Haplotype-aware inference of human chromosome abnormalities

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Introduction

Figure 1. Mosaic (i.e., mitotic) aneuploidy may be compatible with healthy birth.

- Preimplantation genetic testing for aneuploidy (PGT-A) has been devised as an approach to improve IVF outcomes by prioritizing chromosomally normal (i.e. euploid) embryos for transfer based on genetic analysis of embryo biopsies.
- Extra or missing chromosomes (aneuploidy) is the leading cause of human pregnancy loss and congenital disorders.
- While meiotic aneuploidies are unambiguously harmful, mitotic errors, which generate mosaic embryos possessing both normal and aneuploid cells, are common and potentially compatible with healthy live birth.
- The ability to distinguish meiotic- and mitotic-origin aneuploidies during PGT-A may thus prove valuable for enhancing IVF outcomes.

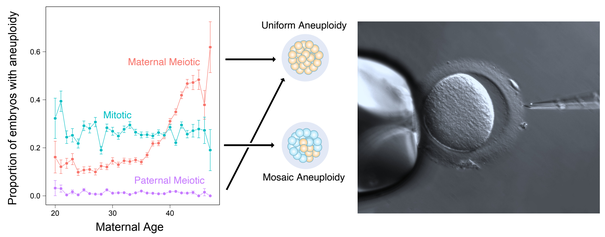

Figure 2. Meiotic and mitotic errors contribute to human aneuploidy

- Aneuploidies of maternal meiotic origin increase in frequency with age.
- Aneuploidies of mitotic origin are prevalent and constant across all ages.
- The current PGT-A comprise low-coverage whole-genome sequencing of DNA extracted from 5-10 trophoblast cells of day-5 embryos.

Motivation

- To date, few methods have explicitly attempted to distinguish the patterns of transmission of individual parental homologous chromosomes, which may inform the classification of meiotic and mitotic aneuploidies.
- The few exceptions require genomic data from parents, as well as embryos, and/or are not designed for low-coverage sequencing data—the current standard for PGT-A.
- Distinguishing viable forms of mosaic aneuploidy from harmful meiotic aneuploidy could recover healthy embryos from IVF cycles otherwise deemed unsuccessful.

Signatures of meiotic and mitotic trisomy

Notably, trisomies of meiotic origin are expected to produce a genetic signature characterized by the presence of three unique parental haplotypes (two from a single parent) and distinct from the mitotic trisomy signature of only two unique haplotypes chromosome-wide.

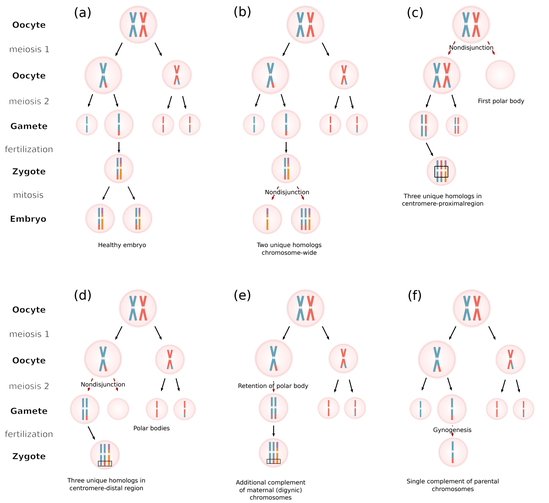

Figure 3. Signatures of various forms of chromosome abnormality with respect to their composition of identical and distinct parental homologs. Normal gametogenesis produces two genetically distinct copies of each chromosome—one copy from each parent—that comprise mosaics of two homologs possessed by each parent. Meiotic-origin trisomies may be diagnosed by the presence of one or more tracts with three distinct parental homologs (i.e., transmission of both parental homologs [BPH] from a given parent). In contrast, mitotic-origin trisomies are expected to exhibit only two genetically distinct parental homologs chromosome-wide (i.e. duplication of a single parental homolog [SPH] from a given parent). Triploidy and haploidy will mirror patterns observed for individual meiotic trisomies and monosomies, respectively, but across all 23 chromosome pairs—a pattern that confounds standard coverage-based analysis of PGT-A data.

Classification approach

Inspired by the related challenge of imputation, our method overcomes the sparse nature of the data by leveraging haplotype structure from a population reference panel.

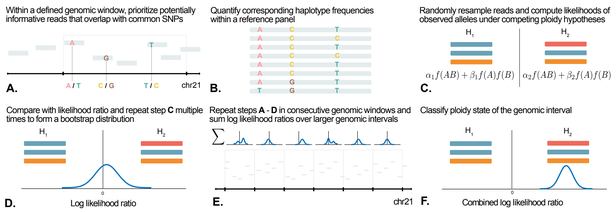

Figure 4. A statistical approach to leverage aneuploidy signatures to classify meiotic and mitotic trisomies using low-coverage sequencing-based data.

Benchmarking with simulation

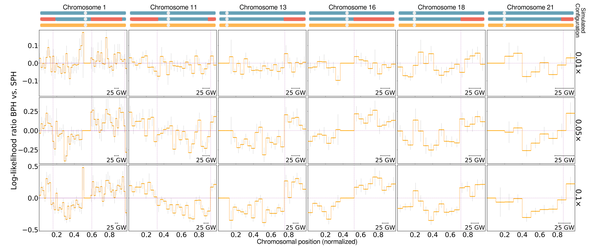

Figure 5. Demonstration of the detection of meiotic crossovers from low-coverage PGT-A data. Trisomies were simulated with varying locations of meiotic crossovers, as depicted in the upper diagrams and varying depths of coverage (0.01×, 0.05×, and 0.1×). Confidence intervals correspond to a z-score of one (confidence level of 68.3%). The size of the genomic windows varies with the coverage, while the size of the bins is kept constant.

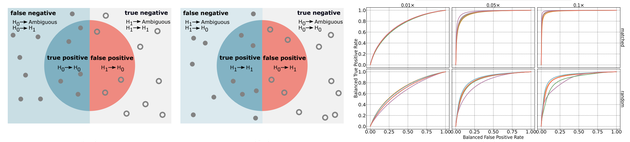

Figure 6. Balanced ROC curves for BPH vs. SPH with matched and random reference panels of non-admixed embryos, varying depths of coverage.

Application to PGT-A data

We applied our method to low-coverage PGT-A data from >8,000 human embryos provided by the Zouves Fertility Center.

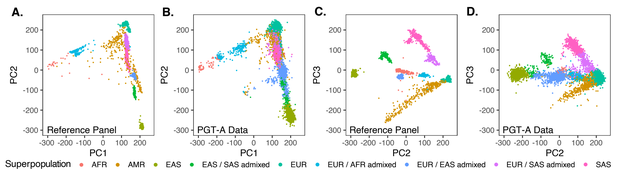

Figure 7. Ancestry inference from low-coverage PGT-A data informs the selection of matched reference panels. PCAs were defined based on analysis of 1000 Genomes reference samples.

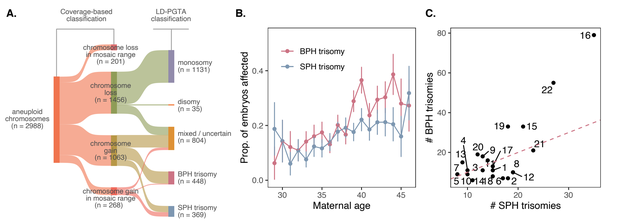

Figure 8. Classification of trisomies of meiotic and mitotic origin (A), their association with maternal age, and their chromosome-specific propensities.

Revealing abnormalities in genome-wide ploidy

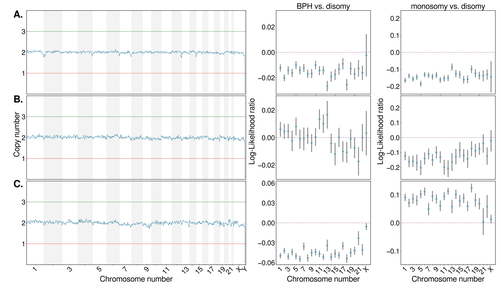

Figure 9. Representative putative diploid (A.), triploidy (B.), and haploid (C.) samples.

Mapping meiotic crossovers

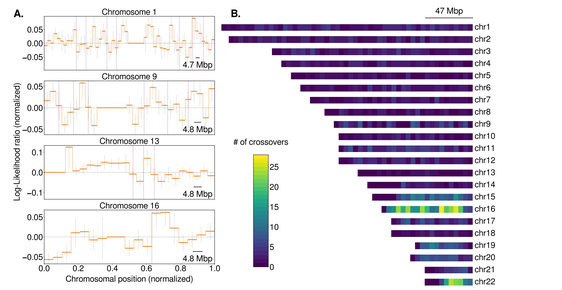

Figure 10. Mapping of meiotic crossovers on putative trisomic chromosomes based on inferred switches between tracts of BPH and SPH trisomy.

Conclusions

- Aneuploidies arising during meiosis and mitosis have distinct impacts on development and possess unique haplotype signatures.
- We distinguish these signatures from low-coverage sequencing.
- Potential to improve IVF outcomes and diagnosis of pregnancy loss.

Acknowledgements

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References

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