UPD1 in a Newborn with Multiple Congenital Anomalies

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ABSTRACT

There have been reports in the literature of uniparental isodisomy of chromosome 1 (UPD), but none has revealed a unifying phenotype. In most cases, the UPD1 led to the unmasking of an autosomal recessive condition. A newborn girl with multiple congenital anomalies was referred for the Claritas Genomics custom SNP chromosomal microarray analysis (CMA), which identified uniparental isodisomy of the entire chromosome 1. The patient originally came to medical attention prenatally for concerns regarding small kidneys, dilated ureters, and oligohydramnios beginning at 26 weeks gestation. Additional ultrasounds and fetal MRI identified bilateral dysplastic kidneys and cardiomegaly. The patient was born at 38 weeks via spontaneous vaginal delivery with Apgars of 2, 5, and 5. Postnatal imaging identified aortic coarctation, right ventricular dysfunction, tricuspid regurgitation and confirmed renal dysplasia/hypoplasia. Physical exam was notable for dysmorphic features including deep set eyes, downslanting palpebral fissures, and 3,4 syndactyly of fingers. She later was noted to have bilateral clavicle fractures and bilateral hip dislocation. Mosaic chromosome analysis to assess for potential aneuploidy rescue was normal. None of the known autosomal recessive disorders related to chromosome 1 sufficiently explained the patient's entire phenotype, raising the possibility of more than one disorder, an atypical presentation of a known disorder, or a novel disorder. The patient's fractures raised the possibility of hypophosphatasia, associated with autosomal recessive mutations in the *ALPL* gene on chromosome 1; however, plasma ALP levels were not decreased and urine phosphoethanolamine was not increased. Exome sequencing of chromosome 1 is currently pending with the goal of identifying the responsible gene(s) for this patient's features. This case highlights the ability of SNP CMA to identify UPD that likely would not have been otherwise detected. This information helped to refine our search and will hopefully lead to an ultimate molecular diagnosis.

Introduction

A newborn with multiple congenital anomalies (MCA) was assessed by the Genetics Program at Boston Children's Hospital. Per the 2010 ACMG Practice Guideline entitled "Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities," the team recommended that the patient undergo a SNP chromosomal microarray analysis as the first-line test[1] in order to determine the underlying genetic cause for the patient's MCA.

The Claritas Genomics custom SNP CMA (Agilent 4x180k) was conducted on this patient. No copy number variants were detected. SNP probes identified absence of heterozygosity of the entire 1st chromosome indicating likely UPD.

UPD of chromosome 1 is not associated with any specific syndrome, however, there are several reports in the literature of maternal and paternal UPD1 as well as partial UPD1. For instance, one case of maternal UPD1 resulted in features consistent with Zellweger syndrome due to a homozygous single base pair insertion in the *PEX10* gene[2]. In a different case partial maternal UPD1 is hypothesized to be connected to the patient's diagnosis of autism likely due to an autosomal recessive gene located on 1q for which further investigation was needed to identify the causative gene[3]. In cases of UPD1 it is apparent that the patient's phenotype is due to the unmasking of a pathogenic homozygous variant in an autosomal recessive gene located on either arm of chromosome 1.

The Investigation

- The Genetics Team at Boston Children's Hospital used the Genomic Oligoarray and SNP Array Evaluation Tool developed by the University of Miami and Oklahoma University Health Sciences Center to review the autosomal recessive OMIM genes located on chromosome 1.
- The gene *ALPL* associated with hypophosphatasia was raised as a potential cause for the patient's fractures, however, the patient's plasma ALP levels were not decreased and urine phosphoethanolamine was not increased.
- It was felt that the known remaining autosomal recessive OMIM genes located on chromosome 1 were not a phenotypic match for the patient, thus, raising the possibility of more than one disorder, an atypical presentation of a known disorder, or a novel disorder.
- Mosaic chromosome analysis to assess for potential aneuploidy rescue was normal.
- To identify a potential molecular diagnosis by targeting genes only located on chromosome 1, the GeneDx XomeDx Slice was ordered.

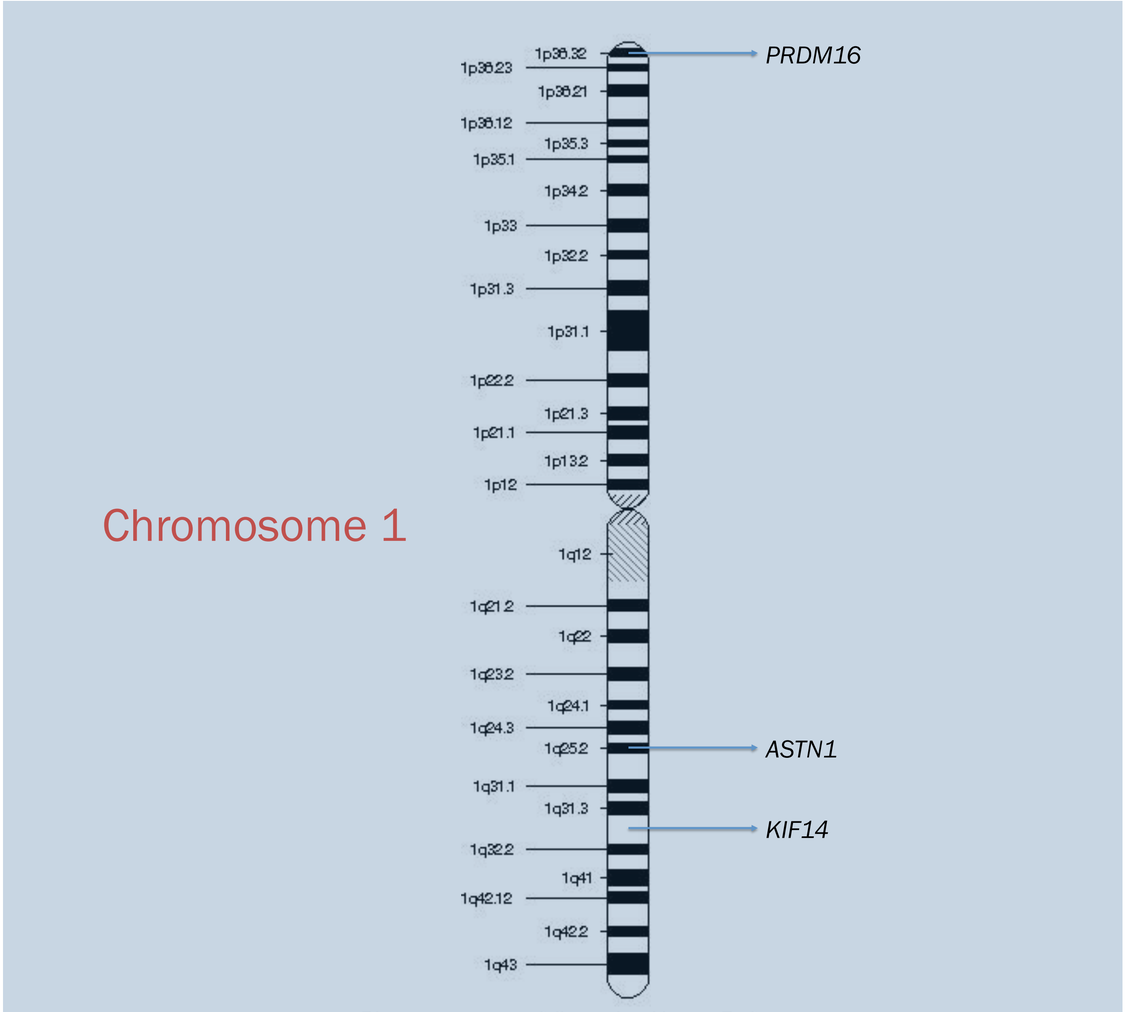

Photo courtesy of Genetics Home Reference

The Result

The XomeDx Slice identified three homozygous variants in the following genes:

1. *PRDM16* – associated with left ventricular noncompaction and dilated cardiomyopathy
2. *ASTN1* – potential risk factor for autism spectrum disorder, ADHD, and other neurodevelopmental disorders[4]
3. *KIF14* – associated with Meckel syndrome characterized by intrauterine growth restriction, microcephaly, dysmorphic features, uterine hypoplasia, renal agenesis, renal hypoplasia, cystic dysplasia, ureteral hypoplasia, arthrogryposis, and brain malformations including cerebral and cerebellar hypoplasia and agenesis of the corpus callosum

These three genes in combination could be the explanation for this patient's findings, however, none of these genes explain the fractures or the bilateral hip dislocation. Additionally, *PRDM16* is inherited in a dominant manner, therefore, the effect of a homozygous change is unknown. The *ASTN1* gene has been associated with neurodevelopmental phenotypes when a disruption of the gene either by deletion or duplication has occurred. The effect of a homozygous sequence variant on this gene is unknown. *KIF14* is inherited in an autosomal recessive manner, which matches the inheritance pattern for this case and the patient has several features overlapping with Meckel syndrome. Therefore, this patient at least has a diagnosis of Meckel syndrome, but could have a couple of other diagnoses as well or she could have an atypical presentation.

Conclusion

SNP CMA continues to be an important diagnostic first-line test for individuals with multiple congenital anomalies. While no copy number variants associated with a known microdeletion or duplication syndrome were identified, the SNP CMA identified absence of heterozygosity of the entire chromosome 1, which was important information in narrowing down the search for the underlying molecular diagnosis. If the UPD1 had not been detected, potentially multiple single gene and multi-gene panel tests would have been ordered in an effort to establish a molecular diagnosis. Negative test after negative test would have come back before eventually utilizing whole exome sequencing, which would have identified the homozygous sequence variants in the three genes identified by the XomeDx Slice. Due to the powerful utility of the SNP CMA, the search for a molecular diagnosis was expedited saving time and financial resources and relieving the family from potential emotional distress related to prolonged diagnosis particularly since the diagnosis potentially results from a combination of three genes.

References

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