Single-cell analysis of human preimplantation embryos reveals widespread and complex patterns of chromosomal mosaicism

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Image Credit: Beata Edyta Mierzwa
Aneuploidy is common in human embryos

• Only approximately half of all conceptions survive to live birth.

• Many pregnancy losses occur early in development and are due to aneuploidy—extra or missing chromosomes.

Image credit: Stefano Santaguida and Angelika Amon
Embryonic aneuploidies originate in meiosis or mitosis

Errors in maternal meiosis

Embryonic aneuploidies originate in meiosis or mitosis

Errors in maternal meiosis

Errors in paternal meiosis

Embryonic aneuploidies originate in meiosis or mitosis

Errors in maternal meiosis

Errors in paternal meiosis

Errors in postzygotic mitosis

Preimplantation genetic testing for aneuploidy is based on embryo biopsies.
Chromosomal mosaicism may confound preimplantation genetic testing

- The incidence of mosaicism is highly contentious, with estimates ranging from 4% to 90%.
- The fitness impacts of mosaicism are uncertain.
- Previous studies have relied on biopsies of few cells.
Can we use single-cell RNA sequencing data to resolve this debate?

1488 single-cell RNA-seq libraries from 75 human embryos

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<th>Embryos</th>
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Detecting aneuploidy from single-cell RNA-seq data

Dosage Effects on Expression

For defined group of cells, calculate score for each chromosome-cell pair.

![Histogram showing dosage effects on expression](image)


Convert to Z-scores and obtain p-values to quantify evidence of chromosome gain or loss.
Detecting aneuploidy from single-cell RNA-seq data

Dosage Effects on Expression

For defined group of cells, calculate score for each chromosome-cell pair.

![Graph showing dosage effects on expression](image)


Convert to Z-scores and obtain p-values to quantify evidence of chromosome gain or loss.

Allele-Specific Expression

Call heterozygous SNPs by pooling data from all cells of a given embryo.

Disomy

Monosomy

Trisomy

Compute ratios of reads supporting reference and alternative alleles.
Examples: meiotic monosomy 13

Dosage Effects on Expression

Chromosome

Z-score

0.00

0

-5

-10

Embryo E7.8
Examples: meiotic monosomy 13

Dosage Effects on Expression

Allele-Specific Expression

Embryo E7.8
Examples: meiotic monosomy 4 and 14, mosaic monosomy 8

Dosage Effects on Expression

Allele-Specific Expression

Embryo E7.17
Examples: euploidy

Dosage Effects on Expression

Allele-Specific Expression
Examples: mosaic haploidy / near-haploidy

**Embryo E7.5**

**Dosage Effects on Expression**

**Allele-Specific Expression**

Z-score

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Multiple testing at multiple levels

Multiple testing at multiple levels

59 of 75 embryos
380 of 1223 cells
1064 of 26,904 chromosomes called aneuploid at 10% FDR

Evidence of cell-type specificity of aneuploidy rates

OR = 2.29 [95% CI: 1.23–4.41],
P = 7.5 x 10⁻³
Conclusions

• Mosaic aneuploidy is detectable from single-cell RNA-seq data.

• Chromosomal mosaicism is common, affecting approximately one-third of blastocyst-stage embryos.

• Reciprocal aneuploidies appear to be rare, pointing to mitotic error mechanisms beyond non-disjunction.

• Preliminary evidence that trophectoderm cells are enriched for aneuploidy.
Looking for postdocs, graduate students, and collaborators!

http://mccoy-lab.org