BOHRING-OPTIZ SYNDROME CAUSED BY AN *ASXL1* MUTATION INHERITED FROM A GERMLINE MOSAIC MOTHER

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Introduction

- Bohring-Opitz syndrome (BOS) is a rare congenital disorder characterized by intrauterine growth retardation, poor feeding, mental retardation, trigonocephaly, prominent metopic suture, exophthalmos, nevus flammeus of the face, upslanting palpebral fissures, hirsutism, and flexion of the elbows and wrists. There have been approximately 60 reported cases of BOS and all have been reported to be due to de novo *ASXL1* gene mutations (1).

Methods

- Genomic DNA was extracted from the submitted specimen(s). Exonic regions and flanking splice junctions of the genome were captured for massively parallel (NextGen) sequencing on an Illumina HiSeq sequencing system. Reads were aligned to reference gene sequences based on human genomebuild GRCh37/ UCSC hg19, and analyzed for sequence variants using a custom-developed analysis tool.
- Clinical records and prior genetic results on the affected fetus were reviewed prior to analysis.
- Variants were interpreted following ACMG guidelines published in 2015.
- Capillary sequencing was used to confirm all potentially pathogenic variants identified in the fetus and the parents.

Case Report

We report a case of a 3 year old female who presented with history of intrauterine growth retardation, failure to thrive, microcephaly, seizures, choanal atresia, atrial septal defect (ASD), chronic respiratory failure, facial hemangioma, and facial dysmorphism.

- Born at 34 weeks to a G4P3-4 34-year-old mother. Delivery induced due to poor umbilical flow. Small for gestational age.
- NICU stay involving choanal atresia, hyperbilirubinemia, polychythemia, frequent vomiting, laryngomalacia, dyspnea. Surgeries included Nissen with fundoplication and tracheostomy. Brain MRI revealed periventricular leukomalacia. Genetic testing included SNP array and CHD7 sequencing – both negative. Discharged at 8 months.
- Readmission at 12 months due to new onset seizures (left sided tonic clonic activity), fever, and shock. Rapid decline led to ordering an expedited exome sequencing test, with underlying suspicion of BOS based on facial dysmorphisms.
- At 30 months old, weight and length are <1st percentile and her head is the 10th percentile. Ophthalmic findings include nystagmus, optic atrophy alternating esotropia, and high myopia.
- Developmentally she is delayed. She cannot hold her head up, poor grasp with her hands, she sometimes responds to a voice by turning her head but more-so her parents voices just calm her. Receives physical, occupational, speech, vision, and hearing services.
- Family history revealed Mother has a history of Crohn's disease, immune thrombocytopenic purpura and degenerative disc disease. Father and three siblings are healthy. No family history of developmental delay or congenital anomalies. No pregnancy losses.

Figure 1. Proband at 30 months old

Results

- Trio exome sequencing revealed a heterozygous pathogenic nonsense variant in *ASXL1* (p.R965X; c.2893C>T). The sequencing data demonstrated that the variant was inherited maternally but indicating that this maternal allele was underrepresented in comparison to the normal allele.
- In this case, the mother has 44/123 (36%) reads with the variant (95% CI = 27.3%-44.9%) indicating she is likely mosaic and not heterozygous. Using a one-proportion Z-test with an expected variant frequency of 47% for heterozygotes (based on our observations and due to capture bias of the reference allele), gives P=0.0126. These results suggested mosaicism for the variant in the mother.
- Additional testing on maternal buccal cell DNA was performed and the sequencing data indicate that the p.R965X variant was present but underrepresented in comparison to the normal allele. Again these results are consistent with somatic mosaicism.
- Additionally, the proband is compound heterozygous for the p.Q730H and p.R422C variants of uncertain significance in the FANCM Gene.

Conclusions

- This is the first report of Bohring-Opitz syndrome caused by a mutation inherited from an unaffected, somatic mosaic parent with presumed germline mosaicism. This phenomenon has been reported for other traditionally *de novo* dominant disorders like CHARGE syndrome and Cornelia de Lange syndrome (2)(3). This case demonstrates that haploinsufficiency of *ASXL1* is not lethal in the germline, and emphasizes the need for accurate low but non-negative recurrence risk counseling for families with children with Bohring-Opitz syndrome

References

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