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CASE REPORT

A new case of Bainbridge–Ropers syndrome (BRPS): delineating the phenotype and review of literature

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ABSTRACT

Background: Bainbridge–Ropers syndrome (BRPS) is characterized by failure to thrive, global developmental delay, feeding problems, hypotonia, profound speech delays, and intellectual disability and dysmorphic features. It is an autosomal dominant condition caused by heterozygous mutations in the additional sex combs like 3 (*ASXL3*) gene (OMIM #615115) on chromosome 18q12. As per the literature available, only 39 cases, including the current patient, were reported with BRPS across the globe.

Case Presentation: A 4-year-old girl with confirmed BRPS. She had the characteristic features of the disease, including psychomotor delay, hypotonia, profound speech impairment, neonatal feeding difficulties, postnatal, and dysmorphic features. The array comparative genomic hybridization and whole exome sequencing (WES) were negative, but the whole genome sequencing (WGS) detected a novel heterozygous *de novo* insertion in the *ASXL3* gene c.3592_3593insGAT; p.Leu1198X.

Conclusion: With the advent of WES/WGS, we would expect to diagnose more cases of BRPS from different ethnic populations. Although the clinical manifestations of BRPS were non-specific, finding a motor delay, hypotonia, intellectual disability, and feeding difficulty may raise the clinicians' suspicion for the diagnosis. Further clinical and functional studies are needed to delineate the long-term course of the disease and to elaborate on the exact role of the *ASXL3* gene in the brain development.

Keywords: Bainbridge–Robers syndrome, *ASXL3* gene, psychomotor delay, hypotonia, dysmorphic features.

Introduction

The additional sex combs like (ASXL) family consists of three genes, *ASXL1*, *ASXL2*, and *ASXL3*. The resulting three proteins share the same structural domains, however, ASXL3 is the largest (1). The additional sex combs like 3 (*ASXL3*) gene (OMIM #615115) is located on chromosome 18q12 and encodes for a translational factor named Putative Polycomb group protein (ASXL3). This protein is considered as a scaffold that binds to other transcription factors and epigenetic regulators like Ubiquitin carboxyl-terminal hydrolase (BAP1), forming a complex [Polycomb repressive deubiquitinase (PR-DUB)], that catalyzes the deubiquitination of H2A histone. The deubiquitination of H2A maintains the repression of certain genes during the development (1–3). Germline heterozygous truncating mutations in *ASXL3* were reported to be associated with Bainbridge–Roper's syndrome (BRPS) (OMIM #615485), which is characterized by failure to thrive, global developmental delay, feeding problems, hypotonia, dysmorphic features, profound speech delays, and intellectual disability (3). So far, there are 38 reported cases in the literature. All of them share these non-specific symptoms. In this report, we present the first reported case of BRPS in Saudi Population caused by a novel *de novo* truncating mutation. Additionally, we also performed a comprehensive literature review of all the previously reported patients.

Case Report

A 4-year-old girl, a daughter of a consanguineous Saudi couple. She was born by spontaneous normal vaginal delivery at term with birth weight at 2.8 kg (10th–25th centile), length 48 cm (25th–50th centile), and head circumference 32.5 cm (5th–10th centile). The first concern

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Table 1. *Clinical phenotype of previously reported BRPS cases.*

Total reported cases		39	Percentage
Gender		21 male & 28 females	
Birth		14 NVD; 14 CS	
Growth failure		16/34	47
Psychomotor development			
Motor delay		38/38	100
Free walking		17/33	51.5
Intellectual disability		36/36	100
Speech impairment		38/38	100
Craniofacial			
Long face/temporal narrowing		14/35	40
Prominent forehead		17/34	50
Arched eyebrows/synophrys		17/34	50
Down or upslanting palpebral fissures		29/34	85
Strabismus		11/34	32
High/narrow palate		14/31	45
Prominent columella/small alanasi		14/33	42
Anteverted nares		13/34	38
Microcephaly		16/36	44
Dental anomalies		3/17	17.6
Gastrointestinal			
Feeding difficulty		33/35	94
Skeletal			
Pectus deformity/scoliosis		9/30	30
Hand abnormalities		17/35	48.5
Deep hand creases		5/5	100
Central nervous system			
Hypotonia		30/35	85.7
Hypertonia		4/36	11
Seizures		13/39	33
MRI		12/34	35
Skin and appendages			
Hypertrichosis		5/28	17.5
Synophrys		3/28	10.7
Other	Autistic spectrum disorder	9	23
	Hypersalivation	1	~3
	Hyperinsulinism	1	~3
	Fixed contractures	1	~3
	Primary Insulin like growth factor-1 deficiency	1	~3
Remark		The difference between the total number of reported cases and the positive characters is due to either negative characters or due to non-reporting.	

was at the age of 2 months when the parents noticed poor weight gain, feeding difficulty, and excessive crying. The patient underwent medical evaluation and was found to have hypotonia, dysmorphic features, and delay in the motor development. The patient's global developmental delay persisted, she began to sit at the age of 3 years, crawling at 3.5 years, and currently, she could walk only on the furniture and with support. She was able to catch by her hands and transfers toys from hand to hand. She says mama and baba with a total of five words. Thereafter, the patient was referred to as the genetic service for the evaluation. Upon examination, her growth parameters were all below the average, weight 10.5 kg (<5th centile); height 88 cm (<5th centile), and the HC 47 cm (<5th centile). She had dysmorphic features, including microcephaly and dolichocephaly, temporal narrowing, prominent forehead, synophrys with arched eyebrows, long eyelashes, down-slanting palpebral fissures, anteverted nares, prominent columella, high arched palate, and enamel hypoplasia. The neck was supple and no neck masses. There was pectus excavatum deformity. The heart sounds were normal and no appreciated murmuring was observed. The abdomen was distended, with no organomegaly. She had a normal external female genitalia. She was hypotonic with decreased power 3/5 in the upper and lower limbs. She had a mild increase in the deep tendon reflexes. Extensive biochemical investigations were unremarkable, including a very long chain fatty acid, urine for organic acids, normal pattern for mucopolysaccharides, and oligosaccharides. The initial molecular investigations were also unremarkable, including karyotype, array comparative genomic hybridization, fluorescence *in situ* hybridization for Prader–Willi syndrome, in addition to negative whole exome sequencing (WES). Finally, the whole genome sequencing (WGS) showed a *de novo* insertion in the *ASXL3* gene (NM_030632.1) c.3592_3593insGAT, p.Leu1198X. This insertion interrupts the reading frame prematurely where Leucine at codon 1198 is replaced by a stop codon. This finding confirmed the diagnosis of Bainbridge–Robers syndrome. The Brain Magnetic Resonance Imaging (MRI) revealed a delay in myelination according to the patient's age. All the remaining imaging studies including skeletal survey and renal ultrasound were unremarkable.

Discussion

BRPS was first described when Bainbridge et al. (4) reported *de novo* truncating mutations in four unrelated probands with feeding difficulties, failure to thrive, neurological abnormalities, and significant developmental delay. In addition to the current patient,

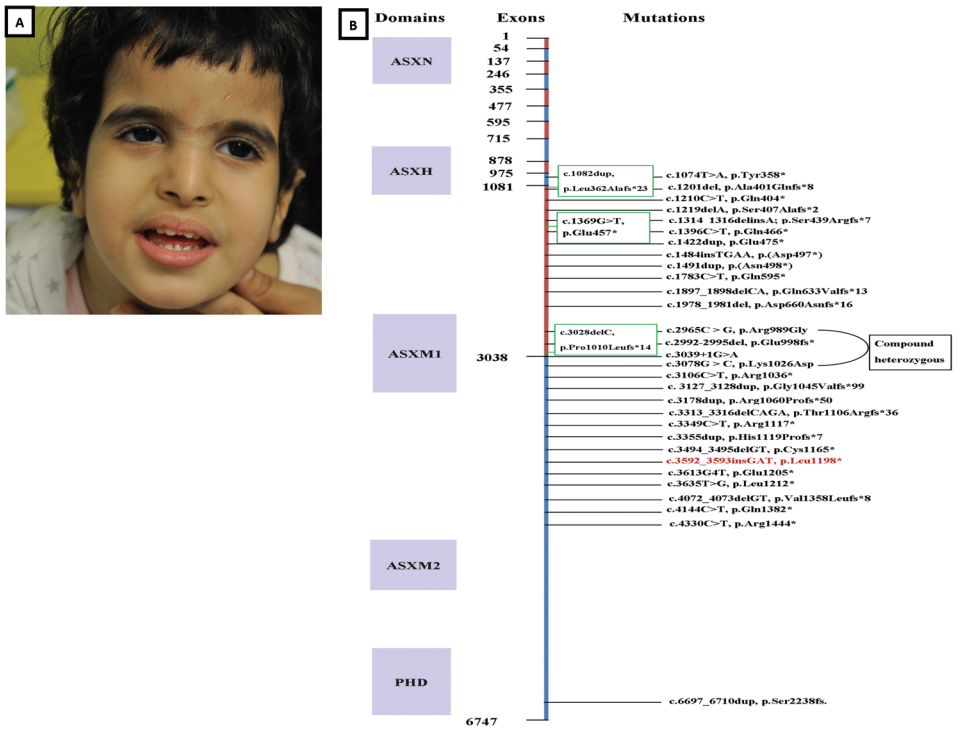

Figure 1. *(A) Four-year-old patient with BRPS. Facial features include microcephaly and dolichocephaly, temporal narrowing, prominent forehead, synophrys with arched eyebrows, long eyelashes, down-slanting palpebral fissures, anteverted nares, and prominent columella. (B) Scheme of ASXL3 gene exons with protein's domains and summary of all the reported mutations. The current case is highlighted in red.*

only 39 cases of BRPS were described in the literature. Interestingly, all the reported cases were diagnosed through the WES or WGS. This could be due to the non-specific signs and symptoms of presentation, in addition to the relatively low number of reported cases. Table 1 summarizes the main clinical features of all the reported cases in addition to the current case (3–15). All the cases had motor development delay. Furthermore, only around half of them were ambulating. Intellectual disability and speech impairment were common features among all of the patients. Thirty-three of the patients were reported to suffer from feeding difficulty. Hypotonia was commonly reported (30/35 patients). Almost half of the patients (47%) were suffering from growth failure. A near percentage was reported for some dysmorphic features, microcephaly, and hands anomalies as well. Seizures and structural brain abnormalities were reported in around one-third of the patients. The proband shared the common symptoms of other patients, including motor delay, intellectual disability, hypotonia, feeding difficulty, and microcephaly. *ASXL3* gene harbors 12 exons. Most of the reported mutations aggregate in exon 11 in addition to the first half of exon 12. The majority of the reported mutations were frameshift truncating (Figure 1B). The only two exceptions were the case reported by Hori et al. (10), which was a splice site mutation, and the compound heterozygous mutation reported by Giri et al. (9) All the reported cases had a *de novo* heterozygous mutation, with the exception again of Giri et al. (9) reported patient, who inherited two novel heterozygous variants of *ASXL3* gene from his parents. Although missense mutation in *ASXL3* was reported previously to be associated with the autism spectrum disorder (16), the parents of this patient were healthy (9). Verhoeven et al. (14) reported multiple affected siblings and probably the mother, which may indicate that the mutation could be inherited from the mother; however, she was not tested. The truncating heterozygous mutations in *ASXL3* may jeopardize the expression through nonsense-mediated decay (5). The ASXL3 protein contains five domains, ASX conserved domain at the N-terminus (ASXN), ASX homology (ASXH), ASX conserved domain in the middle part 1 (ASXM1), ASXM2, and plant homeodomain (PHD) from N terminal to C terminal, respectively. ASXH domain is responsible for binding to BAP1 to form the PR-DUB complex, while PHD domain (Zinc finger) is the DNA binding domain (1). The distribution and the nature of the reported mutations may point to the essential role of PHD domain in the function of the protein. All the reported truncating mutations lead to the complete loss or partial loss of the PHD domain.

Conclusion

With the advent of WES/WGS, we would expect to diagnose more cases of BRPS from different ethnic populations. Although the clinical manifestations of BRPS were non-specific, finding a motor delay, hypotonia, intellectual disability, and feeding difficulty may raise the clinicians' suspicion for the diagnosis. Further clinical and functional studies are needed to delineate the long-term course of the disease and to elaborate on the exact role of the *ASXL3* gene in the brain development.

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Declaration of conflicting interests
The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
This study was approved by the Institutional Review Board at King Abdullah International Medical Research Centre (KIMARC) (Study number: RC16/113/R).

Consent for publication
Informed consent was obtained from the parents.

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