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Clinical findings in 39 individuals with Bohring–Opitz syndrome from a global patient-driven registry with implications for tumor surveillance and recurrence risk

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Abstract

Bohring–Opitz syndrome (BOS) is a rare genetic condition caused by pathogenic variants in *ASXL1*, which is a gene involved in chromatin regulation. BOS is characterized by severe intellectual disabilities, distinctive facial features, hypertrichosis, facial nevus simplex, severe myopia, a typical posture in infancy, variable anomalies, and feeding issues. Wilms tumor has also been reported in two individuals. We report survey data from the largest known cohort of individuals with BOS with 34 participants from the ASXL Patient-Driven Registry and data on five additional individuals with notable findings. Important or novel findings include hepatoblastoma ($n = 1$), an additional individual with Wilms tumor, two families with a parent who is mosaic including a pair of siblings, birth weights within the normal range for the majority of participants, as well as presence of craniosynostosis and hernias. Data also include characterization of communication, motor skills, and care level including hospitalization frequency and surgical interventions. No phenotype–genotype correlation could be identified. The ASXL Registry is also presented as a crucial tool for furthering ASXL research and to support the ASXL community.

KEYWORDS
ASXL1, Bohring–Opitz syndrome, craniosynostosis, hepatoblastoma, mosaicism, Wilms tumor

1 | INTRODUCTION

Bohring–Opitz syndrome (BOS) was first phenotypically described in 1975 by Oberklaid and Danks with further clinical delineation by Bohring et al. in 1999 who distinguished it from Opitz Trigoncephaly C syndrome (Bohring et al., 1999; Oberklaid & Danks, 1975). The molecular etiology was uncovered in 2011 by Hoischen et al. who reported de novo truncating variants in the ASXL Transcriptional Regulator 1 gene or Additional Sex Combs-Like 1 (*ASXL1*) on chromosome 20q11.21 in 7 out of 13 individuals with a clinical diagnosis of BOS (Hoischen et al., 2011). To date, all *ASXL1* variants associated with clinical features of BOS are truncating variants in the last two exons. No missense or truncating pathogenic variants outside this region have been reported in the literature (Russell et al., 2018). While clinical diagnostic criteria of BOS were proposed by Hastings et al. (2011) based on 30 individuals, this predates the identification of the molecular etiology, and several individuals, including a pair of siblings (participants 1 and 2 in that report), have subsequently been diagnosed with

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other syndromes (Bruel et al., 2017). Nonetheless, the initial clinical descriptions have remained relevant such that BOS is now typically defined by characteristic clinical features and truncating variants in the last two exons of *ASXL1*. Ultimately, there remains multiple individuals with BOS-like clinical features without identifiable *ASXL1* variants, some of whom may have other BOS-like syndromes or have *ASXL1* variants that are missed on routine genetic testing (Hoischen et al., 2011).

BOS is characterized by distinctive facial features and an unusual posture of the upper limbs in infancy, growth failure, variable but typically severe to profound intellectual disability, and a wide range of structural birth defects. The facial features may include microcephaly or trigonocephaly with prominent but not fused metopic ridge, hypotonic facies with full cheeks, synophrys, glabellar and eyelid nevus simplex, proptosis, widely set eyes, palate anomalies, and micrognathia. The BOS posture, which resolves with age, includes flexion at the elbows with ulnar deviation and flexion of the wrists and metacarpophalangeal joints. Most individuals also experience feeding difficulties during early childhood that improve with age. Severe vomiting can occur in a cyclic pattern that often improves with typical management for cyclic vomiting. Seizures are also common, and two individuals with Wilms tumor have been reported (Russell et al., 2015, 2018).

Interpretation of *ASXL1* variants can be challenging. While BOS is inherited in an autosomal dominant pattern, there is one publication with transmission from an asymptomatic mother with somatic mosaicism to her child (Bedoukian et al., 2018). Moreover, truncating variants in *ASXL1* are common in hematologic malignancies such as chronic myelomonocytic leukemia (40%–50%) and acute myeloid leukemia (almost 40%). Individuals also commonly acquire age-related loss-of-function *ASXL1* variants due to clonal hematopoiesis (Jaiswal & Ebert, 2019). These somatic variants are typically the same or similar to constitutional truncating variants in the last two exons that cause BOS (Micol & Abdel-Wahab, 2016), and their presence in control databases of reportedly healthy individuals, further complicates variant interpretation (Carlston et al., 2017). This, coupled with reports of unaffected mosaic parents, makes variant classification of *ASXL1* difficult and has likely resulted in under-reporting of BOS patients.

The canonical transcript of *ASXL1* consists of 13 exons. *ASXL1* is named after the *Drosophila* ortholog, Additional sex combs (Asx), which is a Polycomb group protein that regulates the transcription of specific homeotic *Hox* genes. *Hox* genes are critical for the formation of the body axis, as well as interacting with other genes, possibly by regulating the methylation and ubiquitination of specific lysine residues on certain histones (Fisher et al., 2006; Micol & Abdel-Wahab, 2016). *ASXL2* and *ASXL3* are similarly named with some overlapping function. The ASXL genes are considered nonenzymatic "readers" of the epigenetic code by playing a role in histone modification and chromatin regulation. They are part of a growing group of syndromes known as chromatinopathies or Mendelian disorders of the epigenetic machinery (MDEMs) that are characterized by intellectual disability and atypical growth (Fahrner & Bjornsson, 2019).

In this text, we review clinical data for 34 individuals in the ASXL Patient Driven Registry along with five additional individuals with Wilms tumor, hepatoblastoma, and two families with gonadal mosaicism including an affected sibship.

2 | METHODS

2.1 | Registry design and data collection

The ASXL Registry is a multisite patient-driven registry designed in close collaboration with the ASXL family communities including the Bohring–Opitz Syndrome Foundation, the Bohring–Opitz Syndrome Support Group, and the ASXL Rare Research Endowment (ARRE). It has approval by the institutional review boards at all sites (UCLA, Boston Children's Hospital, Cincinnati Children's Hospital, and Duke University). This publication primarily includes information collected through a survey completed by parents or guardians of the participants. The survey is shown in Table SS1. Review of medical records was undertaken for those with a tumor or have parents who are mosaic for an *ASXL1* variant. Genetic test results confirming the presence of a pathogenic *ASXL1* variant were reviewed by the registry clinical team. Participants were recruited through family support groups, at family gatherings, from ClincalTrials.gov (ClinicalTrials.gov Identifier: NCT03303716), and through referrals from healthcare providers. All participants were consented per study protocol.

2.2 | Data analysis

Survey question responses were reviewed in detail by the registry team. In order to classify clinical severity for each participant, specific survey questions were assigned weighted points that were summated to generate an overall severity score. Table SS2 includes details for score generation. All 34 participants had sufficient data to determine a severity score based on a standardized scale of points out of 100 such that 1–49 points is mild, 50–74 points is moderate, and greater than 75 points is severe.

3 | RESULTS

3.1 | Demographics

A total of 34 participants from the United States ($n = 24$), Canada ($n = 2$), Australia ($n = 2$), the Netherlands ($n = 2$), Portugal ($n = 1$), Poland ($n = 1$), Italy (n = 1), and Germany ($n = 1$) completed this survey. The survey was submitted by a parent (biologic, adoptive, or step) in all but 2 instances where a grandparent or a foster parent completed it. Per the caregivers who completed the survey, data from 22 out of 34 (65%) of participants are not known to have been published, while another 4 out of 34 (11%) were unsure whether their

data have ever been published. Nineteen individuals were male (56%) and 15 were female (44%). Mean age of the participants was 7 years (range: 1–23 years). Three of the 34 surveys were completed on behalf of deceased individuals, with the causes of death being seizures, respiratory failure, or cardiac failure (Table 1). Molecular confirmation of BOS was obtained through whole exome or genome sequencing in 19 of 34 individuals (56%), ASXL gene family sequencing in 13 of 34 individuals (38%), and large gene panel sequencing in 2 of 34 individuals (6%). Figure 1 demonstrates facial features at different ages for six participants.

3.2 | Phenotype and genotype

The *ASXL1* variants of the 34 participants with severity scores were plotted on an *ASXL1* gene diagram. Variants from the additional five individuals reported here were also included but without severity scores as they did not complete the survey. Previously published individuals who were not in the registry do not have severity scores but are included in part B of the diagram. No clear genotype–phenotype correlation was observed. All variants were truncating and occurred in the final two exons (Figure 2).

3.3 | Clinical history

Data on demographics, severity, birth weight, hospitalizations (including ICU stays), surgeries, feeding, communication, motor skills, and survival are reported in Table 1. The majority of individuals had appropriate birth weight for gestational age (Figure 3). When a denominator of less than 34 is used in Table 1, it is due to incomplete survey responses. Multiple responses were allowed for questions about surgeries, communication, and motor skills. All reported surgeries are shown in the table, with many individuals having multiple surgeries. For communication and motor skills, the highest level of attained abilities is listed. Many participants listed "understands more than can communicate" and an expressive skill. This value was therefore presented separately as well as in the expressive skill set when it was the only answer provided.

3.4 | Inheritance

In addition to the data reported herein, we report an affected sib pair and a family with paternal constitutional mosaicism. In the sibship, both siblings have the c.1282C>T p. Q428X (NM_015338.5) variant, but neither parent, both of whom were unaffected, had the variant in their peripheral blood samples. We also identified another family in which the unaffected father was mosaic for his daughter's ASXL1 variant: c.1934dupG p.G646YfsX12 (NM_015338.5) in 1.58% of 190 next generation sequencing reads. Neither of these families were included in the survey data, but they are currently enrolled in the registry.

3.5 | Neoplastic processes

Additional oncologic cases from two registrants not included in the survey dataset are also reported. We identified a previously unpublished 33-year-old woman with classic features of BOS (*ASXL1* c.1762C>T p.Q588X, NM_015338.5) who had unilateral Wilms tumor identified at age 4 on abdominal examination and was treated successfully with nephrectomy, chemotherapy, and radiation. We also report a 3 years old female with classic features of BOS (*ASXL1* c.1433delG p.G478VfsX224, NM_015338.5) who had hepatoblastoma found on surveillance abdominal ultrasounds for Wilms tumor at 18 months of age. She required partial liver resection and chemotherapy with subsequent remission.

4 | DISCUSSION

Previous case reports and series on BOS had limited natural history data and included patients without molecular confirmation, so different genetic diagnoses could have been included. Medical care has also advanced significantly with more aggressive interventions, so previously published case reports may not reflect current treatment paradigms. Our registry provides an opportunity to better understand BOS, develop management and treatment strategies, generate data that may facilitate basic science research, and collate data on a pool of patients who may be eligible for future clinical trials. This initial publication reports baseline data from 34 participants who completed our enrollment survey as well as data from five additional individuals who did not complete the survey. While longitudinal data and a larger sample of patients are needed to further characterize the full clinical spectrum of BOS, this is the largest cohort of BOS patients in the published literature, and we have demonstrated an expanded phenotype.

Despite the expanded clinical spectrum, there remains a clear phenotypic pattern for BOS that is well recognized with characteristic facial features and neurocognitive impairments. While the majority of the participants (56%; 19/34) were diagnosed by whole exome sequencing, it is noteworthy that 38% (13/34) of participants were identified on targeted ASXL gene family testing, which suggests that nearly 40% of the healthcare providers recognized, or suspected, BOS based on the clinical phenotype.

When using our survey data to evaluate symptom severity, we could not identify any genotype–phenotype correlations (Figure 2). This is not surprising given that all the pathogenic variants are truncating and occur in the last two exons, likely resulting in a similar impact. It is possible that a milder or different phenotype associated with other types of variants or variants outside the last two exons may be identified in the future.

In regards to the clinical presentation, our data supported what has been reported as "classic BOS" in the literature, but they also highlighted some additional features. Novel findings include four individuals with hernias (inguinal [$n = 2$, hiatal; $n = 1$]) and two with craniosynostosis (Table 1). Although BOS has been associated with

TABLE 1 Clinical data for ASXL Registry participants

Severity	
Mild	9/34 (26.5%)
Moderate	**16/34 (47%)**
Severe	9/34 (26.5%)
Birth weight[a]	
Small for gestational age	4/31 (13%)
Appropriate for gestational age	**26/31 (84%)**
Large for gestational age	1/31 (3%)
Hospital admissions[a]	
Total number of hospitalizations	
0–5	**16/32 (50%)**
6–15	10/32 (31%)
More than 15	6/32 (19%)
Hospitalizations in ICU	20/32 (63%)
Unknown number of ICU stays	3/20 (15%)
1 ICU stay	7/20 (35%)
2–6 ICU stays	7/20 (35%)
>6 ICU stays	3/20 (15%)
Surgeries[b]	
Surgical feeding tube	**19/34 (56%)**
Myringotomy	**14/34 (41%)**
Orthopedic surgery (Scoliosis repair [3], surgical contracture management [hip, knee, feet], lower extremity epiphyseodesis, tibial fibular derotation, tendon release, femur fracture fixation)	6/34 (18%)
Gastric fundoplication	6/34 (18%)
Supraglottoplasty	5/34 (14%)
Tracheostomy	4/34 (12%)
Cleft lip or palate repair	5/34 (14%), 3/34 (9%)
Hernia (inguinal [2], hiatal)	3/34 (9%)
Genitourinary surgery	3/34 (9%)
Renal surgery	3/34 (9%)
Cardiac repair (congenital)	1/34 (3%)
Craniosynostosis	2/34 (6%)
Ophthalmologic surgery	1/34 (3%)
Feeding	
No oral feeds	7/34 (20.5%)
Oral tastes for pleasure only	7/34 (20.5%)
Some oral feeds	4/34 (12%)
All oral feeds	**16/34 (47%)**
Communication	
Expressive (*highest ability*)[a]	
Too young to communicate	5/26 (19%)
Understands more than communicates	3/26 (12%)
Nonverbal communication/gestures	**6/26 (23%)**
Uses a communication device/signing	4/26 (15%)
Uses a few basic words	5/26 (19%)
Mostly communicates verbally	1/26 (4%)
Has a normal vocabulary	2/26 (8%)

Receptive	
Understands more than communicates	**27/34 (79%)**
Motor skills (highest ability)	
Under age of 8 months	1/34 (3%)
No independent movement	4/34 (12%)
Rolls over, reaches/holds objects	2/34 (6%)
Sits with support	**10/34 (29%)**
Sits independently	4/34 (12%)
Crawls/scoots	4/34 (12%)
Walks with support	5/34 (14%)
Full mobility	4/34 (12%)
Survival	
Deceased	3/34 (9%)
Cause of death	
Respiratory	1/3 (33%)
Cardiac	1/3 (33%)
Seizure	1/3 (33%)

Note: Most frequent features in bold.
[a]Not all respondents provided answers.
[b]Multiple responses allowed, total does not equal 100%.

intrauterine growth retardation (IUGR), the majority (84%; 26/31) of the participants in our cohort had birth weights in the normal range for gestational age (Figure 3). While there is likely ascertainment bias in the registry data, a large number of BOS individuals survive past infancy and into adulthood (31/34), which differs from early reports of a high infant mortality rate (Russell et al., 2018). Feeding intolerance with recurrent vomiting that typically improves with age was thought to be prevalent (Russell et al., 2015), yet 47% (16/34) of participants fed entirely orally with another 32% (11/34) taking some amount of oral feeds for nutrition or pleasure. While oral feeding was attained by the majority of participants, 56% (19/34) of the participants had a surgically placed feeding tube with 32% (6/19) of those individuals receiving a gastric fundoplication, likely related to chronic vomiting in infancy (Table 1). Thus, severe feeding issues are not universally present and likely decrease with age given that 79% of registrants take at least some oral tastes, but it remains noteworthy that 20% of individuals do not take oral feeds.

From a communication standpoint, the majority of participants were able to understand more than they could communicate (79%; 27/34). For those with expressive language skills, nonverbal cues was the highest level of communication for 23% (6/26) of individuals, while 15% (4/26) used signs or communication devices, and 31% (8/26) of the families reported some amount of verbal language. Early developmental services and use of augmentative and alternative communication (AAC) devices and/or sign language could therefore be beneficial in improving expressive communication for many individuals. Gross motor skills showed a similar large spectrum with 26% (9/34) of individuals who walk with or without support. This again emphasizes that around at least a quarter of affected individuals do attain higher level functioning. It is therefore important to recognize strengths and range of ability in order to maximize individual potentials. Introducing nonverbal gestures, assistive devices, as well as early physical and occupational therapy, will allow for greater autonomy, less frustration and associated behavioral issues, increased communication, as well as improved mobility.

The number of surgical procedures and need for hospitalization are also variable. Overall, 50% (16/32) of respondents have had six or more hospitalizations. Intensive care (ICU) level stays are common, with 63% (20/32) of participants requiring at least one ICU stay. This result is not unexpected given the multiple organ system manifestations, hypotonia, and feeding issues. The most common surgery is feeding tube placement with or without gastric fundoplication (56%; 19/34), followed by myringotomy (41%; 14/34), various orthopedic procedures (18%; 6/34) and airway management surgeries (supraglottoplasty 14%; 5/34 and tracheostomy 12%; 4/34). This likely reflects that major care challenges are often centered on feeding, chronic infections, mobility, hypotonia, and airway issues. Although not captured through a one-time survey, we have observed a decrease in hospitalizations and overall disease burden after the first few years of life.

Our data also further support that rates of mosaicism in the ASXL-related disorders are higher than what is typically seen in the majority of autosomal dominant neurocognitive disorders. By adding to the literature a pair of BOS sibs with negative parental *ASXL1* sequencing and a BOS individual with an unaffected father who is mosaic for the pathogenic variant, there are now three BOS families that demonstrate gonadal or constitutional mosaicism (Bedoukian et al., 2018).

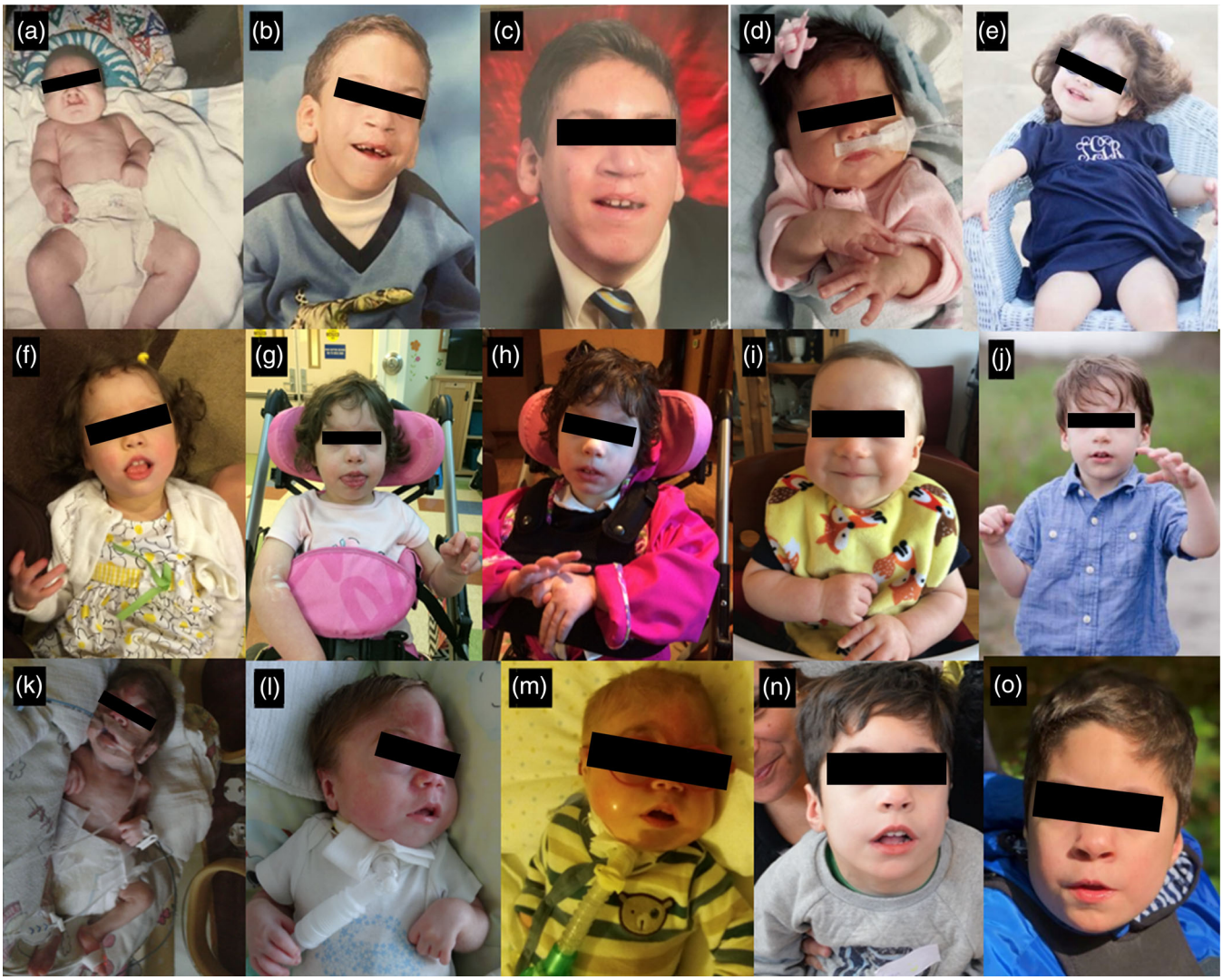

FIGURE 1 Photographs of Bohring-Opitz syndrome patients at various ages. (a–c) Patient 1 at 3 months, 5 years, and 22 years. (d, e) Patient 2 at birth and 3 years. (f–h) Patient 3 at 2 years, 3 years, and 4 years. (i, j) Patient 4 at 8 months and 02 years. (k–m) Patient 5 at 2 months, 8 months, and 1 year. (n, o) Patient 6 at 5 years and 7 years

For the ASXL3-related disorder (Bainbridge–Ropers syndrome), 5 families out of 90 published individuals have an unaffected mosaic parent, siblings with no parental variant identified, or an affected individual with 30%–35% mosaicism on blood and saliva testing (Koboldt et al., 2018; Schirwani et al., 2020, 2021).

While it remains a challenge to determine true prevalence in the population, the ASXL-related disorders are ultra-rare neurodevelopmental conditions with eight families harboring gonadal or constitutional mosaic ASXL variants. This occurrence appears higher than the typically cited 1%–2% expected recurrence risk due to gonadal mosaicism. However, we are unable to determine the true rate of gonadal and constitutional mosaicism through a survey due to the relatively small sample size and potential biases. It is notable that this increased risk is not unique to the ASXL disorders as gonadal mosaicism is well reported in other autosomal dominant neurodevelopmental disorders with mechanisms that impact chromatin and cohesion pathways such as CHARGE syndrome (*CHD7*) and Cornelia de Lange syndrome (*NIPBL*, *SMC1A*) (Jongmans et al., 2008; Lalani et al., 2006; Slavin et al., 2012). There is no clearly defined mechanism resulting in increased rates of mosaicism for these conditions.

Of note, Greenhalgh et al., 2003 reported a sibling pair with clinically diagnosed BOS but subsequent *ASXL1* sequencing was negative with an ultimate diagnosis of *KLHL7*-related disorder (Bruel et al., 2017). Given that these individuals do not have BOS, they should not be considered when discussing rates of mosaicism in this population.

While Wilms tumor has previously been reported in two individuals, as published by Russell et al., 2015, we now report a third individual with this rare pediatric tumor along with the first individual with BOS known to have a hepatoblastoma. Wilms tumor rates in the pediatric population are 7 per 1 million (Grovas et al., 1997) while hepatoblastoma rates are 0.5–1.5 per 1 million children (Mann et al., 1990). Because the prevalence of BOS cannot be accurately predicted, determining an accurate tumor risk is not feasible but given

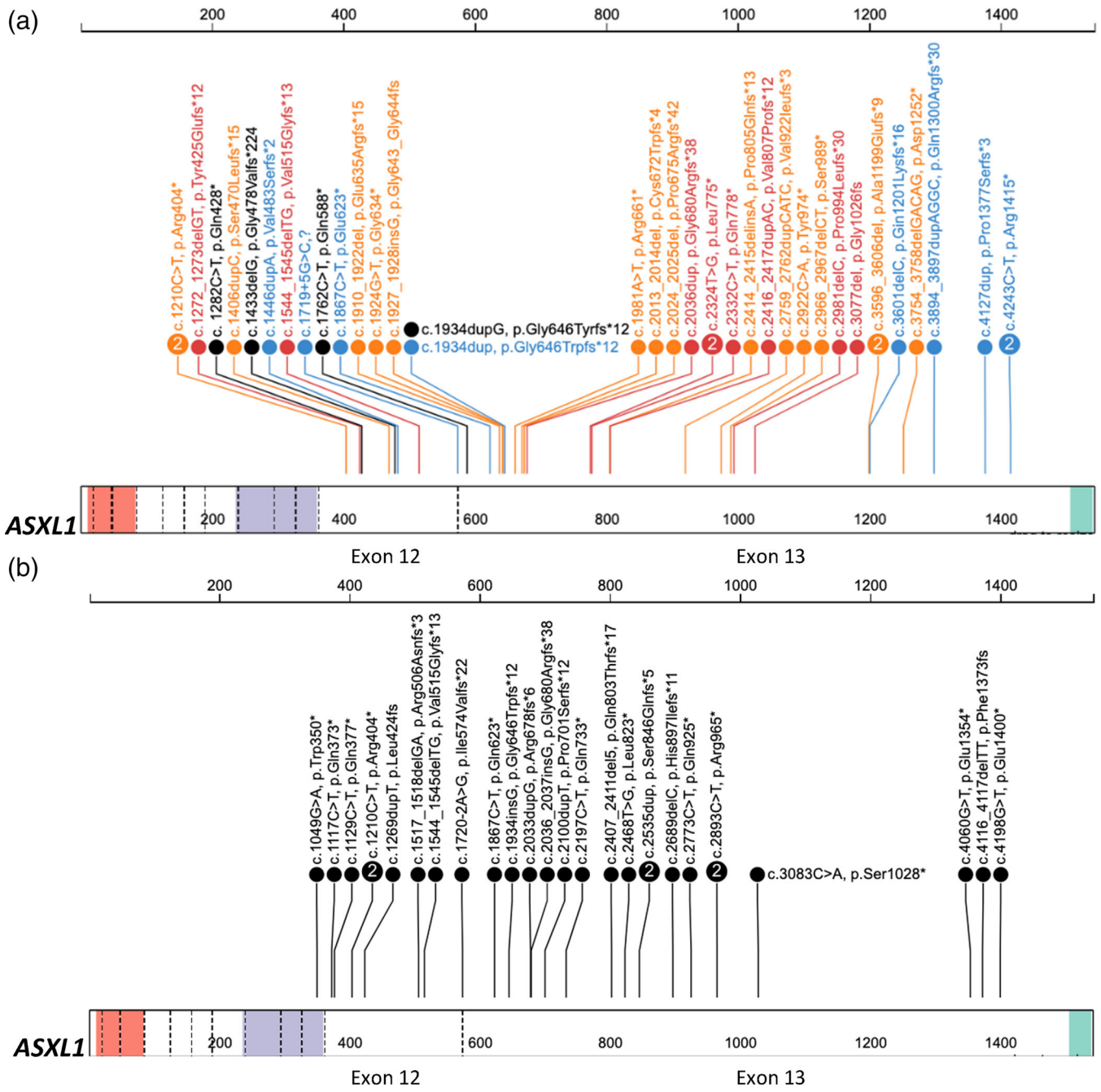

FIGURE 2 Schematic of the ASXL1 protein with variants from the ASXL Patient Registry with Associated Severity Scores and Published ASXL Variants. Dashed lines denote exon borders. (a) ASXL1 variants from the 34 individuals who completed the ASXL Registry survey with severity scores are shown in red, orange, and blue. Red lollipops represent severely affected individuals, orange are moderately affected individuals, and blue are mildly affected individuals. Five additional individuals without severity scores are shown in black. The variant c.1282C>T, p.Gln428* is reported only once in the image but occurs in affected siblings. (b) ASXL1 variants reported in the literature in association with BOS that are not included in registry dataset. References in Supplemental Data S3. *Source*: Image generated using St. Jude Protein Paint with ASXL transcript NM_015538 and hg19 build

the rarity of both these pediatric tumors and their frequency in an ultra-rare genetic condition, screening with abdominal ultrasound every 3 months until age 8 for Wilms tumor was previously recommended (Russell et al., 2015). While a single case of hepatoblastoma does not necessarily warrant recommendations to implement regular surveillance with serum alpha-fetoprotein (AFP) levels, if additional patients were identified, hepatoblastoma surveillance could become a critical component of future management guidelines. Of note, abdominal ultrasound every 3 months until age 8 would be part of the recommendation for hepatoblastoma surveillance. It also remains of interest that somatic variants in the ASXL genes (primarily *ASXL1* and *ASXL3*), are common in many hematologic and solid tumor oncologic

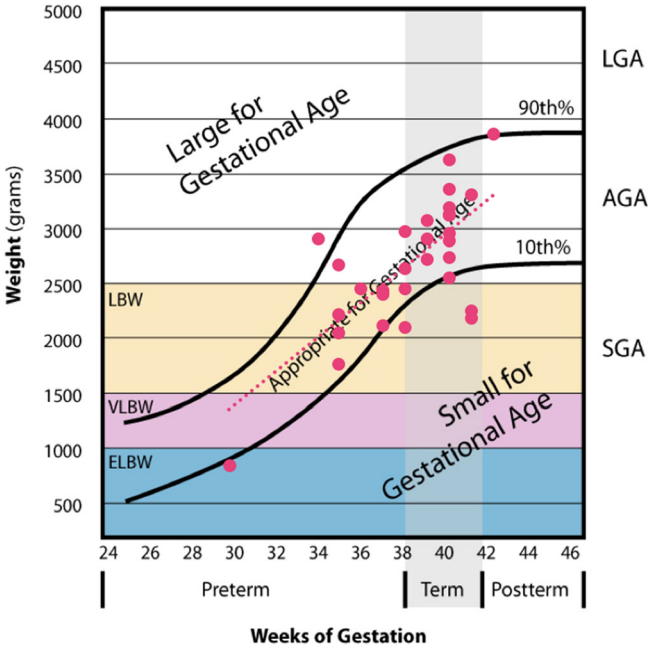

FIGURE 3 Birthweight for gestational age in patients with Bohring–Opitz syndrome. Data are plotted as weight in grams against gestational age in weeks. Values plotted over normative data with designations for birthweight norms, including small for gestational age, appropriate for gestational age, and large for gestational age. *Source*: Wikipedia commons provided the graphic with normative values

processes (Micol & Abdel-Wahab, 2016). To date, other forms of cancer have not been reported in BOS, although very few adults have been identified, so the prevalence of adult-onset cancers is unknown.

Ultimately, the ASXL-Patient Driven Registry is essential for our understanding of BOS and developing management strategies. Data collected directly from families have limitations regarding accuracy, yet the data presented here are within the scope of what families can reliably recount regarding their children's medical history. A survey is also biased toward those who respond so it does not always capture the full spectrum of manifestations and complications. Nonetheless, given the rarity of BOS and the high response rate for our survey, the data reported herein likely have broad applicability. Other rare disease registries, such as the Duchenne Registry for Duchenne Muscular Dystrophy (DMD) and the Global Angelman syndrome (AS) Registry, have shown continued value for parent and participant reported data. The DMD community uses the Duchenne Registry to collect longitudinal natural history information and develop therapeutic interventions through a mutually beneficial collaboration between academic investigators and patients (Wang et al., 2014). The AS registry further demonstrates success in informing research that will identify treatments for AS, and ultimately improving the lives of individuals and families living with AS (Napier et al., 2017). The ASXL registry shares a similar designs to these successful resources with direct surveys and medical record support as needed.

In conclusion, further expansion of the disease spectrum is characterized here, including novel features of hepatoblastoma, absence of IUGR or low birth weight, and presence of craniosynostosis and hernias. An additional occurrence of Wilms tumor as well as two families with mosaicism continues to support previously reported findings. We seek to increase the number of participants globally and to gather data on other aspects of BOS. This registry has also been integrated into a biobank study at UCLA will correlate natural history data with biological specimens as a resource for laboratory studies that can further elucidate the underlying disease mechanisms and lead to the development of therapeutics.

AUTHOR CONTRIBUTIONS

Bianca E. Russell designed the study, oversaw all aspects of the study and completed much of the writing for the manuscript. **Rebecca R. Kianmahd** assisted in study coordination and completed the majority of data analysis, figure and table design, and authored major portions of the manuscript. **Rebecca R. Kianmahd**, **Chelsea Munste**, **Anna Yu**, and **Leena Ahad** enrolled study participants, managed the study, assisted with data generation and data analysis. **Wen-Hann Tan**, in the role of senior author, assisted in study design, execution, and in writing the manuscript. All authors contributed to the manuscript editorial and revision process.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Bedoukian, E., Copenheaver, D., Bale, S., & Deardorff, M. (2018). Bohring-Opitz syndrome caused by an ASXL1 mutation inherited from a germline mosaic mother. *American Journal of Medical Genetics*, *176*(5), 1249–1252. https://doi.org/10.1002/ajmg.a.38686

Bohring, A., Silengo, M., Lerone, M., Superneau, D. W., Spaich, C., Braddock, S. R., Poss, A., & Opitz, J. M. (1999). Severe end of Opitz trigonocephaly (C) syndrome or new syndrome? *American Journal of Medical Genetics*, *85*(5), 438–446. https://doi.org/10.1002/(sici)1096-8628(19990827)85:5<438::aid-ajmg2>3.0.co;2-a

Bruel, A. L., Bigoni, S., Kennedy, J., Whiteford, M., Buxton, C., Parmeggiani, G., Wherlock, M., Woodward, G., Greenslade, M.,

Williams, M., St-Onge, J., Ferlini, A., Garani, G., Ballardini, E., van Bon, B. W., Acuna-Hidalgo, R., Bohring, A., Deleuze, J. F., Boland, A., … Thevenon, J. (2017). Expanding the clinical spectrum of recessive truncating mutations of KLHL7 to a Bohring-Opitz-like phenotype. *Journal of Medical Genetics*, *54*(12), 830–835. https://doi.org/10.1136/jmedgenet-2017-104748

Carlston, C. M., O'Donnell-Luria, A. H., Underhill, H. R., Cummings, B. B., Weisburd, B., Minikel, E. V., Birnbaum, D. P., Exome Aggregation Consortium, Tvrdik, T., MacArthur, D. G., & Mao, R. (2017). Pathogenic ASXL1 somatic variants in reference databases complicate germline variant interpretation for Bohring-Opitz syndrome. *Human Mutation*, *38*(5), 517–523. https://doi.org/10.1002/humu.23203

Fahrner, J. A., & Bjornsson, H. T. (2019). Mendelian disorders of the epigenetic machinery: Postnatal malleability and therapeutic prospects. *Human Molecular Genetics*, *28*(R2), R254–R264. https://doi.org/10.1093/hmg/ddz174

Fisher, C. L., Randazzo, F., Humphries, R. K., & Brock, H. W. (2006). Characterization of Asxl1, a murine homolog of additional sex combs, and analysis of the Asx-like gene family. *Gene*, *369*, 109–118. https://doi.org/10.1016/j.gene.2005.10.033

Greenhalgh, K. L., Newbury-Ecob, R. A., Lunt, P. W., Dolling, C. L., Hargreaves, H., & Smithson, S. F. (2003). Siblings with Bohring-Opitz syndrome. *Clinical Dysmorphology*, *12*(1), 15–19. https://doi.org/10.1097/00019605-200301000-00003

Grovas, A., Fremgen, A., Rauck, A., Ruymann, F. B., Hutchinson, C. L., Winchester, D. P., & Menck, H. R. (1997). The National Cancer Data Base report on patterns of childhood cancers in the United States. *Cancer*, *80*(12), 2321–2332. https://doi.org/10.1002/(sici)1097-0142(19971215)80:12<2321::aid-cncr14>3.0.co;2-w

Hastings, R., Cobben, J. M., Gillessen-Kaesbach, G., Goodship, J., Hove, H., Kjaergaard, S., Kemp, H., Kingston, H., Lunt, P., Mansour, S., McGowan, R., Metcalfe, K., Murdoch-Davis, C., Ray, M., Rio, M., Smithson, S., Tolmie, J., Turnpenny, P., van Bon, B., … Newbury-Ecob, R. (2011). Bohring-Opitz (Oberklaid-Danks) syndrome: Clinical study, review of the literature, and discussion of possible pathogenesis. *European Journal of Human Genetics*, *19*(5), 513–519. https://doi.org/10.1038/ejhg.2010.234

Hoischen, A., van Bon, B. W., Rodríguez-Santiago, B., Gilissen, C., Vissers, L. E. L. M., de Vries, P., Janssen, I., van Lier, B., Hastings, R., Smithson, S. F., Newbury-Ecob, R., Kjaergaard, S., Goodship, J., McGowan, R., Bartholdi, D., Rauch, A., Peippo, M., Cobben, J. M., Wieczorek, D., … de Vries, B. B. B. A. (2011). *De novo* nonsense mutations in *ASXL1* cause Bohring-Opitz syndrome. *Nature Genetics*, *43*(8), 729–731. https://doi.org/10.1038/ng.868

Jaiswal, S., & Ebert, B. L. (2019). Clonal hematopoiesis in human aging and disease. *Science*, *366*(6465), eaan4673. https://doi.org/10.1126/science.aan4673

Jongmans, M. C., Hoefsloot, L. H., van der Donk, K. P., Admiraal, R. J., Magee, A., van de Laar, I., Hendriks, Y., Verheij, J. B., Walpole, I., Brunner, H. G., & van Ravenswaaij, C. M. (2008). Familial CHARGE syndrome and the CHD7 gene: A recurrent missense mutation, intrafamilial recurrence and variability. *American Journal of Medical Genetics. Part A*, *146A*(1), 43–50. https://doi.org/10.1002/ajmg.a.31921

Koboldt, D. C., Mihalic Mosher, T., Kelly, B. J., Sites, E., Bartholomew, D., Hickey, S. E., McBride, K., Wilson, R. K., & White, P. (2018). A de novo nonsense mutation in ASXL3 shared by siblings with Bainbridge-ropers syndrome. *Cold Spring Harbor Molecular Case Studies*, *4*(3), a002410. https://doi.org/10.1101/mcs.a002410

Lalani, S. R., Safiullah, A. M., Fernbach, S. D., Harutyunyan, K. G., Thaller, C., Peterson, L. E., McPherson, J. D., Gibbs, R. A., White, L. D., Hefner, M., Davenport, S. L., Graham, J. M., Bacino, C. A., Glass, N. L., Towbin, J. A., Craigen, W. J., Neish, S. R., Lin, A. E., & Belmont, J. W. (2006). Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation. *American Journal of Human Genetics*, *78*(2), 303–314. https://doi.org/10.1086/500273

Mann, J. R., Kasthuri, N., Raafat, F., Pincott, J. R., Parkes, S. E., Muir, K. R., Ingram, L. C., & Cameron, A. H. (1990). Malignant hepatic tumours in children: Incidence, clinical features and aetiology. *Paediatric and Perinatal Epidemiology*, *4*(3), 276–289. https://doi.org/10.1111/j.1365-3016.1990.tb00651.x

Micol, J. B., & Abdel-Wahab, O. (2016). The role of additional sex combs-like proteins in cancer. *Cold Spring Harbor Perspectives in Medicine*, *6*(10), a026526. https://doi.org/10.1101/cshperspect.a026526

Napier, K. R., Tones, M., Simons, C., Heussler, H., Hunter, A. A., Cross, M., & Bellgard, M. I. (2017). A web-based patient driven registry for Angelman syndrome: The global Angelman syndrome registry. *Orphanet Journal of Rare Diseases*, *12*(1), 134. https://doi.org/10.1186/s13023-017-0686-1

Oberklaid, F., & Danks, D. (1975). The Opitz Trigonocephaly syndrome: A case report. *American Journal of Diseases of Children*, *129*(11), 1348–1349.

Russell, B., Johnston, J. J., Biesecker, L. G., Kramer, N., Pickart, A., Rhead, W., Tan, W. H., Brownstein, C. A., Kate Clarkson, L., Dobson, A., Rosenberg, A. Z., Vergano, S. A. S., Helm, B. M., Harrison, R. E., & Graham, J. M., Jr. (2015). Clinical management of patients with ASXL1 mutations and Bohring-Opitz syndrome, emphasizing the need for Wilms tumor surveillance. *American Journal of Medical Genetics - Part A*, *167*(9), 2122–2131. https://doi.org/10.1002/ajmg.a.37131

Russell, B., Tan, W. H., & Graham, J. M., Jr. (2018). Bohring-Opitz syndrome. In M. P. Adam, D. B. Everman, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, L. JH Bean, K. W. Gripp, A. Amemiya (Eds.), *GeneReviews® [Internet]*. University of Washington.

Schirwani, S., Albaba, S., Carere, D. A., Guillen Sacoto, M. J., Milan Zamora, F., Si, Y., Rabin, R., Pappas, J., Renaud, D. L., Hauser, N., Reid, E., Blanchet, P., Foulds, N., Dixit, A., Fisher, R., Armstrong, R., Isidor, B., Cogne, B., Schrier Vergano, S., … Balasubramanian, M. (2021). Expanding the phenotype of ASXL3-related syndrome: A comprehensive description of 45 unpublished individuals with inherited and de novo variants in ASXL3. *American Journal of Medical Genetics - Part A*, *185*, 3446–3458. https://doi.org/10.1002/ajmg.a.62465

Schirwani, S., Hauser, N., Platt, A., Punj, S., Prescott, K., Canham, N., study, D. D. D., Mansour, S., & Balasubramanian, M. (2020). Mosaicism in ASXL3-related syndrome: Description of five patients from three families. *European Journal of Medical Genetics*, *63*(6), 103925. https://doi.org/10.1016/j.ejmg.2020.103925

Slavin, T. P., Lazebnik, N., Clark, D. M., Vengoechea, J., Cohen, L., Kaur, M., Konczal, L., Crowe, C. A., Corteville, J. E., Nowaczyk, M. J., Byrne, J. L., Jackson, L. G., & Krantz, I. D. (2012). Germline mosaicism in Cornelia de Lange syndrome. *American Journal of Medical Genetics. Part A*, *158A*(6), 1481–1485. https://doi.org/10.1002/ajmg.a.35381

Wang, R. T., Silverstein Fadlon, C. A., Ulm, J. W., Jankovic, I., Eskin, A., Lu, A., Rangel Miller, V., Cantor, R. M., Li, N., Elashoff, R., Martin, A. S., Peay, H. L., Halnon, N., & Nelson, S. F. (2014). Online self-report data for Duchenne muscular dystrophy confirms natural history can be used to assess for therapeutic benefits. *PLOS Currents*, *6*, 6. https://doi.org/10.1371/currents.md.e1e8f2be7c949f9ffe81ec6fca1cce6a

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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