncating variants, mostly located in the first half of exon 11. Similarly, a novel de novo frameshift variant, p.P1010L*fs**14, found in the present patient also located in *ASXL3* exon 11. Pathogenic missense variants in *ASXL3* have not been identified in patients with BRPS; however, such variants have been reported in ASD cases [3]. The clinical phenotype of ASD individuals with missense variants in *ASXL3* has not been clearly identified by brain imaging. Brain MRI assessments of BRPS patients (including the present patient and those from previous reports) show mild white matter volume loss in 50% (6/12), mild corpus callosum hypoplasia in 42% (5/12), and mild cerebellar vermis hypoplasia in 42% (5/12) of patients (Table 1) . Secondary findings affected by white matter volume loss might be mild enlargement of lateral ventricles and mild prominence of the sulci. The present patient had autistic features, including whispering face and hand-wringing and the ability to say only a few meaningful words. Differences in cortical thickness were observed between individuals with ASD and controls at the bilateral inferior frontal gyrus, pars opercularis, pars triangularis, the right caudal middle frontal and left rostral middle frontal

Table 1. Brain MRI assessments of BRPS patients from this study and previous reports.

Patients with BRPS	A	B	C		D	E						F
Number of patients assessed by brain MRI/total number	1/4	1/1	2/3		1/1	6/6						1/1
Mild white matter volume loss	+	+	+	+	–	–	–	–	–	+	–	+
Mild prominence of the sulci	–	+	–	–	–	–	–	–	–	–	–	+
Mild enlargement of lateral ventricles	–	+	–	–	–	–	–	–	+	–	+	–
Mild brain stem hypoplasia	+	–	–	–	–	–	–	–	–	–	–	–
Mild corpus callosum hypoplasia	–	–	+	+	–	–	–	–	+	+	–	+
Hypoplasia/dysplasia of bilateral cerebellar tonsils	+	–	–	–	–	–	–	–	–	–	–	–
Mild cerebellar vermal hypoplasia	+	–	+	+	–	–	+	–	–	–	–	+

References: A [1]; B [4]; C [16]; D [5]; E [9]; F, the present case; +, present; –, absent/normal.

regions, and the left frontal pole [17]. Mild prominence of the Sylvian fissure might be affected by white matter volume loss or reduced cortical thickness at the bilateral inferior frontal gyrus, pars opercularis, and pars triangularis. Further brain imaging characteristics in patients with BRPS might be useful for assessing ASD individuals with missense variants in *ASXL3*.

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Authorship

YC: was the principal investigator of this article and contributed to the conception, analysis of data, and reporting of the work described in the article. He performed patient follow-up. SN: contributed to clinical management and neurological assessment. AK: contributed to estimate hearing ability and data analysis. SH: contributed to an array-based comparative genomic hybridization analysis. JI: contributed to an array-based comparative genomic hybridization analysis. KY: contributed to DNA analysis of whole-exome sequencing and data analysis. KN: contributed to data analysis and reporting of the work described in the article. TK: contributed to the planning, data analysis, and reporting of the work described in the article. KN: contributed to data analysis and reporting of the work described in the article.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Gene variations with phenotype-causing potentiality.