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Case Review

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Metabolic Dysfunction in Shashi-Pena Syndrome: A Novel Pathologic ASXL2 Frameshift Variant

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Abstract

ASXL2 is a member of the Additional sex combs (Asx)-like gene family, essential for embryonic development and homeostasis. Germline truncating variants are associated with Shashi-Pena syndrome (SHAPNS), an ultra-rare disorder, characterized by macrocephaly, dysmorphic features, feeding difficulties, hypotonia, and developmental delay. Metabolic dysfunction has been less well described. We report clinical presentation, genetic evaluation, and hospital course of a neonate with dysmorphic features and persistent hypoglycemia. Whole exome sequencing (WES) was performed using next-generation sequencing with high coverage and quality thresholds. A 34-week male infant, born via cesarean section to a primigravida with chronic hypertension and intrauterine growth restriction, developed hypoglycemia on day 2 of life with inappropriately elevated insulin levels consistent with neonatal hyperinsulinism requiring diazoxide. Dysmorphic craniofacial features (frontal bossing, depressed nasal bridge, low set ears, retrognathia, bulging eyes, temporal wasting), truncal hypotonia, and congenital heart defects (patent foramen ovale and a mid-muscular ventricular septal defect) were additionally noted. Chromosomal microarray and brain magnetic resonance imaging were unremarkable. WES revealed a novel heterozygous frameshift variant in ASXL2 (NM_018263.4, c.2889_2293del, p.Gln764Serfs*2), classified as likely pathogenic. The patient required prolonged neonatal intensive care (72 days), and gastrostomy tube placement for feeding difficulties and metabolic instability. This case identifies a novel ASXL2 variant and broadens the phenotypic spectrum of SHAPNS, highlighting its association with neonatal hyperinsulinism and multisystem involvement.

Introduction

The Additional sex combs (Asx)-like (ASXL) genes are human homologues of the Drosophila Asx gene, essential for recruiting Polycomb group repressor complexes and Trithorax group activator complexes during embryogenesis. ASXL2 is a member of the ASXL family of paralogs, consisting of ASXL1, ASXL2, and ASLX3 [1]. In mice, ASXL2 has been implicated in the regulation of skeletal, lipid, and glucose homeostasis, as well as cardiac development [2,3]. Homozygous deletion of ASXL2 in mice exhibited significant phenotypic abnormalities, including premature death, growth retardation, impaired cardiac function, and vertebral anomalies, underscoring its essential role in embryonic and postnatal development [4]. Germline mutations in ASXL1 and ASXL3 have been respectively associated with Bohring-Opitz and Bainbridge-Ropers syndromes [5,6]. Recent reports have linked germline truncating mutations in ASXL2 with Shashi-Pena syndrome. Affected individuals typically present with a consistent constellation of features such as macrocephaly, prominent eyes, arched eyebrows, hypertelorism, a glabellar nevus flammeus, neonatal feeding difficulties, hypotonia, and developmental disabilities [7].

Here we report on a patient who presented with feeding difficulties, hypoglycemia secondary to hyperinsulinism, ventricular septal defect (VSD), hypotonia, dysmorphic features, and developmental delay. Following full-exome sequencing, she was found to have a novel variant in the ASXL2 gene (NM_018263.4, c.2889_2293del, p.Gln764Serfs*2) which, to our knowledge, has not been previously published as pathologic or benign. The result was interpreted as a likely pathogenic variant.

Methods

Copy number variant sequencing

Copy number variant (CNV) analysis utilized next-generation sequencing (NGS) data from the patient's genomic DNA, extracted directly from the specimen. Enrichment of coding regions and splice site junctions was achieved using

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GeneDx's proprietary capture system for NGS-CNV analysis. Paired-end sequencing on an Illumina platform generated bi-directional reads, which were aligned to National Center for Biotechnology Information (NCBI) Reference Sequence (RefSeq) transcripts and human genome build GRCh37/UCSC hg19. Data underwent rigorous filtering to detect clinically significant deletions and duplications involving three or more exons. Variants were reported following Human Genome Variation Society (HGVS) guidelines, with confirmation by orthogonal methods as needed. Only pathogenic and likely pathogenic variants were reported, while variants of uncertain significance and benign variants were excluded.

Clinical exome sequence analysis

In our patient, the genetic sample was obtained using an oral swab from buccal mucosa. Clinical exome sequence analysis was sent to GeneDx. The quality metrics reported were mean depth of coverage and quality threshold. The mean depth of coverage denotes the average count of sequence reads obtained throughout the entire exome, specifically targeting the coding exons and splice junctions of protein-coding RefSeq genes using massively parallel NGS. The quality threshold denotes the proportion of the test region covered by at least 10 sequence reads (10x), the threshold needed for reliable exome variant detection, with average coverage typically exceeding 90–95%, though a small portion may still lack sufficient depth for confident analysis. Our patient's sample had a mean depth of coverage of 92x and a quality threshold of 97.8%.

Case Presentation

Clinical presentation

Our patient was delivered via urgent cesarean section at 34 weeks 2 days gestation to a G1P1 mother with chronic hypertension, intrauterine growth restriction, and footling breech presentation. After initial resuscitation with APGARs of 4 and 8 respectively at 1 and 5 minutes of life, the baby was transferred to neonatal intensive care unit (NICU) on room air. On day of life (DOL) 2, the patient developed persistent hypoglycemia in the setting of an inappropriately elevated insulin level of 2.4 µU/mL, consistent with hyperinsulinism secondary to presumed intrauterine growth restriction. Endocrinology was consulted and the patient was transitioned to continuous fortified feeds. Owing to consideration of initiating diazoxide, pre-treatment echocardiogram revealed a patent foramen ovale (PFO) and a small, restrictive mid-muscular ventricular septal defect (VSD). Due to dysmorphic features (frontal bossing, depressed nasal bridge, low set ears, retrognathia, bulging eyes, and temporal wasting), chromosomal microarray (CMA) and brain magnetic resonance imaging (MRI) were performed and found to be unremarkable. Diazoxide therapy was initiated with prophylactic hydrochlorothiazide following dose escalation. The 72-day NICU course was otherwise complicated by Klebsiella sepsis and meningitis treated with a 21-day course of cefepime.

Following an initial outpatient newborn visit, an outpatient EEG was obtained due to concern for seizure-like activity which was unremarkable in both awake and drowsy states. Family history was negative for neurological disorders. Neurologic examination revealed mild hypotonia, more pronounced truncally, along with dysmorphic features. The whole exome gene sequencing sent for further investigation identified a likely pathogenic variant in the ASXL2 gene, associated with Shashi-Pena syndrome.

Furthermore, due to inadequate oral intake and an unsuccessful trial off diazoxide, the patient underwent gastrostomy tube placement and esophagogastroduodenoscopy. Cardiology follow-up included discussion of possible PDA closure, pending family preference. The patient continues to receive physical and occupational therapy.

Genetic findings

A novel variant in the ASXL2 gene (NM_018263.4, c.2889_2293del, p.Gln764Serfs*2) was found in our patient. The inheritance pattern was identified as autosomal dominant, with the variant present in a heterozygous state. It is unknown whether the patient inherited the disease from her biological mother or father due to the absence of exome sequencing in the parents. Regardless, this mutation was classified as a likely pathogenic variant. The frameshift variant in the ASXL2 gene located in exon 13 is predicted to result in an abnormal protein length. This variant has not been observed at significant frequency in large population cohorts (including gnomAD). Given the gene analysis and the clinical phenotype consistent with an ASXL2 variant, the p.Gln764Serfs*2 alteration in the ASXL2 gene was determined to be the likely cause of the patient's symptoms.

Discussion

ASXL2 is a member of the ASXL gene family involved in embryonic development and homeostasis [1-3]. Germline truncating variants in ASXL2 have been associated with Shashi-Pena syndrome, characterized by macrocephaly, feeding difficulties, hypotonia, and developmental delay [7]. Initially described in 2016 by Dr. Vandana Shashi and Dr. Loren Pena in a group of six children with overlapping facial features and clinical findings, it remains an ultra-rare disease with only 23 cases identified as of 2023 per National Organization for Rare Disorders registry [8,9]. Our patient's presentation was consistent with dysmorphic features, hypotonia, cardiac malformations, and feeding difficulties, with the most prominent concern being persistent hypoglycemia due to hyperinsulinism.

In the case report by Yuan et al., the patient exhibited persistent hypoglycemia caused by inappropriately high insulin levels following diagnostic fasting and glucagon testing. This was in the setting of a de novo truncating mutation in ASXL2 [10]. Similarly, our patient failed several 6-hour challenges with critical labs confirming hyperinsulinism. A glucagon stimulation test was performed and produced an adequate response, though she required continuous feeds to help maintain sugars. Though feeding difficulties may have played a role in her hypoglycemia, a larger cause may be due to the ASXL2 deficiency. In the study published by Izawa et

al., [2] researchers found that ASXL2 activates PPARγ in the osteoclastogenic process. PPARγ itself plays a central role in insulin sensitivity. In fact, ASXL2-deficient mice exhibited insulin-resistant glucose intolerance, as evidenced by elevated baseline glucose levels, impaired glucose clearance, and disrupted insulin signaling in hepatic and muscle tissues [2]. Therefore, it was postulated that ASXL2 may also promote glucose homeostasis.

ASXL2 plays a critical role in cardiac morphogenesis by regulating chromatin structure and gene expression in the heart. ASXL2 deficiency disrupts histone modification, leading to abnormal cardiac gene expression and progressive ventricular dysfunction, with evidence linking it to VSD and other structural abnormalities [11]. Our patient had a small patent ductus arteriosus (PDA), a trivial left-to-right shunt across a PFO, and a very small mid-muscular VSD with restrictive left-to-right flow. The PFO was deemed a normal variant, the VSD was expected to close spontaneously without clinical significance, and the PDA may be electively closed in the future if the family desires. These findings suggest a possible association of ASXL2 deficiency with disruptions in development and metabolic networks. Further research is needed to elucidate the link, better understand its role in cardiac development and glucose homeostasis, and investigate potential targeted therapies in affected individuals.

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