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 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.

References
1. PRDM16 – associated with left ventricular noncompaction and dilated cardiomyopathy
2. ASTN1 – associated with Meckel syndrome characterized by intracranial 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
3. KIF14 - associated with Meckel syndrome characterized by intracranial 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
4. PRDM16 is inherited in an autosomal recessive manner, which matches the inheritance pattern for this gene. The effect of a homozygous change is unknown. The ASTN1 gene has been linked to a significant reduction in large, novel, and novel SNPs.

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.