**Title**: Uniparental disomy mysteries: How chromosomal microarray and exome sequencing can provide UPD clues that influence the diagnostic odyssey

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**Abstract**: Chromosomal microarray (CMA) and exome sequencing (ES) are recommended first-tier testing for multiple congenital anomalies and neurodevelopmental delay. Patterns of homozygosity detected on these tests can be indicative of uniparental disomy (UPD), in which an individual inherits homologous sections of a chromosome from a single parent. UPD is not inherently pathogenic, but it increases the risk for recessive disease and can be pathogenic if it involves an imprinted chromosome. We present three individuals who received CMA and ES, where combined results suggest the presence of UPD. Case 1, an 18-year-old female with undergrowth, neurodevelopmental features and dysmorphic features, first received CMA, which revealed large regions of homozygosity spanning the majority of chromosome 7. Subsequent Russell-Silver Syndrome methylation testing was negative, but chromosome 7 was not assessed. Finally, trio ES revealed mixed hetero/isodisomic regions on chromosome 7 of maternal origin, suggestive of maternal UPD7. Case 2, a 19-day-old female with multiple congenital anomalies, dysmorphic features, hypoglycemia with hyperinsulinism, and hypotonia initially underwent Beck with Wiedemann Syndrome (BWS) methylation testing which was positive.

CMA revealed genome wide mosaic homozygosity, suggestive of uniparental isodisomy (UPiD). Finally, trio exome testing supported paternal UPiD resulting in BWS and identified a pathogenic variant in PAH, which was heterozygous in the father and not detected in the mother. It was detected in the proband in 24/40 reads (60%). Case 3, a 14-month-old male clinically diagnosed with Gaucher disease underwent GBA sequencing, which revealed a pathogenic homozygous variant, molecularly confirming the Gaucher disease diagnosis. CMA identified a single ROH spanning chromosome 1, which includes GBA. Finally, trio ES identified the same GBA variant as homozygous in proband, heterozygous in the father, and absent in the mother. This combination of findings is suggestive of paternal UPD1.

Our three cases demonstrate the multiple mechanisms by which UPD is implicated in disease: 1) disordered imprinting (Case 1 and 2), 2) homozygous pathogenic variants in UPiD regions (Case 2 and 3). For clinicians navigating a diagnostic odyssey, it is important to understand the limitations of commonly ordered tests in detecting UPD, to understand the clinical significance of UPD, and to recognize the implications this has for test utilization management.