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CLINICAL REPORT
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Bohring–Opitz Syndrome (BOS) With a New *ASXL1* Pathogenic Variant: Review of the Most Prevalent Molecular and Phenotypic Features of the Syndrome

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Bohring–Opitz syndrome (BOS) was first described by Bohring et al. [1999]. The authors reported four cases which had several features in common, including a prominent metopic suture, hypertelorism, exophthalmos, cleft lip and palate, limb anomalies, as well as difficulty feeding with severe developmental delays. In almost 50% of cases that meet the clinical criteria for BOS, de novo frameshift and nonsense mutations in the *ASXL1* gene have been detected, suggesting that loss of function of this gene is a major cause. We report on the clinical characterization of one young female patient who was evaluated because of severe developmental delays, failure to thrive, and multiple minor anomalies and was clinically diagnosed with BOS. Whole exome sequencing analysis detected one novel disruptive frameshift mutation in the *ASXL1* gene and we were also able to confirm the presence of two *CFTR* mutations associated with her chronic pancreatitis with acute severe breakthrough attacks requiring multiple ICU admissions. This latter complication of pancreatitis further contributed to the complexity of the clinical presentation and represents an independent genetic finding. Our case report emphasizes the importance of highly specific phenotypic characterization of patients with complex phenotypes before proceeding with molecular studies. That approach will lead to more accurate molecular data interpretation and better clinical genetic diagnosis, particularly for those patients with rare, difficult-to-diagnose disorders.

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Key words: Bohring–Opitz syndrome; atypical cystic fibrosis; *ASXL1*; chronic pancreatitis; *CFTR*

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INTRODUCTION

In 1999, Bohring et al. reported on four cases with prominent metopic suture, hypertelorism, exophthalmos, cleft lip and palate, limb anomalies, feeding difficulty and severe developmental delays [Bohring et al., 1999].

Later on, diagnostic criteria were defined for the diagnosis of Bohring–Opitz syndrome (BOS), based on the most common phenotypic manifestations. These diagnostic criteria are microcephaly, trigonocephaly, palatal abnormalities, prominent eyes and hypoplastic supraorbital ridges, upslanting palpebral fissures, depressed nasal bridge and anteverted nares, facial nevus flammeus, low-set, posteriorly angulated ears, failure to thrive, and severe developmental delays. Other minor anomalies may also be observed in patients with BOS, including low frontal and temporal hairline with hirsutism, hypertelorism, exophthalmos and retrognathia [Hastings et al., 2011].

Patients with BOS have a particular and characteristic limb posture, described as the "BOS posture", which consists of the external rotation and/or adduction of shoulders, with flexion at the elbows and wrists and ulnar deviation of the wrists and/or fingers at the level of the metacarpophalangeal (MCP) joint [Magini et al., 2012]. Also, in some cases, the patients with BOS have severe scoliosis.

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Early in life, BOS patients tend to gain weight disproportionally, in comparison with their length, leading to central obesity [Pierron et al., 2009]. Systemic manifestations which are nonspecific but may be associated with BOS include cardiac anomalies in approximately 50% of cases. The most frequent are atrial septal defects, patent ductus arteriosus, and valvular abnormalities (most commonly pulmonary stenosis). Gastrointestinal anomalies may include intestinal malrotation and inguinal hernias among others. Ophthalmologic manifestations comprise strabismus and retinal abnormalities which are observed in up to 50% of cases and, to a lesser extent, anterior chamber abnormalities (20%) and myopia (33%).

Finally, 70% of patients have structural brain abnormalities. Among those, ventriculomegaly, delayed myelination, Dandy–Walker malformation, generalized atrophy involving the corpus callosum and brainstem, and neuronal migration abnormalities have been described. Seizures may be present in some patients [Hastings et al., 2011].

Life expectancy in BOS patients is decreased because they are more prone to infections and they may experience cardiac arrhythmias and/or apneas. Moreover, previous reports on BOS describe a high rate of infant mortality (40%), which is directly correlated with the previously described complications [Russell and Graham, 2013].

The molecular basis of BOS was recently identified, making molecular diagnosis possible [Hoischen et al., 2011]. For almost 50% of cases that meet the clinical criteria for BOS, de novo frameshift and nonsense mutations in the *ASXL1* gene have been detected. This suggests that the molecular correlation is loss of function of this gene, although, from a more comprehensive perspective, other putative genes might be involved. Moreover, upon further review on the literature, we observed that some reported cases with the typical phenotype did not carry mutations, suggesting genetic heterogeneity.

The *ASXL1* gene, which is located at HSA 20q11.21, encodes the additional sex combs–like protein 1, which contains 1,543 amino acids. This protein belongs to the polycomb group (PcG) and trithorax complexes family. Polycomb group genes are involved in chromatin based gene silencing, while trithorax group genes counteract the silencing effects of chromatin to maintain gene activity, suggesting that additional sex combs–like protein 1 is required for maintenance of both activation and silencing of *HOX* genes, which are involved in body patterning, as well as in chromatin remodeling [Fisher et al., 2003].

To date, current literature reports a total of 9 patients who have been clinically diagnosed with BOS, and confirmed by molecular analysis of *ASXL1*.

Magini et al. [2012] reported on two unrelated patients with Bohring–Opitz syndrome confirmed by molecular analysis. One was a female patient that presented with congenital microcephaly and hypotonia. The patient displayed typical facial features, including frontal bossing, facial nevus flammeus, prominent eyes, hypertelorism, mild hirsutism low-set, posteriorly rotated ears, long philtrum, highly arched, narrow palate, and everted lower lip. Additionally, she presented abnormal posture with elbow contractures. Systemic manifestations included failure to thrive, severe myopia and seizures. CNS malformation was demonstrated by brain MRI which showed dilatation of lateral ventricles, mildly thin corpus callosum, and apparent moderate atrophy of the spinal cord. By 3 years of age the patient was noted to have mild hepatomegaly and thoracolumbar scoliosis. She had severe psychomotor retardation and she was still nonverbal. An unrelated affected male presented with trigonocephaly secondary to partially fused metopic suture, a facial capillary hemangioma and upslanting palpebral fissures, prominent eyes with hypoplastic supraorbital ridges, highly arched, narrow palate, low-set ears, marked hirsutism and short neck. This patient also presented with truncal hypotonia, scoliosis, cryptorchidism, and the typical BOS posture with contractures of the hips, knees, and ankles, as well as talipes valgus deformity of the feet. In terms of systemic manifestations, the patient had feeding difficulties with failure to thrive and myopia. Brain MRI showed enlarged cerebral ventricles, hypomyelination of the periventricular white matter and a hypoplastic corpus callosum. At around 7 years of age, the boy had severe neurodevelopmental delay and he was nonverbal although he was able to communicate through images, letters, and signs, and had social interaction as well.

Hoischen et al. [2011] reported 13 patients who clinically met the diagnostic criteria established by Bohring et al. The majority of cases were infants. In this series, 7 out of 13 patients were found to have mutations in the *ASXL1* gene. Two of the seven patients reached adult age (only one of those two patients, a 24 year-old, is mentioned and picture illustrated five more subjects, who were children up to 11 years of age). The fact that only **7** out of 13 subjects had *ASXL1* mutations, suggested that mutations or structural alterations in other genes may cause this syndrome.

Kaname et al. [2007] reported a mutation in *CD96* in a patient with diagnosis of C syndrome based on typical clinical features, including unusual facies, wide alveolar ridges, multiple buccal frenula, limb defects, visceral anomalies, redundant skin, psychomotor retardation, and hypotonia. They sequenced *CD96*, which was associated with a phenotype resembling Opitz C-syndrome, in nine karyotypically normal Japanese patients with a clinical diagnoses of the C or C-like syndrome. Two of the patients were reported as having C-like syndrome, which displays some phenotypic overlap with *Bohring-Opitz syndrome*. In the remaining patients, neither deletions nor mutations were identified in two candidate genes(*CD96* and *ZEBD2*). Moreover, at some point, BOS was proposed as the most severe end of the same clinical spectrum which includes C-syndrome but always manifests with exophthalmos.

Bainbridge et al. [2013] identified four individuals with de novo truncation mutations in a related gene, *ASXL3* (chromosome 18). In all four families, the affected children displayed features of BOS. Dysmorphic features consisted of arched eyebrows, anteverted nares, and ulnar deviation of the hands. These features overlap with Cornelia de Lange Syndrome (CdLS) and BOS, except that these patients did not present with trigonocephaly, which is characteristic of BOS. Systemic manifestations included severe postnatal growth retardation, difficulty feeding and severe psychomotor delay.

Of note, *ASXL3* is in the same gene family as *ASXL1* and mutations in *ASXL3* are known to be associated with a disorder

that is paralogous to BOS. The phenotype presented in the affected individuals was variable in terms of presentation and severity, a phenomenon that is also associated with *ASXL1* mutations and is currently under study (Fig. 1).

A more recent report described a heterozygous frame shift variant in the additional sex combs-like 3, (*ASXL3*) gene on a proband who also displayed considerable overlap with the BOS phenotype [Dinwiddie et al., 2013]. Dinwiddie et al. reported a 6 year-old, nonverbal African American with craniosynostosis, prominent eyes, global developmental delay and autism, although this patient did not present with flammeus nevus, micro- or retrognathia, abnormal palate and the typical BOS posture. This was the second report and fifth patient with pathogenic mutations in *ASXL3*. The authors conclude that truncating frameshift mutations in the *ASXL3* gene phenotypically correlate with a distinct disorder that shares significant clinical features with Bohring–Opitz syndrome and is characterized by craniofacial anomalies and global developmental delay.

In terms of inheritance, although the large majority of reported cases are sporadic, Greenhalgh et al. [2003] described a brother and sister with Bohring–Opitz syndrome, suggesting the possibility of autosomal recessive inheritance or germ line mosaicism [Greenhalgh et al., 2003].

We report on the clinical characterization of one young adult female patient who was recently diagnosed with BOS and pancreatitis in whom we detected a novel disruptive frameshift mutation in *ASXL1* and two *CFTR* mutations (c.1521_1523delCTT;p.F508del and c.958T>G; p.L320V).

Clinical Report

Our patient is a 17 year-old girl who was born at term with a birth weight of 2500 g to a 35 year-old G3P2 mother. She was born to non-consanguineous Caucasian parents. Pregnancy was complicated by IUGR. She presented with a post-natal history of profound neurodevelopmental delay and failure to thrive. Feeding was a significant problem, with pharyngeal dysphagia and gastro-esophageal reflux. She required Nissen fundoplication and gastrostomy. She also presented with severe scoliosis requiring spinal fusion surgery, and dysfunctional uterine bleeding. Her care was further complicated by intestinal resection following volvulus necessitating ostomy and by chronic pancreatitis with severe recurrent acute episodes requiring admission to the intensive care unit. She had a negative family history for congenital abnormalities and pancreatitis.

The patient was microcephalic (HC < 3rd centile), her height was below the 3rd centile and her weight was on the 10th centile. She had a "triangular" face, hypertelorism, low anterior hairline, synophrys, upslanting palpebral fissures, some degree of exophthalmos, flat nasal bridge, anteverted nares, low set ears, small mouth, wide spaced teeth, retrognathia, finger pads, thoracic scoliosis, was wheelchair-dependent, with hypermobile joints fixed flexion contractures of both wrists and fingers as well as flexion contractures of her legs and feet.

The patient was non-verbal, did not track objects and did not follow commands. Neurologic exam revealed tremor and choreiform movements. CAT scan of the head revealed cerebral volume loss and ventriculomegaly. EEG revealed mild diffuse slowing suggestive of underlying multifocal cerebral dysfunction, as well as frequent multifocal and generalized spike and wave discharge. Abdominal ultrasound showed bilateral renal cysts and splenic cysts. Also, she presented with long QT on an EKG.Previous genetic work up included normal karyotype, SNP microarray and molecular analysis of *SPINK1* for pancreatitis.

MATERIALS AND METHODS

Exome sequencing was performed on DNA obtained from the peripheral blood of the patient. Briefly, exome sequencing libraries were prepared from genomic DNA from the proband and the parents using Agilent SureSelect XT Human All Exome v5+UTRs kit according to the manufacturers' protocol. Paired-end sequencing was performed on the Illumina HiSeq 2500 platform to provide a mean sequence coverage of more than 150X, with more than

FIG. 1. Our patient with *ASXL1* mutation. This picture depicts our patient's most prominent facial features including: triangular face, hypertelorism, synophrys, upslanting palpebral fissures, some degree of exophthalmos, low set ears and wide spaced teeth.

99% of the target bases having at least 10Xcoverage. The data were analyzed and annotated using Nextgene (Softgenetics, LLC. PA) software, an in-house developed "pipeline" for clinical interpretation.

RESULTS

Exome sequencing analysis revealed a two base pair deletion (c.4116_4117delTT) in the *ASXL1* gene that results in a frameshift (p.F1373fs). Sanger sequencing of the patient and parental DNA specimens confirmed the variant to be de novo. In addition to the pathogenic *ASXL1* variant identified in this patient, exome sequencing confirmed the presence of two heterozygous changes in *CFTR* (c.1521_1523delCTT; p.F508del and c.958T>G; p.L320V) which were detected by CF testing.

Based on the previously described clinical picture, our patient most likely has Bohring–Opitz syndrome, which is known to be autosomal dominant, the patient also is a compound heterozygote for the *CFTR* gene. This genetic finding explains the chronic and the recurrent severe pancreatitis that she had from early childhood.

Genetic counseling was provided. The de novo nature of the *ASXL1* mutation was explained as was the very low, but not negligible, recurrence risk due to the possibility of gonadal mosaicism. The inheritance of *CFTR* mutations was explained and the 25% recurrence risk was reviewed. Testing for the *CFTR* mutations was offered to the family.

DISCUSSION

A summary of clinical features of our patient and previously reported ASXL1-positive BOS cases are in Tables I, II and III. Our patient was initially evaluated regarding severe developmental delay, failure to thrive, and minor anomalies. Her clinical picture was complicated by chronic pancreatitis. Exome sequencing revealed a de novo frameshift mutation in *ASXL1*, which was predicted to be pathogenic. This mutation is associated with *Bohring-Opitz syndrome* which is consistent with our patient's phenotype.

De novo truncating and/or frameshift mutations in *ASXL1* are associated with Bohring–Opitz syndrome [Bainbridge et al., 2013]. Although the variant identified in this patient has not been previously reported, it was predicted to abolish the Zinc finger domain of the protein that is essential for the normal function of *ASXL1* and is considered pathogenic.

ASXL1 [Katoh, 2013] encodes a chromatin-binding protein required for normal determination of segment identity in the developing embryo. The protein is a member of the Polycomb group of proteins, which are implicated in embryogenesis and carcinogenesis through transcriptional regulation of target genes. The *ASXL1* protein is thought to disrupt chromatin in localized areas, enhancing transcription of certain genes while repressing the transcription of other genes. The protein encoded by this gene functions as a ligand-dependent co-activator for retinoic acid receptor in cooperation with nuclear receptor co-activator.

TABLE I. Prevalence of *ASXL1* Mutation Based on Clinical Features in Patients Diagnosed With BOS

Clinical features	*ASXL1* mutation n /%	No *ASXL1* mutation n /%	*ASXL1* mut. n/% with our case
Feeding difficulties	8/8 (100)	6/6 (100)	9/9 (100)
Severe/profound LD	8/8 (100)	6/6 (100)	9/9 (100)
IUGR	8/9 (89)	4/6 (67)	9/10 (90)
Seizures	5/8 (62)	3/6 (50)	6/9 (70)
Arrhythmias	2/8 (25)	0/4 (0)	3/9 (33)
Prominent eyes	9/9 (100)	6/6 (100)	10/10 (100)
Trigonocephaly	8/9 (89)	5/6 (83)	9/10 (90)
Microcephaly	9/9 (100)	5/6 (83)	10/10 (100)
Nevus flammeus	8/9 (89)	6/6 (100)	9/10 (90)
Micro/retrognathia	8/9 (89)	6/6 (100)	9/10 (90)
Depressed nasal bridge	4/8 (50)	5/6 (83)	5/9 (55)
Low-set ears	6/9 (67)	5/6 (83)	7/10 (70)
Upslanting palp. fissures	6/9 (67)	3/6 (50)	7/10 (70)
Broad alveolar ridges	7/8 (87)	5/5 (100)	8/9 (88)
Anteverted nares	4/8 (50)	4/5 (80)	5/9 (55)
Hypertelorism	5/9 (55)	5/6 (83)	6/10 (60)
Low hairline	6/9 (67)	3/6 (50)	7/10 (70)
Hirsutism	8/9 (89)	1/6 (17)	9/10 (90)
BOS posture	9/9 (100)	6/6 (100)	10/10 (100)
Brain abnormalities	7/9 (78)	4/6 (67)	8/10 (80)
Fixed contractures	8/9 (89)	4/6 (67)	9/10 (90)
Hypotonia	7/9 (78)	4/6 (67)	8/10 (80)
Renal abnormalities	2/9 (22)	2/6 (33)	3/10 (30)

Modified from Magini et al. [2011].

TABLE II. Prevalence of Clinical Features That are Not Present in our Case Compared to Previous BOS Reports

Features not present in our case	*ASXL1* mutation	No *ASXL1* mutation
Recurrent infections	5/8 (62)	4/5 (80)
Cardiac abnormalities	3/9 (33)	2/6 (33)
Apneas	4/8 (50)	1/4 (25)
Genital abnormalities	2/9 (22)	2/6 (33)
Cleft palate	3/9 (33)	nr
Epicanthal folds	2/9 (22)	1/6 (17)

Modified from Magini et al. [2011].

Previous reports on BOS were based on clinical characteristics, although not confirmed by molecular identification of the causative mutation [Oberklaid and Danks, 1975; Bohring et al., 1999; Hastings et al., 2011]. Current molecular diagnostic methods lead to better definition of this syndrome by making a more accurate phenotypical-genotype correlation.

Only 10 cases (including the two previous reports and our report) of clinically diagnosed BOS have been confirmed by molecular analysis of the*ASXL1 gene,* as per current literature. All cases (100%) present with feeding difficulties, severe/profound learning disability, prominent eyes, microcephaly and the typical BOS posture. Also, most of cases (80 to 90%) present with IUGR, trigonocephaly, nevus flammeus during early infancy, low-set ears, broad alveolar ridges, micro/retrognathia, fixed contractures, hirsutism, hypotonia and brain abnormalities. Additionally, a high percentage of cases (60 to 80%) present with upslanting palpebral fissures and low hairline, recurrent infections and seizures.

Four patients are described with a BOS phenotype but lacking mutations in the *ASX1* gene but with pathogenic mutations in *ASXL3*. The clinical features of these four patients include severe feeding difficulties present from birth (3/4), severe post-natal growth retardation and severe psychomotor delay (4/4). Physical findings include small size at birth (3/4), microcephaly (3/4), high and broad forehead, periorbital fullness, arched eyebrows, anteverted nares, ulnar deviation of the hands (3/4) and high arched palate (3/4). Of note, none of those patients with *ASXL3* mutations, presented with trigonocephaly, nevus flammeus, prominent eyes, broad alveolar ridges, hirsutism or the typical 'BOS posture' of elbow and wrist flexion, features that are common for most patients with *ASXL1* mutations.

A more recent report on *ASXL3* mutations (which is the second report and fifth patient with pathogenic mutations in *ASXL3*) mentions trigonocephaly, prominent eyes, and metopic craniosynostosis, microcephaly, upslanting palpebral fissures, and low set ears, which further contribute to the phenotypic overlap with BOS, although the patient did not present with flammeus nevus, hirsutism, broad alveolar ridges and typical BOS posture.

Patients with known *ASXL3* mutations, represent an overlapping but distinct entity from BOS, since they do not fully display the most common features of this latter condition.

In summary, we review the most prevalent phenotypic features among the patients who have a clinical diagnosis of BOS and were further confirmed by molecular analysis (of *ASXL1* mutation). Our case report emphasizes the importance of highly specific phenotypic characterization of patients before proceeding with molecular studies which will lead to more accurate molecular data interpretation and better clinical genetic diagnosis, particularly for those patients with rare, difficult-to-diagnose disorders.

TABLE III. Most Frequent Features in BOS Cases With *ASXL1* Mutation Detected

100% of cases	80 to 90% of cases	60 to 80% of cases
Feeding difficulties	IUGR	Recurrent infections
Severe/Profound LD	Trigonocephaly	Upslanting palpebral fissures
Seizures	Flammeus nevus	Low hairline
Prominent eyes	Micro/Retrognathia	
Microcephaly	Fixed contractures	
BOS posture	Low-set ears	
	Hirsutism	
	Broad alveolar ridges	
	Hypotonia	
	Brain abnormalities	

Modified from Magini et al. [2011].

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