Identification of uniparental disomy events in a cohort of 29,723 exome sequencing samples

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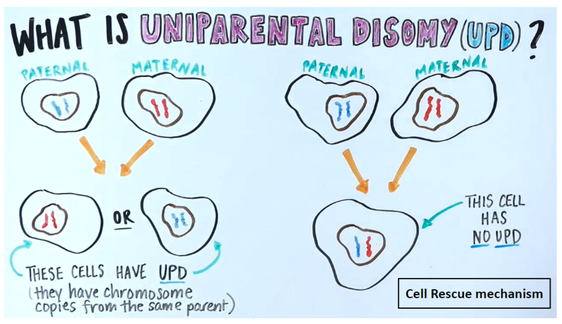
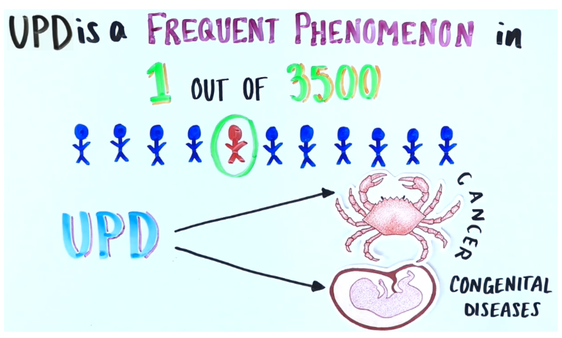
Introduction

Uniparental disomy (UPD) is a copy-neutral structural variation leading to the occurrence of two homologous chromosomes originating from the same parent : **uniparental isodisomy (iUPD)** where a single parental homologue is transmitted in duplicate and **uniparental heterodisomy (hUPD)** where a pair of chromosome homologues is transmitted from a single parent. A UPD can be **segmental** with the isodisomic region originating from one parent, whereas the remainder of the chromosome is of biparental origin.



Although the majority of UPDs does not have phenotypic consequences, particular events may lead to disease due to **imprinting effects**, an underlying **homozygous** pathogenic disease variant or a **low mosaic trisomy**.



UPDs are typically identified through SNP microarray. In recent years **exome sequencing** (ES) has become a routine diagnostic investigation. Although it is theoretically possible to identify UPDs through ES data, these events are **not routinely detected as part of a genetic diagnosis**.

We investigated the sensitivity of UPD detection by ES and the prevalence of medically relevant UPD events.

Methods

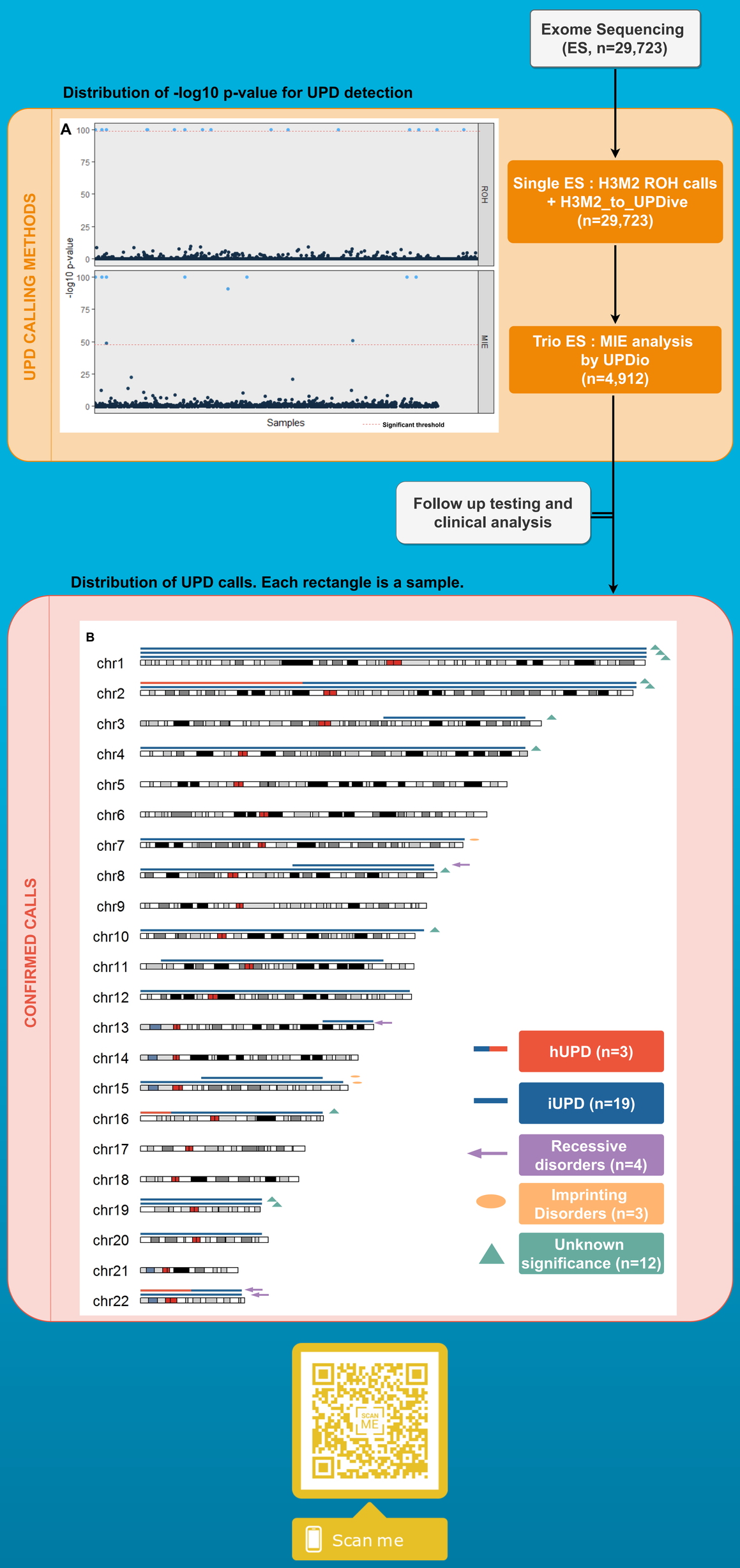
Samples : Anonymized collection of **29,723 single cases**, which contains **4,912 ES trios** from Genome Diagnostics Nijmegen.

Single ES : **Regions of homozygosity** (ROH) identification using the `H3M2` algorithm. **Median absolute deviation** (MAD) to scale the total ROH size per chromosome with `robustscale` function from `quantable` package. Exclusion of samples with > 2 chr. with large ROH (MAD > 3 - **consanguinity filter**). Log & p-value transformation after normal distribution verification and Bonferroni correction (n=653906).

Trio ES : **Mendelian inheritance errors** (MIE) detection by `UPDio`. CNV bias filter and Bonferroni correction (n=4912) applied.

All scripts of UPDive study are available at https://github.com/kyauy/UPDive.

UPDive: Accurate detection of clinically relevant uniparental disomy from exome sequencing data.



Results

Type	Origin	Array	MIE	ROH
Validation dataset				
hUPD	mat 3/3	3/3	3/3	NA
iUPD	mat 2/3, pat 1/3	3/3	3/3	3/3
seg. UPD	mat 2/2	2/2	2/2	0/2*
New cases				
iUPD	mat 1/11, pat 1/11, NA 9/11	NA	3/3	11/11
seg. UPD	mat 1/3, pat 1/3, NA 1/3	NA	2/2	2/3

Table 1: UPD calls performance. mat= maternal, pat= paternal, NA = not applicable, seg. = segmental, * = low -log10 p value.

For all **14 patients with novel UPD events** we re-evaluated the existing WES analysis:

For **three** cases, the detected UPD events would give rise to an **imprinting disorder**.

In **two** cases a **homozygous pathogenic variant** was identified in the UPD region, meaning that only a single parent would be heterozygous carrier of the respective variant. This **changed the genetic counselling** for their families, for which there is almost no recurrence risk in this case.

UPD identification is a **UPD of unknown significance (UUS)** for the remaining **eight** patients.

Discussion

ES is able to diagnose UPD and all others types of molecular alterations observed in **imprinting disorders** (SNV, CNV duplication & deletion and UPD) except for idiopathic DNA methylation change. This can lead to a **change in imprinting disorders genetic testing strategies** and to be more time and money effective, especially for multi locus imprinting disorders.

Conclusion

UPD can easily be identified using both single and trio ES. UPDs may be clinically relevant and affect genetic counselling, given the reduced risk of recurrence for affected families.

Recommended pipeline :

Single ES : H3M2 + H3M2_to_UPDive.py

Trio ES : UPDio

UPD pictures reference http://tiny.cc/ngaa5y