Transcriptomic signatures of genomic instability during human preimplantation embryo development characterized at single cell resolution by G&T-seq

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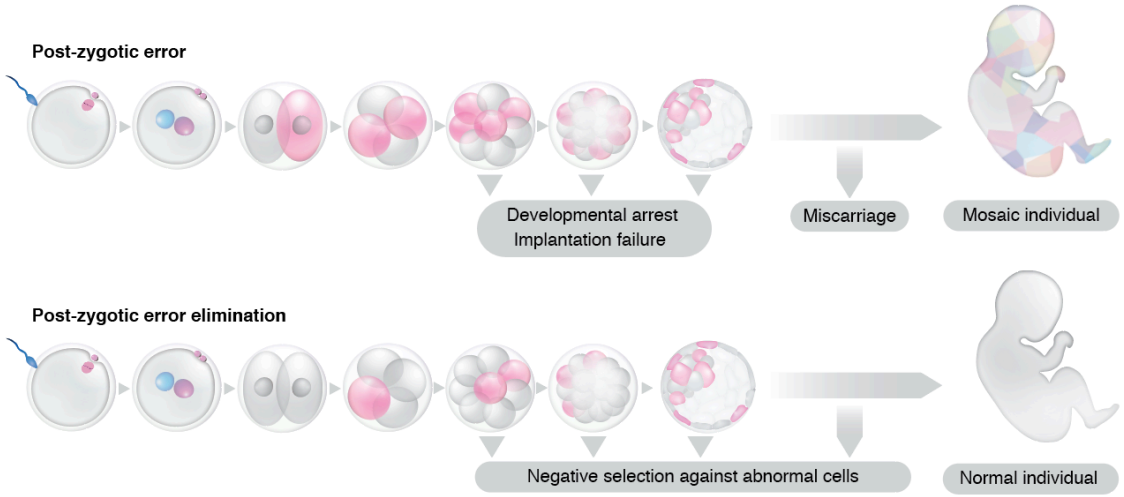
INTRODUCTION

- **Genomic instability** is common in human preimplantation embryos and is the leading cause of pregnancy loss, but still its **causes and consequences remain unknown**.
- It is characterized by the frequent occurrence of **mitotic errors** in the first cell divisions after fertilization and results in genetic **mosaicism** in the embryo.
- The diverse outcomes of embryo mosaicism and its high prevalence represent a **challenge** when interpreting results of **preimplantation genetic diagnosis**.

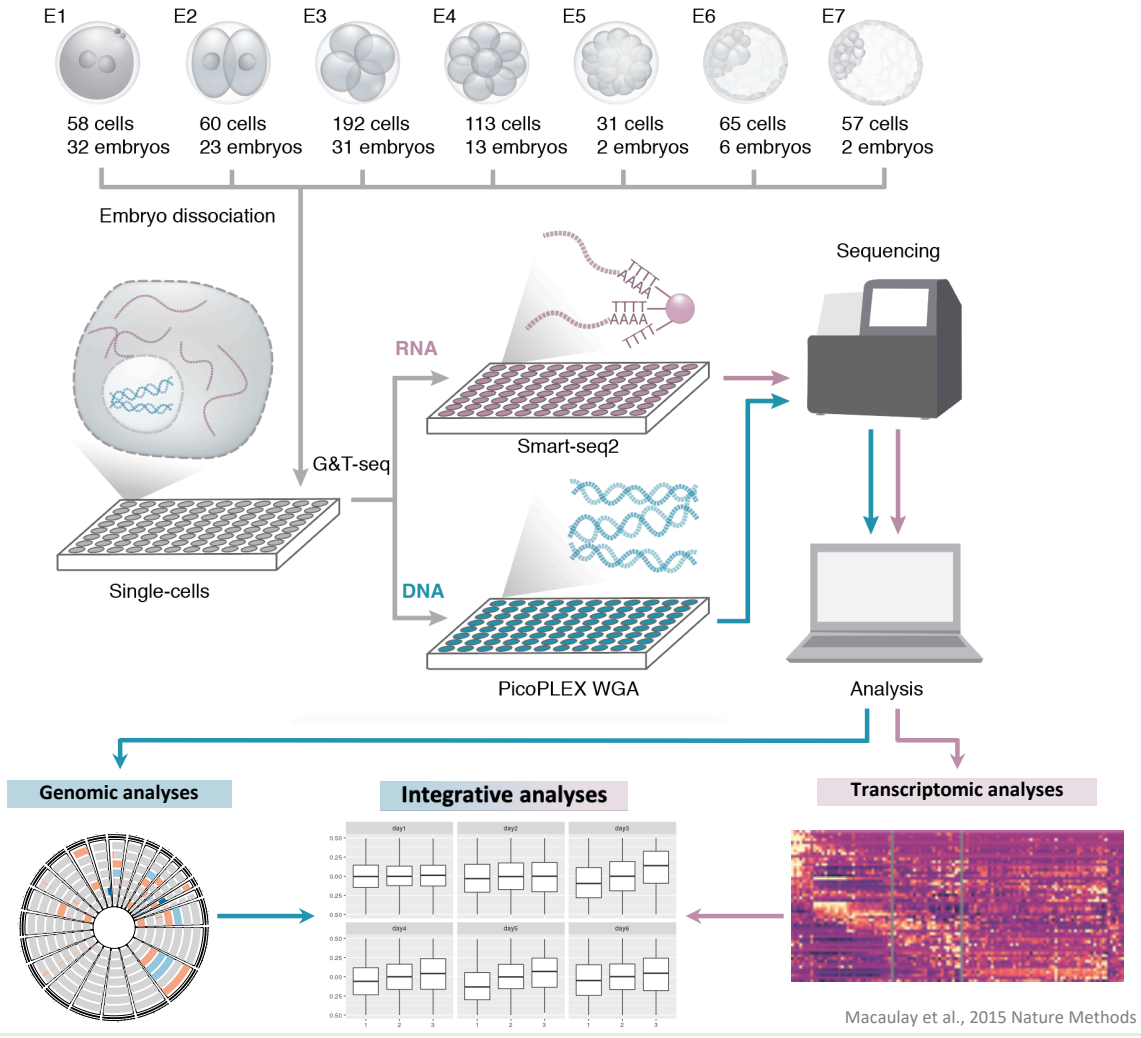


Tšuiko and Fernandez Gallardo et al., 2020 Reproduction; Van-Echten Arends et al., 2011 Human Reproduction; Popovic et al., 2018 Human Reproduction; Popovic et al., 2019 Hum Reproduction; Greco et al., 2015 New England Journal of Medicine; Santaguida et al., 2015 Nature Reviews.

AIM

Investigate the impact of genetic abnormalities on cellular phenotypic states and development of the early human embryo using single-cell multi-omics for parallel genome and transcriptome sequencing (G&T-seq).

MATERIAL AND METHODS

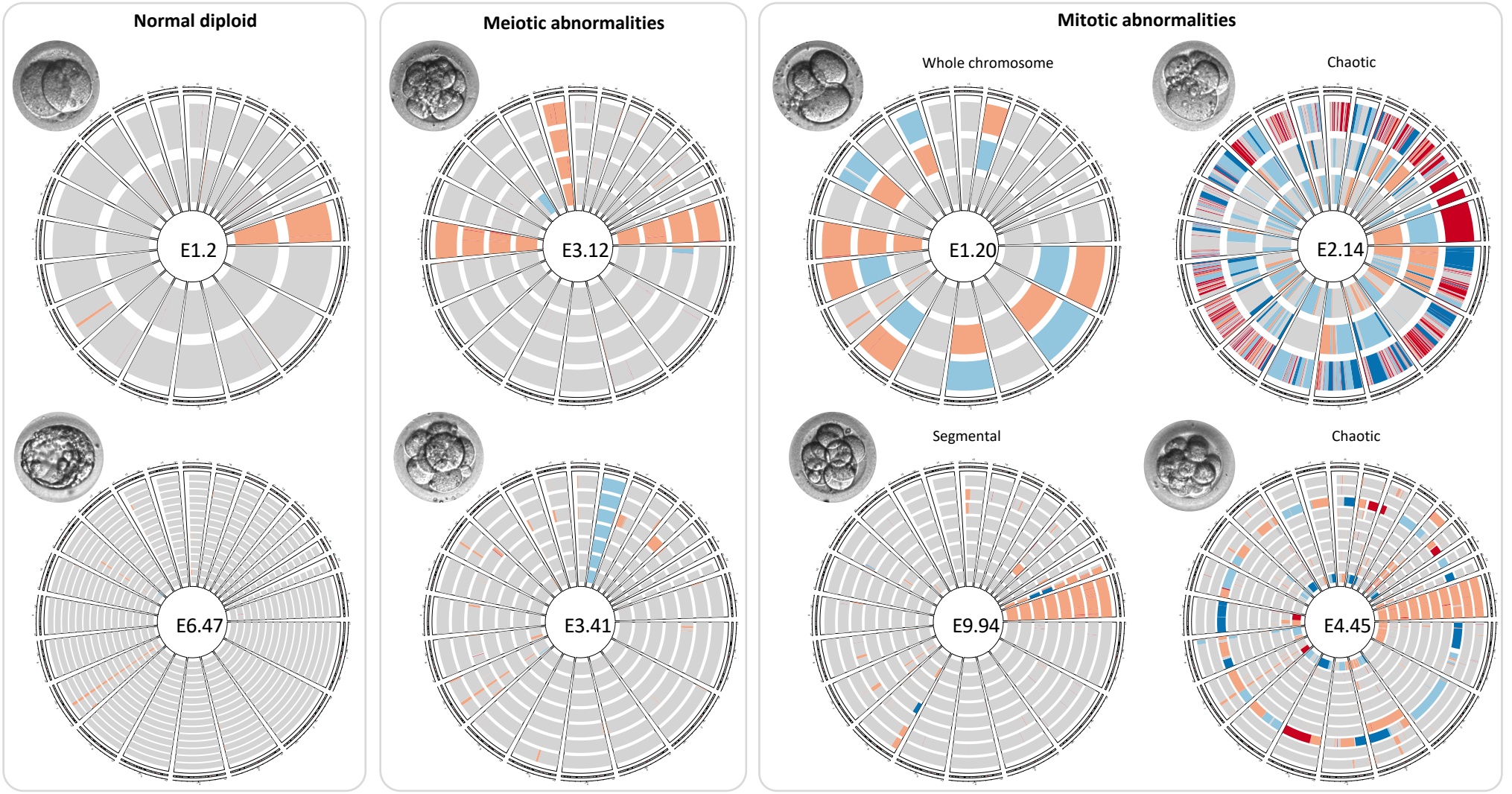


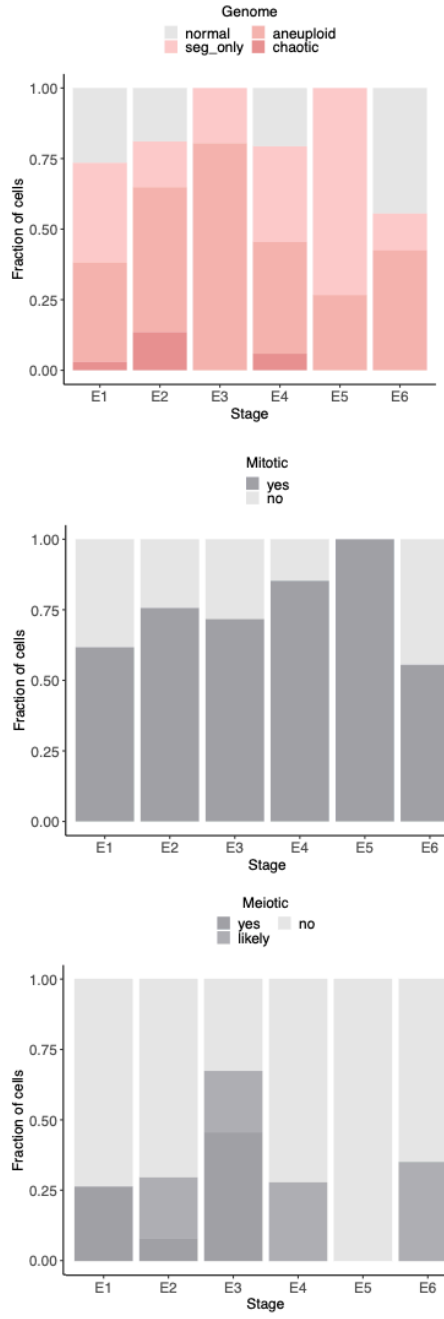
Macaulay et al., 2015 Nature Methods

GENOMIC ANALYSES

Single-cell genome-wide CNV profiles of preimplantation human embryos

	Origin of abnormality		Type of abnormality		
	Mitotic	**Meiotic**	**Segmental**	**Whole chromosome**	**Chaotic**
Cells	74%	36%	25%	50%	4%
Embryos	92%	18%	39%	63%	10%

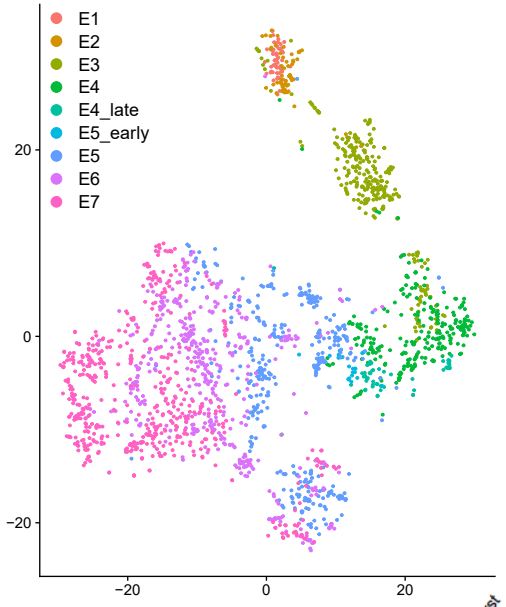


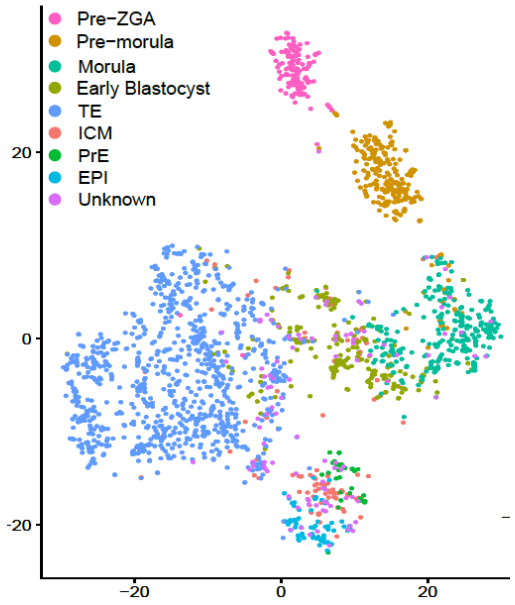


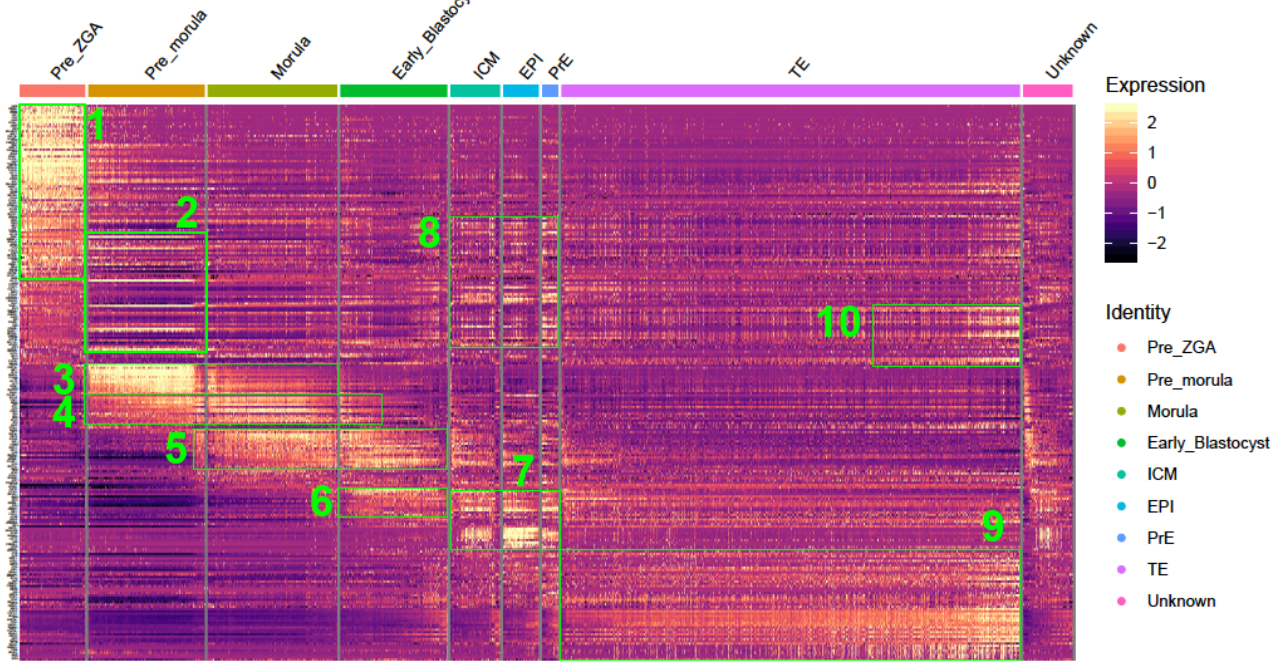
RESULTS

TRANSCRIPTOMIC ANALYSES

Gene regulatory landscape and cell differentiation of human preimplantation development

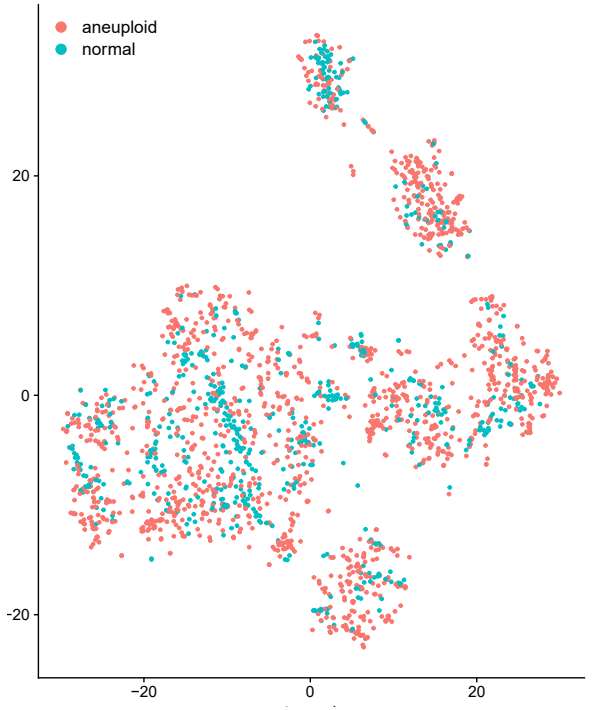




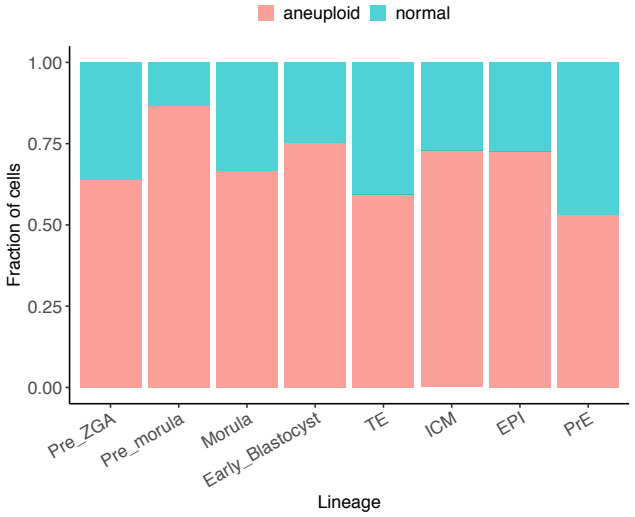


INTEGRATIVE ANALYSES

Lineage allocation of aneuploid cells

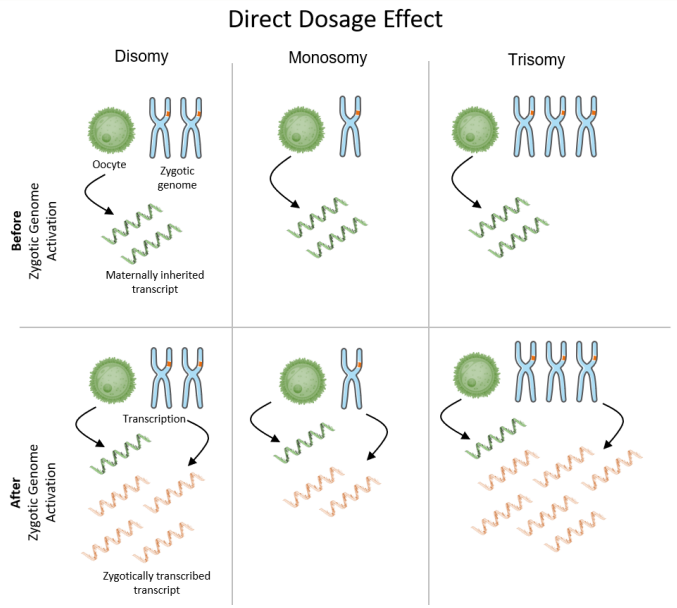


Aneuploid cells distribute equaly between lineages and along development.

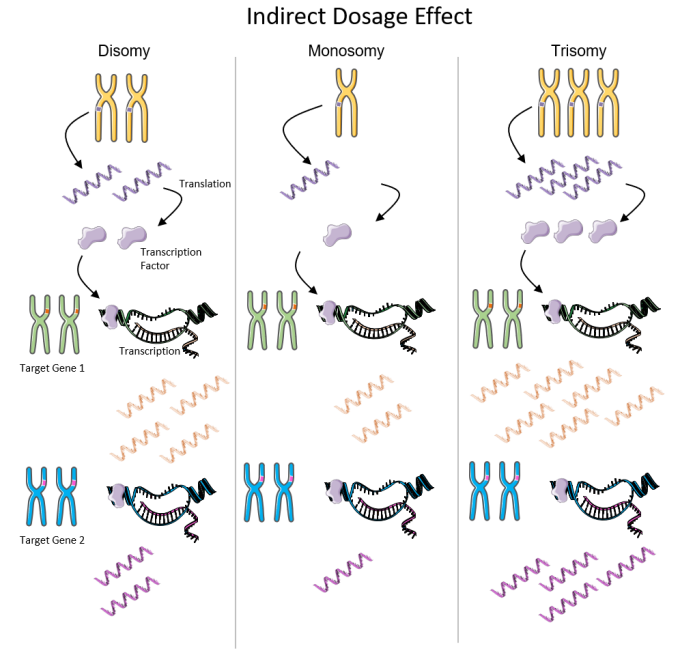


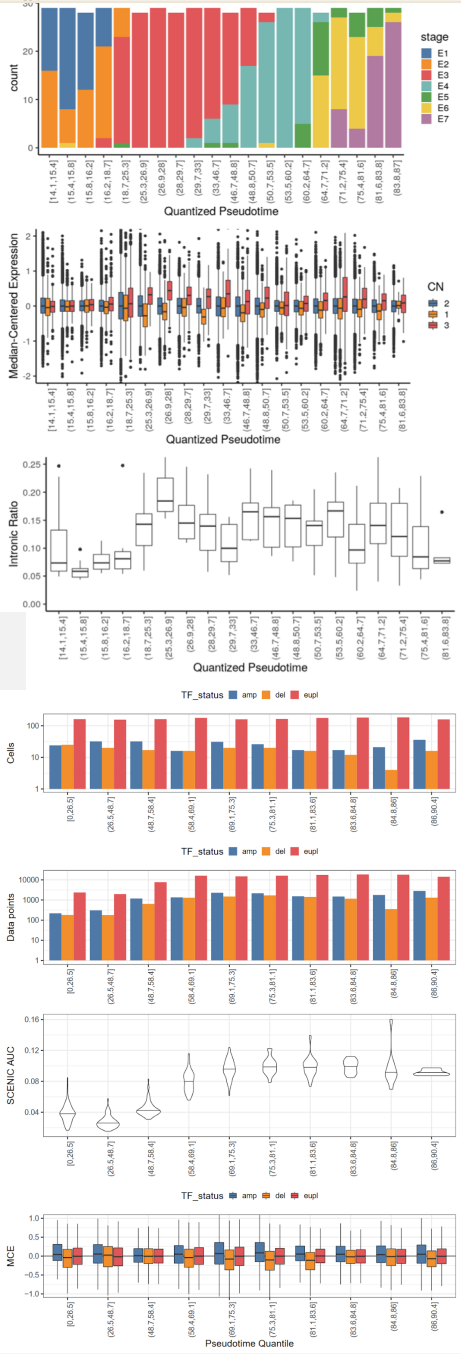
RESULTS

INTEGRATIVE ANALYSES

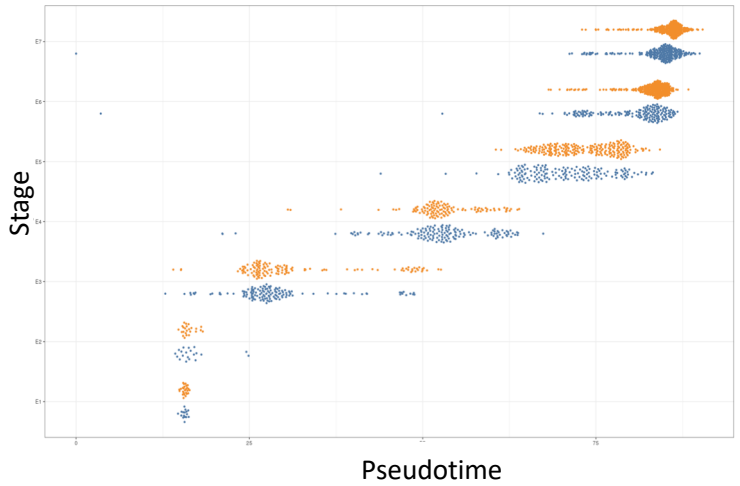


Direct and indirect dosage effects are evident after embryonic genome activation and vary with transcriptional activity along pseudotime.





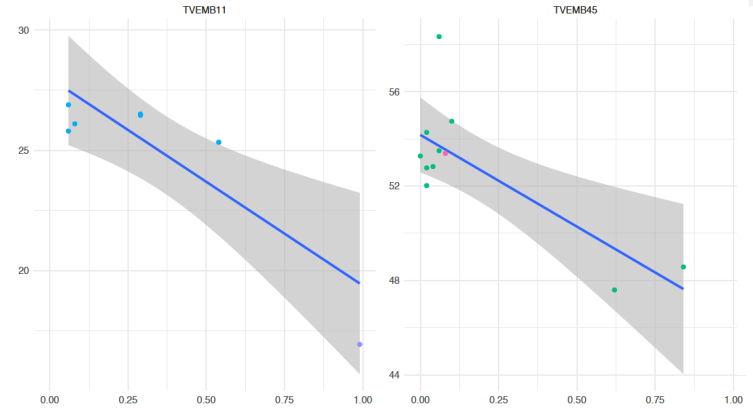
Global effects of aneuploidy



Aneuploid cells in E5-E7 show a significant delay in pseudotime.

cnv_profile
- aneuploid
- normal

Negative correlation between pseudotime (x) and % of abnormal genome (y) in cells within the same embryo.



SUMMARY

- Recapitulation **of transcriptional signatures of embryo development** using G&T.
- **Genomic instability effects** in general are more **subtle** than expected during preimplantation development.
- **Aneuploidy rate** is **similar** than previously detected with stand alone single cell genome analysis in human embryos.
- Complete **gene regulatory landscape** of human preimplantation embryo development.
- Common **effects of aneuploidy** observed show a **developmental delay** of cells with abnormal genome.
- First time description of when **direct and indirect gene dosages** occur and their effect size on genes prior, during and after EGA.