Clinical Vignette

Bohring-Opitz Syndrome: Report of a Patient with a Novel Variant in the *ASXL1* Gene & Review of Literature

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Abstract

Bohring-Opitz Syndrome (BOS) is a very rare genetic disorder with multiple anomalies caused by heterozygous pathogenic variants in the *ASXL1* gene. The child reported here had the classic presentation of BOS due to a novel pathogenic variant in the *ASXL1* gene.

Keywords: Bohring-Opitz syndrome, *ASXL1* gene

Introduction

Bohring-Opitz syndrome (BOS) is a very rare genetic disorder with multiple anomalies that primarily affects infants and young children and causes delay in growth and development, with involvement of various organ systems. This complex disorder presents with a wide spectrum of symptoms caused by *de novo* mutations in the *ASXL1* gene. The *ASXL* (additional sex comb-like) group of genes *(ASXL1, ASXL2, ASXL3)* play a critical role in the regulation of gene expression, particularly during development. They are involved in chromatin remodelling that are responsible for epigenetic and transcriptional regulation (Katoh, 2013) These genes have similar functions and variants in these genes present with overlapping clinical phenotypes Molecular diagnosis helps in delineating the various syndromes caused by the *ASXL* genes. Heterozygous pathogenic variants in the *ASXL1* gene are associated with the severe congenital-onset Bohring-Optiz syndrome, an autosomal dominant genetic disorder.

The child reported here had a classic presentation of BOS due a novel pathogenic variant in the *ASXL1* gene.

Clinical Description

This one-year-old female baby, the first offspring of a non-consanguineous couple, presented with low weight, global developmental delay (GDD), breathing difficulty, and failure to thrive. The antenatal history revealed that it was a spontaneous conception and the mother's antenatal sonograms were insignificant except for intrauterine growth restriction (IUGR) noted in the last trimester. During the antenatal period, the mother had severe anemia and hypothyroidism, requiring two blood transfusions and a daily dose of 100 micrograms of thyroxine tablets respectively. The baby was born full-term by normal vaginal delivery with a birth weight of 1.5 kg and cried immediately after birth. The Apgar score was 7/10 and 9/10 at one minute and 5 minutes respectively. The baby developed respiratory distress and required treatment in the neonatal intensive care unit (NICU) for 5 days. Starting from the 5th day, she was fed expressed breast milk. Due to poor weight gain and weak suckling efforts, her hospital stay was extended to 30 days. She remained on breast milk until 2 months of age, after which she was transitioned to formula feeding.

The baby had frequent respiratory tract infections, feeding difficulties, failure to thrive, and sleep disturbances. The developmental history revealed that the child had severe developmental delay and had not attained age-appropriate milestones, including gross motor skills such as neck control, rolling over, sitting, or standing. She had minimal speech development (only cooing), had not achieved social smile, and was not recognizing family members. Family history

Figure 1 Clinical findings in the patient. (A) Photograph of the patient showing typical BOS posture as described by Hastings et al., 2011. (B) Glabellar flammeus nevus, characterised by a distinctive port-wine stain marking on the forehead, typically associated with BOS, seen in the patient. (C) Oral inspection showing a high arched palate and an incomplete cleft. (D) Dermatological observation highlights deep palmar creases and a sacral dimple. (E) Neuroimaging through MRI showing posterior thinning of the corpus callosum indicative of atypical neural development associated with BOS.

revealed that one maternal uncle had died at 9 years of age with congenital skeletal anomalies and intellectual disability.

On examination, at one year of age, the baby's length was 58 cm (< - 3 Z score), weight was 3.5 kg (< -3 Z score), and head circumference was 39 cm (< -3 Z score). She had craniofacial dysmorphic features including scaphocephaly and microcephaly, bitemporal narrowing, long face, retrognathia, prominent forehead, proptosis, hypertelorism, arched eyebrows, up slanting palpebral fissures, glabellar flammeus nevus, depressed nasal bridge and low set ears. Oral examination revealed a cleft/notched lip, a deep and narrowed palate with a small mouth and unerupted deciduous dentition. On ophthalmic evaluation, she had large eyes with strabismus, ptosis in the left eye and mild myopia. She had the typical "BOS posture" with elbow and wrist flexion, camptodactyly, ulnar deviation of the wrists and metacarpophalangeal joints. Extremities were hypertonic with truncal hypotonia. Reverse phenotyping extended findings like deep palmar, plantar creases, and sacral dimples (**Figure 1**).

Magnetic resonance imaging (MRI) of the brain showed posterior thinning of the corpus callosum, mild dilatation of the trigone of both lateral ventricles and mild reduction in bilateral periventricular deep white matter volume with associated T2 FLAIR hyperintensities. Mutation analysis through whole exome sequencing revealed a novel heterozygous frameshift variant c.3125dup (p.Leu1043Thrfster7) in exon13 of the *ASXL1* gene [transcript ID NM_015338.6 (ENST00000375687.4 GRCH37/hg19 build)] Parental targeted testing was done through Sanger sequencing and both parents were negative for the variant (**Figure 2**). This indicates that this variant was most likely *de novo* in the proband. The variant is classified as 'likely pathogenic' (PVS1+PM2) according to the American College of Medical Genetics and Genomics & Association for Molecular Pathology (ACMG-AMP) guidelines. This established the diagnosis of Bohring-Opitz syndrome (OMIM # 605039) in the child.

Detailed genetic counselling was given to the parents outlining the reduced likelihood of another child inheriting the same disorder. The proband is being monitored regularly and

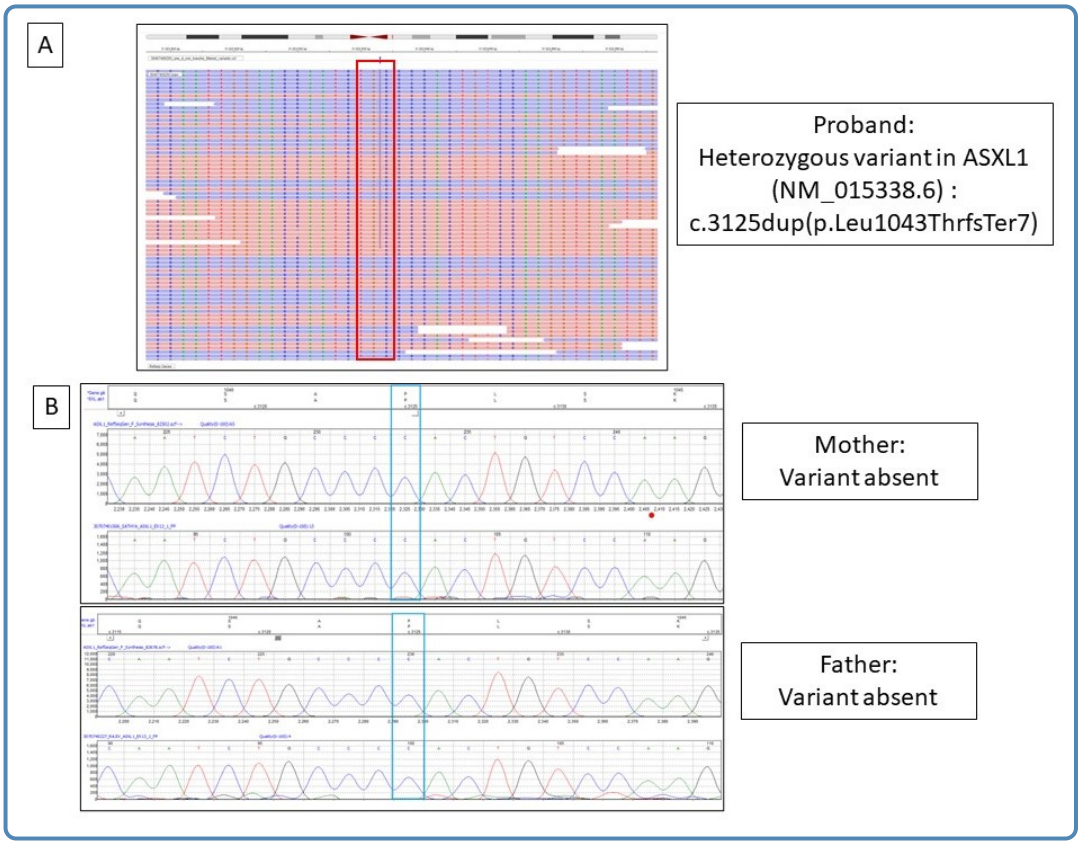

Figure 2 (A) Integrative Genome Viewer (IGV) image showing presence of the heterozygous variant c.3125dup (p.Leu1043Thrfster7) in exon13 of the *ASXL1* gene (ENST00000375687.4; GRCH37/hg19 build) in the proband. (B) Targeted variant testing in parents by Sanger sequencing showing absence of the variant in both parents.

ultrasonography of the abdomen once in four months up to eight years of age has been recommended as a part of renal tumour surveillance (Russell et al., 2023)

Discussion

Bohring - Opitz syndrome (BOS) was first described by the German paediatrician Helga V Bohring in 1999 and the American clinical geneticist John M Opitz in 2004. Bohring-Opitz Syndrome (BOS) is a rare genetic disorder characterised by a range of congenital anomalies and developmental delays caused by *de novo* mutations in the *ASXL1* gene. The ASXL group of genes plays a role in regulating tumour suppression and helps maintain the proper expression of genes necessary for cell differentiation and growth of the neural crest cells. Pathogenic variants in *ASXL2* and *ASXL3* are associated with Shashi-Pena and Bainbridge-Ropers syndrome, respectively (Cuddapah et al., 2021). All these syndromes exhibit overlapping clinical phenotypes like craniofacial dysmorphism, developmental delay, skeletal abnormalities and neurological manifestations (**Table 1**). Literature reports that *KLHL7* gene-associated Perching syndrome also exhibits BOS-like clinical features.

Clinical diagnostic criteria for BOS were given by Hastings et al. in 2011(Hastings et al., 2011). The typical clinical phenotype of BOS includes global developmental delay, failure to thrive, IUGR, microcephaly, craniofacial malformations, flammeus nevus, cleft lip/palate, retrognathia, prominent eyes with strabismus, and the typical "BOS posture" with flexion of the wrist and elbow, ulnar deviation of the metacarpophalangeal joints. As reviewed by Zhao and colleagues in 2021 (Zhao et al., 2021), 40 cases have been reported with *ASXL1* variants in literature. Mostly they occur

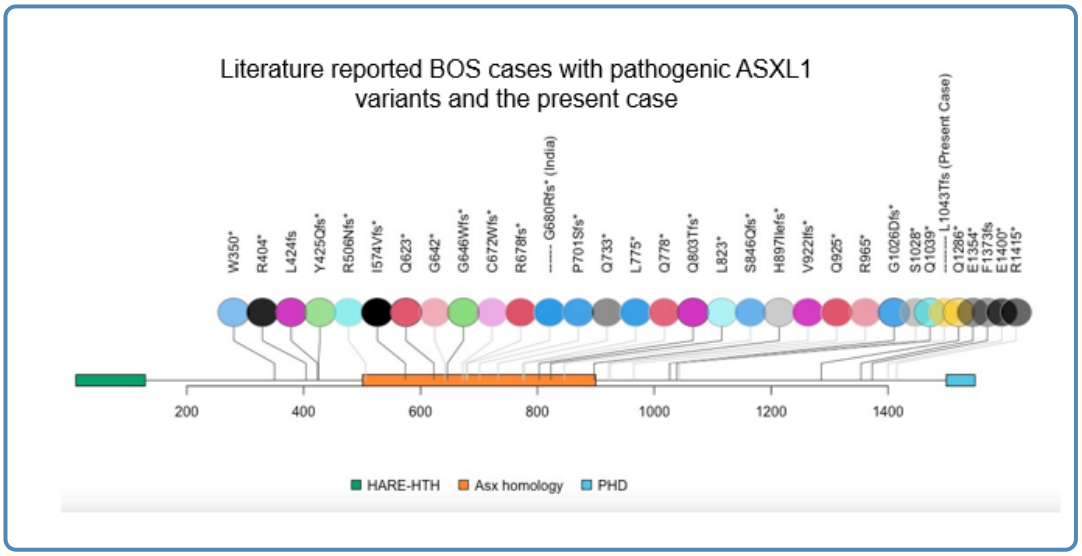

Figure 3 The schematic outlines the ASXL1 protein domain structure, which includes the HARE-HTH, ASX homology, and PHD domains, depicted in green, orange, and blue, respectively. The lollipop plot shows the *ASXL1* variants in the literature-reported cases of Bohring-Opitz Syndrome (Zhao et al. 2021; Russell et al., 2023) and highlights the variant identified in the present patient.

de novo with two cases in literature suggesting germline mosaicism so far (Greenhalgh et al.2003; Cuddapah et al. 2021). In India, among the cases that were reported as BOS, only one case was molecularly confirmed to the best of our knowledge (Arunachal et al., 2016).

In 2023, Russel and colleagues (Russell et al., 2023) described the clinical findings in 39 patients with BOS along with recommendations for tumour surveillance. They reported Wilms tumour in five patients and a novel finding of hepatoblastoma in one patient with BOS. They emphasised the importance of renal tumour surveillance in BOS patients every three to four months up to eight years of age (Russell et al., 2023) Though the somatic mutations in the *ASXL1* gene are associated with many haematological and solid tumours (Katoh, 2013; Micol & Abdel-Wahab, 2016) to date, other forms of cancers have not been reported with BOS except Wilms tumour and hepatoblastoma (Russell et al., 2023)

Here we have presented a case of Bohring-Opitz syndrome which fulfils the clinical criteria given by Hastings et al. (2011) and is molecularly confirmed with a heterozygous duplication variant in *ASXL1*. A genotype-phenotype correlation was established. Our variant has not been reported previously in any literature or databases like HGMD (https://www.hgmd.cf.ac.uk/), OMIM (https://www.omim.org/), UCSC Genome Browser (https://genome.ucsc.edu/), Ensembl (https://ensembl.org/index.html), dbSNP (`https://www.ncbi.nlm.nih.gov/snp/`) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). All the previously reported pathogenic variants in literature have been reviewed as a lollipop plot with the present case indicated in the disease-causing protein domain (**Figure 3**). We have submitted our variant to ClinVar (ID: 3338642 Accession ID: VCV003338642.1).

Due to the rarity and severity of Bohring-Opitz Syndrome and in view of the phenotypic heterogeneity of the *ASXL1* gene, clinical diagnosis of BOS and its management are highly challenging. Medical care typically focuses on managing the symptoms and providing supportive care to improve the quality of life for affected individuals. Thorough clinical examination with genotype-phenotype correlation helps in arriving at a confirmatory diagnosis in very rare genetic disorders like BOS.

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Table 1 Clinical features differentiating the ASXL family of genes and their syndromes

Clinical Features	Bohring-Opitz syndrome *(ASXL1)*	Shashi Pena syndrome *(ASXL2)*	Bainbridge Ropers syndrome *(ASXL3)*
'BOS' posture	Y	N	N
Trigonocephaly	Y	N	N
Microcephaly	Y	N	Y
GDD	Y	N	Y
Prominent eyes	Y	N	Y
Ptosis	N	N	Y
Aggressive behaviours	N	N	Y
Hand flapping, rocking behaviours	N	N	Y
Macrocephaly	N	Y	N
Normal height & weight	N	Y	N
Epilepsy	Y	Y	N
Nevus flammeus	Y	Y	N
Precocious puberty	Y	N	N
Thick hair	Y	-	-
Arched eyebrows	Y	Y	Y
Hypertelorism	Y	Y	Y
Feeding difficulties	Y	Y	Y
Hypotonia	Y	Y	Y
Cognitive disabilities	Y	Y	Y

○ - Overlapping phenotypes, ○ - Specific for Bohring Opitz, ○ - Specific for Shashi Pena, ○ - Specific for Bainbridge Ropers. Y-Yes: N-No

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