Uniparental Disomy Detection in a Clinical Trio Genome Sequencing Cohort

Yuan Liu[1], Pengfei Liu[1,2], Weimin Bi[1,2], Nichole Owen[1,2], Eric C. Kao[1,2], Wilson C. Wu[1,2], Xi Luo[1,2], Casey A. Thornton[1,2], Robert Rigobello[1], Michael Santana[1], Linyan Meng[1,2], Fan Xia[1,2], Christine M. Eng[1,2], Hongzheng Dai[1,2*] Bo Yuan[1,2*]

1. Baylor Genetics, Houston, TX, USA
2. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

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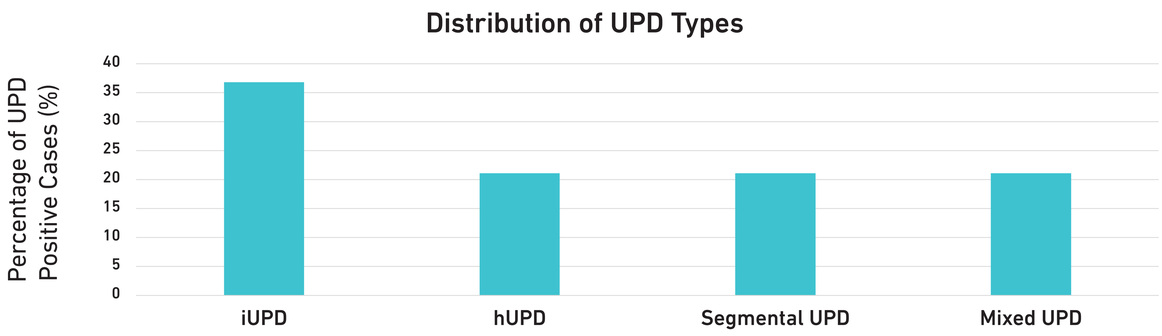
Background

- Uniparental disomy (UPD) refers to the inheritance of both homologous chromosomes from a single parent.
- UPD can lead to diverse clinical outcomes through several mechanisms, including disruption of genomic imprinting, homozygosity for deleterious recessive alleles, or association with mosaic aneuploidy[1].
- These conditions are often missed by targeted testing approaches, such as multigene panels, chromosomal microarray (CMA) and genome sequencing (GS) without parental sample. In particular, heterodisomy (hUPD) is more easily missed because no absence of heterozygosity (AOH) regions is present to alert to underlying UPD.
- Here, we describe our experience with UPD detection by clinical trio GS.

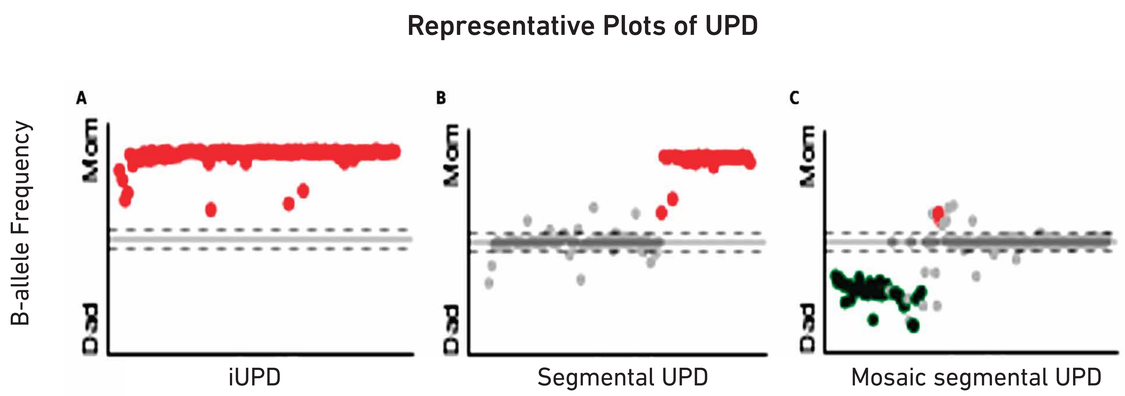
Results

- In a cohort of 2322 consecutive trio GS, 19 (0.82%) were identified to have a UPD. None of these findings had been detected by prior genetic testing.
- Twelve cases (63.2%) were diagnostic with UPD finding. The remaining six were nondiagnostic, as these findings have not yet been correlated with clinical features.
- Among cases with diagnostic findings, the most frequently involved chromosomes were 15 (4/12), 16 (4/12) and 14 (3/12).
- Maternal UPD was detected in 13 individuals (68%) and paternal UPD in 6 individuals (31%).
- Isodisomy (iUPD) (7/19, 36.8%) was the most frequent type, followed by hUPD (4/19, 21.1%), segmental UPD (4/19, 21.1%) and mixed UPD (4/19, 21.1%).
- Of note, although some UPD findings have not been correlated with clinical phenotypes, they may reflect an underlying trisomic rescue event. A case in our cohort demonstrated maternal hUPD (16) in the blood sample and mosaic trisomy 16 in the buccal sample. Given that UPD (16) has not been associated with a consistent clinical phenotype, the clinical features in this case were resolved by mosaic trisomy 16.
- These UPD findings comprise nine imprinting disorders including 4 cases of Prader-Willi syndrome. Mosaic segmental paternal UPD (11) was identified in one case, which is associated with Beckwith-Wiedemann syndrome. In another two cases, UPD unmasked recessive disorders involving pathogenic (P) or likely pathogenic (LP) variants in the *DGAT1* and *PERCC1* genes. The remaining four individuals had dual molecular findings of UPD and additional variant(s).
- Notably, one proband carried a mosaic whole-genome paternal UPD, presenting with growth abnormalities, metabolic and endocrine dysfunction, dysmorphic features, and cardiac involvement that resembles partial Beckwith-Wiedeman syndrome.



Methods

- We retrospectively reviewed trio GS performed at our clinical laboratory in which a UPD was identified.
- The indication for testing, prior genetic evaluations, results, and other relevant clinical information were reviewed.



Cases with Diagnostic UPD Findings

UPD Type	Chr	Parental	ROH	Clinical Significance	Disease Mechanism
iUPD	8	Paternal	Yes	Homozygous c.1183C>T, p.R365* in *DGAT1* (P)	Unmasked recessive disorder
Mosaic Segmental	11	Paternal	No	Beckwith–Wiedemann syndrome	Imprinting disorder
iUPD	14	Maternal	Yes	Temple syndrome	Imprinting disorder
iUPD	14	Paternal	Yes	Kagami-Ogata syndrome	Imprinting disorder
Segmental	14	Maternal	Yes	Temple syndrome	Imprinting disorder
Segmental	15	Maternal	Yes	Prader-Willi syndrome	Imprinting disorder
hUPD	15	Maternal	No	Prader-Willi syndrome	Imprinting disorder
hUPD	15	Maternal	No	Prader-Willi syndrome	Imprinting disorder
Mixed	15	Maternal	Yes	Prader-Willi syndrome	Imprinting disorder
Segmental	16	Maternal	Yes	Homozygous c.348C>G, p.Y116* in *PERCC1(LP)*	Unmasked recessive disorder
hUPD	16	Maternal	No	Trisomy 16	Post-zygotic trisomy rescue
Mosaic	Genome-wide	Paternal	No	Beckwith-Wiedeman syndrome	Imprinting disorder

Conclusions

- UPD detection identifies imprinting disorders as well as recessive conditions. Incorporating UPD analysis increases diagnostic yield for conditions that might be missed by targeted panel testing approaches, CMA or GS without parental comparators.
- These observations support integrating UPD analysis into the clinical GS workflow. This would allow for evaluation of UPDs and other variant types simultaneously, ultimately increasing the diagnostic yield of genome sequencing.

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References:

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