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Bohring-Opitz Syndrome Case Report of a Libyan child with a Novel Heterozygous Variant in the ASXL1 Gene and Review of Literature

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Abstract

Bohring-Opitz Syndrome (BOS) is a very rare genetic disorder and malformation syndrome with multiple anomalies caused by heterozygous pathogenic variants in the ASXL1 gene. Individuals with BOS have a wide collection of symptoms. Some of these symptoms are present in all individuals with BOS and some are present only in some cases but not all. Our patient was born at 36 weeks gestation via normal vaginal delivery with a birth weight of 3100 grams. She had mild Atrium Septal Defect (ASD) discovered immediately after birth. Mother had gestational diabetes for which she received treatment. Physical examination after birth revealed small head and generalized hypotonia. The child reported here had the classic presentation of BOS. Whole Exome Sequence (WES) identified a novel variant in ASXL1 not previously reported in the literature. It is classified as likely pathogenic.

Introduction

Bohring-opitz syndrome

(OMIM 605039, ORPHA 97297, MONDO 0011510, SNOMEDCT 720565000, ICD-10: Q87.8, UMLS: C0796232, MeSH: C537419, GARD: 10140)

SYNONYMS: Bohring-Opitz syndrome, BOS, BOPS, Bohring syndrome, C-like syndrome, Oberklaid - Danks syndrome, Opitz trigonocephaly-like syndrome

HGNC APPROVED GENE SYMBOL: ASXL1 (responsible gene for Bohring-Opitz syndrome)

CYTOGENETIC LOCATION: 20q11.21 (genes position on chromosome)

GENOMIC COORDINATES (GRCh38): 20:32,358,061-32,439,318 (from NCBI) (Fisher OMIM.2003) [

Bohring-Opitz Syndrome (BOS) is a congenital genetic and malformation syndrome characterized by severe developmental delay, feeding challenges, Intrauterine Growth Restriction (IUGR), and failure to thrive. The characteristic facial features and typical BOS-posture that are interpreted in several expressions include micro and/or trigonocephaly, Naevus flammeus, prominent eyes, puffy cheeks, flexion at the elbows and wrists, truncal hypotonia, and increased muscle tone of the extremities.

When BOS was first described, diagnosis was usually based only on symptoms because genetic testing was not yet available. Since then, genetic testing and research studies have advanced significantly. In 2011, a group of researchers found that more than half of the children they looked at with a clinical diagnosis of BOS had a de novo mutations in a gene called ASXL1 (located on the long arm (q) of chromosome 20 within band 20q11.21).

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The three genes in the ASXL group—ASXL1, ASXL2, and ASXL3—are essential for controlling gene expression, especially during development. They participate in chromatin remodeling, which controls transcription and epigenetics [2]**.** Variants in these genes may exhibit clinical symptoms that overlap. There might be additional genetic causes of BOS because this variation was not present in every child. The ASXL1 gene produces the ASXL1 protein, which is important in regulating the synthesis of proteins from other genes. Certain proteins may be produced more frequently while others may be produced less frequently. The disease can affect a wide range of body system since the protein is involved in regulating the expression of numerous other genes. The many disorders brought on by the ASXL genes can now be recognized with the aid of molecular diagnosis. The severe form of congenital-onset Bohring-Optiz syndrome is linked to heterozygous pathogenic mutations in the ASXL1 gene. We still do not know everything about the function of ASXL 1 gene protein.

Prevalence

Bohring-Opitz Syndrome is quite uncommon ultra-rare disease. Medical literature and patient advocacy groups believe that there are about 300 diagnosed cases worldwide, while the precise prevalence is yet unknown. Only few cases are specifically reported in scientific and medical journals. Worldwide organizations like the ARRE Foundation and the BOS Foundation, however, estimate that there are only about 300 living people with a clinical or proven molecular diagnosis, with many more perhaps going undiagnosed. Most of the Interactive Visual Aid and list of BOS are based on published medical literature and case studies between 2006 – 2024 and are for information only, and do not claim to be complete, but can be used as a guide. The scholarly literature reports just 46 cases [3,4]. However, since May 2024, nearly 70 people with Bohring-Opitz Syndrome have been fully enrolled in the BOS/ASXL Patient registry, and the number is continually growing. The BOS family support network had brought together roughly 350 families from 60 countries worldwide [5].

Clinical description of our case

This fifteen-month-old girl is the fourth child of a non-consanguineous marriage. She has hypotonia, failure to thrive, and global developmental delay.

With the exception of maternal gestational diabetes mellitus, which was discovered in the first trimester and for which mother needed treatment, the rest of the antennal history was insignificant. The mother's prenatal sonograms and follow-up were unremarkable. The prenatal history showed that the conception was spontaneous. The girl weighed 3100 grams at birth and cried right away after being delivered vaginally at 36 weeks gestation. The Apgar scores were eight and nine out of ten at one minute and five minutes, respectively. The infant required attention in the intensive care unit (NICU) for two days because to minor respiratory distress and ASD murmurs. She was fed on both breast milk and formula. The baby experienced poor weight gain, recurrent respiratory tract infections, one seizure episode accompanied by fever, and myopia for which glasses were prescribed. According to the neurodevelopmental history, the child's gross motor skills and other developmental milestones were delayed. She was able to roll over but not able sit up on her own at the time of her one-year checkup. She could vocalize but not able to babble. Her posterior fontanel was barely open, whereas her anterior fontanel was one fingerbreadth. She was unable to identify family members and had not developed a social smile. She was able to focus on her parent's face. Family history did not reveal any significant information.

Upon her routine assessment at fifteen months of age, the baby's head circumference was 45 cm (normal for age), length was 65 cm (< -3rd percentile), and weight was 7 kg (<-3rd percentile). Her long face, retrognathia, broad forehead, arching eyebrows, glabellar flammeus nevus, depressed nasal bridge, low-set ears, small mouth, and un-erupted deciduous dentition were among her dysmorphic traits. Her ophthalmological examination revealed myopia. Her extremities were hypertonic with truncal hypotonia, and her elbow and wrist flexion were typical of the "BOS posture."

Brain Magnetic Resonance Imaging (MRI) revealed a mild dilatation of the supraventricular system and posterior thinning of the corpus callosum. Her entire spine MRI came out normal. Right renal aplasia was discovered by high-resolution abdominal ultrasonography.

Variant analysis through whole exome sequencing revealed the ASXL 1 variant; c.2717del p. (Glu906GlyfsTer2) creates a shift in the reading frame at codon 906 in exon(s) no.13 (of 13).

To the best of our knowledge, this is a novel variant not previously reported in the literature *(table 1)***.** It is classified as likely pathogenic based on implementation of the ACMG/AMP/ClinGenSVI guidelines. This established the diagnosis of Bohring-Opitz syndrome (OMIM # 605039 & ORPHA 97297) in the child.

Main finding in whole exome sequence

Table 1: Variant annotation based on CentoCloud pipeline * Splicing prediction: Ada and RF scores ** Genome Aggregation Database (gnome AD), Exome Sequencing Project (1000G). *** Based on ACMG recommendations.

Sequences variants							
Gene	Variant Coordinates	Amino Acid Changes	SNP	Zygosity	In Silico Parameters *	Allele Frequencies**	Type And Classification***
ASXL 1	**NM_015338.5: c.2717del**	**p.(Glu906GlyfsTer2)**	N/A	Heterozygous	PolyPhen: N/A SIFT: N/A Mutation Taster: N/A Conservation_nt:	gnomAD: ESP: -1000G: -	Frameshift Likely Pathogenic

Variant interpretation

ASXL 1, c.2717del p. (Glu906GlyfsTer2)

The ASXL 1 variant, c.2717del p. (Glu906GlyfsTer2) creates a shift in the reading frame at codon 906 in exon(s) no.13 (of 13). To the best of our knowledge, this is a novel variant not previously reported in the literature. It is classified as likely pathogenic based on implementation of the ACMG/AMP/ClinGen SVI guidelines.

Review of the literatures

We searched the PubMed database, Human Gene Variant Database (HGMD), Online Mendelian Inheritance in Man (OMIM), moreover, we used "ASXL1" to search for variants in

the gene associated with BOS in the ClinVar database.

The German Pediatrician Helga V. Bohring in 1999 and the American Clinical Geneticist John M Opitz first described Opitz Syndrome (BOS) in 2004 [6]. Bohring-Opitz Syndrome (BOS) is a rare genetic disorder characterized 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 tumor 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 [7]. All these syndromes exhibit overlapping clinical phenotypes like craniofacial dysmorphism, developmental delay, skeletal abnormalities and neurological manifestations. Literature reports that *KLHL7* gene-associated Perching syndrome also exhibits BOS-like clinical features. Hastings et al. gave clinical diagnostic criteria for BOS in 2011[8].

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 with ulnar deviation of the metatarsophalangeal joints. As reviewed by Zhao and colleagues in 2021[9], 40 cases have been reported with ASXL1 variants in literature. Mostly they occur de novo with two cases in literature suggesting germline mosaicism so far [7,10]. In India, among the cases that were reported as BOS, only one case was molecularly confirmed [11].

Hyeju Kim demonstrated that Asxl1 deletion in mice induces microcephaly, primarily caused by a reduction in the size and number of cortical neurons. Asxl1 ablation disrupts Neural Stem Cell (NSC) maintenance, as evidenced by decreased proliferation and increased apoptosis [12].

Chellappa reported 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. This indicated that the variant was most likely *de novo* in the proband. The variant was classified as 'likely pathogenic' (PVS1+PM2) according to the American College of Medical Genetics and Genomics & Association for Molecular Pathology (ACMG-AMP) guidelines [13].

Visayaragawan et al concluded in their case report that the chromosomal analysis in addition to the clinical features that the patient had 46 xx-Bohring Opitz Syndrome overlapped with C syndrome. C syndrome or Opitz Trigonocephaly Syndrome usually has overlapping features with BOS and is caused by mutations in the TACTILE gene [14].

Hoischen reported seven unrelated patients with Bohring-Opitz syndrome due to de novo heterozygous mutations in the ASXL1 gene [15]. All patients fulfilled the main criteria proposed by Bohring [6]. There were six females and one male, ranging in age from 2.5 to 24 years, although two died at ages 6 years and 23 hours after birth, respectively.

Magini reported two unrelated patients with Bohring-Opitz syndrome confirmed by molecular analysis [16].

Leon reported a 5-year-old girl with a mild case of Bohring-Opitz syndrome. She had typical facial features of BOPS [17].

ASXL1 mutations attract much attention; the ASXL1 mutations has been identified in a variety of hematologic malignancies and always predicts poor prognosis. It was found that the C-terminal truncating mutants of the ASXL1 or ASXL1 deletion induced Myelodysplastic Syndrome (MDS) like diseases in mouse. In addition, it has recently been reported that ASXL1 mutations are frequently found in clonal hematopoiesis in healthy elderly people, who frequently progress to hematologic malignancies [18].

Discussion

Here we have presented a child with Bohring-Opitz syndrome that fulfils the diagnostic features of Bohring Opitz Syndrome, which are, glabellar flammeous nevus, low-set ears, retrognathia, prominent forehead, arched eyebrows and a typical BOS posture and is molecularly confirmed with the ASXL 1 heterogonous variant, c.2717del p. (Glu906GlyfsTer2). To the best of our knowledge this is a novel variant which is not previously reported in the literature like HGMD (https://www.hgmd.cf.ac.uk/),OMIM (https://www.omim.org/), UCSC Genome Browser (https://genome.ucsc.edu/), Ensemble (https://ensembl.org/index.html), dbSNP (https://www.ncbi.nlm.nih.gov/snp/) and ClinVar (https://www.ncbi.nlm.nih.gov/ClinVar/).It is classified as likely pathogenic based on implementation of the ACMG/AMP/ClinGen SVI guidelines. A genotype-phenotype correlation was established.

Our child also had thinning of the corpus callosum, myopia, atrial septal defect, and failure to thrive that is consistent with many other cases of Bohring–Opitz Syndrome reported in the medical literatures so far. High-resolution abdominal ultrasound revealed right renal aplasia, which is not common finding in BOS.

Author declarations

Statement

Informed consent to participate in this study was provided by the parents who are the legal guardian of the child. Consent was given for the publication of any potentially identifiable images or data included in this article.

Author contributions

AZ drafted the manuscript and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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