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

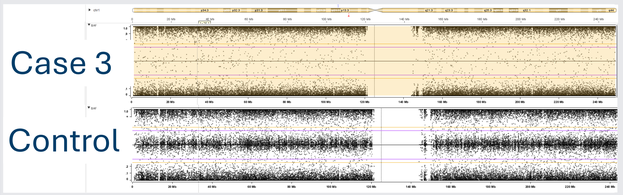
Lana Sheta[1], Andrew Giles[1], Abigail Kosmin[1], Erica Smith[1], Ginger Tsai[1]. [1]Ambry Genetics lsheta@ambrygen.com Ambry Genetics, Aliso Viejo, CA

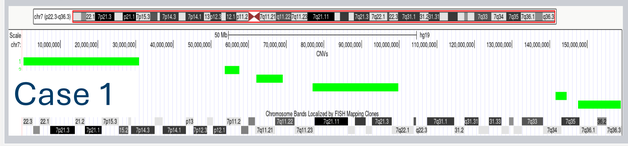
Background

Chromosomal microarray (CMA) and exome sequencing (ES) are recommended first-tier testing for multiple congenital anomalies and neurodevelopmental delay[1]. 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[2]. 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.

Clues of UPD from first-tier testing

SNP Array	Trio Exome
Large contiguous ROH impacting a single chromosome	Homozygous variants in the proband which are heterozygous in one parent and absent from the other parent.
Segmental ROH impacting a single chromosome, including terminal	Multiple heterozygous variants in trans in the proband, which are all identified in only one parent





Case Descriptions

Patients were ascertained via clinical genetic testing. Each patient underwent CMA and ES.

Case 1: 18-year-old female with undergrowth, neurodevelopmental delay and dysmorphic features.

Case 2: 19-day-old female with multiple congenital anomalies, dysmorphic features, hypoglycemia with hyperinsulinism, and hypotonia.

Case 3: 14-month-old male clinically diagnosed with Gaucher disease.

Results

	Chromosomal microarray	Trio exome sequencing	Methylation analysis	Diagnosis
Case 1	6 ROH involving 49% of chr7	Mixed hetero/isodisomic regions on chr7 of maternal origin	11p15.5 testing, non-diagnostic	Russell-Silver syndrome
Case 2	Genome wide mosaic homozygosity	*PAH* c.516G>T (p.Q172H), 60% allele fraction in proband, heterozygous in father, not detected in mother	Consistent with Beckwith Wiedemann syndrome (BWS)	BWS, possible phenylalanine hydroxylase deficiency
Case 3	Whole chr1 ROH	*GBA* c.1448T>C (p.Leu483Pro), homozygous in proband, heterozygous in father, not detected in mother	N/A	Gaucher disease

Methylation analysis of Case 2 reveals mosaic hypermethylation of ICR1

Methylation patterns of the imprinting control region 1 (ICR1) in Case 2 compared to an unaffected individual. Red indicates 5-methylcytosine (5mC) and blue indicates unmethylated cytosine. The methylation pattern in Case 2 is consistent with mosaic chr11 paternal uniparental isodisomy (UPiD).

TAKE HOME POINTS

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 clinical significance of UPD and consider the signals of UPD relevant to managing test utilization.

References

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2. Del Gaudio D, Shinawi M, Astbury C, Tayeh MK, Deak KL, Raca G; ACMG Laboratory Quality Assurance Committee. Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020 Jul;22(7):1133-1141. doi: 10.1038/s41436-020-0782-9. Epub 2020 Apr 16. PMID: 32296163.