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ORIGINAL ARTICLE

Contribution of uniparental disomy in a clinical trio exome cohort of 2675 patients

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Abstract

Background: Uniparental disomy (UPD) is the inheritance of two homologous chromosomes from the same parent. UPD may result in clinical phenotypes when occurring on chromosomes with specific imprinting pattern, when leading to homozygosity of a deleterious recessive allele inherited from one carrier parent, or when associated with a mosaic aneuploidy. Due to the importance of UPD in genetic disease etiology, UPD analysis has started to be implemented in the context of exome sequencing (ES) or genome sequencing.

Methods: We developed an in-house algorithm TRIPS (Trio Parentage/UPD Studies) to identify UPD events in trio ES cases. This method identifies regions with uniparental inheritance by utilizing the trio genotyping data obtained from the concurrent SNP array to delineate the parental origin of the SNPs in the proband.

Results: We identified 16 UPD events from 2675 ES trios. Among those, four events led to imprinting disorders, seven unmasked a pathogenic/likely pathogenic variant in a recessive disease gene, and two were consistent with a mosaic genome wide paternal UPD pattern. Twelve of these UPD events directly contributed to the molecular diagnosis of the patients.

Conclusion: Our study demonstrated the contribution of UPD to the molecular diagnosis in one clinical ES cohort, thus UPD analysis should be incorporated into routine clinical ES interpretation.

KEYWORDS
algorithm, SNP array, trio exome sequencing, uniparental disomy

Bo Yuan and Hongzheng Dai should be considered joint senior author.

1 | INTRODUCTION

Uniparental disomy (UPD) is a chromosome variation that two homologous chromosomes (or a segment of the homologous chromosomes) are transmitted from one parent without the contribution of the other parent. UPD events can be classified into different types. Uniparental isodisomy (iUPD), where two identical chromosome homologs are inherited from one parent, leads to whole chromosome homozygosity; while uniparental heterodisomy (hUPD) is the presence of two different homologs from the same parent. A mixture of iUPD and hUPD on the same affected chromosome, which we refer to as segmental iUPD with hUPD, is also possible because of meiotic recombination. In addition, segmental iUPD can occur due to mitotic recombination, in which only a segment of the chromosome pair originate from one parent while the rest of the pair are of bi-parental origin.

UPD can result in clinical consequences when it disrupts the normal imprinting pattern on certain chromosomes, or results in homozygosity of a parental disease-causing variant in autosomal recessive genes. It can also be associated with other chromosomal aberrations such as low-level mosaic aneuploidy, which may contribute to phenotypic abnormalities. UPD can be detected by distinguishing polymorphic loci originated from parents using short tandem repeats analysis or SNP array. Up to now, at least over 3300 UPD cases have been reported (Nakka et al., 2019), and it has been estimated that UPD event occurs at a rate of 1 in 3500 to 1 in 5000 based on clinical case data (Liehr, 2010; Robinson, 2000). However, a recent report suggested that the prevalence of UPD in general population is 1 in 2000 births (Nakka et al., 2019), occurring more frequently than previously thought.

Exome sequencing (ES) has been successfully applied to provide molecular diagnoses for patients with a wide spectrum of genetic conditions, and the diagnostic rates range from 20.1% to 36.1% depending on different phenotypic categories (Yang et al., 2013, 2014). ES has been performed in conjunction with chromosomal microarray (CMA) or SNP array for the detection of copy number variant (CNV) and copy neutral runs of homozygosity (ROH) suggestive of UPD or identity-by-descent (Yuan et al., 2020). A retrospective analysis of 11,020 ES cases with concurrent or sequential CMA or SNP array indicated that pathogenic CNV/UPD could contribute in 10.6% of all molecularly diagnosed cases (Dharmadhikari et al., 2019). Various robust algorithms have been developed over the years to identify potential UPD events from ES data (King et al., 2014; Magi et al., 2014; Nakka et al., 2019; Scuffins et al., 2021; Yauy et al., 2020). Yauy et al. identified 22 UPD events from 4912 ES trios and 29,723 single ES cases, 9 of which were clinically relevant to the patients' phenotype (Yauy et al., 2020). Another recent study detected 112 whole-chromosome or segmental UPD events in 32,067 ES trios, resulting in diagnostic findings in 0.14% of the cases (Scuffins et al., 2021). Hence, implementation of UPD analysis is critical for patients subjected to ES testing.

In our laboratory, SNP array is used as a quality control measure, running in parallel with next-generation sequencing (NGS), for all ES samples. In trio ES, by differentiating the parental origins of the SNPs in the proband based on the trio SNP arrays, chromosomal regions with uniparental inheritance and Mendelian inheritance error may be revealed with or without apparent and extended ROHs. Driven by this concept, we have developed an in-house algorithm TRIPS for trio ES cases to trace the parental origins of the genotyping SNPs in the proband, aiming for detecting various types of UPD. Here we report the contribution of UPD identified by TRIPS to the molecular diagnosis in a clinical trio ES cohort ($N = 2675$).

2 | MATERIALS AND METHODS

2.1 | TRIPS analysis

A total of 2675 patients, along with their parental samples sent to Baylor Genetics Laboratory for clinical trio ES were analyzed. SNP array analysis (Illumina HumanCoreExome-24v1 array, Illumina, San Diego, CA) and ES were performed as previously described (Dharmadhikari et al., 2019). In-house algorithm TRIPS using R scripts was created to process and present the SNP data from SNP array for each trio case, incorporating origin of parentage information assigned on each SNP.

2.2 | GenBank reference sequence

ZMPSTE24 (NM_005857.4, OMIM: 606480), *ABCA4* (NM_000350.2, OMIM: 601691), *PARK7* (NM_007262.4, OMIM: 602533), *KCTD3* (NM_016121.5, OMIM: 613272), *LBR* (NM_002296.4, OMIM: 600024), *RAB3GAP1* (NM_012233.3, OMIM: 602536), *PCDH12* (NM_016580.4, OMIM: 605622), *POLG* (NM_002693.2, OMIM: 174763).

3 | RESULTS

In order to identify potential UPD events from trio ES cases, we have developed an in-house algorithm TRIPS, which, by taking advantage of the trio SNP array data, automatically assigns one of the seven categories of parental origin, which included father only, mother only, possibly father only, possibly mother only, possibly either only,

UPD unlikely, and de novo, to each SNP in the proband based on simple Mendelian rule and the evaluation of the likelihood of UPD (assignment principle in Figure 1a). The assignment of the category of possibly one parent only (possibly father only or possibly mother only) to the heterozygous SNPs in the proband that are heterozygous in one parent and homozygous in the other parent helps to expand our scope of UPD interrogation from ROH to non-ROH and increases the sensitivity for hUPD detection (Figure S1). A normal TRIPS pattern without UPD shows roughly equal contribution of each parent to the SNPs on every chromosome (Figure 1b,c left panel), while the abnormal pattern suggestive of UPD shows the whole chromosome or a chromosome segment with SNPs originating from one parent only (Figure 1c right panel) or possibly one parent only, regardless of the presence of an ROH. The UPD calling can be corroborated by examining the inheritance patterns of all the variants identified by NGS in the corresponding region.

TRIPS identified 16 (0.6%) UPD events (Table 1) among 2675 ES trios, including five iUPD (two on chromosome 1, three on chromosome 2), three mosaic iUPD (one on chromosome 1, two genome-wide), one hUPD (chromosome 14), six segmental iUPD with hUPD on the same chromosome (two on chromosome 1, three on chromosome 15, one on chromosome 16), and one segmental iUPD (chromosome 5) (Figure 2a). No mosaic aneuploidy was identified by SNP array associated with these UPD events.

Out of the 16 UPD events, 12 (75%) were clinically significant findings that were causative for or contributory to the clinical symptoms of the patients via different mechanisms (Figure 2b).

Four UPD events resulted in well-characterized imprinting disorders (Table 1, Figures S1 and S4). Three patients (P11, P12, and P13) were identified to have upd(15) mat which would lead to Prader–Willi syndrome (PWS). Patient P10 did not have any ROH as shown by the SNP array result, but TRIPS revealed that all the SNPs on chromosome 14 were of maternal origin, leading to a molecular diagnosis of Temple syndrome. This case highlighted the utility of TRIPS in complementing SNP arrays for hUPD identification in trio cases.

Seven UPD events led to homozygosity of pathogenic/likely pathogenic variants in autosomal recessive genes inherited from unaffected carrier parents (Table 1), providing molecular diagnoses that contributed to the clinical features of the corresponding patients (Figures S2 and

(a)

Father genotype	Mother genotype	Proband genotype	Origin of two alleles	UPD Assignment
AB	BB	AA	Father only	F
AB	BB	AB	Possibly father only	FP
AA	BB	BB	Mother only	M
BB	AB	AB	Possibly mother only	MP
AB	AB	AB	Possibly either only	W
AA	BB	AB	UPD unlikely/Not UPD	NUPD
AA	AA	AB	De novo change	DeNovo

(b)

	F	FP	M	MP	W	NUPD	DeNovo
1	0	2553	1	3008	42201	1648	0
2	4	2579	6	2857	34844	1888	2
3	8	2082	0	2270	29734	1491	0
4	0	1946	2	2693	23410	1295	0
5	5	1896	4	2076	24281	1314	0
6	2	2008	4	2558	28384	1421	0
7	3	1678	4	2158	22731	1093	0
8	2	1494	4	1922	19933	1075	0
9	0	1340	3	1542	19307	964	0
10	2	1502	3	1496	20498	1104	0
11	3	1440	2	2005	26118	1095	0
12	1	1446	1	1769	22963	947	0
13	2	1095	1	1077	12354	801	0
14	2	1013	3	991	14717	796	0
15	3	936	0	1060	14756	580	0
16	3	984	2	1048	17095	720	0
17	0	898	2	1078	19273	547	0
18	0	809	2	1324	9463	666	0
19	0	739	1	978	19935	521	0
20	2	741	3	825	11607	489	0
21	0	489	0	524	5753	301	0
22	1	475	0	489	8139	263	0
X	0	7	3155	5	9888	8	1
Y	1434	61	0	0	548	0	0
Total	1477	30211	3203	35753	457932	21027	3

(c)

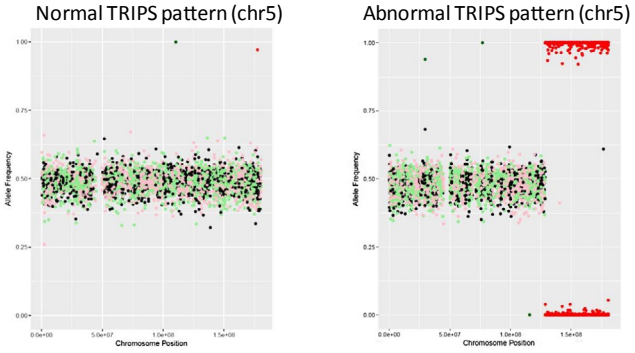

FIGURE 1 Principles and example data output of TRIPS analysis. (a) Principle of seven assignments (F, FP, M, MP, W, NUPD, DeNovo) on SNP allele pairs for possible parental origin. DeNovo, de novo change; F, father only; FP, possibly father only; M, mother only; MP, possibly mother only; NUPD, UPD unlikely/not UPD; W, possibly either only. Color dots represent the color scheme for parental origin assignments: red (F), pink (FP), dark green (M), light green (MP), grey (W), black (NUPD). (b) An example of the parental origin assignments of the allele pairs on different chromosomes. Numbers of the allele pairs assigned with the seven categories of possible parental origins were listed accordingly under each assignment for each chromosome. (c) Examples of a normal (left) and an abnormal (right) TRIPS patterns composed of colored dots that represent the corresponding SNP allele pairs. *X* axis shows the coordinates along the chromosome. *Y* axis shows the b allele frequency retrieved from SNP array. Color scheme for parental origin assignments as described in 1a. For the abnormal pattern of chromosome 5 on the right, paternal segmental iUPD was shown as the ROH region composed of red dots only

TABLE 1 Summary of the UPD findings by TRIPS in our trio ES cohort ($N = 2675$)

Patient #	Chr	Type of UPD	Parental origin	ROH	Clinical significance	Disease mechanism	Ref[a]
P1	1	iUPD	Maternal	Yes	Uncertain		
P2	1	Mosaic iUPD	Maternal	Yes	Possible mosaicism for homozygous *ZMPSTE24* c.1085dup (p.L362Ffs*19) (pathogenic)[b]	Unmasked recessive disorder	Cassini et al. (2018), Dharmadhikari et al. (2019)
P3	1	iUPD	Paternal	Yes	Homozygous *ABCA4* c.1805G>A (p.R602Q) (pathogenic) and *PARK7* c.331del (p.A111Lfs*7) (pathogenic)	Unmasked recessive disorder	
P4	1	Segmental iUPD with hUPD	Maternal	Yes	Homozygous *KCTD3* c.166C>T (p.R56*) (likely pathogenic) (disease candidate gene)	Unmasked recessive disorder	
P5	1	Segmental iUPD with hUPD	Maternal	Yes	Homozygous *LBR* c.1535G>A (p.R512Q) (likely pathogenic)	Unmasked recessive disorder	
P6	2	iUPD	Maternal	Yes	Uncertain		
P7	2	iUPD	Maternal	Yes	Homozygous *RAB3GAP1* c.1247del (p.P416Lfs*9) (pathogenic)	Unmasked recessive disorder	
P8	2	iUPD	Maternal	Yes	Uncertain		
P9	5	Segmental iUPD	Paternal	Yes	Homozygous *PCDH12* c.309del (p.C104Afs*15) (pathogenic)	Unmasked recessive disorder	
P10	14	hUPD	Maternal	No	Temple syndrome	Imprinting disorder	
P11[c]	15	Segmental iUPD with hUPD	Maternal	Yes	Prader-Willi syndrome, homozygous *POLG* c.2209G>C (p.G737R) (pathogenic)	Imprinting disorder + unmasked recessive disorder	Dharmadhikari et al. (2019)
P12	15	Segmental iUPD with hUPD	Maternal	Yes	Prader-Willi syndrome	Imprinting disorder	
P13	15	Segmental iUPD with hUPD	Maternal	Yes	Prader-Willi syndrome	Imprinting disorder	
P14	16	Segmental iUPD with hUPD	Maternal	Yes	Uncertain		
P15	Whole genome	Mosaic iUPD	Paternal	Yes	Multiple diseases	Partial features of various imprinting disorders	Dharmadhikari et al. (2019)
P16	Whole genome	Mosaic iUPD	Paternal	Yes	Multiple diseases	Partial features of various imprinting disorders	Dharmadhikari et al. (2019)

Note: GenBank reference sequence: *ZMPSTE24* (NM_005857.4), *ABCA4* (NM_000350.2), *PARK7* (NM_007262.4), *KCTD3* (NM_016121.5), *LBR* (NM_002296.4), *RAB3GAP1* (NM_012233.3), *PCDH12* (NM_016580.4), *POLG* (NM_002693.2)

[a]Patients P2, P11, P15, P16 have been previously reported in the cited reference.

[b]Variant allele frequency (98/118).

[c]A de novo 10q24.31q24.32 duplication was also identified by the SNP array.

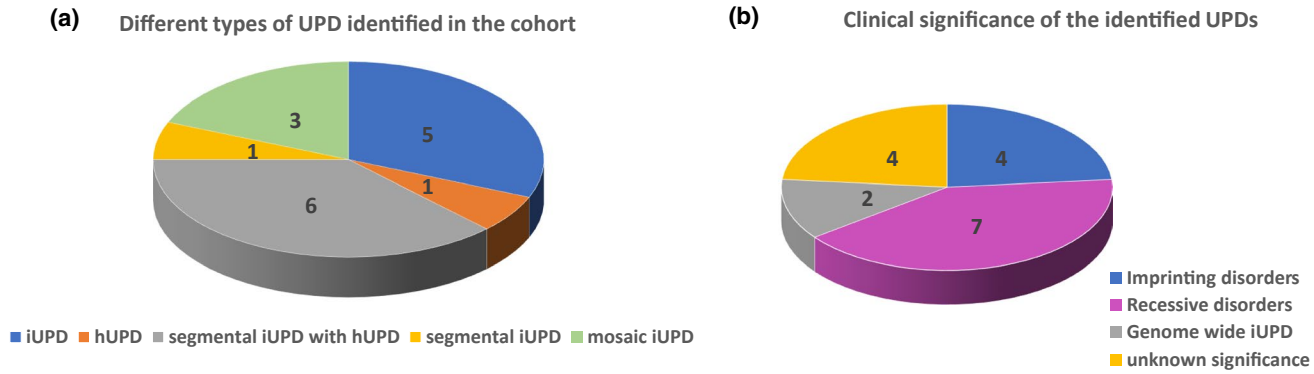

FIGURE 2 (a) Pie chart illustrating the different types of UPD identified in our trio ES cohort ($N = 2675$). (b) Pie chart showing the categories of clinical significance associated with the identified UPD events. Of note, patient P11 was included in both categories of imprinting disorders and recessive disorders because of the exposure of the pathogenic variant in *POLG* by upd(15)mat

S4). Of note, although *KCTD3* has not been documented as a disease-associated gene in OMIM database (Online Mendelian Inheritance in Man), biallelic truncating variants including the one identified in patient P4 have been reported by multiple studies as causative findings in patients with a consistent phenotype of epileptic encephalopathy, cognitive impairment, developmental delay, and cerebellar hypoplasia (Teng et al., 2019).

Mosaic UPD events were detected in three patients (Figures S2 and S3). Patient P2 with maternal iUPD of chromosome 1 at a mosaic level of ~80%–90% was identified by ES with a mosaic pathogenic variant in the *ZMPSTE24* gene located in 1p34.2 (Cassini et al., 2018; Dharmadhikari et al., 2019). Pathogenic variants of *ZMPSTE24* are associated with mandibuloacral dysplasia with type B lipodystrophy (OMIM: 608612), consistent with the phenotype of this patient. In addition, mosaic genome-wide paternal isodisomy was identified in two patients (P15, P16) (Dharmadhikari et al., 2019). This is a rarely reported UPD event, and the affected patients manifested variable phenotypes including partial features of various paternal imprinting disorders, such as Beckwith–Wiedemann syndrome, Angelman syndrome, transient neonatal diabetes, and adrenal nodular hyperplasia (Inbar-Feigenberg et al., 2013; White et al., 2016). The UPD findings were consistent with the complex clinical presentations of patient P15 and P16.

Dual molecular diagnoses were made in two patients (P3, P11) associated with the UPD events (Figure S4). Patient P3 with upd(1)pat was identified by ES to have a homozygous pathogenic variant in the *ABCA4* and the *PARK7* genes, respectively, both located on chromosome 1, leading to the diagnoses of *ABCA4*-related retinal diseases and early onset Parkinson disease in this patient. Patient P11 was identified with upd(15)mat and a homozygous maternally inherited pathogenic variant in *POLG* that was unmasked by UPD15, adding *POLG* related autosomal recessive disorders to the diagnostic picture of this patient besides PWS. Moreover, SNP array identified a de novo duplication of 10q24.31q24.32 associated with Split-hand/foot malformation 3 (OMIM: 246560) in patient P11. These findings demonstrated the strength of integrating NGS, copy number analysis and UPD calling in the cases with a complex clinical phenotypic spectrum.

In the remaining four patients (P1, P6, P8, and P14), the UPD events involved chromosomes 1, 2, and 16 (Figure S5). The existence of an imprinting phenotype associated with UPD on these chromosomes is still under debate to our knowledge (Bertola et al., 2011; Hansen et al., 1997; Scheuvens et al., 2017). No deleterious recessive variants on these chromosomes were detected by ES. Therefore, the clinical significance of these UPD events in these patients remained uncertain.

4 | DISCUSSION

In order to increase the detection of UPD events in ES, our laboratory has developed an in-house algorithm, TRIPS, which can designate parental origins of the genotyping SNPs from the concurrent SNP arrays in trio ES cases. This analysis identified 16 UPD events from 2675 trio ES cases. Majority of these UPD events (12 of 16, 75%) directly led to or contributed to the clinical presentation of the patients by resulting in imprinting disorders or exposing a deleterious recessive variant. No mosaic aneuploidies associated with the UPD events were identified in our study.

Our TRIPS analysis can serve as a valuable complement to SNP array for UPD detection in ES trios, evidenced by the identification of hUPD lacking ROH on the array in patient P10, who was subsequently diagnosed with Temple syndrome. In addition, although the extended ROH caused by segmental iUPD or segmental iUPD with hUPD appears similar on a SNP array, TRIPS can readily

distinguish these two different genetic events by differentiating the bi- and uniparental origin of the SNPs in non-ROH, respectively (Figures S1 and S2).

The identification of mosaic UPD events (3 out of 16) in our cohort also calls for attention to the possible mosaicism when sequencing-based UPD calling algorithms are applied. TRIPS took advantage of the SNP array data which provided more than 500,000 SNP data points at the genome-wide level, more than those normally provided in ES, to increase the sensitivity of mosaic events identification. The skewed allele frequency of the informative variants detected by NGS on the affected chromosomes in these three patients corroborated our mosaic UPD findings from TRIPS.

The prevalence of UPD in our cohort is 0.6%, higher than the previously reported 0.2% from a study which retrospectively analyzed 4912 trio ES cases (Yauy et al., 2020) and 0.3% from a recent study that interrogated 32,067 clinical ES trios (Scuffins et al., 2021). Part of the reason might be that the phenotypic compositions are potentially different among the clinical cohorts used in these studies. UPD might have been represented differently in different cohorts. Patients subjected to ES testing in our laboratory are mostly pediatric patients with a broad spectrum of clinical manifestations, mostly neurological phenotypes (Yang et al., 2014). It has been reported before that pathogenic CNV/UPD detection rate increased in patients with syndromic phenotypes (Dharmadhikari et al., 2019). In addition, the methodologies or algorithms employed in previous studies, likely with different settings and stringencies, might have different sensitivities in the detection of the various types of UPD. Our study demonstrated that our method is capable of identifying mosaic UPD events, the detection of which might be limited by the methods using ES data only (Scuffins et al., 2021), and therefore, could contribute to a relatively higher detection rate.

In conclusion, UPD events had remarkable diagnostic contribution to patients subjected to ES testing. Our study demonstrated that integration of a UPD analysis with the capability to delineate parental origin of the genotyping SNPs could potentially identify variable types of UPD and increase the diagnostic yield in trio ES cases. We have implemented TRIPS analysis as a component of routine trio ES pipeline, and we believe that UPD analysis should be incorporated into ES testing in genetic laboratories.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ETHICAL COMPLIANCE

The aggregated analyses of anonymized samples and reporting of de-identified molecular data with minimum clinical information were approved by the Institutional Review Board of Baylor College of Medicine (protocol H-42680).

AUTHOR CONTRIBUTIONS

HZD, PFL, and YY participated in the study concept and experimental design. HZD designed the algorithm, pipeline, and composed R scripts. HZD, BY, and LW performed the TRIPS analysis and SNP array data interpretation. LW, BY and HZD wrote the manuscript. WB, TS, XW, MW, ML, LM, FX, and CE interpreted WES data with UPD findings.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supporting information of this article. The algorithm program is available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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