Relevance of UPDs in Prenatal Testing

Increased diagnostic yield by UPD calling in a trio cohort of >1.000 prenatal cases

AUTHORS

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Background

Prenatal trio exome sequencing (TES) has become a powerful approach for identifying the underlying genetic cause in fetuses with ultrasound findings. Although some studies show a solving rate of up to 30% with prenatal trio exome sequencing, some genetic causes will still be missed by this approach. In a regular setting, the exomic data will be analyzed for potential pathogenic sequence variants and copy number variants by bioinformatic methods. Although uniparental disomies (UPDs) are a known cause for some severe genetic disorders in most diagnostic setups, UPDs will be missed, especially heterodisomies (hUPDs) and segmental disomies.

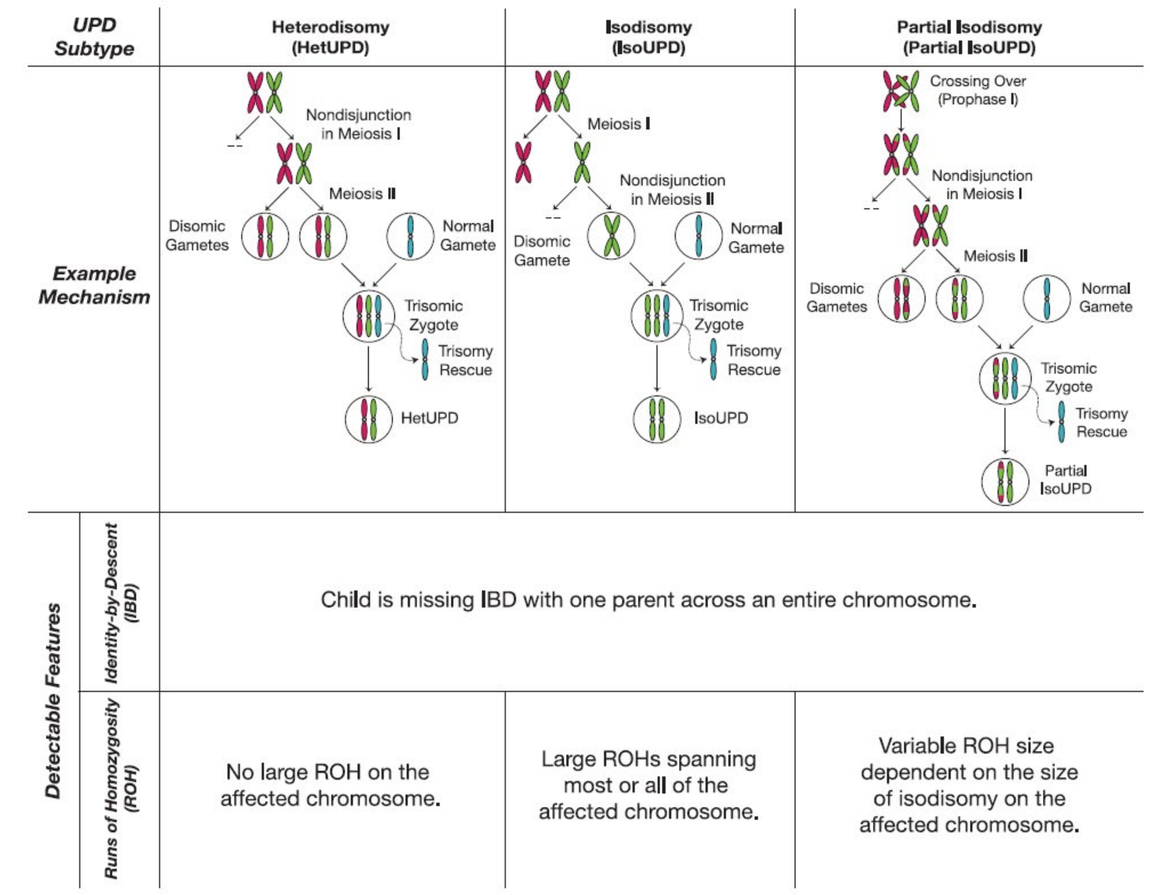

Figure 1: Types of UPD with example mechanisms and detectable features for each UPD type from Nakka et al., 2019 (PMID: 31607426).

Methods

iUPDs can be detected as regions of homozygosity (ROH) in single exomes, based on clusters of homozygous variants. Detection of hUPDs requires data from both parents: For each SNV, zygosity of the index is compared to the parental data and classified as either clearly inherited from one parent, de novo, or unclear. Positions are aggregated with a method similar PLINK ROH caller. Overlapping paternal-UPD and maternal-UPD calls are removed. Suspected UPDs were confirmed by ME-MLPA, when possible.

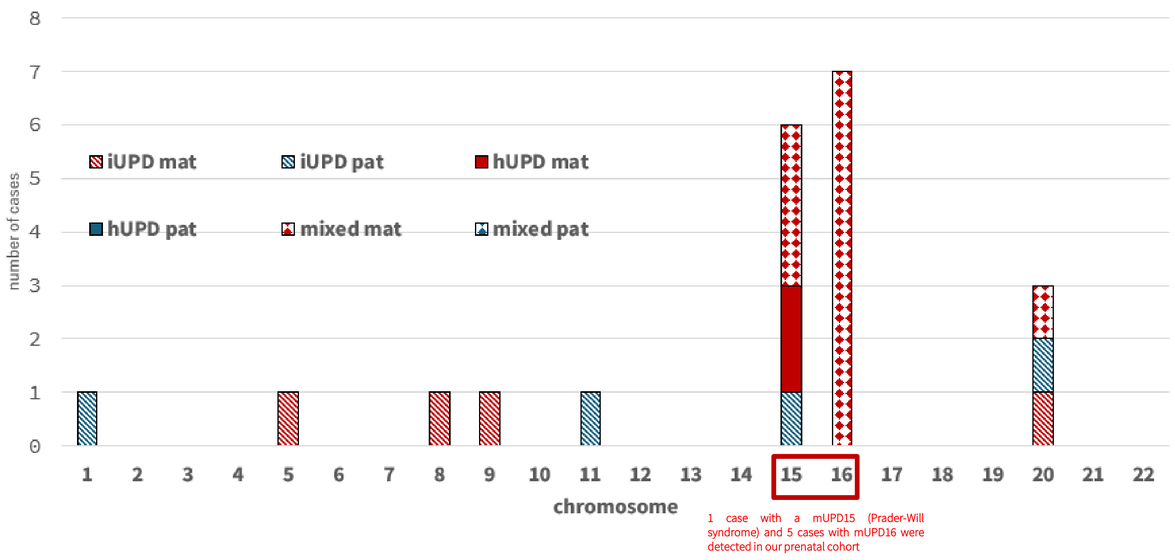

Figure 2: UPDs detected per chromosome for all cases (pre- and postnatal)
Red: maternal origin, blue: paternal origin, cross-striped bar: iUPDs, solid bars: hUPDs.
Chequered bars: mixed UPDs

Preliminary Results

UPDs have so far been confirmed in 21 cases either by ME-MLPA or by comparing identity-by-descent (IBD) variant for variant. In 11 cases, the results were consistent with a mixed i/hUPDs, in 8 cases with an iUPD, and in 2 cases with a hUPD. UPD16 was the most frequently detected UPD to date and accounted for one-third of all cases (7 cases; ~33%), 5 of which were prenatal. Prenatal cases are often characterized by growth retardation or intrauterine growth retardation (IUGR) or cardiac abnormalities, while in the postnatal setting (mild), developmental delay also occurred in some cases. Interestingly, all UPD16 cases were mixed maternal i/hUPDs.

These findings are in line with the literature (Inoue et al., 2019, PMID: 30242100; Scheuvens et al., 2017, PMID: 28032339) where maternal UPD16 is indicative of occult associated with many non-specific and highly variable congenital anomalies, including a Silver-Russell syndrome-like phenotype that includes IUGR, postnatal growth retardation, and heart defects and is the result of trisomic rescue.

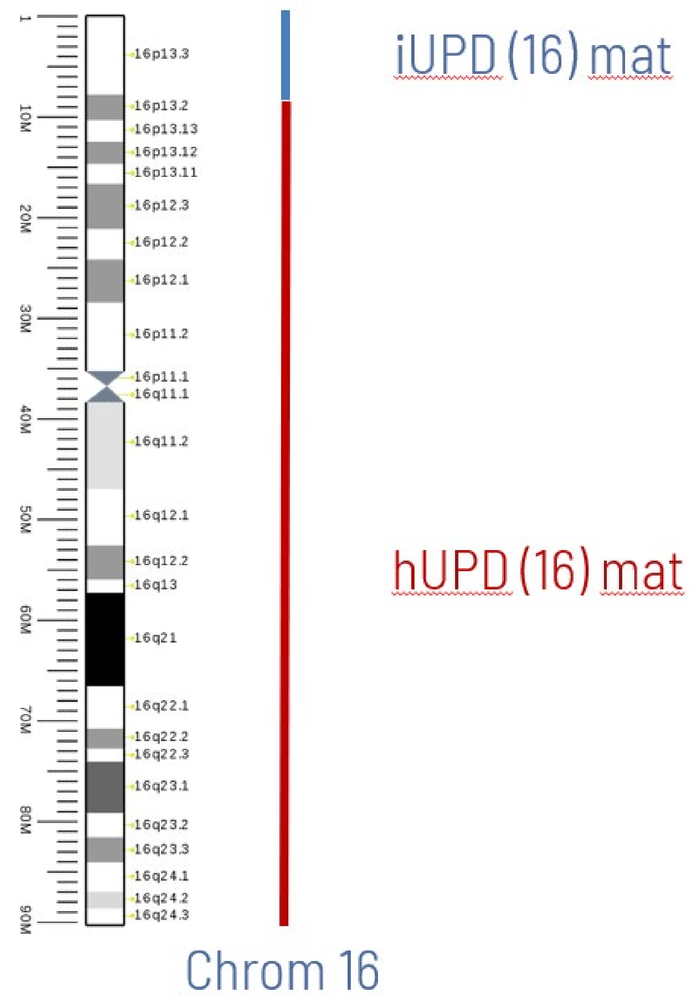

Figure 3: Mixed maternal i/hUPD found in fetus with „suspected cardiomyopathy (or other heartdefect)". Gestation week 18+1.

Conclusion

The phenotypes of four fetuses with the mUPD16 were consistent with UPD16-related IUGR, underlining the relevance of prenatal UPD detection. In one UPD16 fetus, the phenotype was described as „heart defect". IUGR was not reported in this case, but only limited clinical data were available. Although heart defects in association with a UPD16 were described in the literature, it is unclear whether the UPD16 was causative for the observed phenotype.

Besides prenatally detectable disorders, UPDs of some imprinting regions can result in severe genetic disorders with limited ultrasound findings (e.g., Angelman syndrome/Prader-Willi syndrome). It is therefore important to use methods that can also detect such disorders.

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