Common variation in meiosis genes shapes human recombination phenotypes and aneuploidy risk

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Department of Biology
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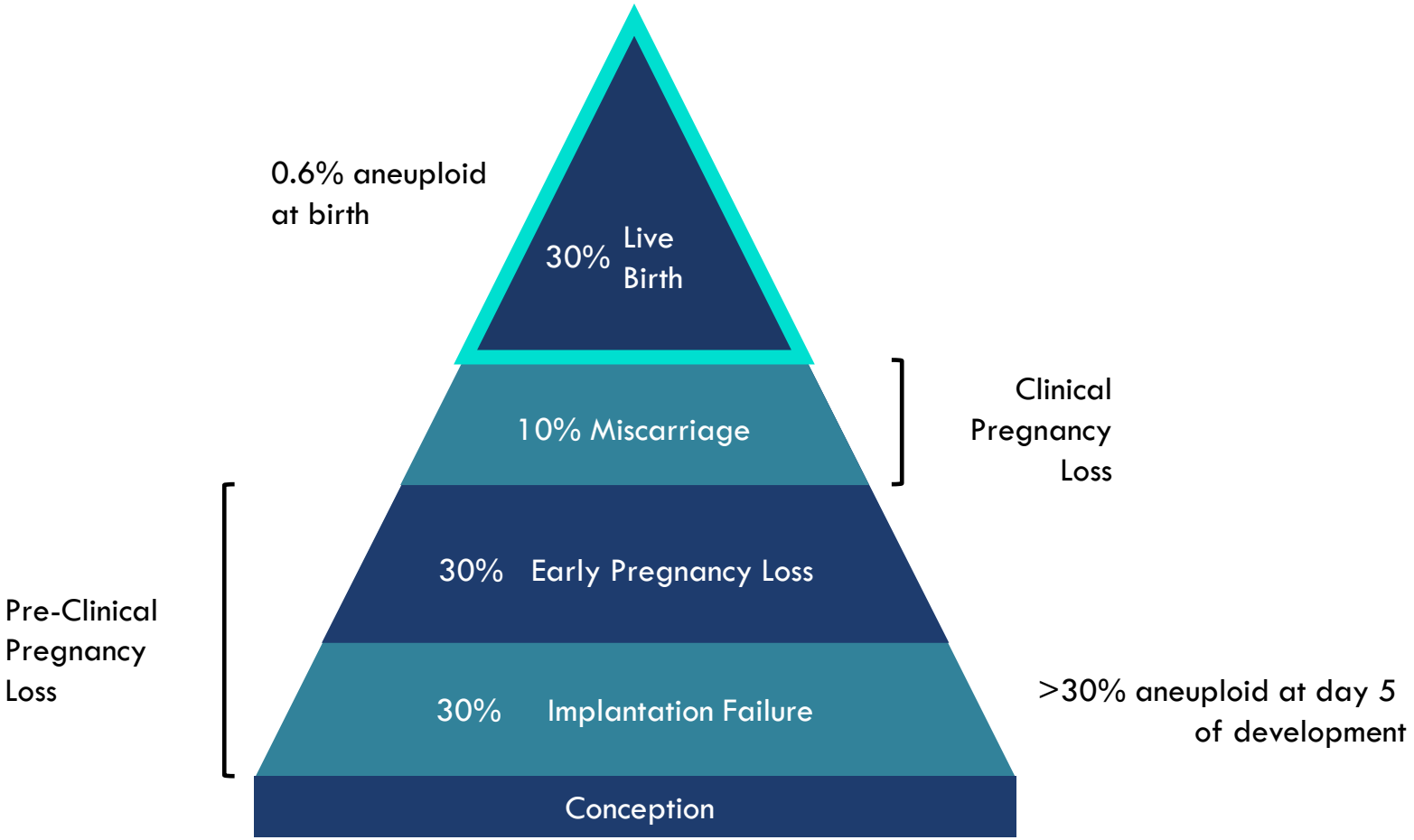
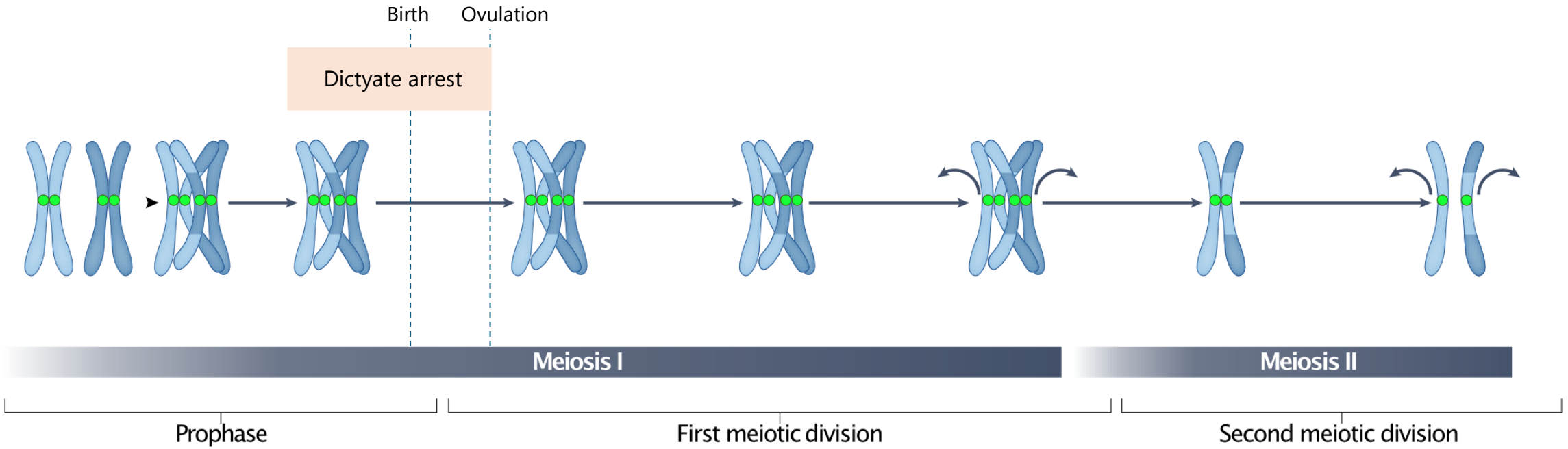
Aneuploidy is the leading cause of human pregnancy loss



Adapted from Macklon et al. (2002). *Hum. Reprod. Update*, 8, 333-343.

Crossovers stabilize paired chromosomes during decades-long female meiotic arrest



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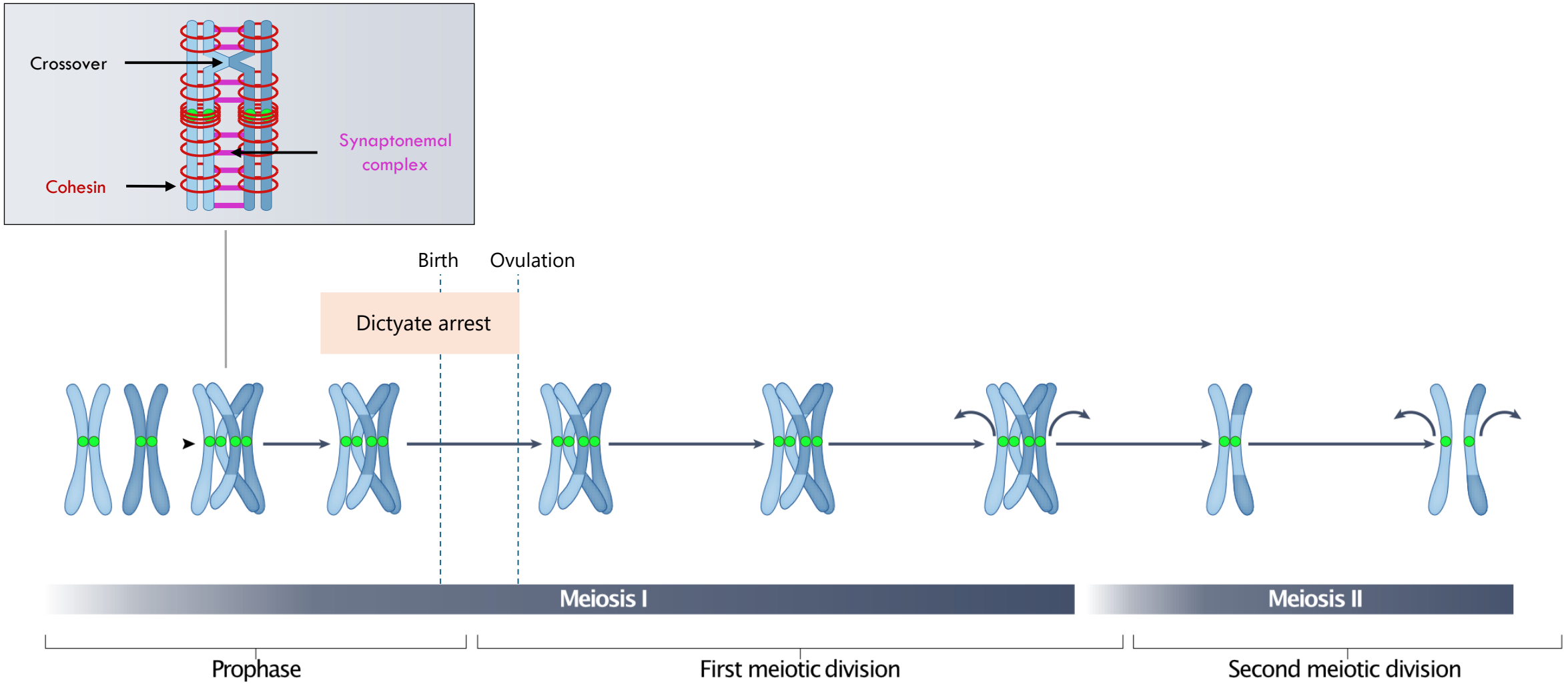

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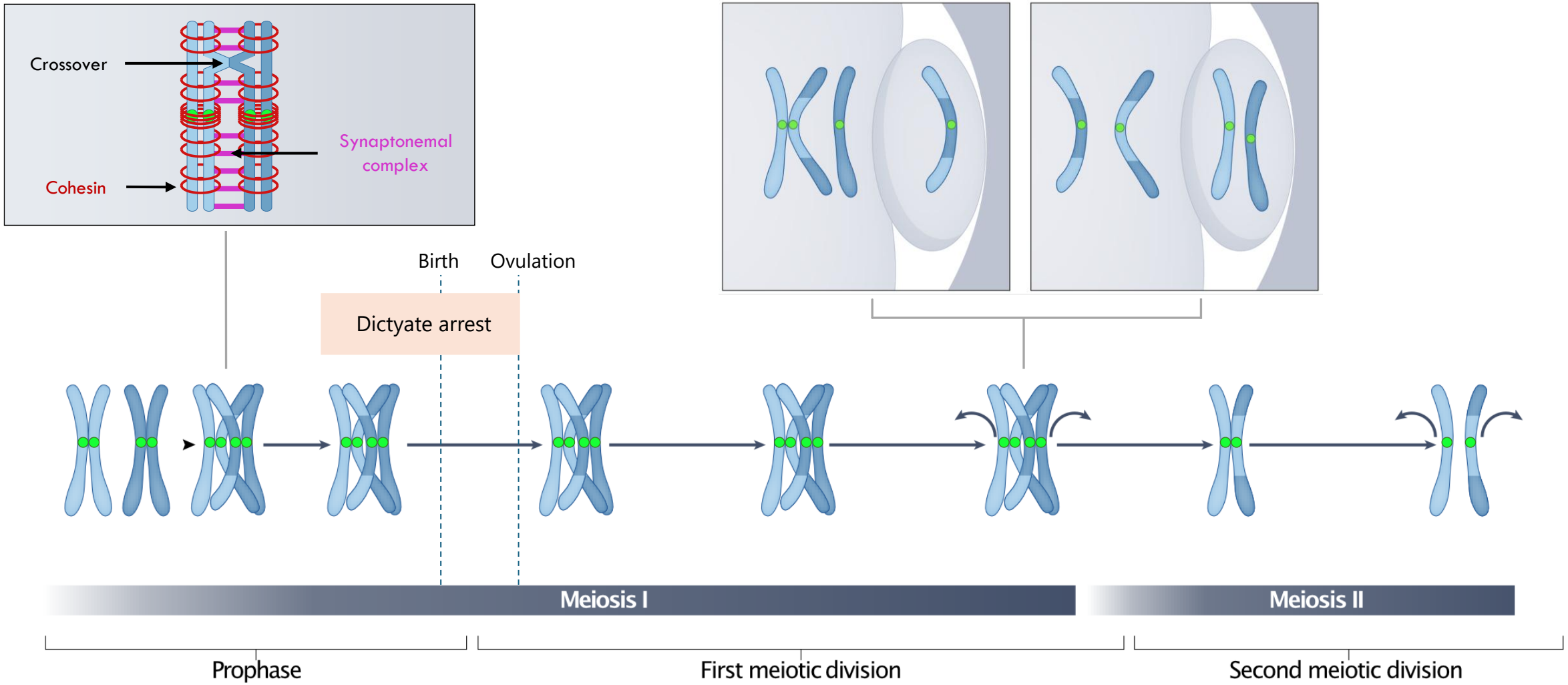

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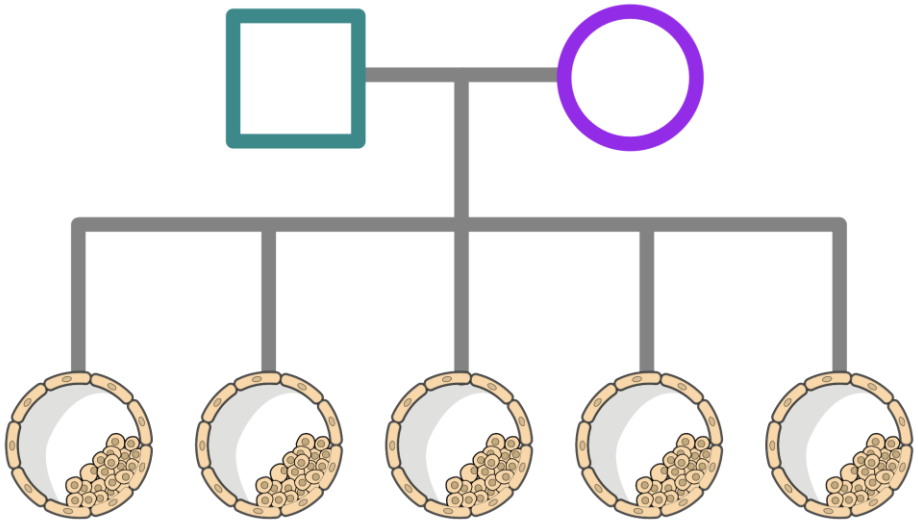
Preimplantation genetic testing (PGT-A) data from Natera



22,850 maternal and paternal DNA samples

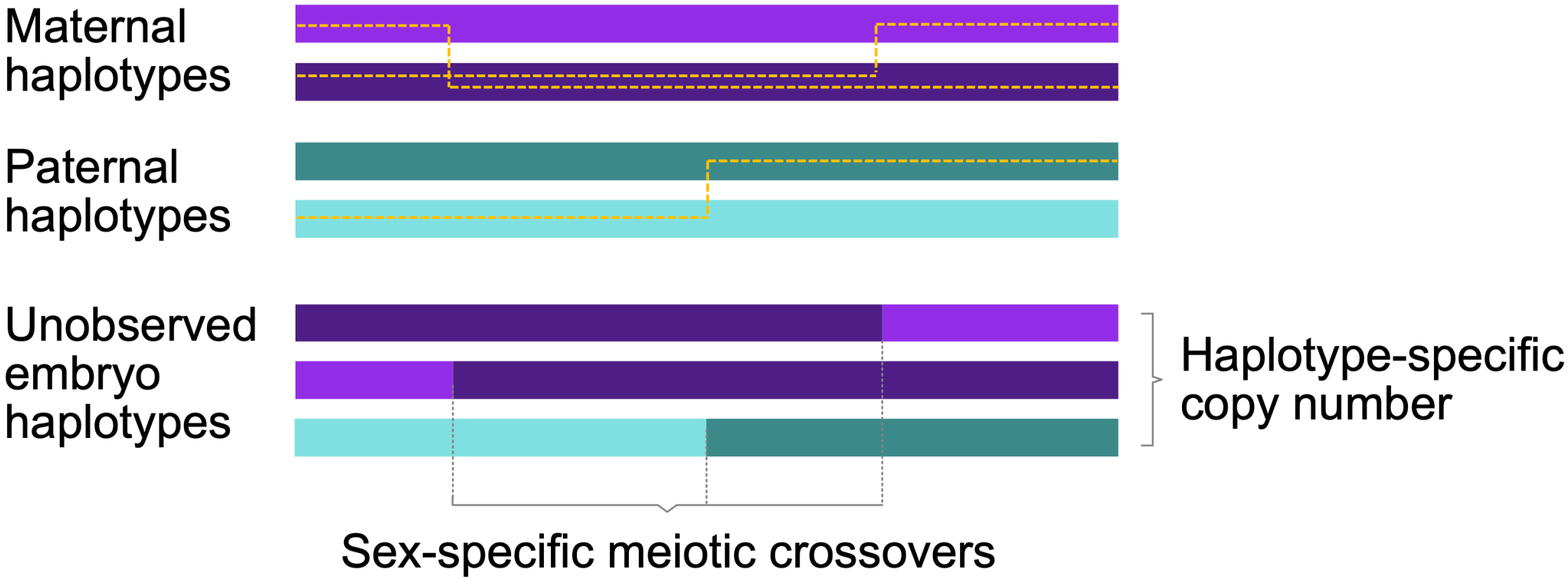
139,416 trophectoderm biopsies of day-5 blastocyst-stage embryos

All samples assayed on Illumina HumanCytoSNP-12 Array (293k sites)

Hidden Markov model for inferring crossovers and aneuploidies

Method inspired by Coop et al. (2008). *Science*, 319, 1395-1398.

Hidden Markov model for inferring crossovers and aneuploidies



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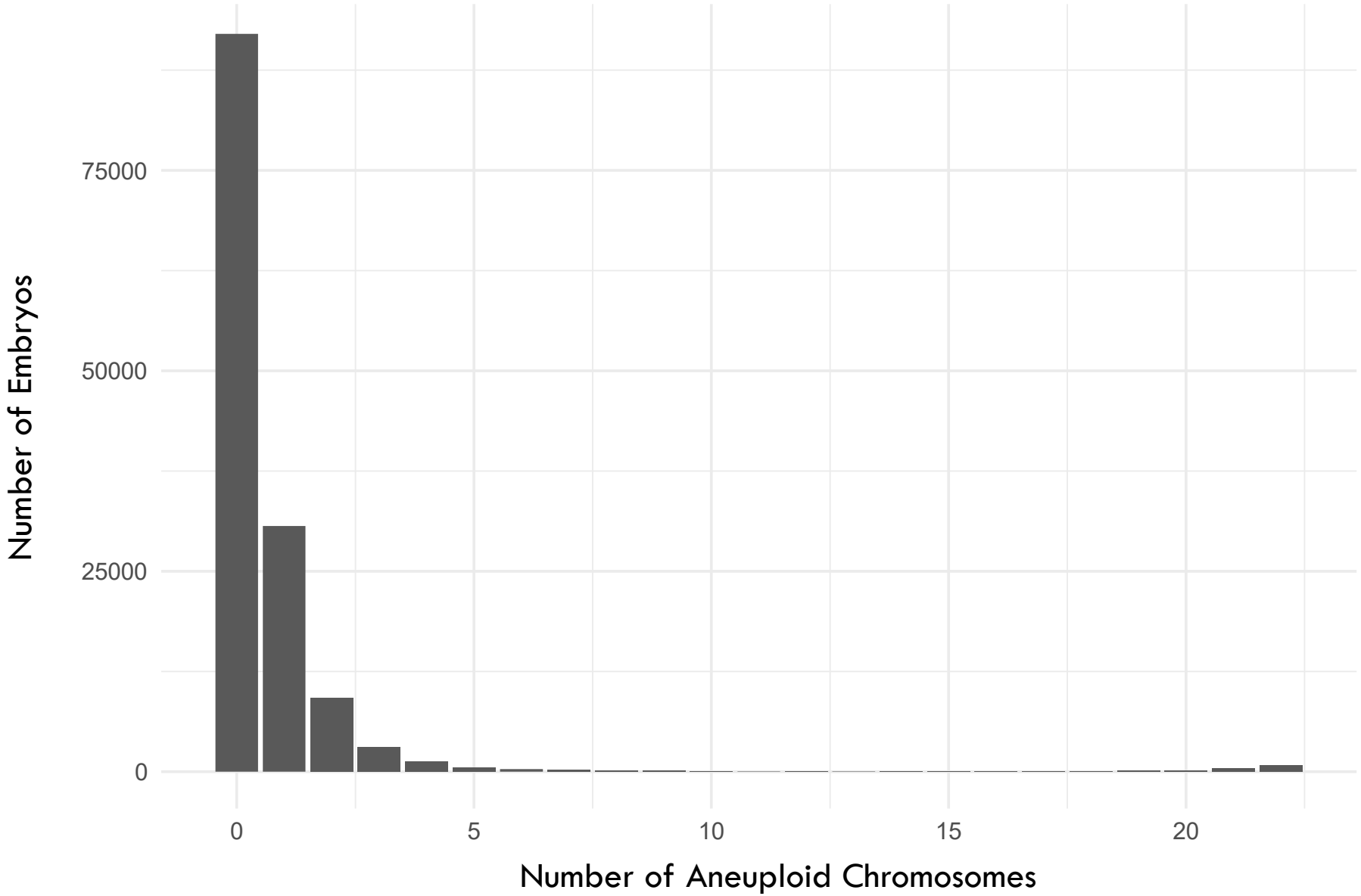
Aneuploidies are common in blastocyst-stage human embryos



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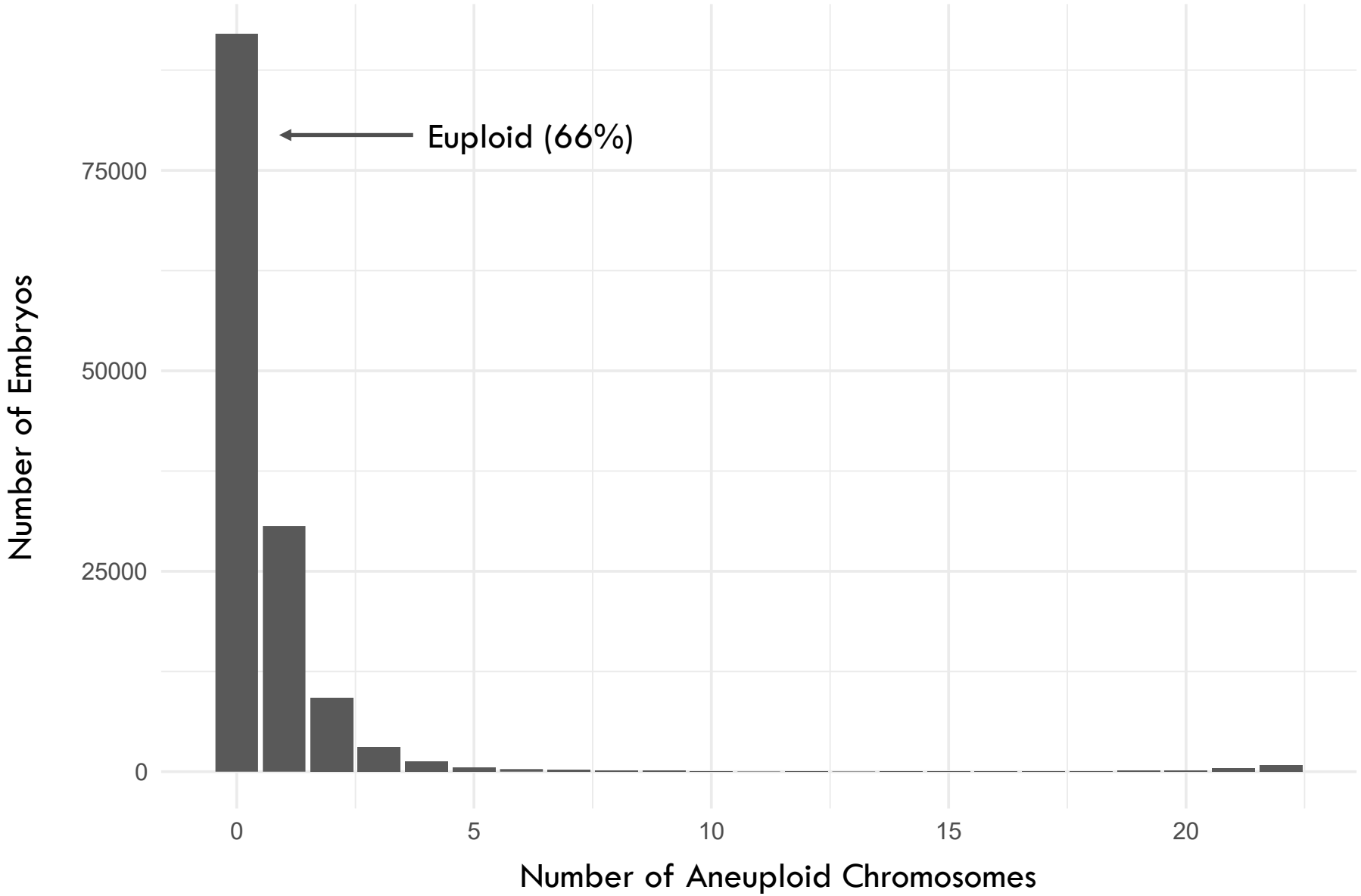

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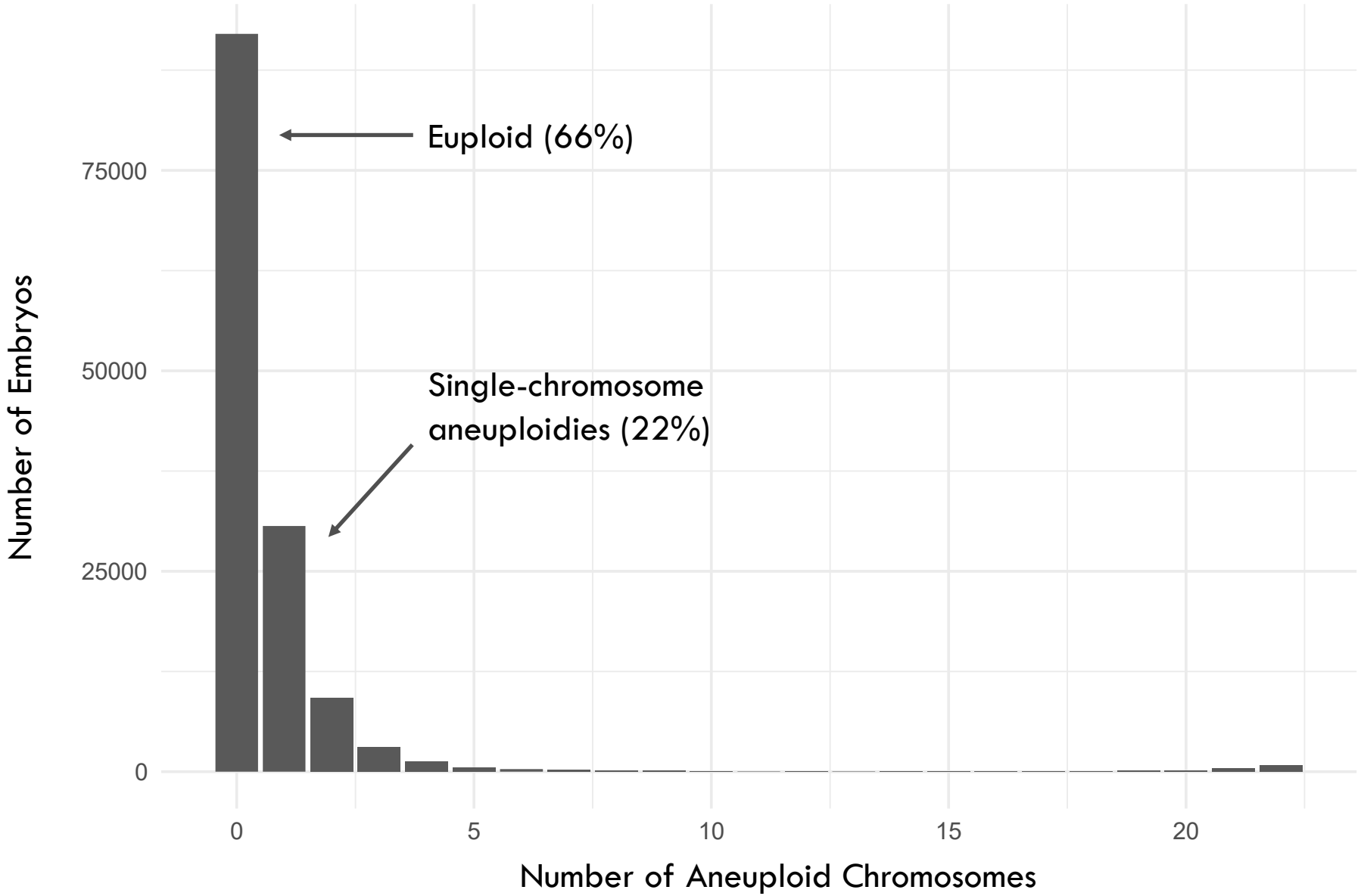

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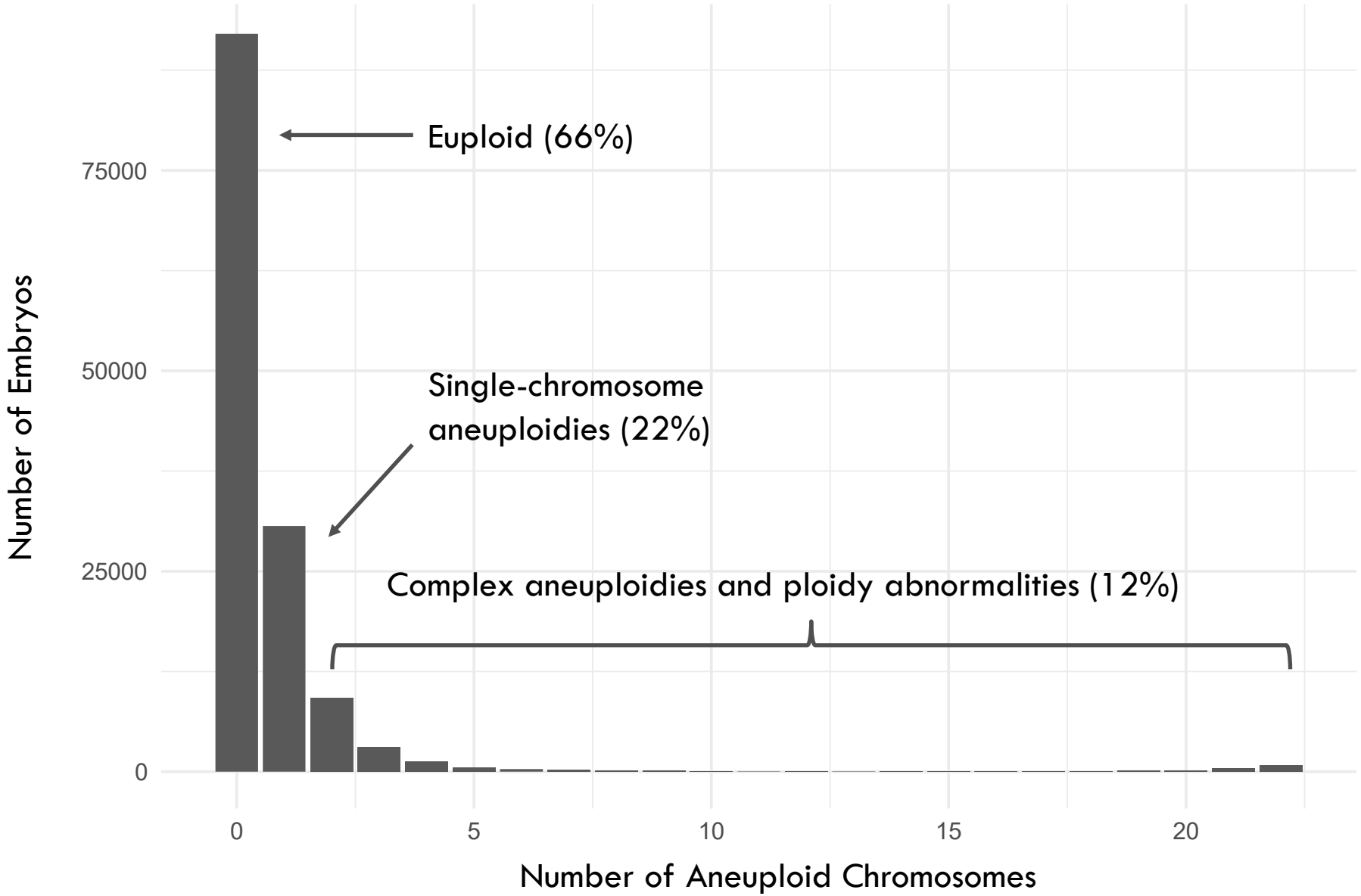
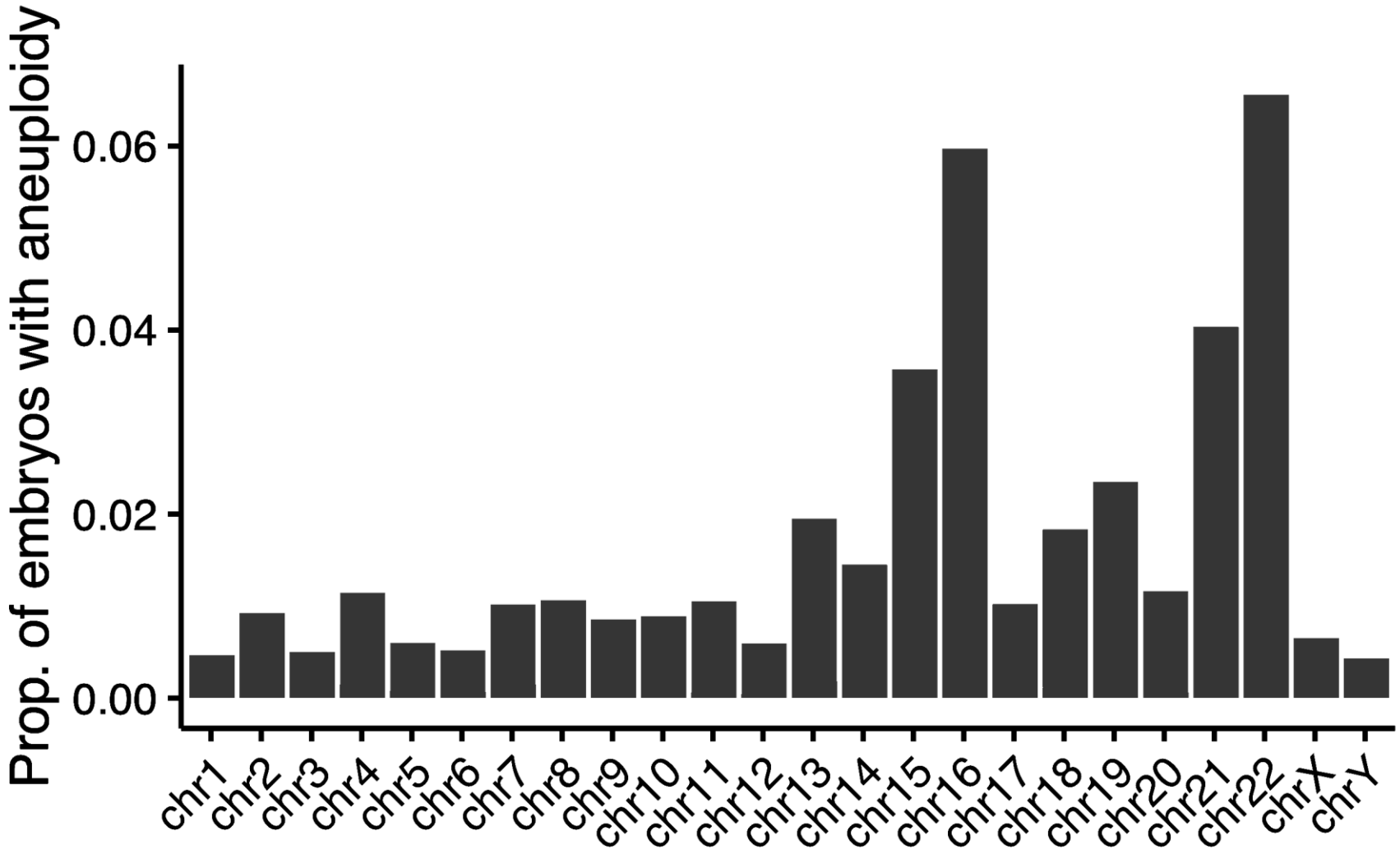


Aneuploidy rates vary across chromosomes



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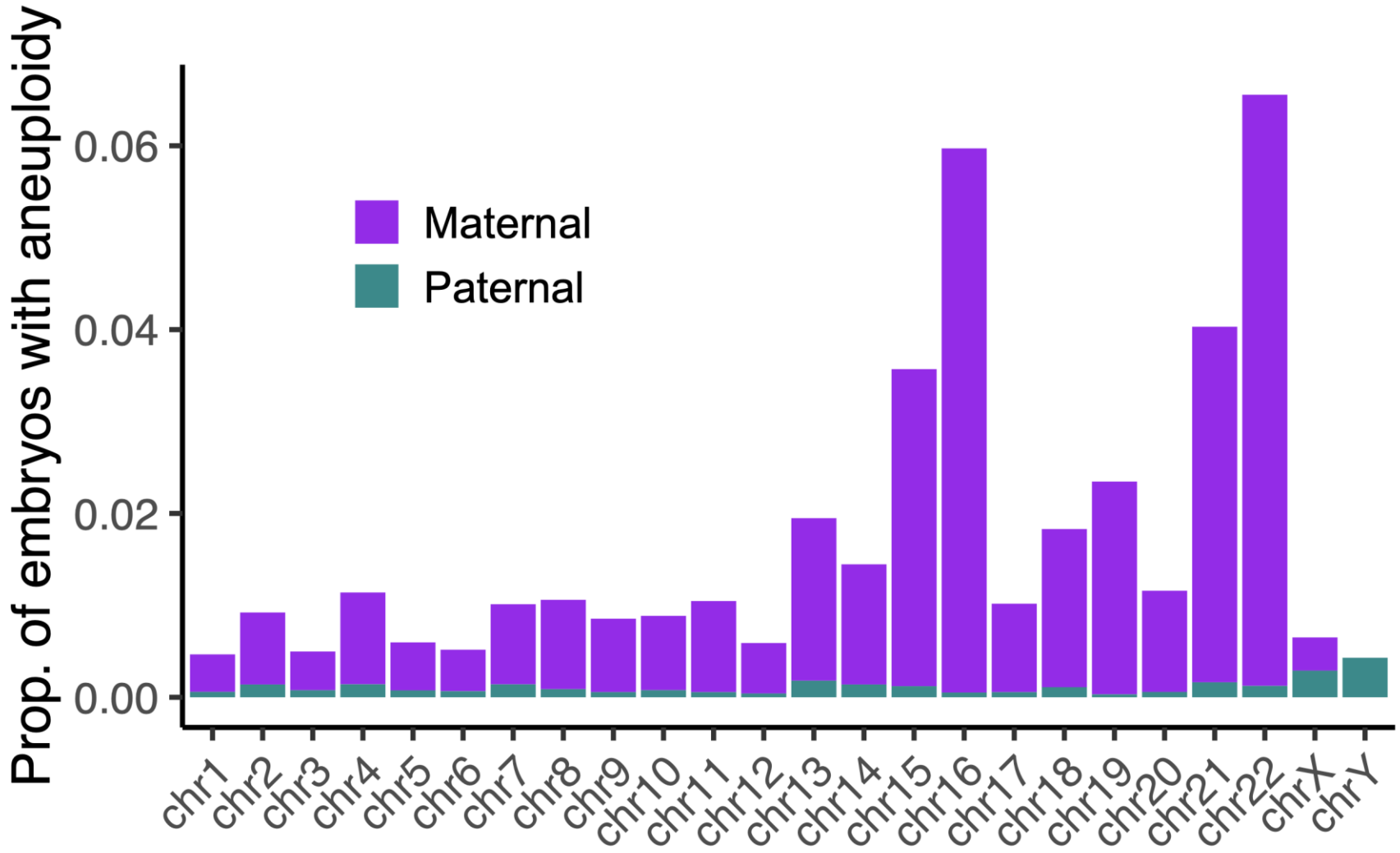
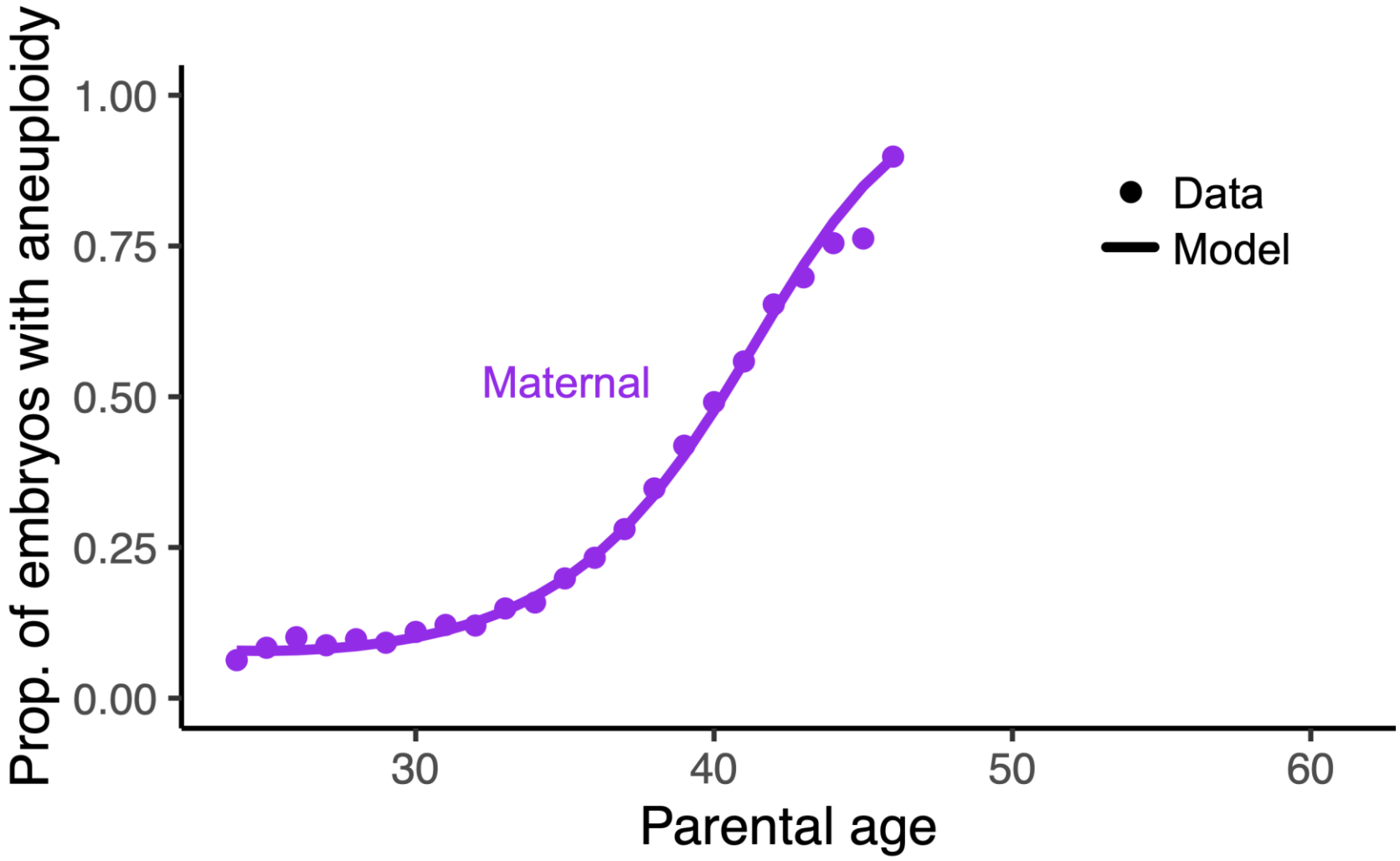


Aneuploidies of maternal meiotic origin increase with maternal age



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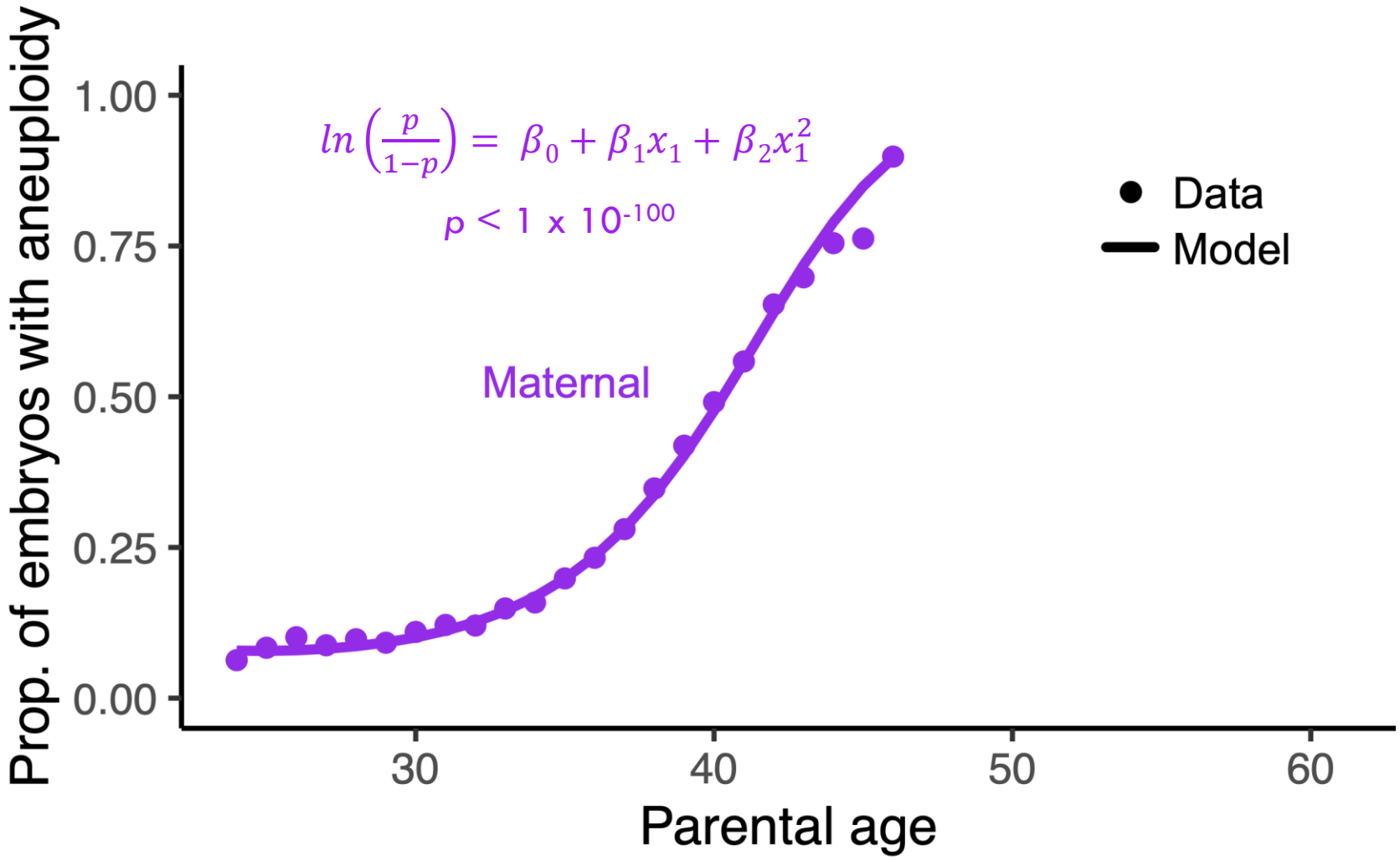

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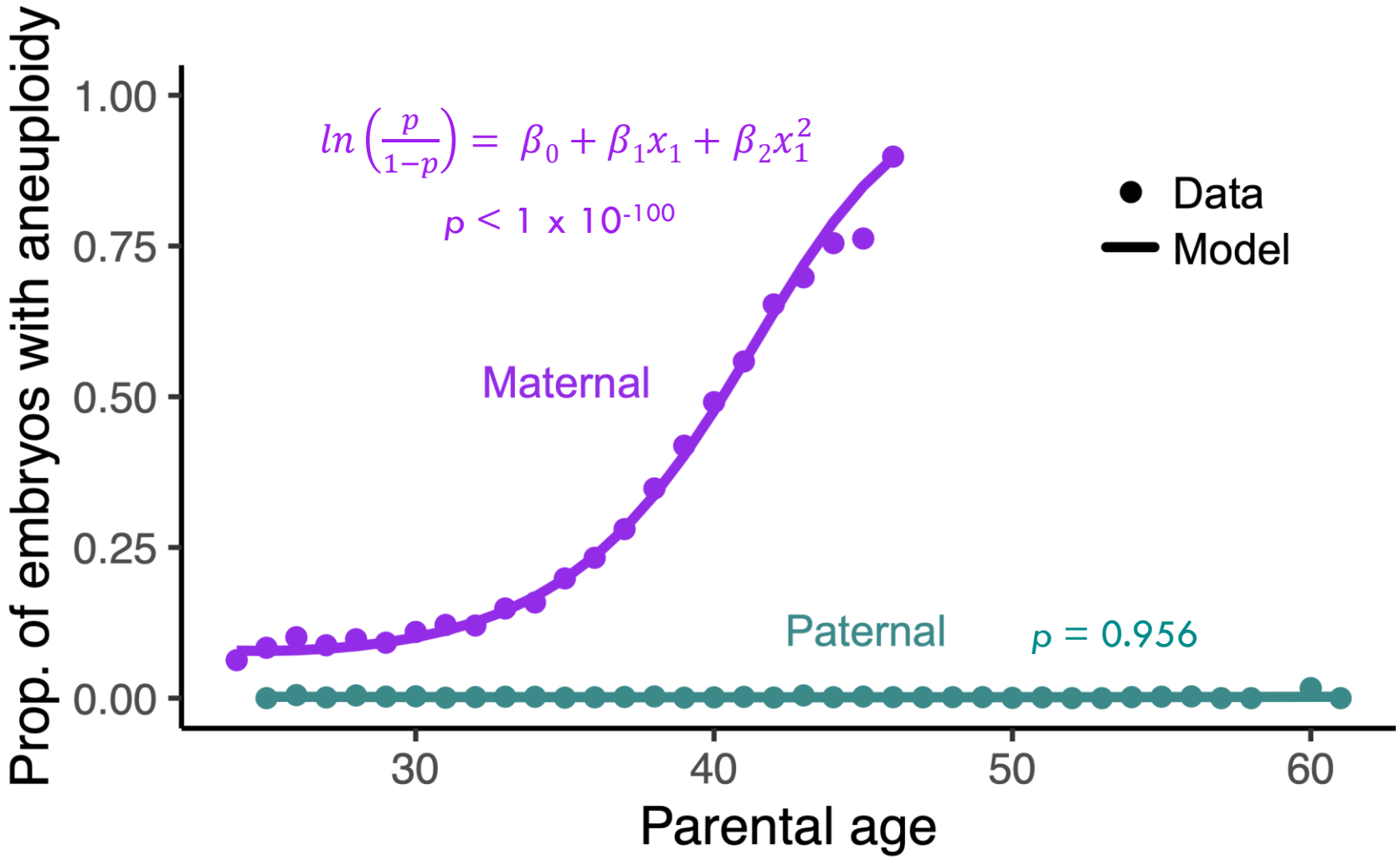
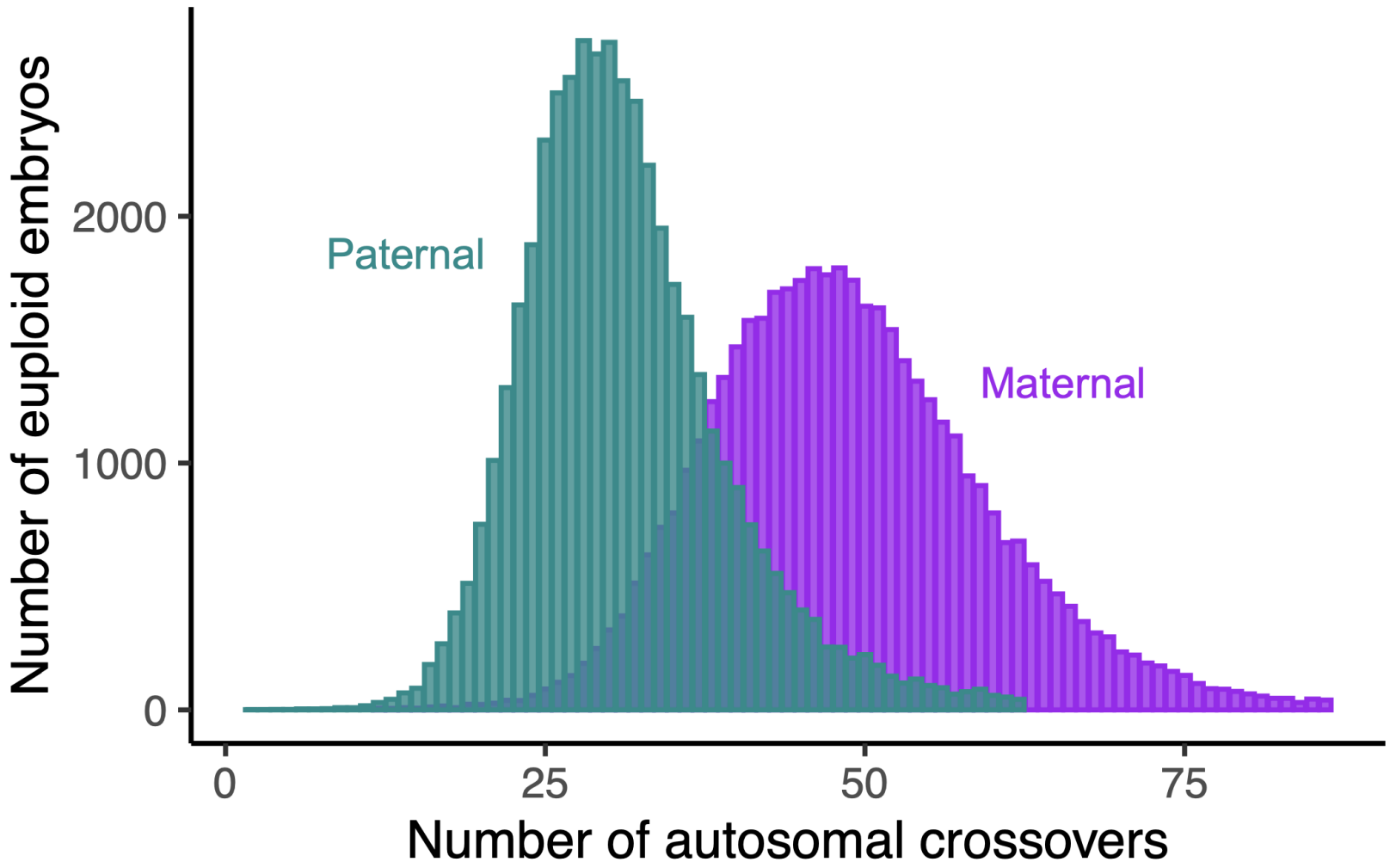
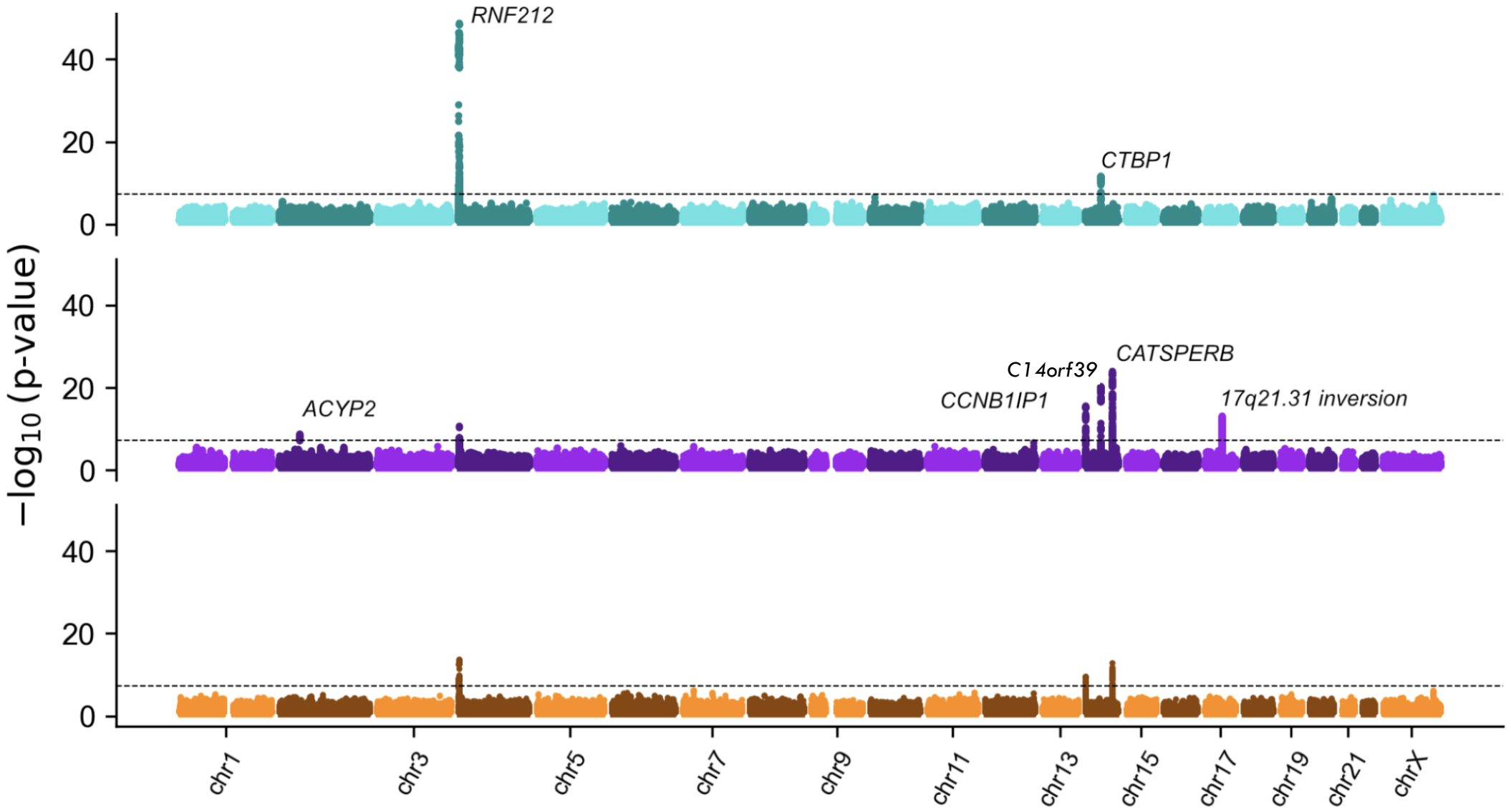


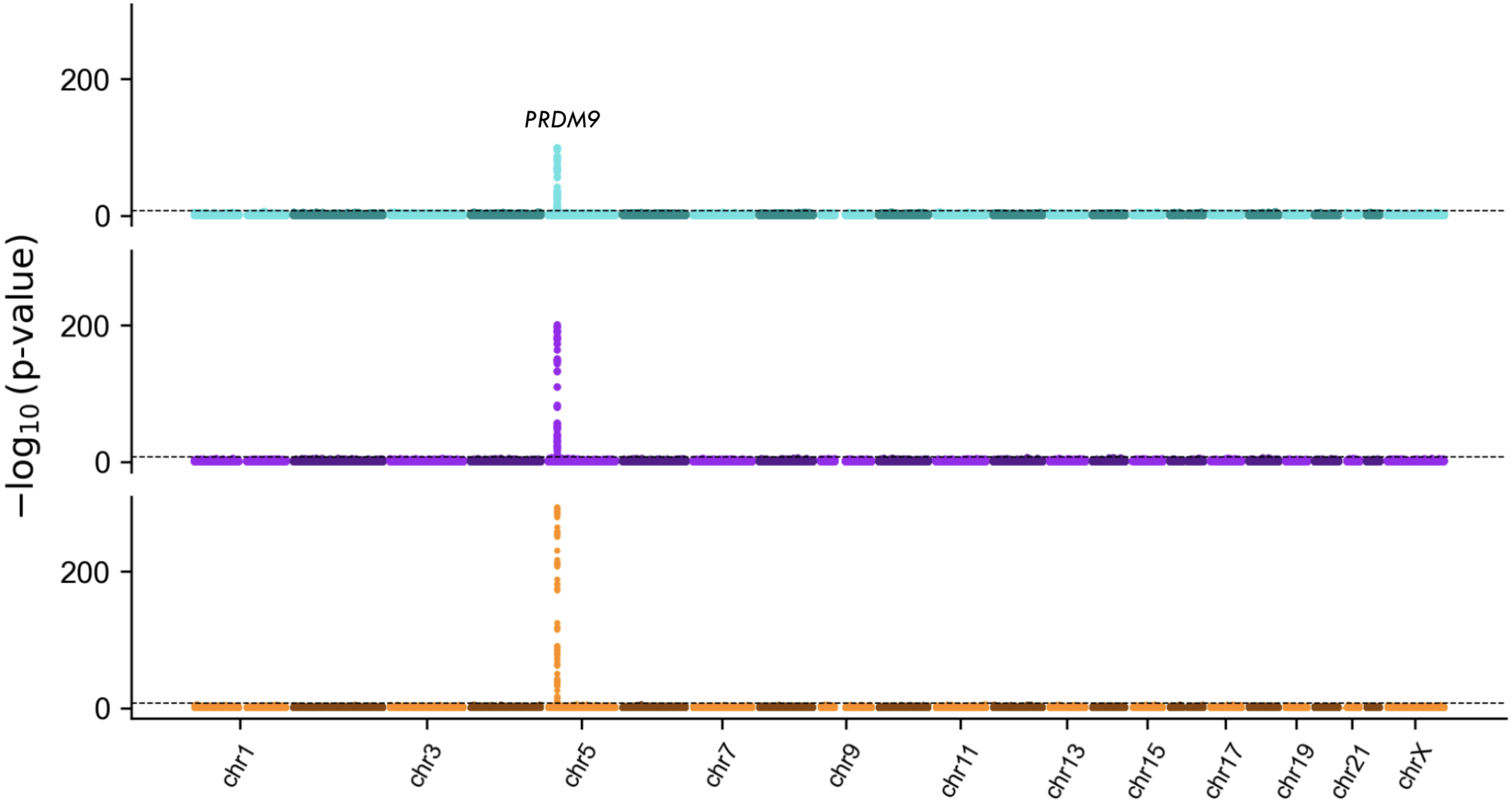
Patterns of crossovers replicate known features of sex-specific genetic maps



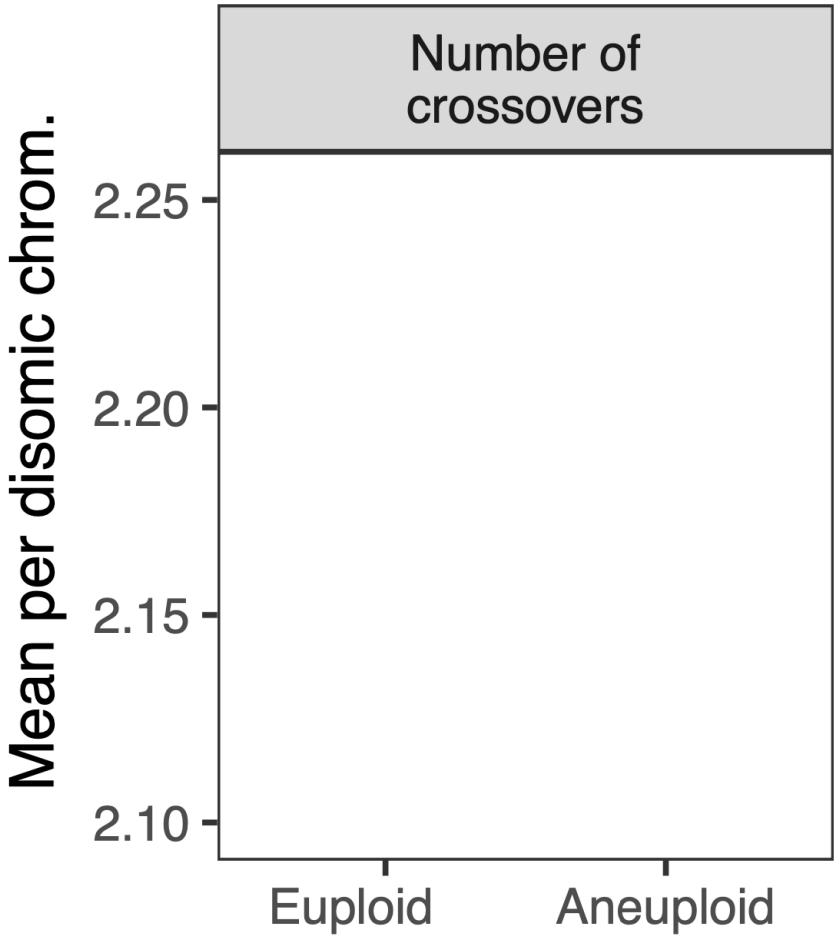
Common variation in meiosis genes is associated with crossover rate



Common variation in meiosis genes is associated with crossover location



Aneuploid embryos are depleted of crossovers compared to euploid embryos



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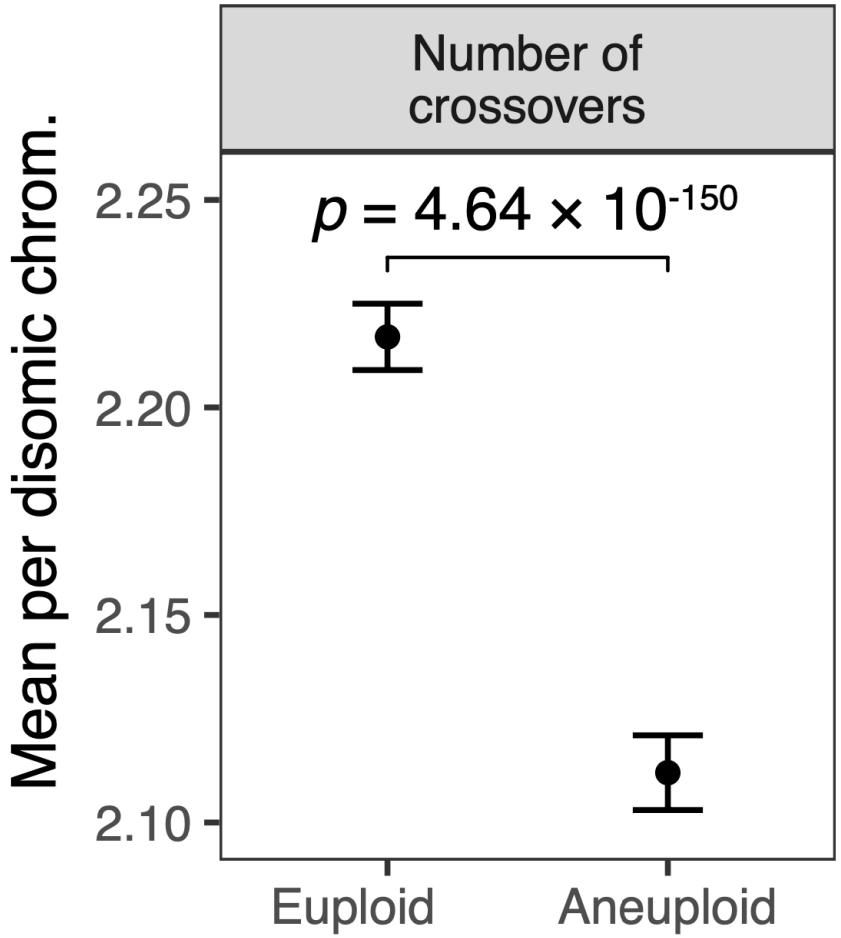
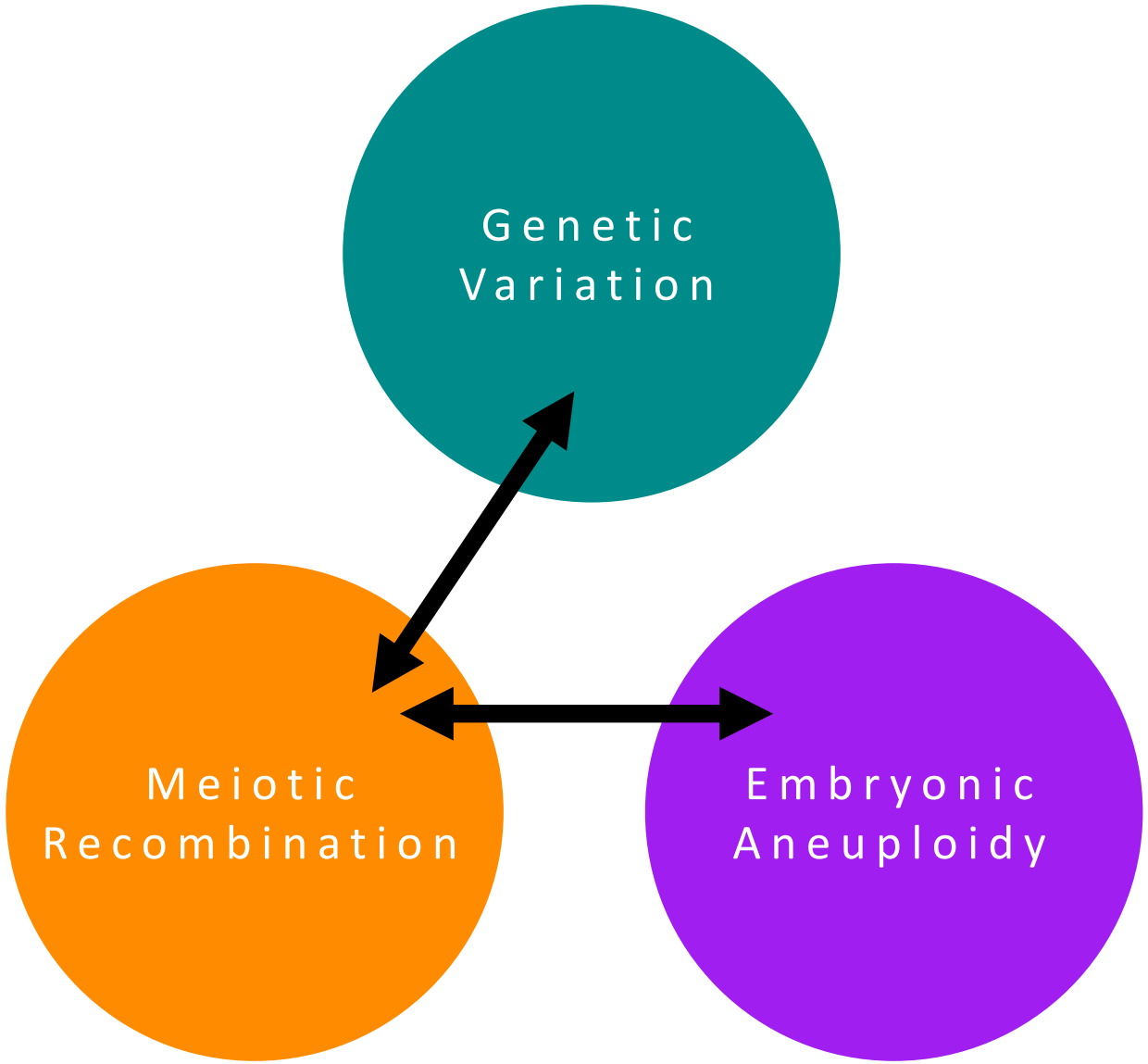
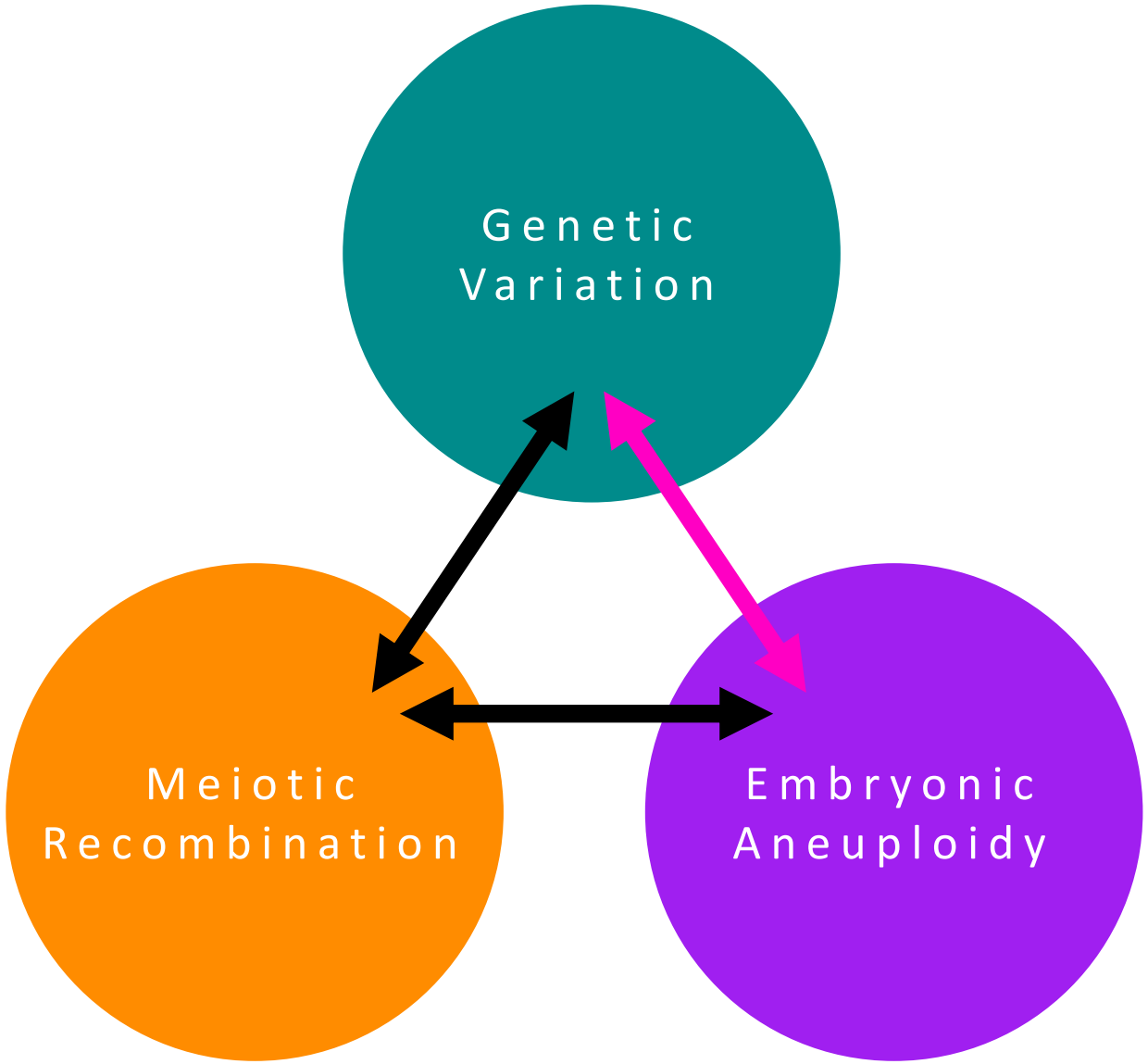



Genetic Variation
Meiotic Recombination
Embryonic Aneuploidy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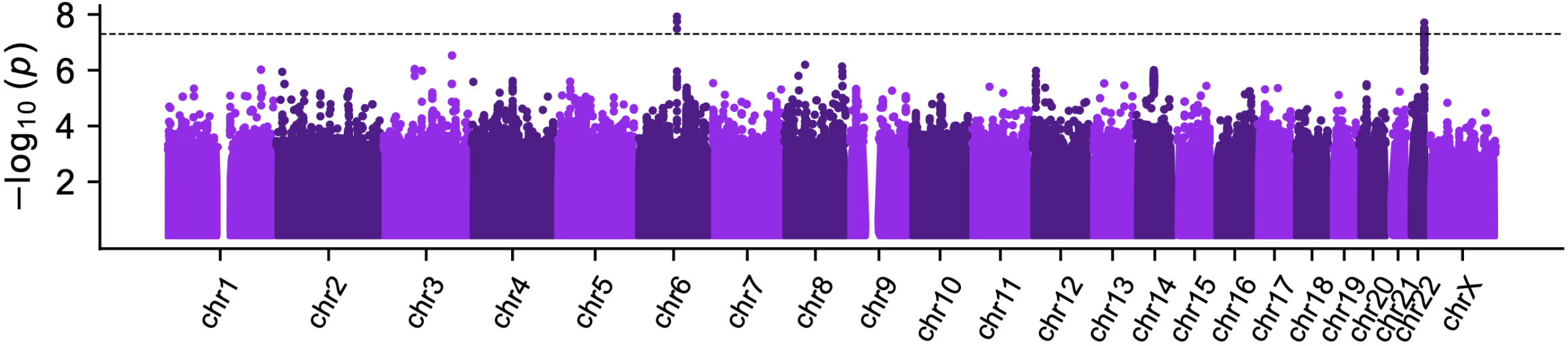
Genome-wide association study of maternal meiotic aneuploidy



Genome-wide association study of maternal meiotic aneuploidy

$p_{discovery\ (85\%)} = 2.93 \times 10^{-8}$

$p_{replication\ (15\%)} = 0.529$

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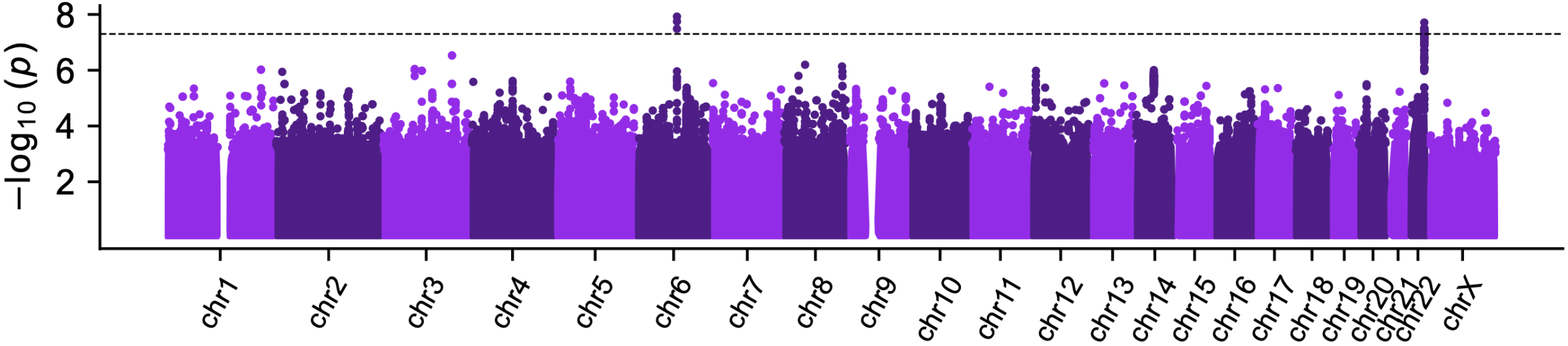
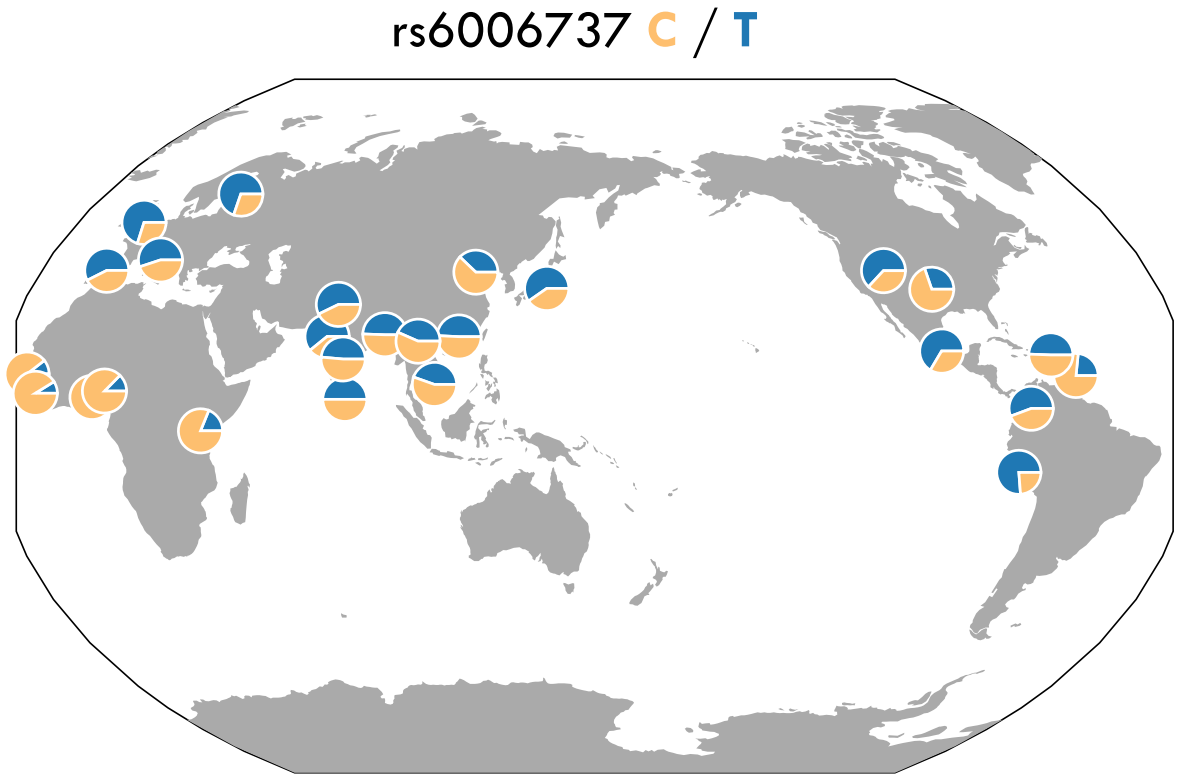
$p_{replication\ (15\%)} = 0.033$



The aneuploidy-associated allele is common across populations and confers a modest additive effect



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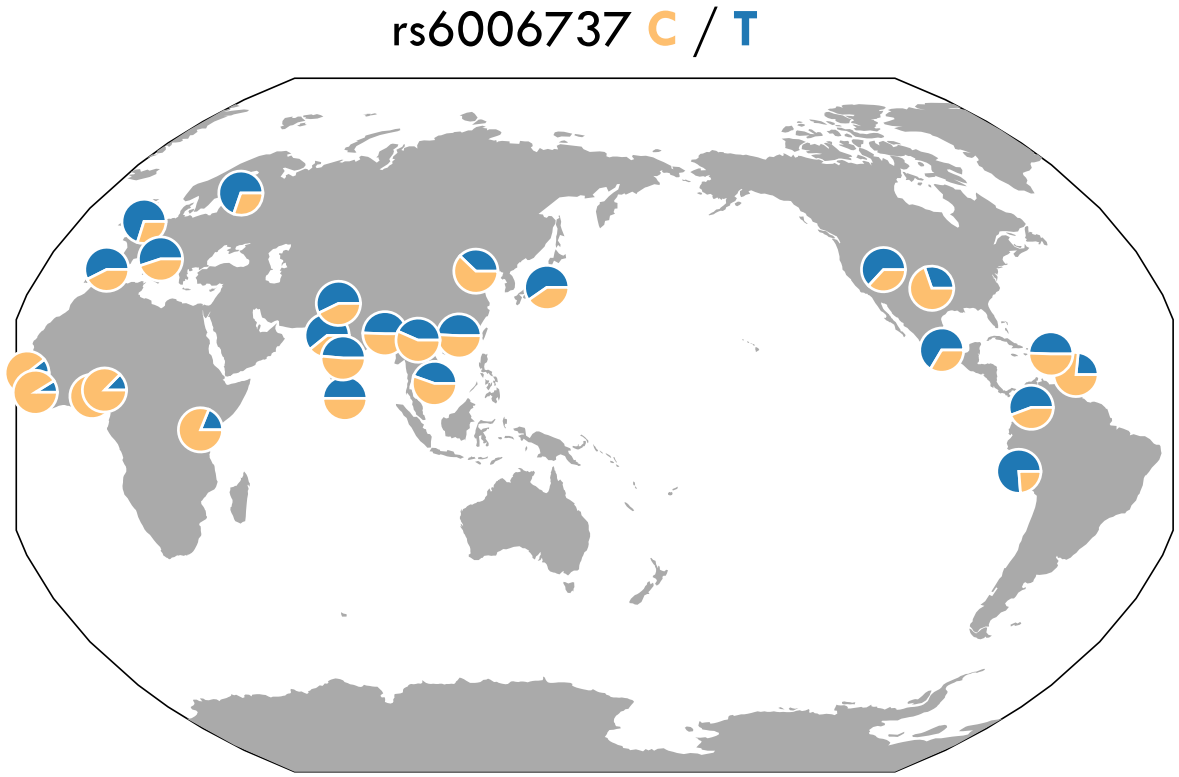

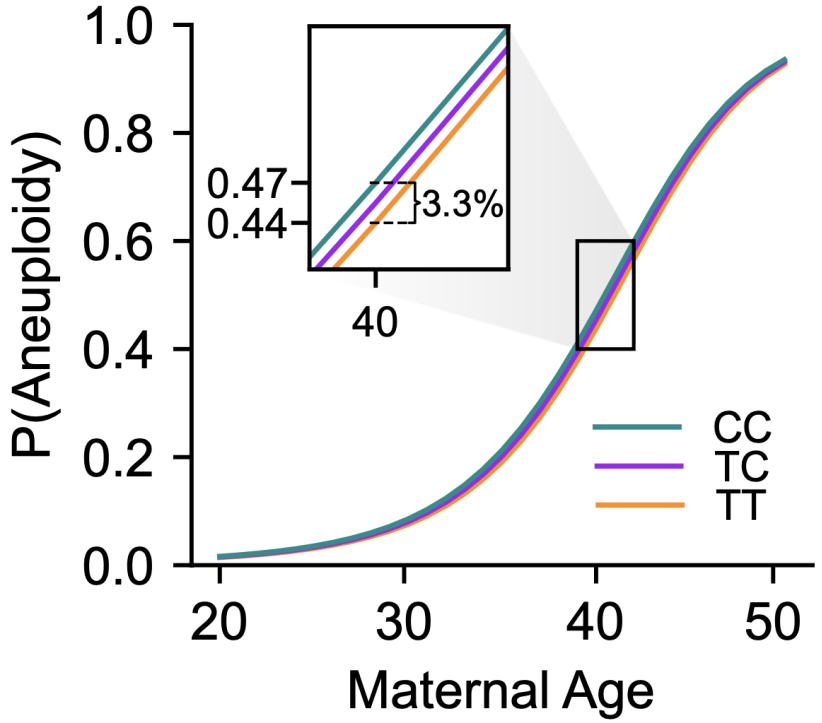

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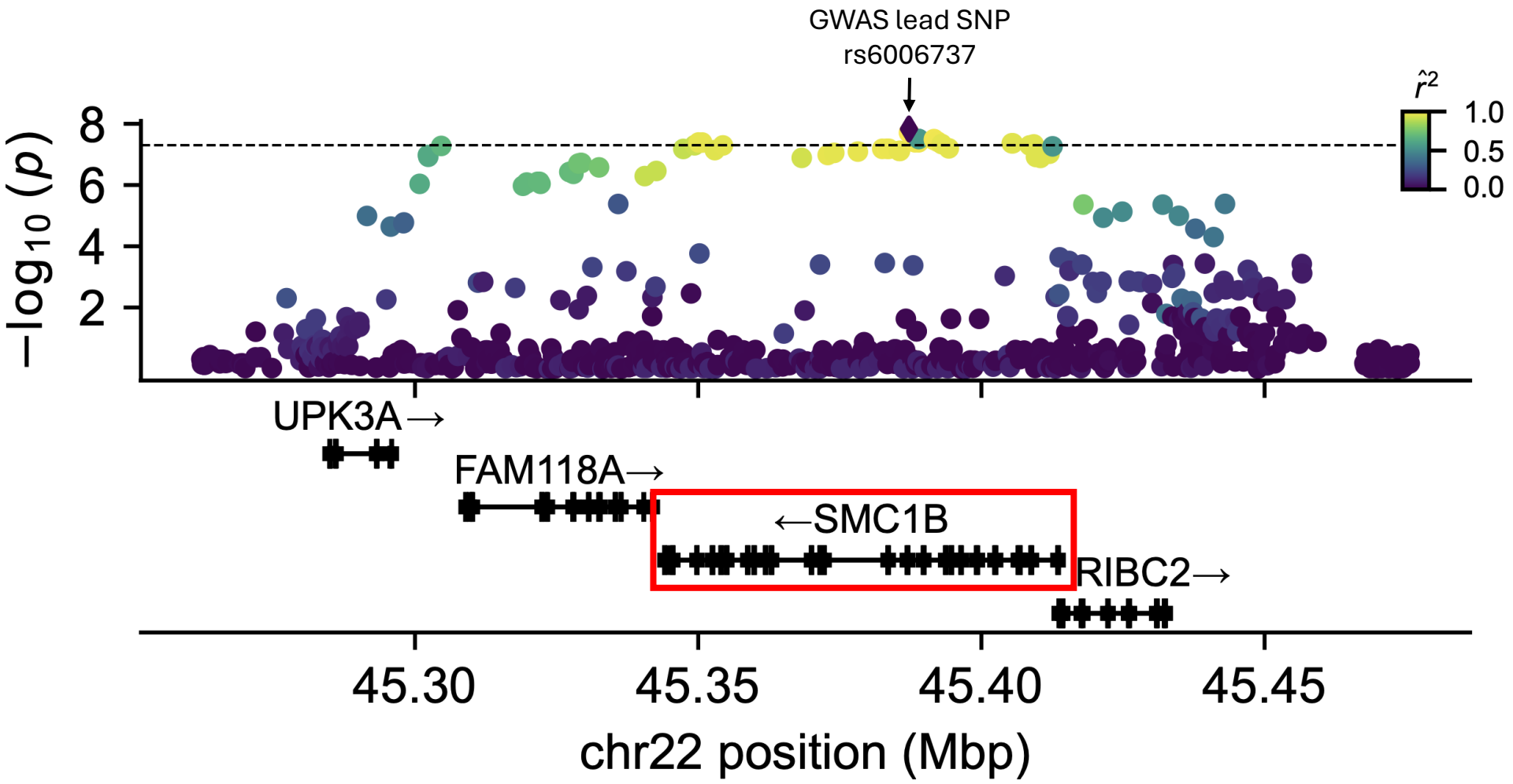
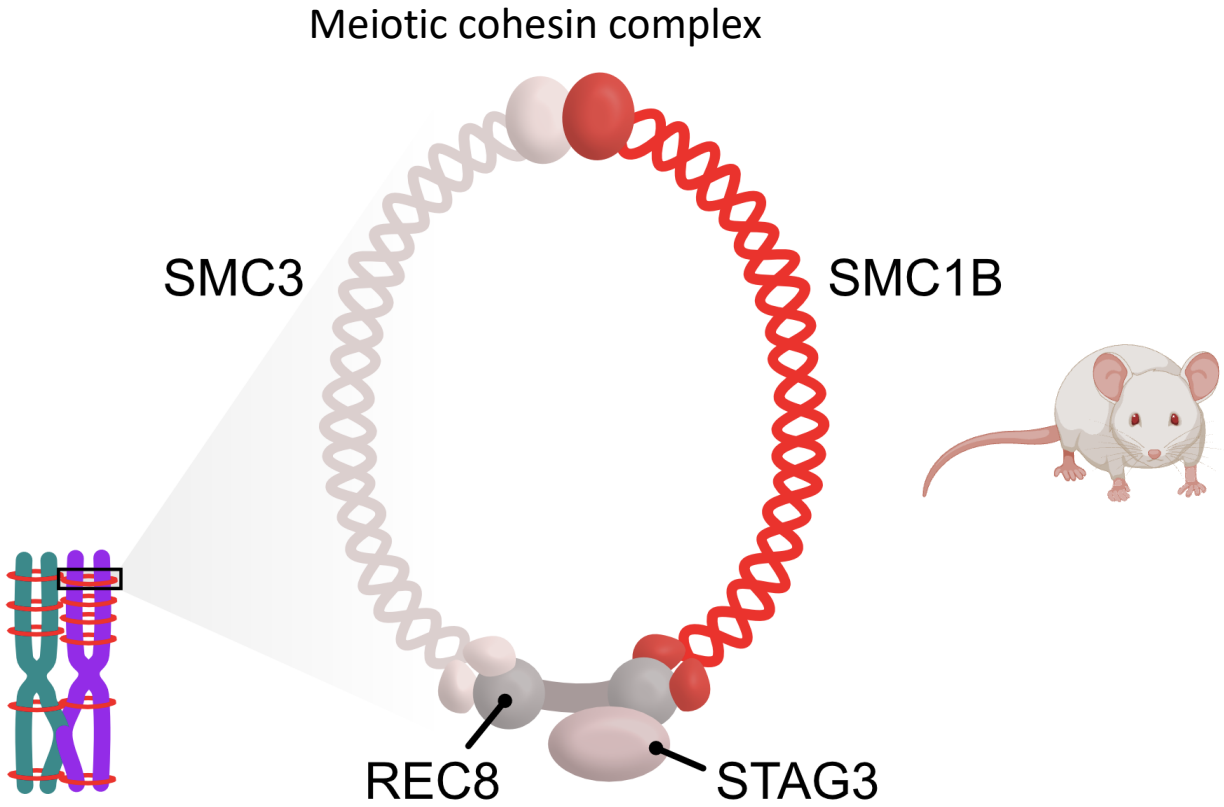
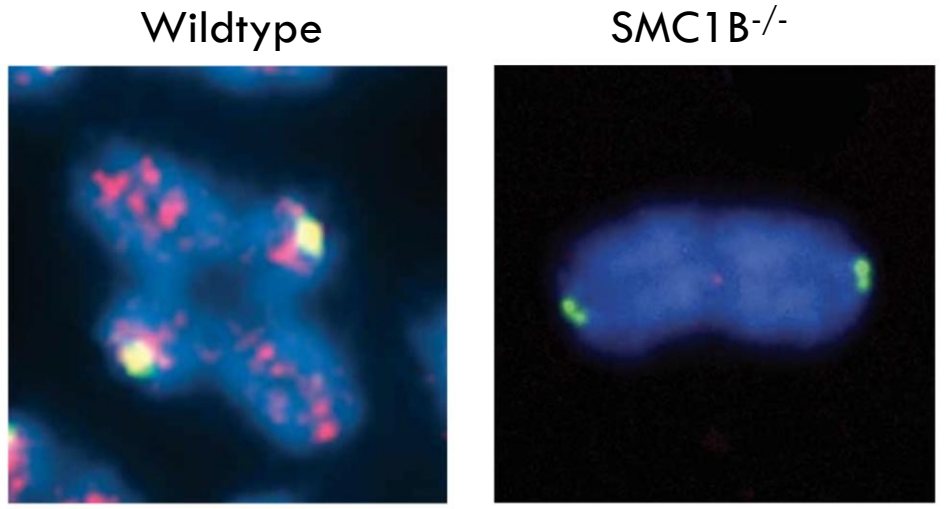
The aneuploidy risk haplotype spans the meiotic cohesin *SMC1B*



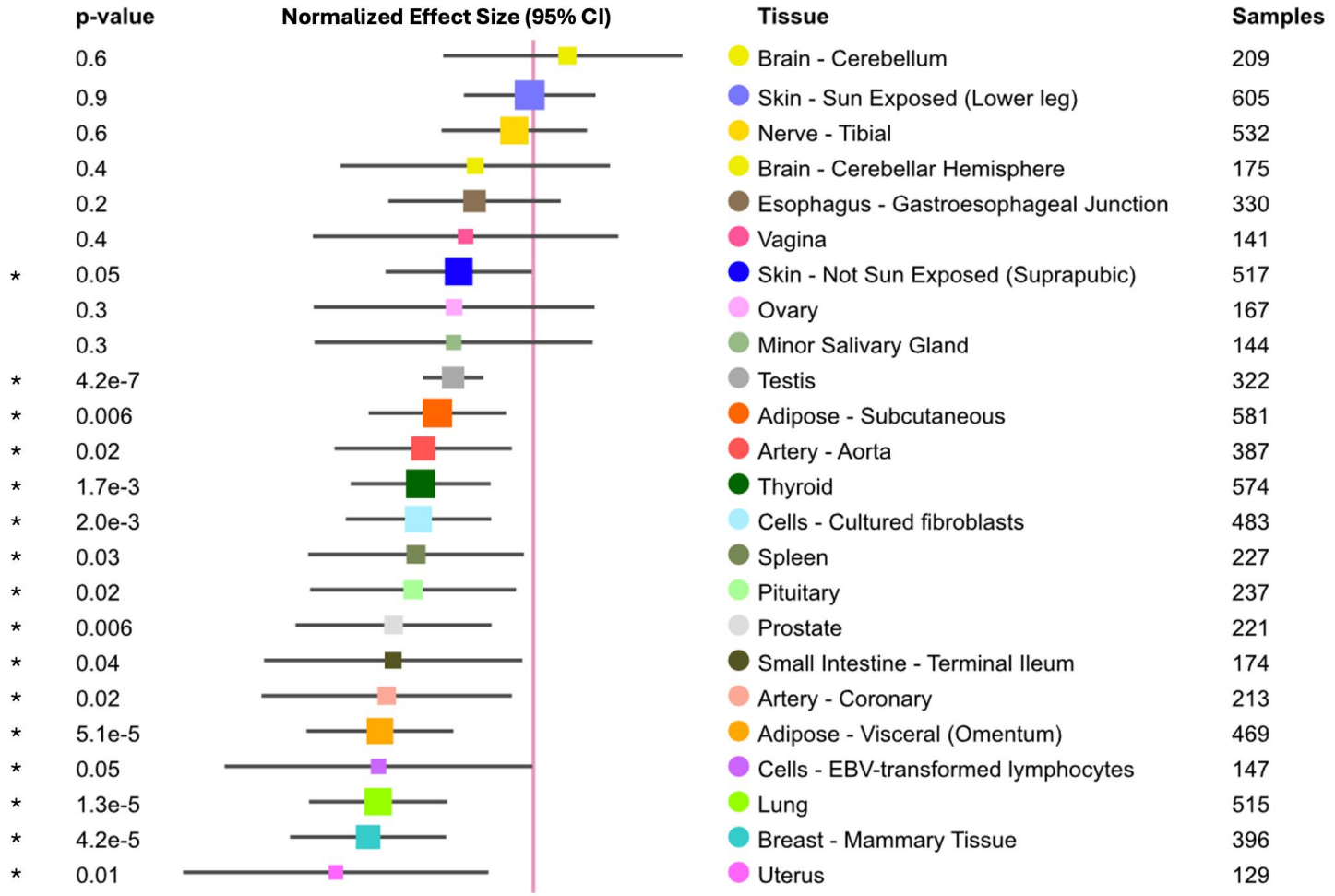
SMC1B-deficient female mice exhibit premature loss of chromosome cohesion





Hodges et al. (2005). *Nat. Genet.*, 37, 1351-1355.
Brooker & Berkowitz (2014). *Methods Mol. Biol.,* 1170, 229-266.

The aneuploidy risk haplotype is associated with reduced *SMC1B* expression



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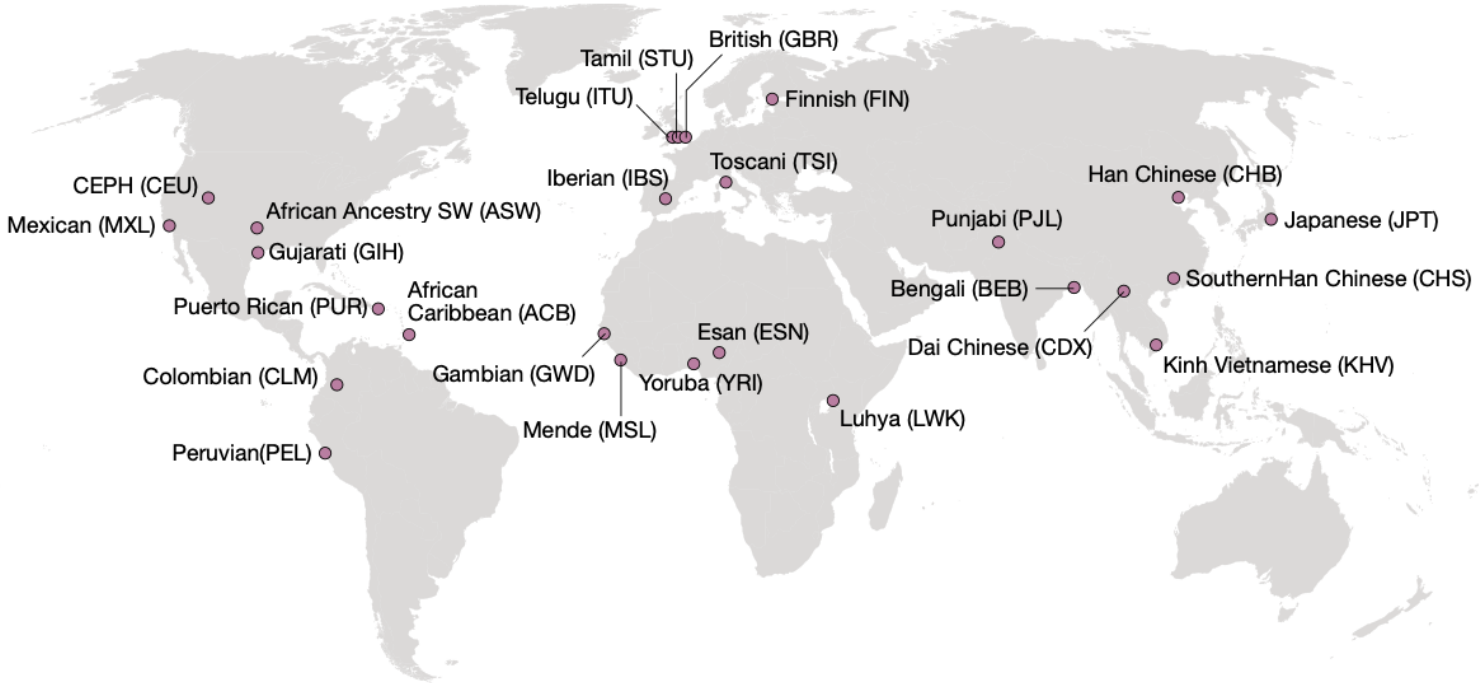
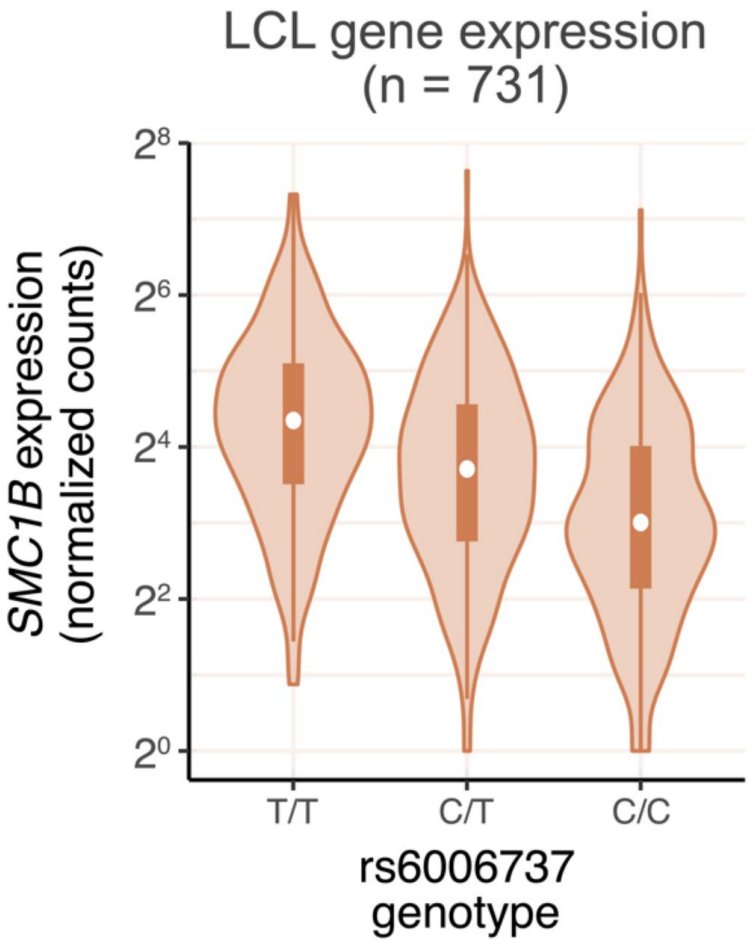
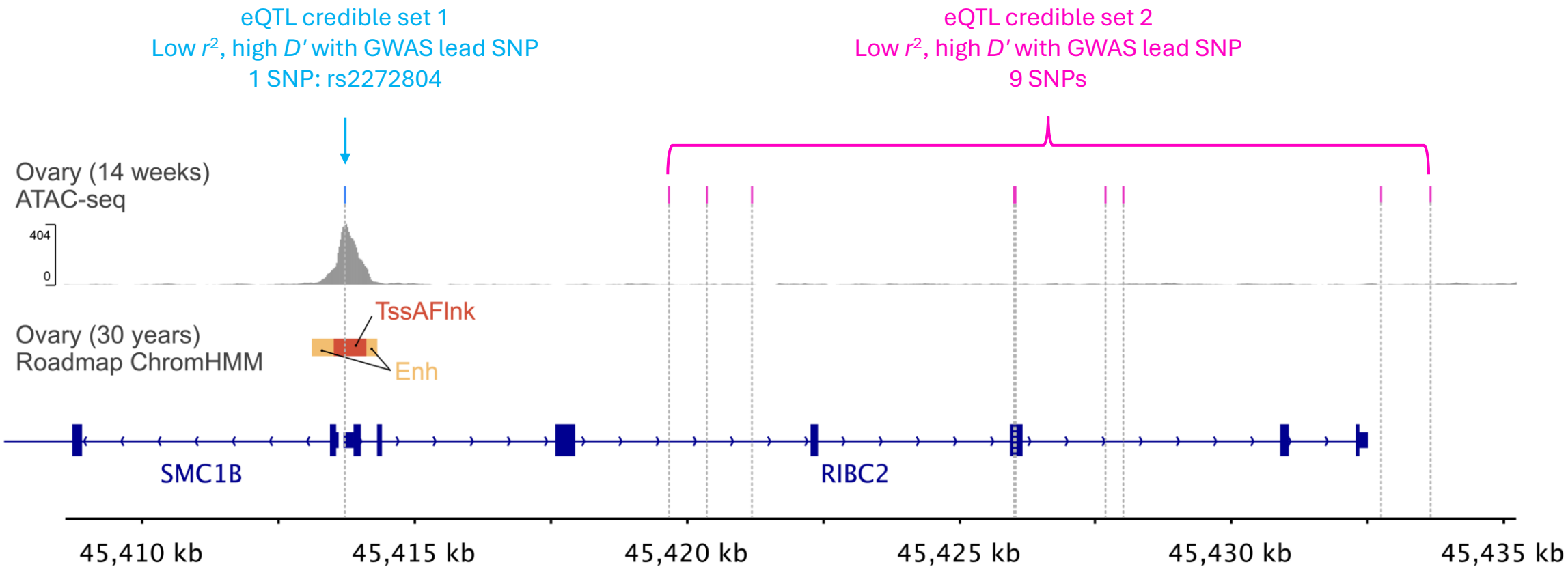




Taylor et al. (2024). *Nature*, 632, 122-130.

Evidence of a non-coding *cis*-regulatory mechanism mediating the aneuploidy association



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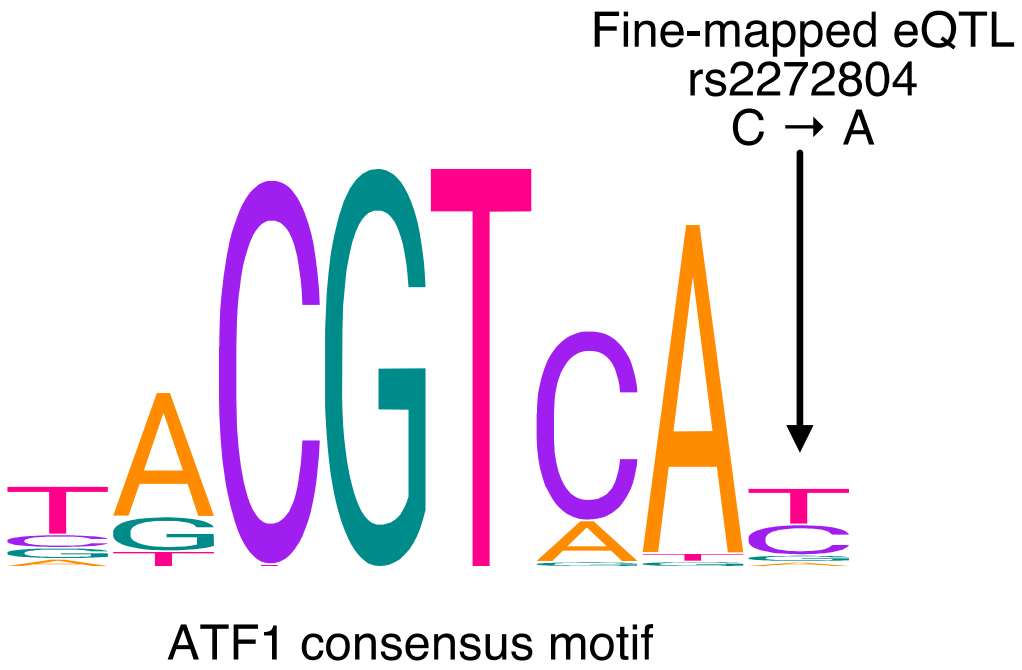

ATF1 consensus motif

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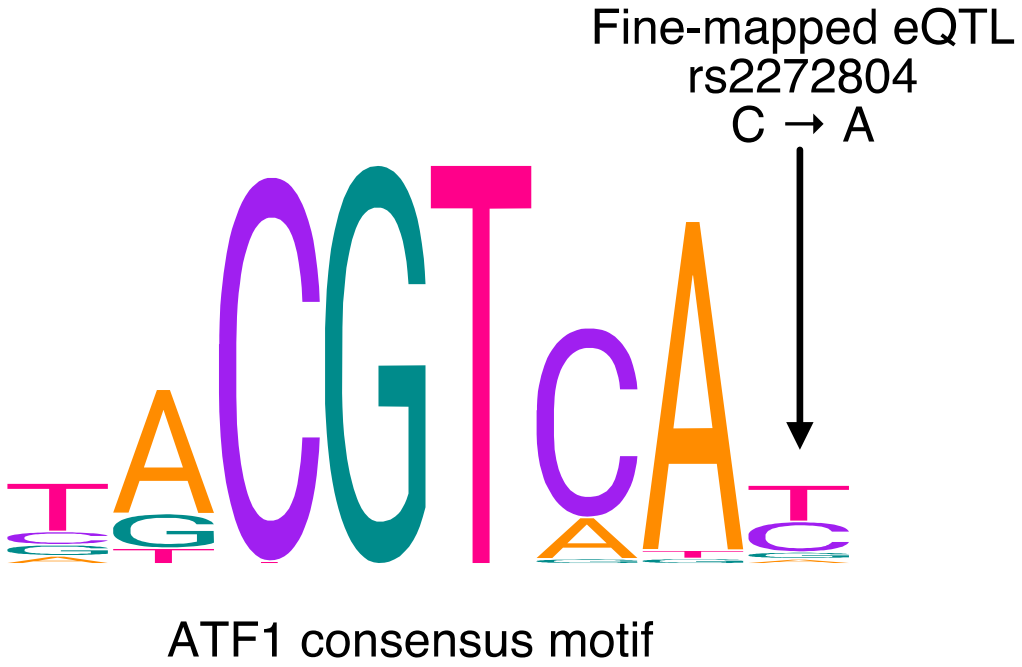

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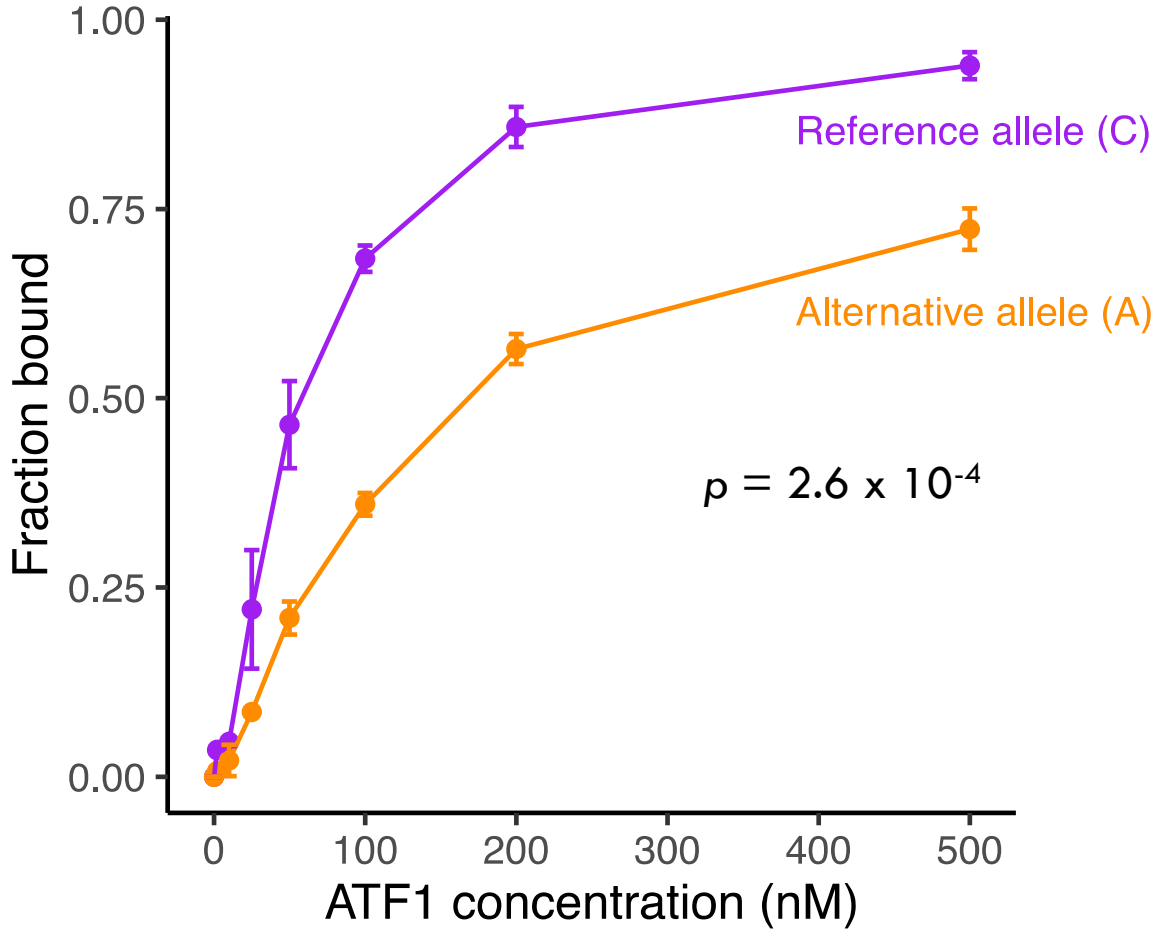
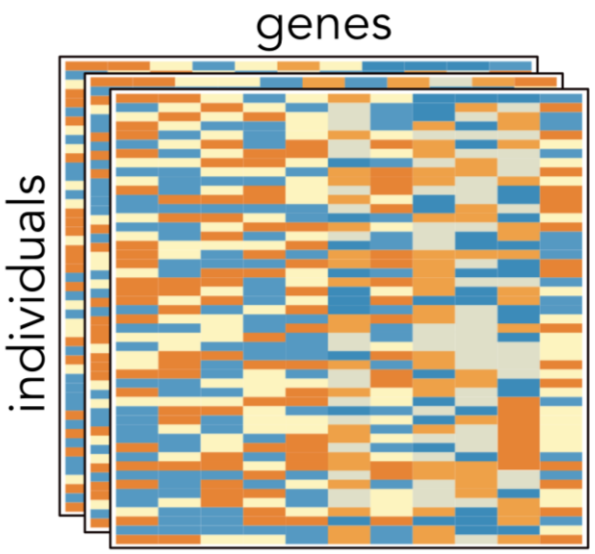


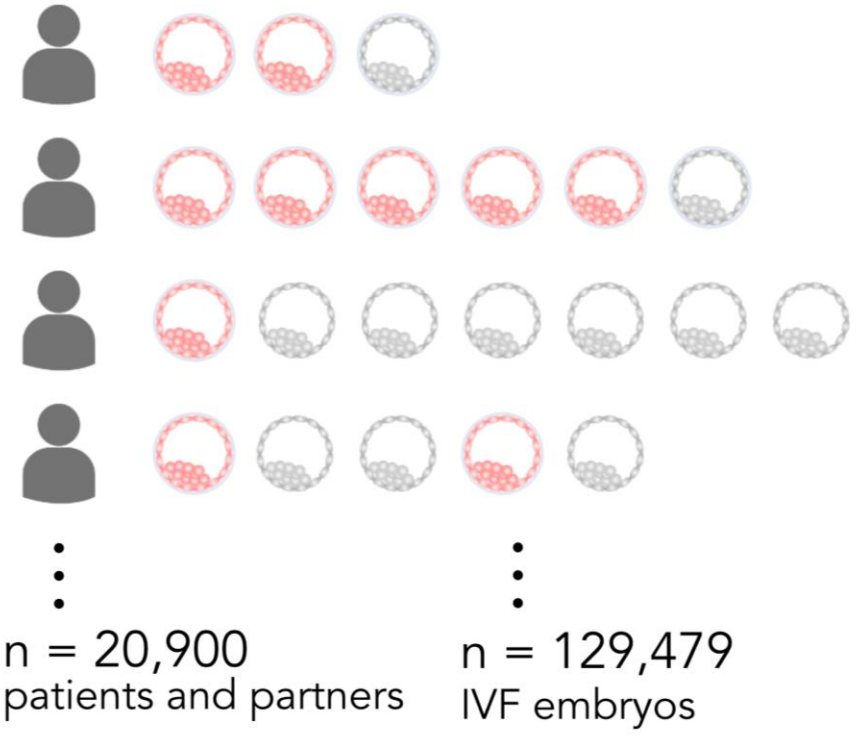
Transcriptome-wide association study (TWAS) of aneuploidy risk

Genetic predictions of gene expression



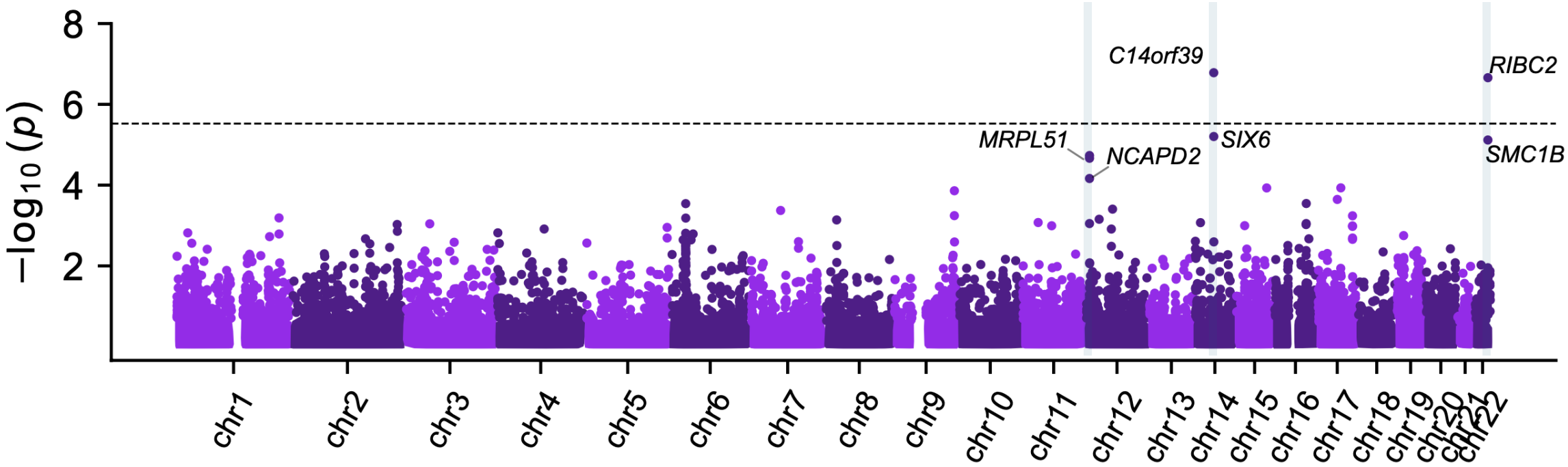
Test association

Measured aneuploidy phenotype



Gamazon et al. (2015). *Nat. Genet.*, 50, 956-967.
GTEx Consortium (2020). *Science*, 369, 1318-1330.
Barbeira et al. (2021). *Genome Biol.*, 22, 1-24.

Predicted expression of other key meiotic components is further associated with aneuploidy risk



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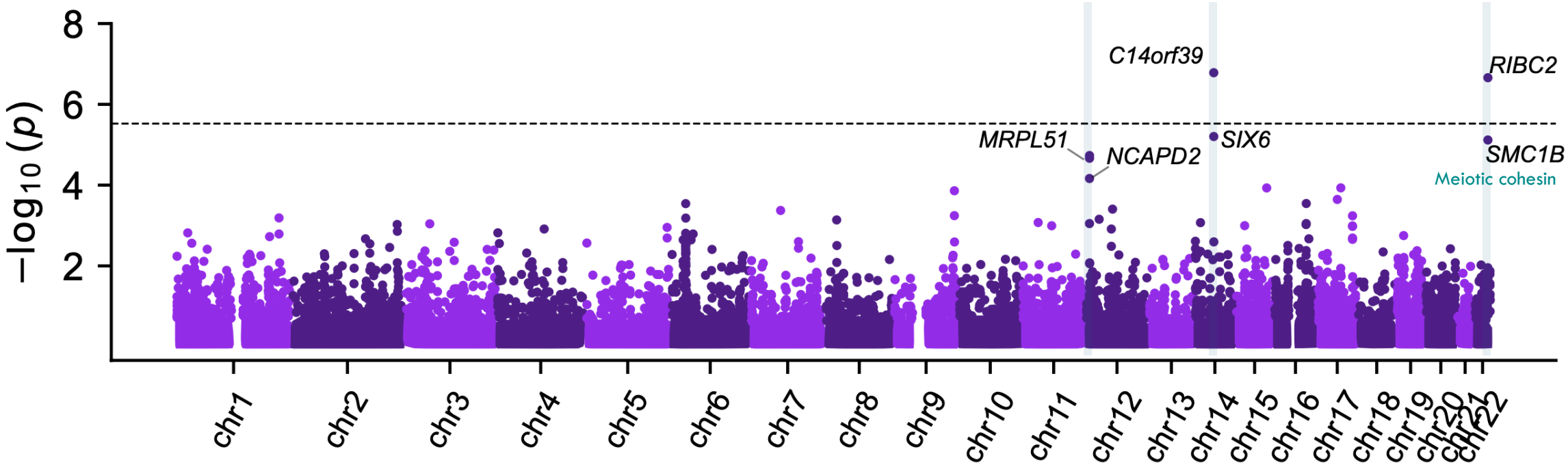

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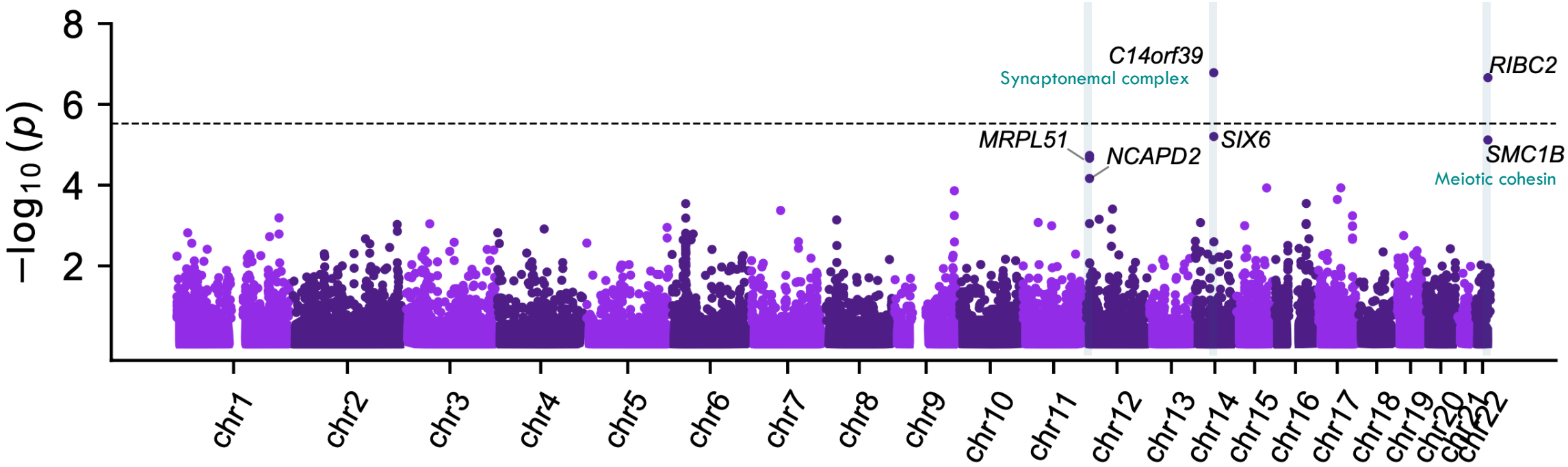

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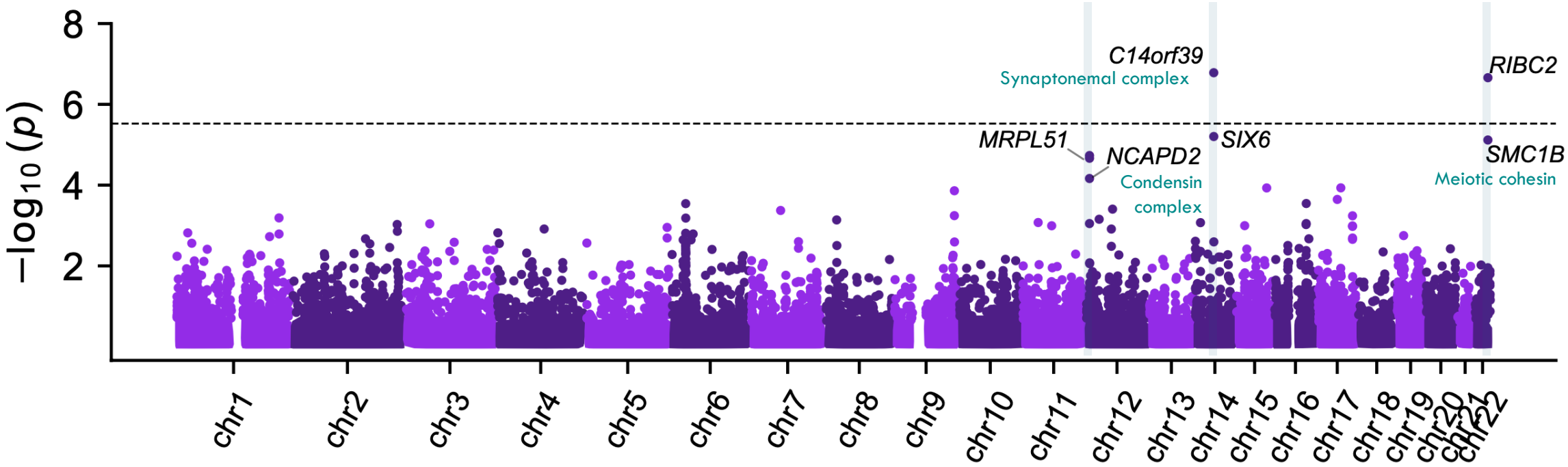
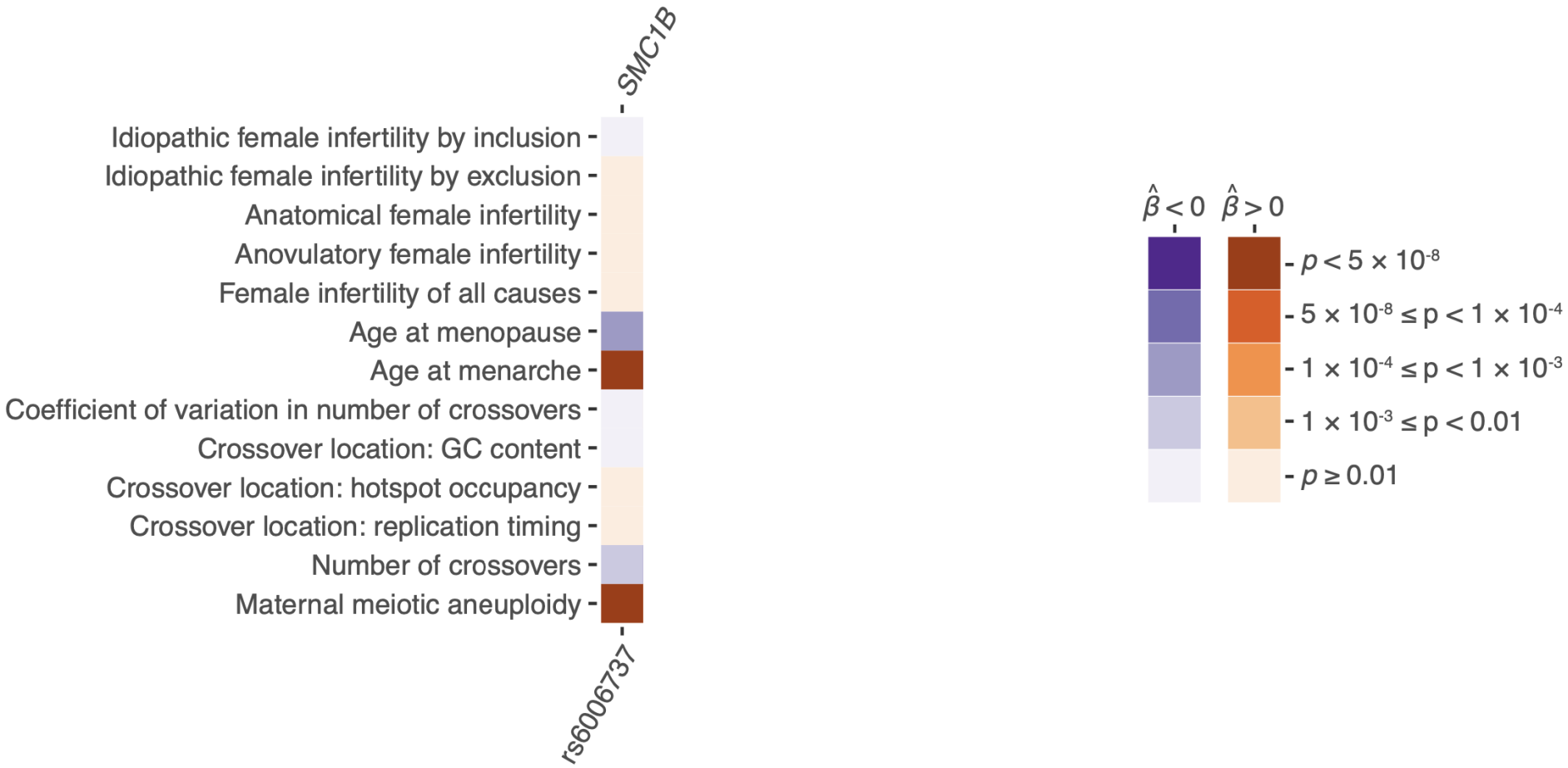


A shared genetic basis of recombination, aneuploidy, and reproductive aging



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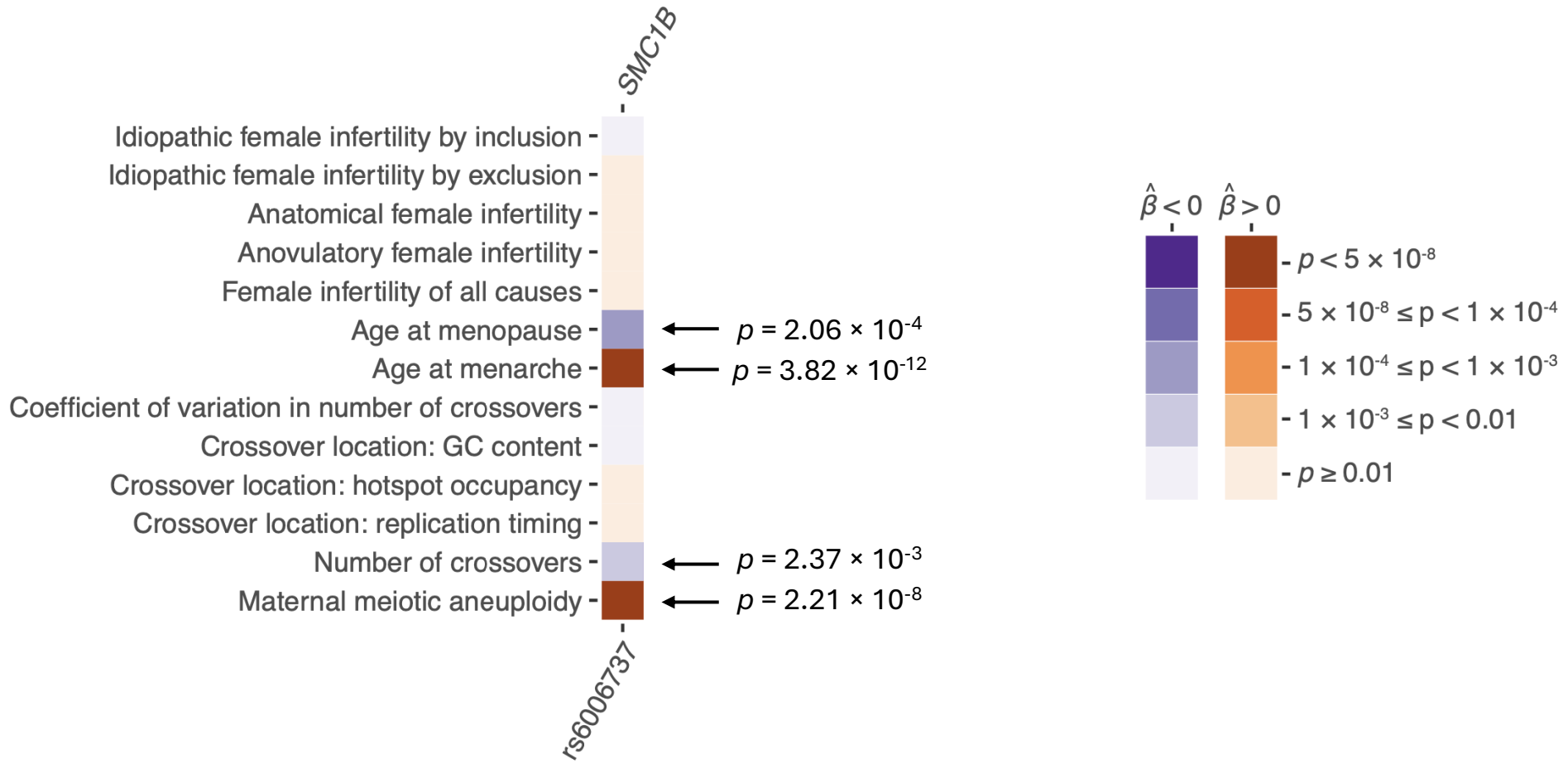

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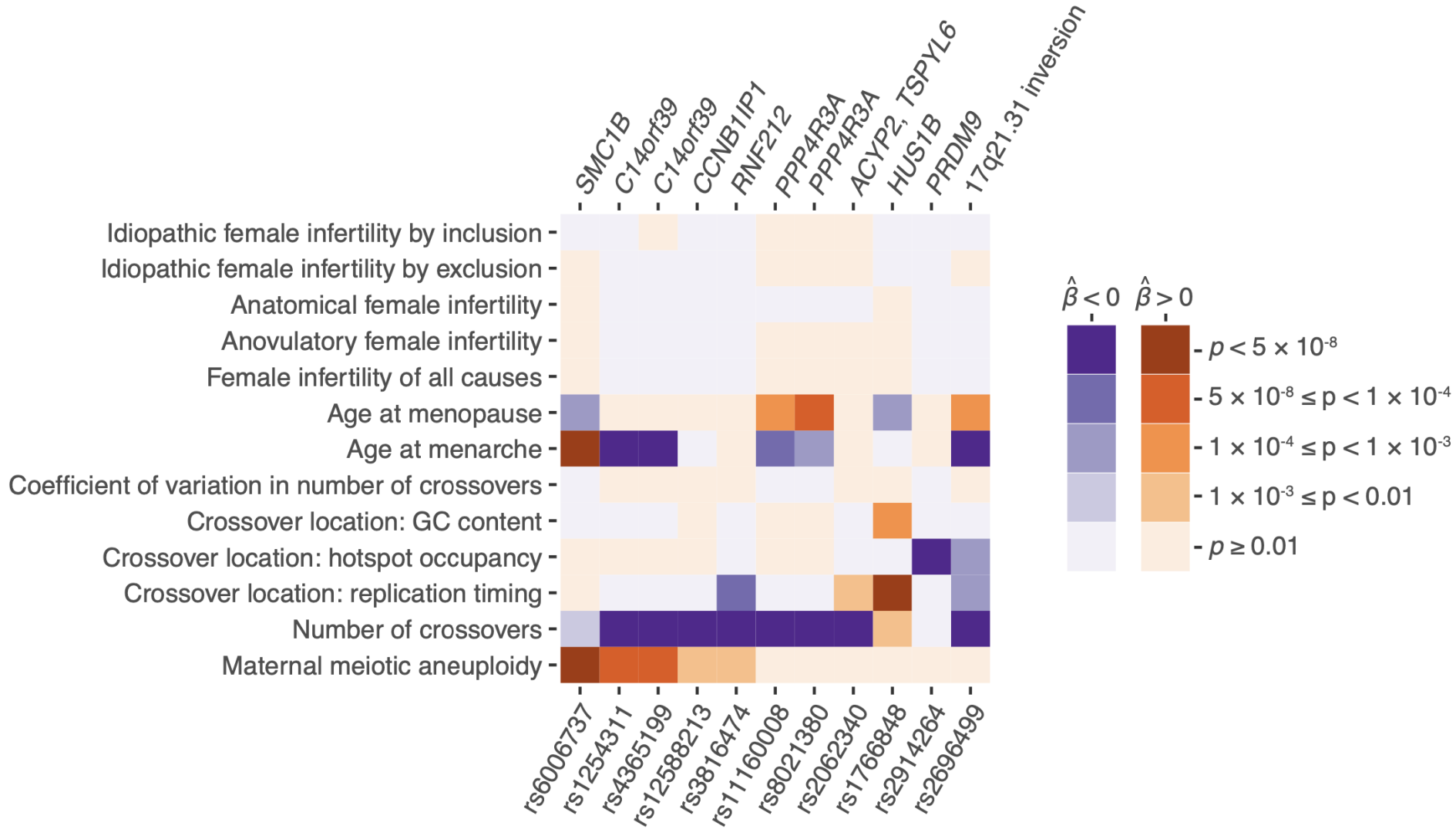

Conclusions

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- These include a haplotype spanning the meiotic cohesin component *SMC1B*, with evidence of a non-coding *cis*-regulatory mechanism driving the effect.

Conclusions

- Common genetic variation in meiotic machinery is associated with variation in number and location of crossovers, as well as maternal-origin aneuploidy.

- These include a haplotype spanning the meiotic cohesin component *SMC1B*, with evidence of a non-coding *cis*-regulatory mechanism driving the effect.

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- Our findings highlight the dual role of meiotic recombination in generating genetic diversity, while ensuring accuracy of chromosome segregation.

Common variation in meiosis genes shapes human recombination phenotypes and aneuploidy risk

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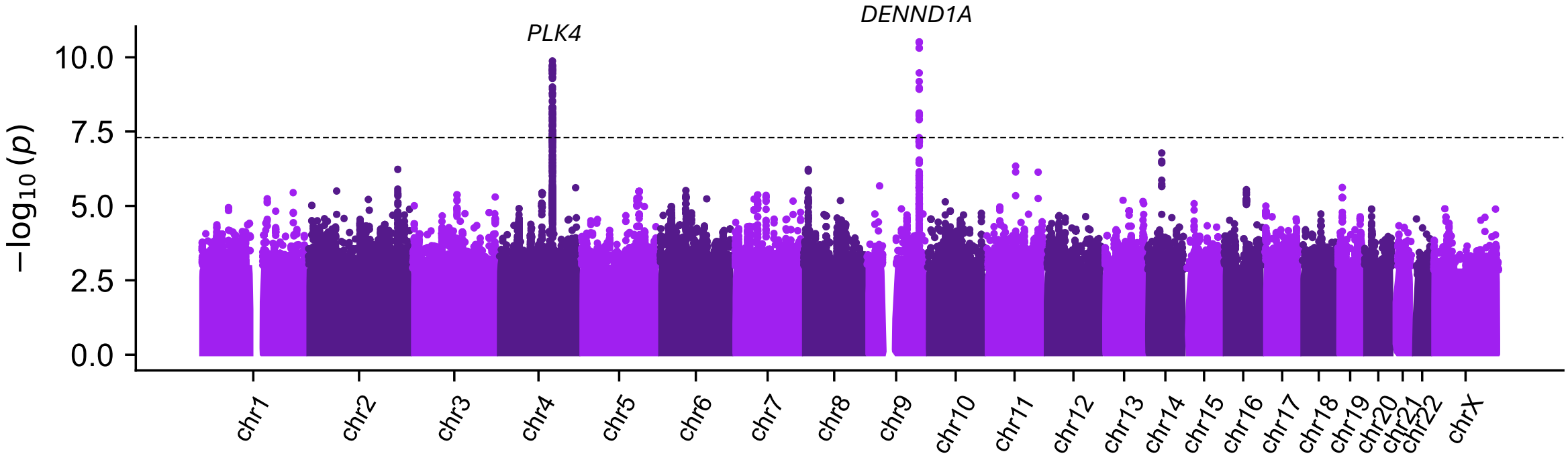
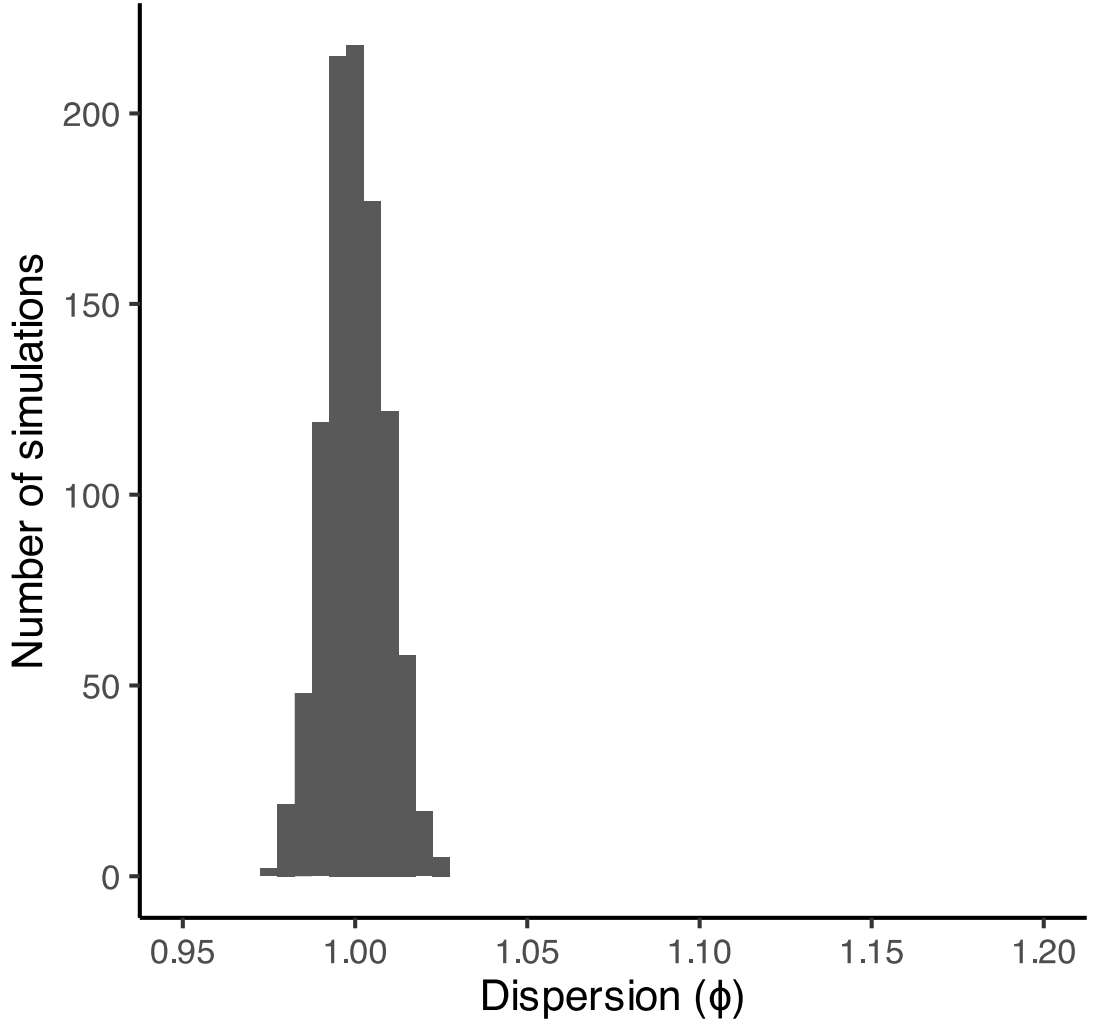
Genome-wide association study of number of blastocysts tested



Patients exhibit individual-specific variance in aneuploidy beyond maternal age



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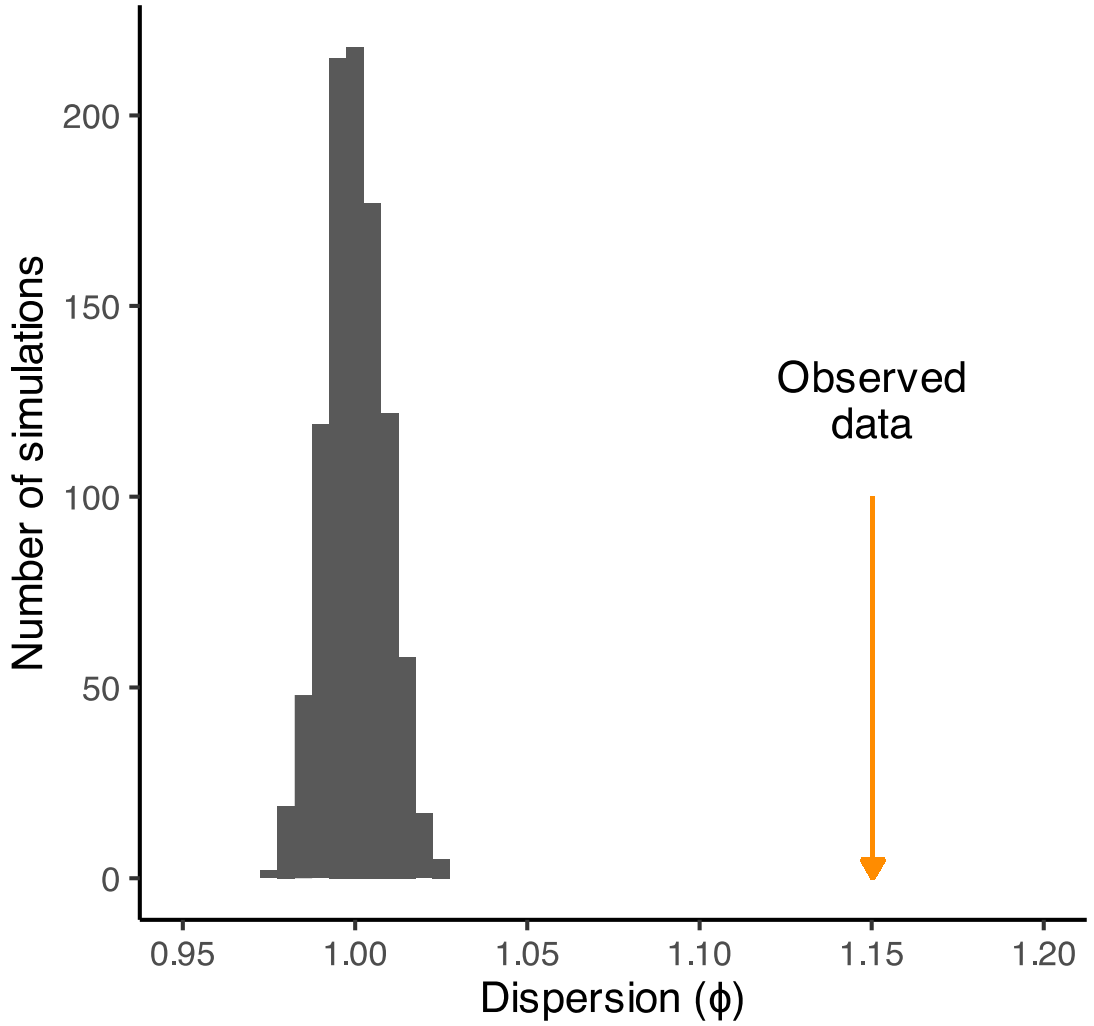
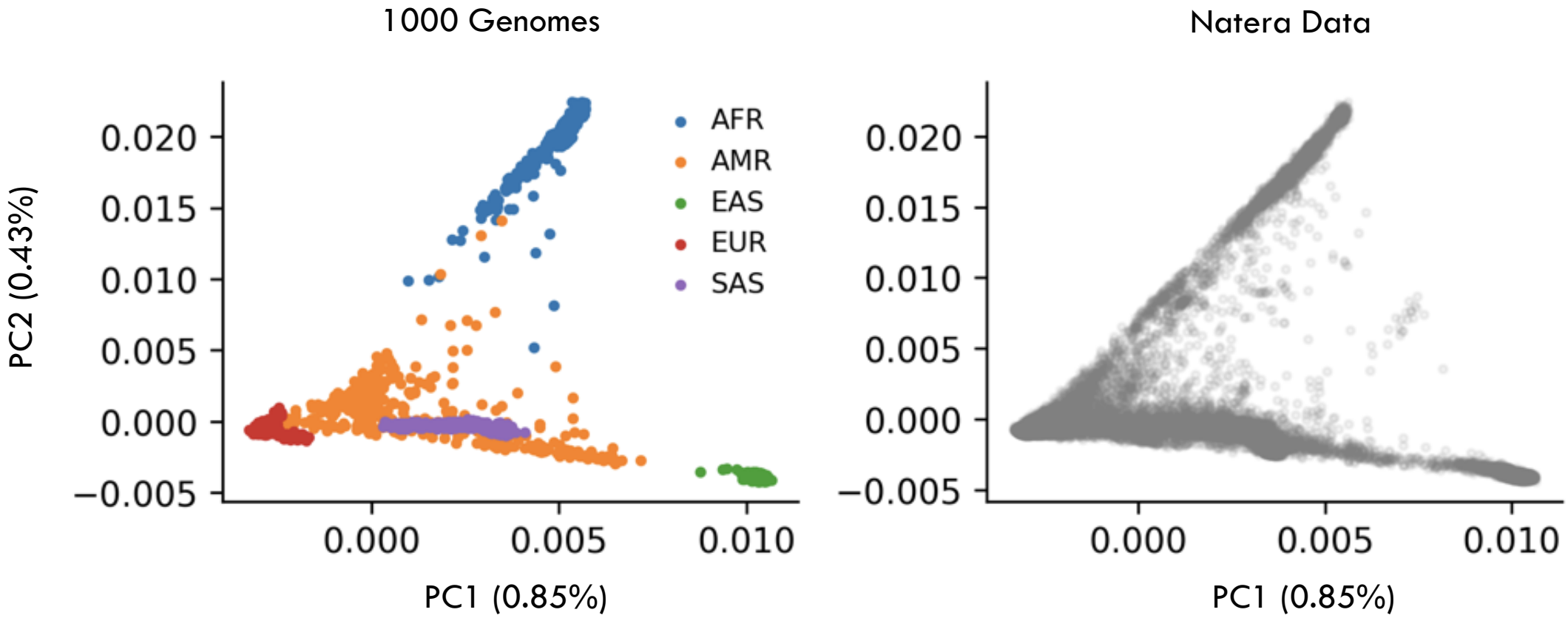


Ancestry of parental samples in the Natera dataset



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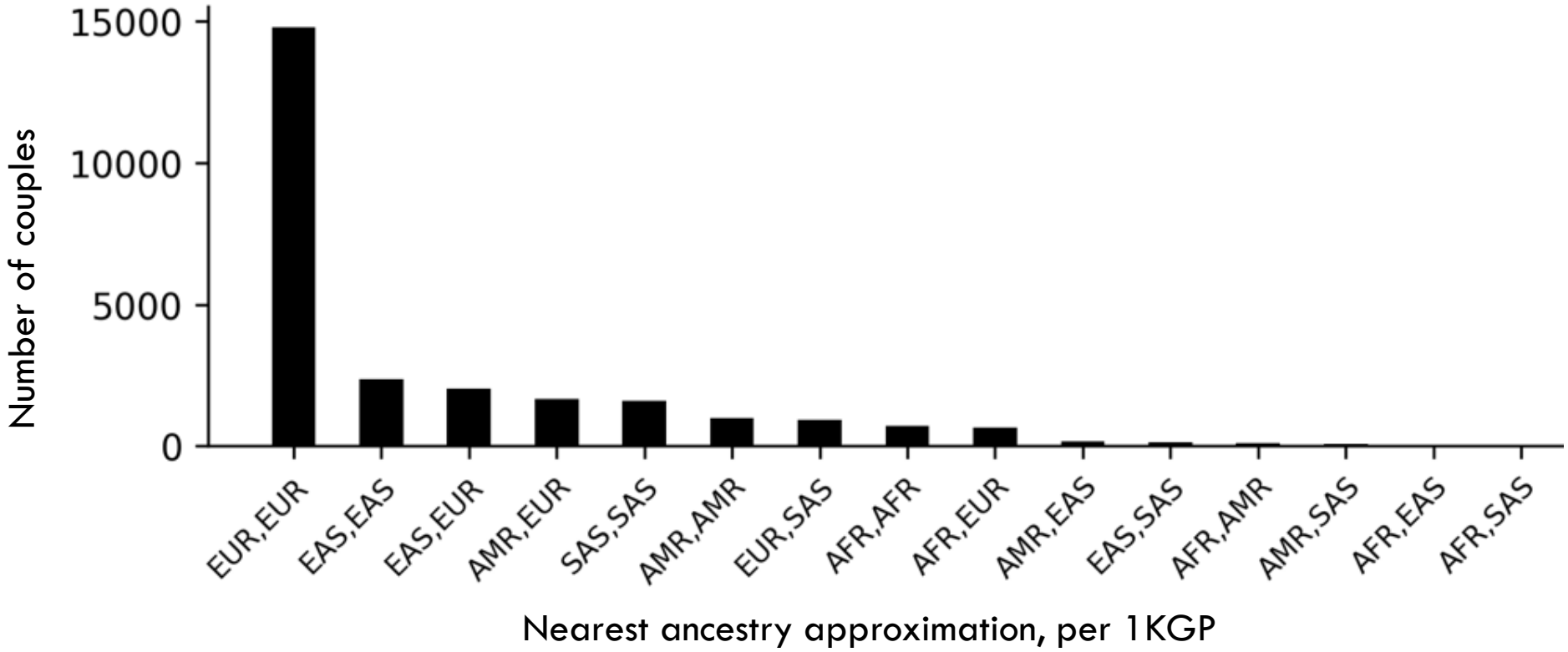
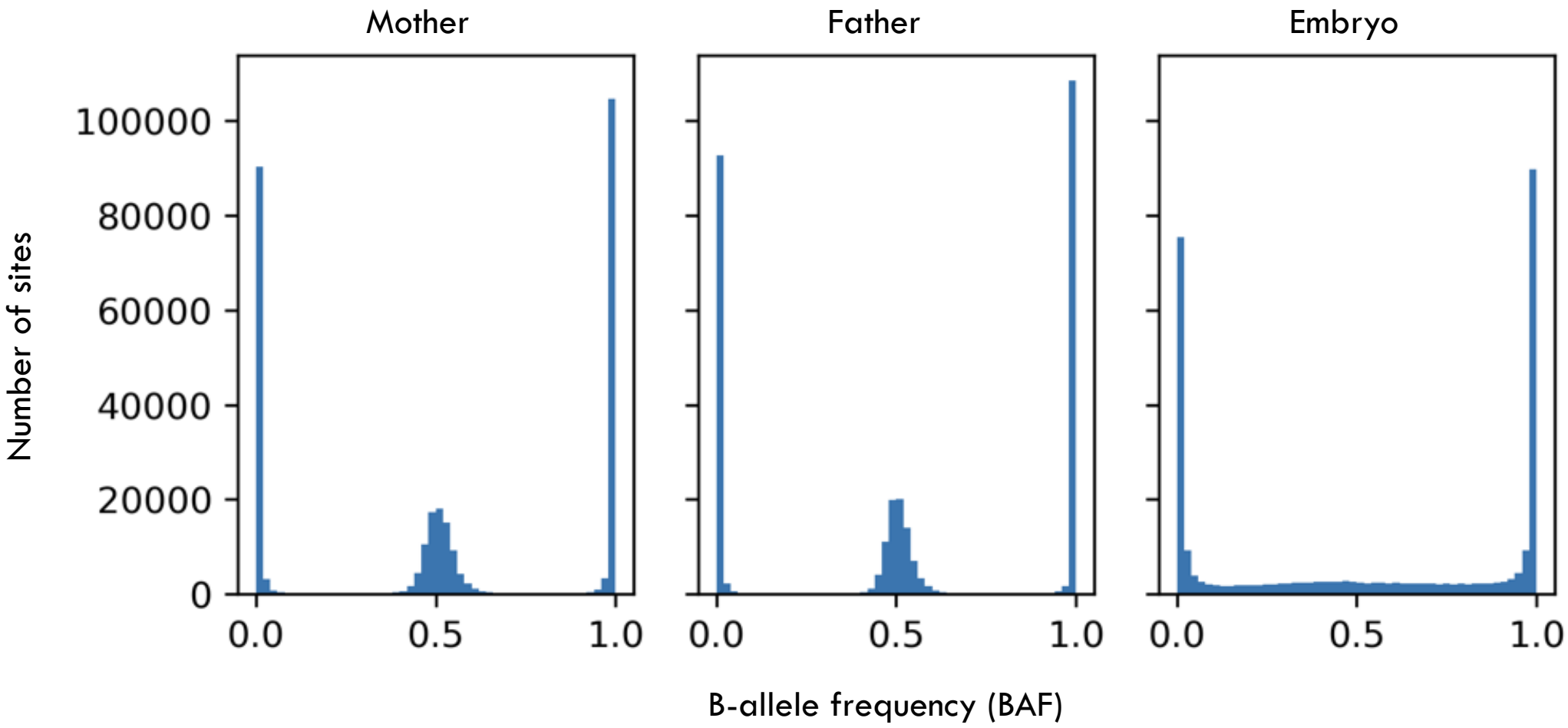
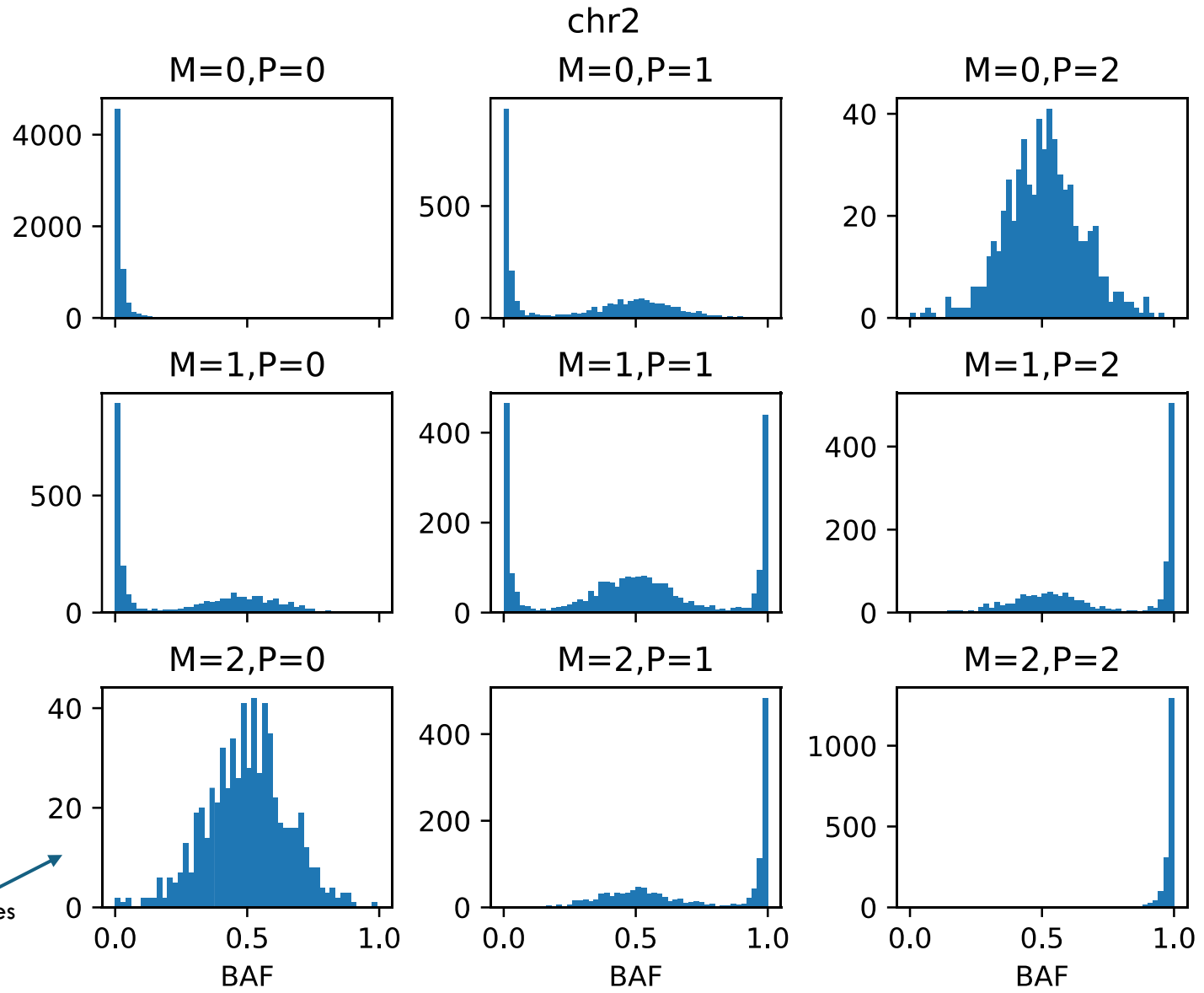


Noisy embryo samples cannot be genotyped directly

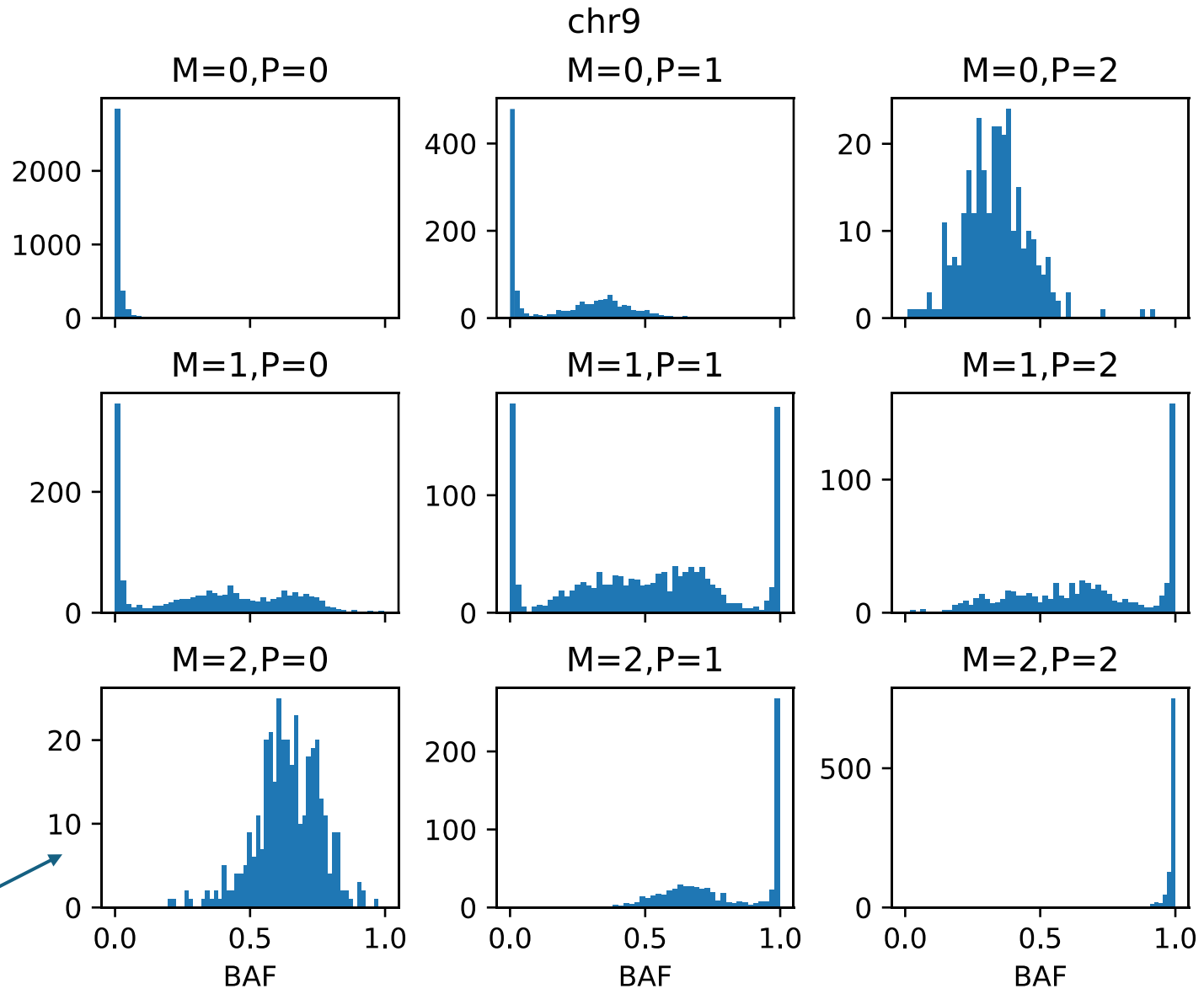


Conditioning on the parental genotypes to model embryo allele intensity



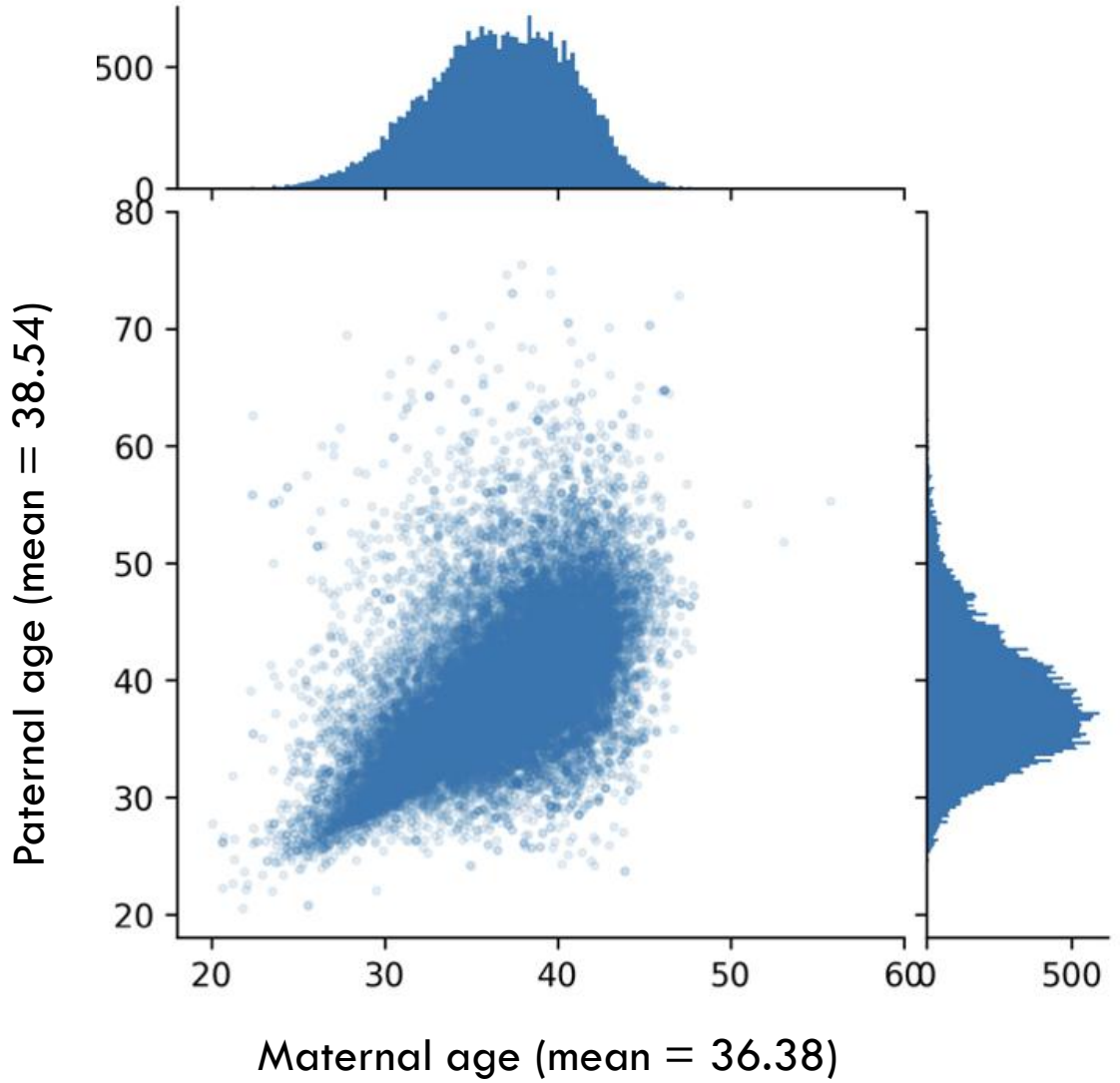
Opposite parental homozygotes are informative

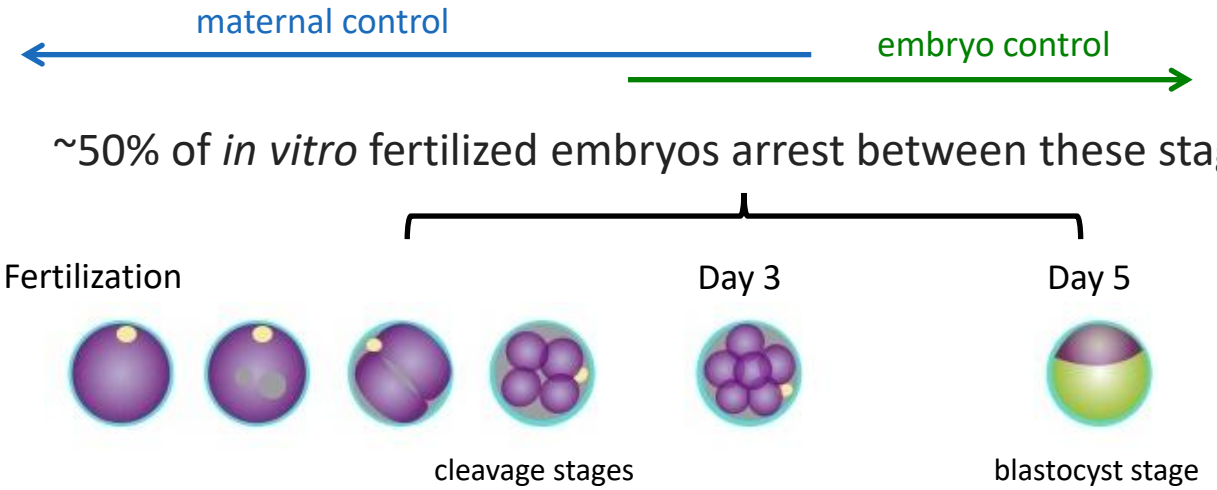
Conditioning on the parental genotypes to model embryo allele intensity

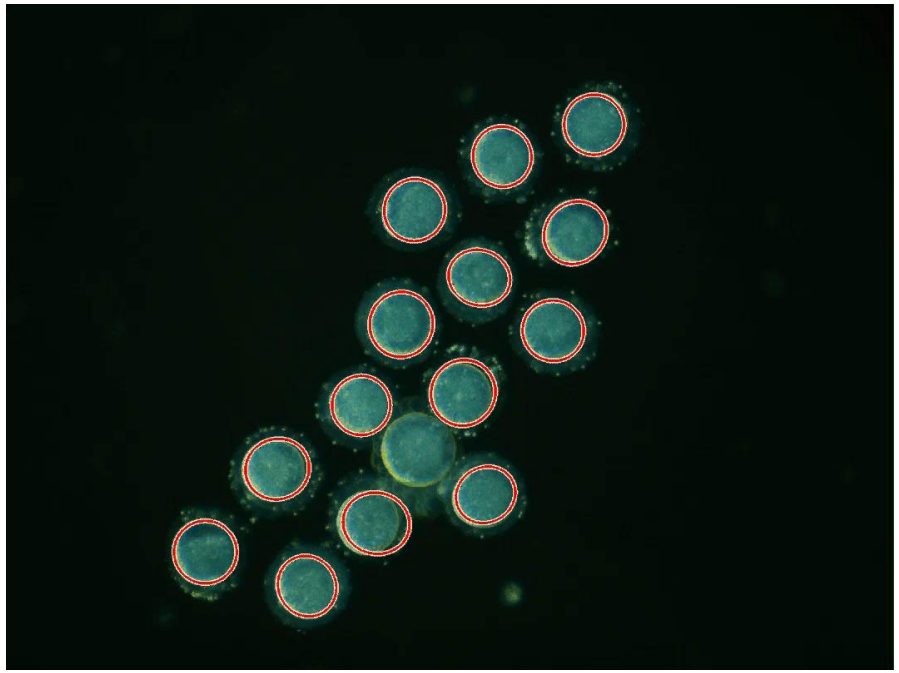


The intensity shifts closer to 2/3 for a trisomy

Age distribution of patient and partner population reflects ascertainment

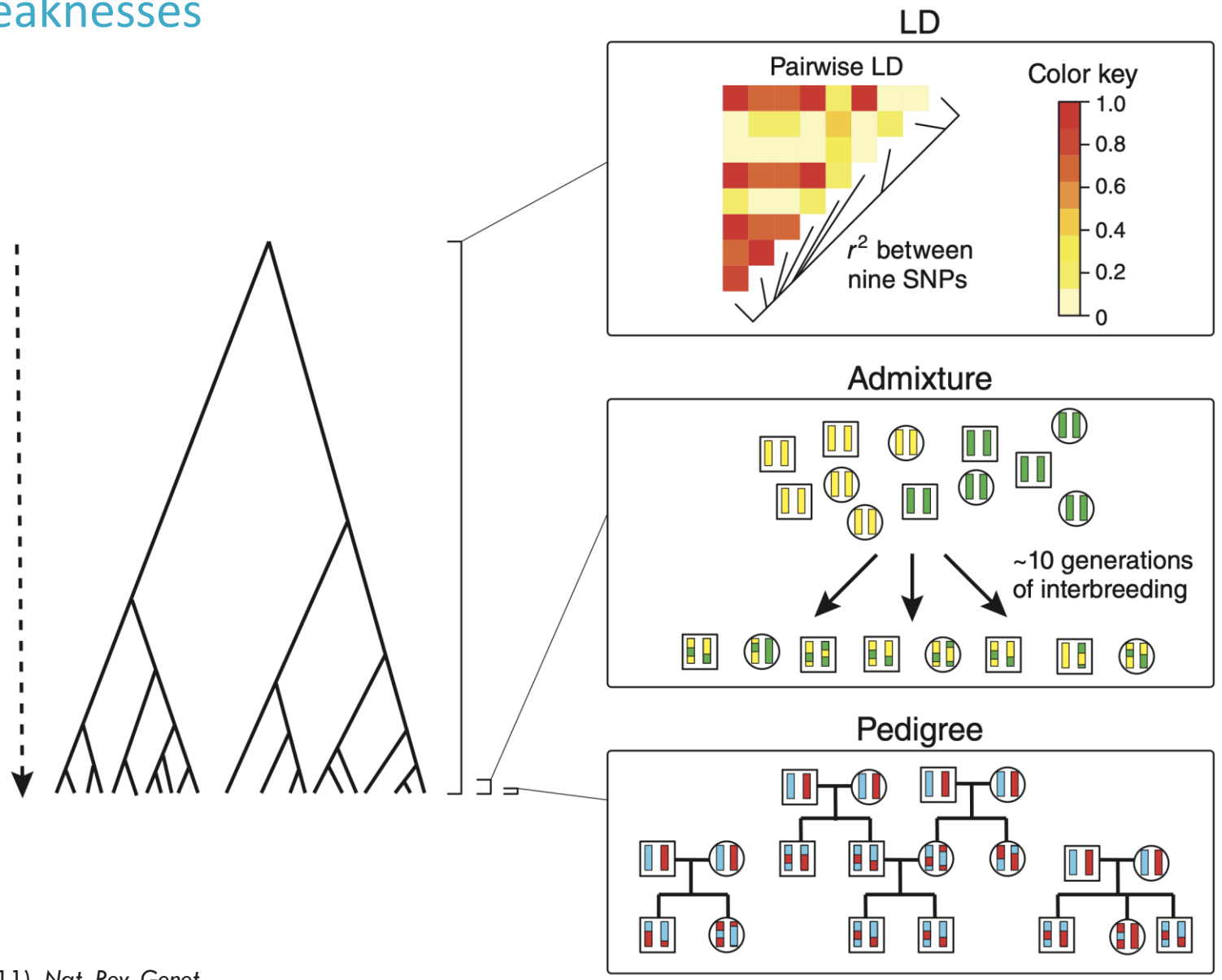






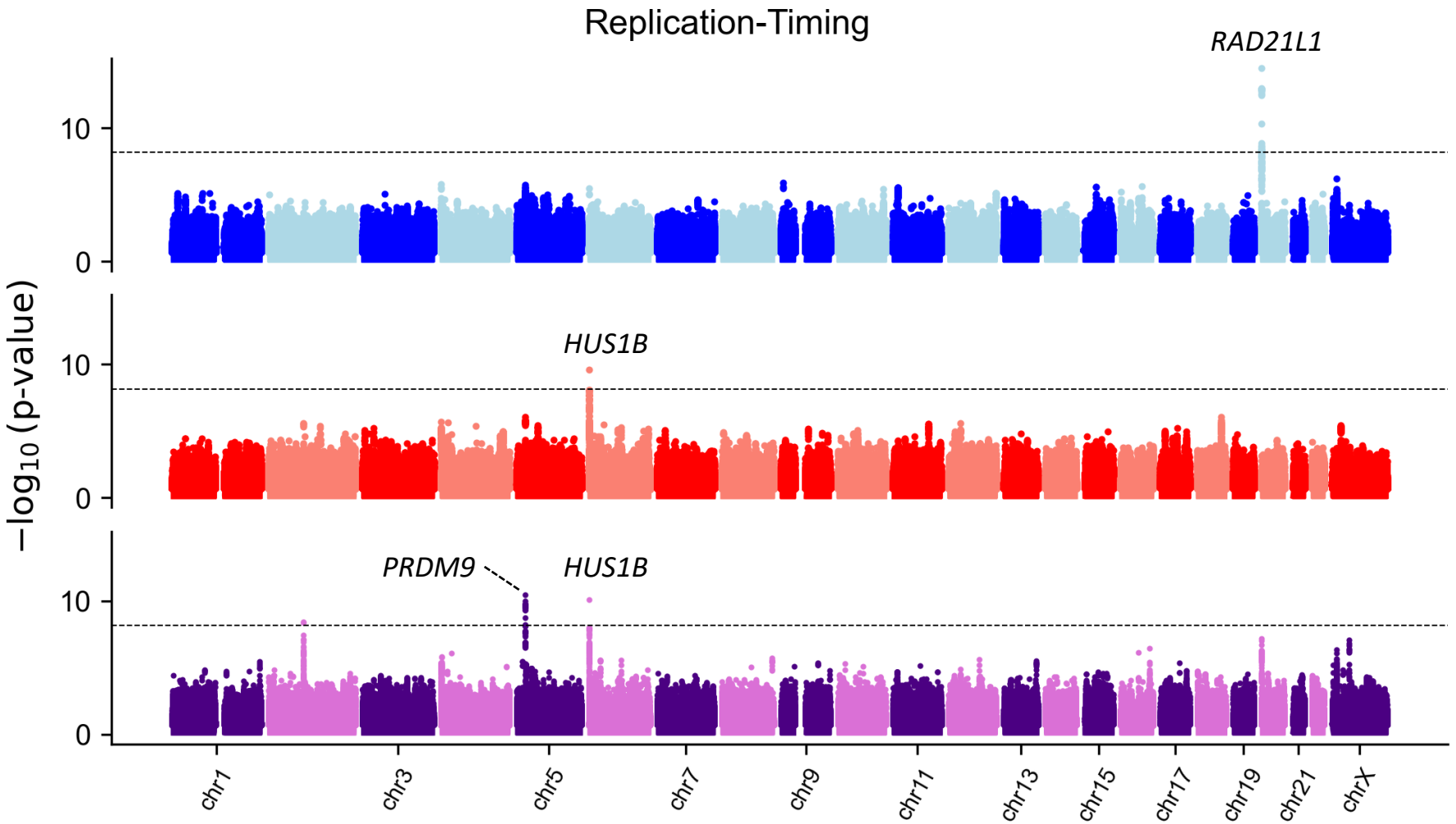
Wong et al. (2010). *Nature Biotechnology*, *28*, 1115–1121.

Alternative approaches for mapping crossovers possess unique strengths and weaknesses



Adapted from O'Reilly & Balding. (2011). *Nat. Rev. Genet.*

Common variation in meiosis genes drives variation in crossover phenotypes



What causes the high rates of IVF embryo loss?

Test embryos regardless of survival or morphological grade

n = 1232 total 2PN embryos

n = 622 blastocysts (50.5%)

n = 610 arrested (49.5%)

n = 909 tested with PGT-A

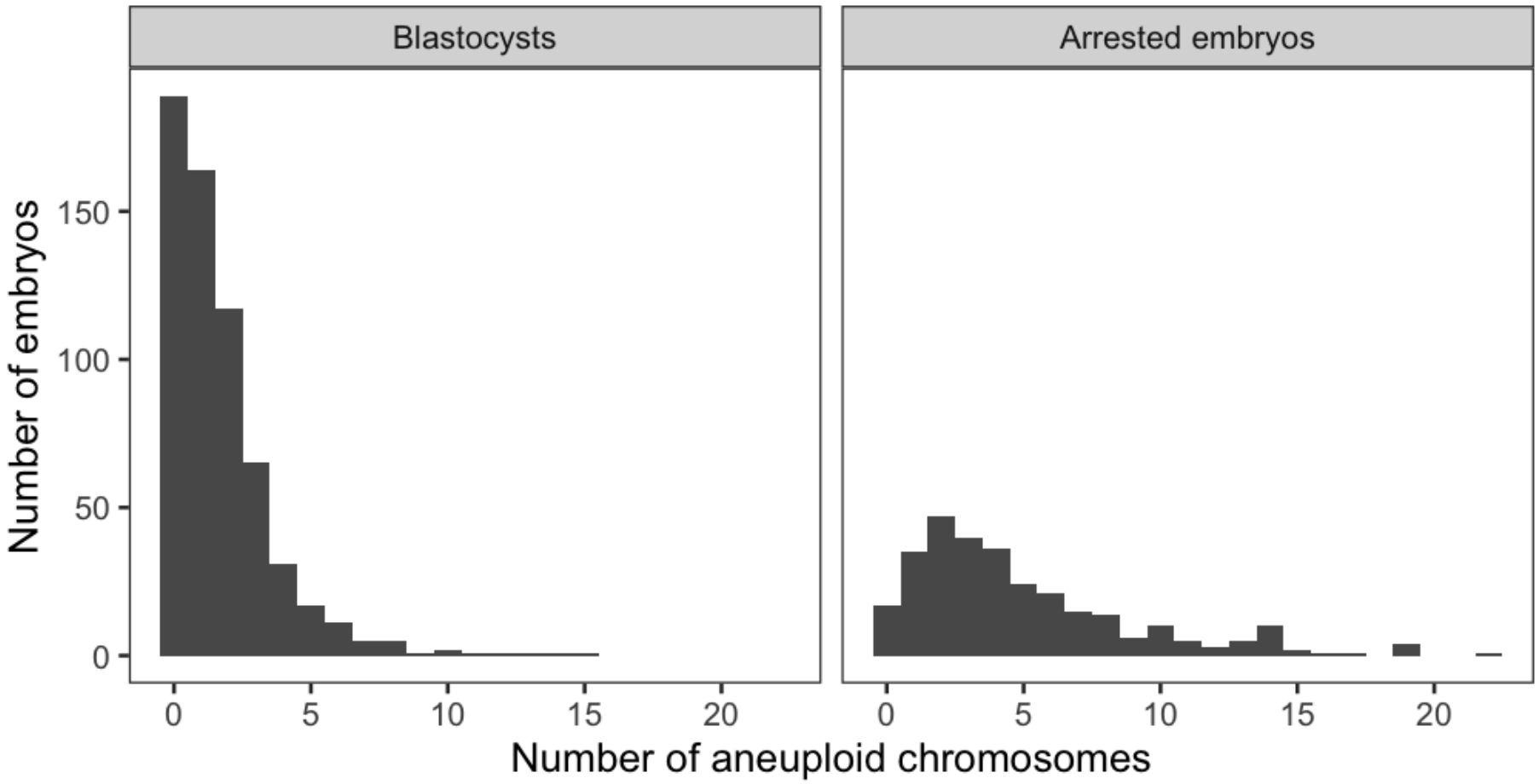
n = 843 tested with time-lapse

Alan Handyside
University of Kent

Michael Summers
London Women's Clinic

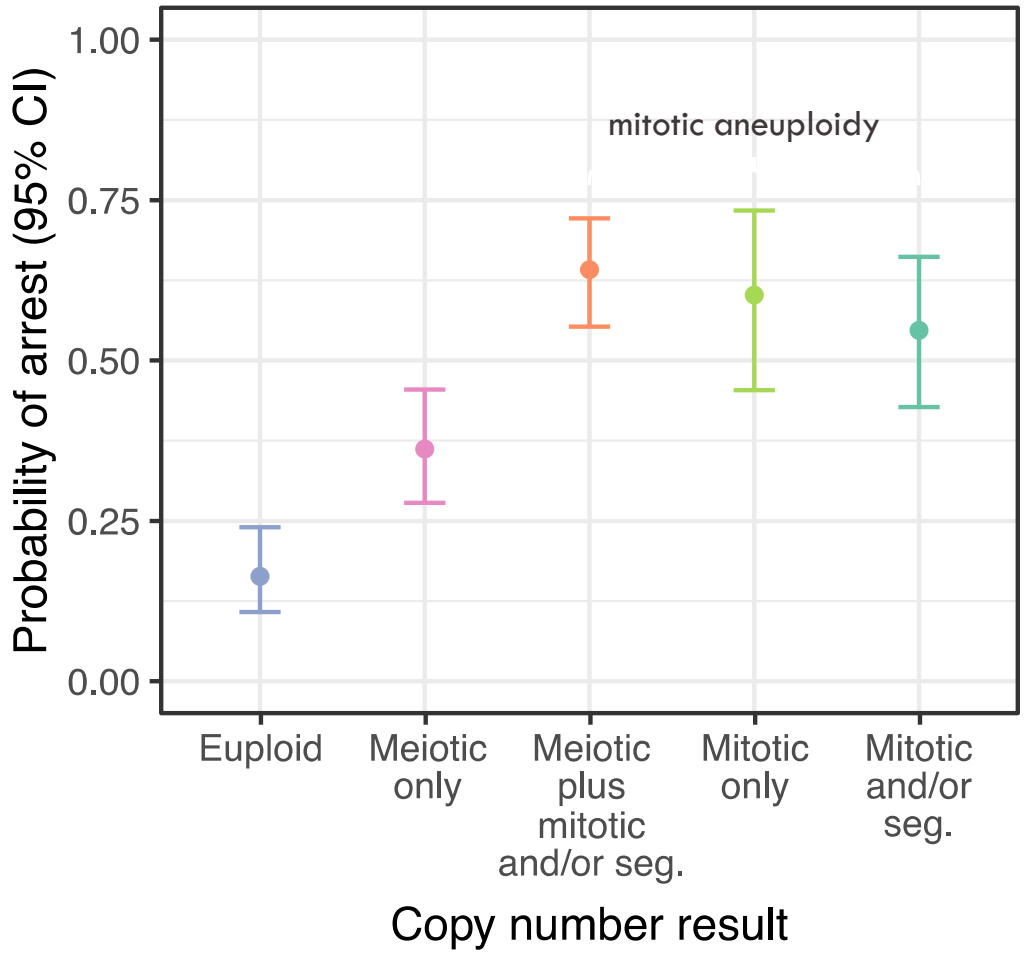
Christian Ottolini
Juno Genetics

Arrested embryos are enriched for aneuploidy affecting multiple chromosomes



McCoy, R. C. et al. (2023). *Genome Med.*, 15: 77.

Estimating the probability of arrest conditional on aneuploidy status



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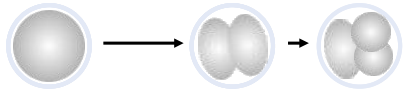
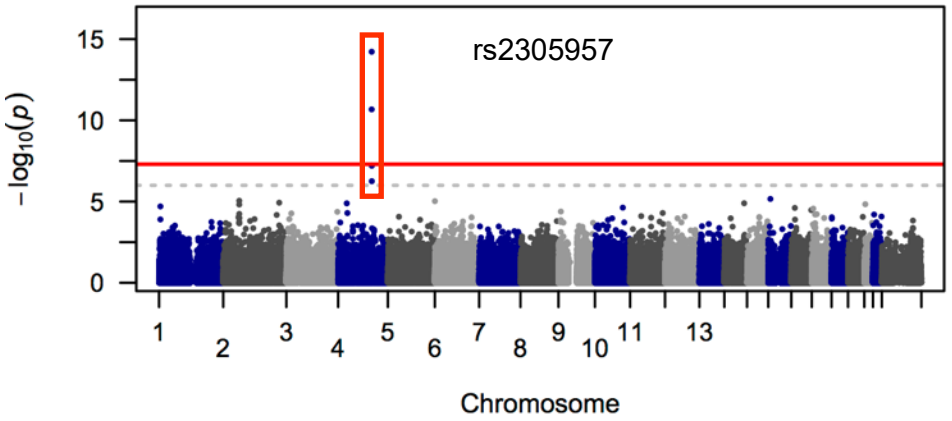
Abnormal cell divisions drive lethal complex mitotic aneuploidies

	Incidence	Mitotic Aneuploidy	Prob. Arrest
Normal 	64.0%	37.3%	24.9%
Precocious 	24.2%	66.1%	77.2%
Reverse 	0.6%	100%	100%
Multipolar 	9.4%	80.7%	80.1%
Failed 	5.3%	62.5%	77.5%

McCoy, R. C. et al. (2023). *Genome Med.*, 15: 77.

Maternal effect quantitative trait locus is associated with mitotic aneuploidy

MATERNAL GENOTYPE



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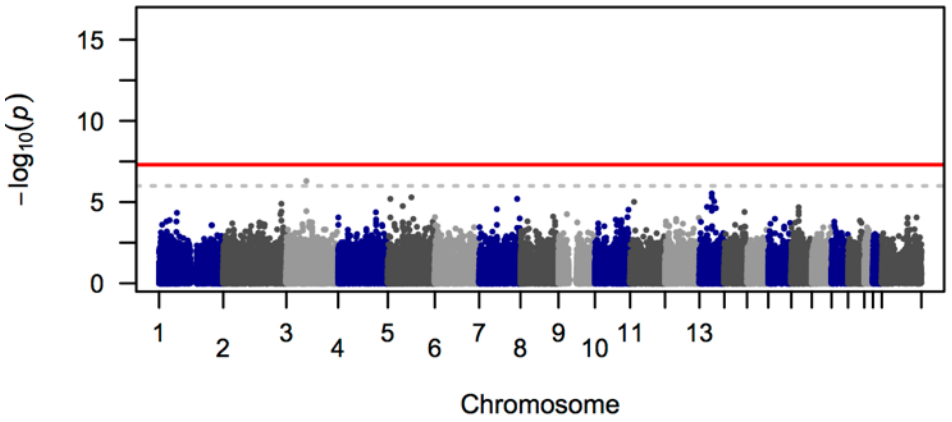
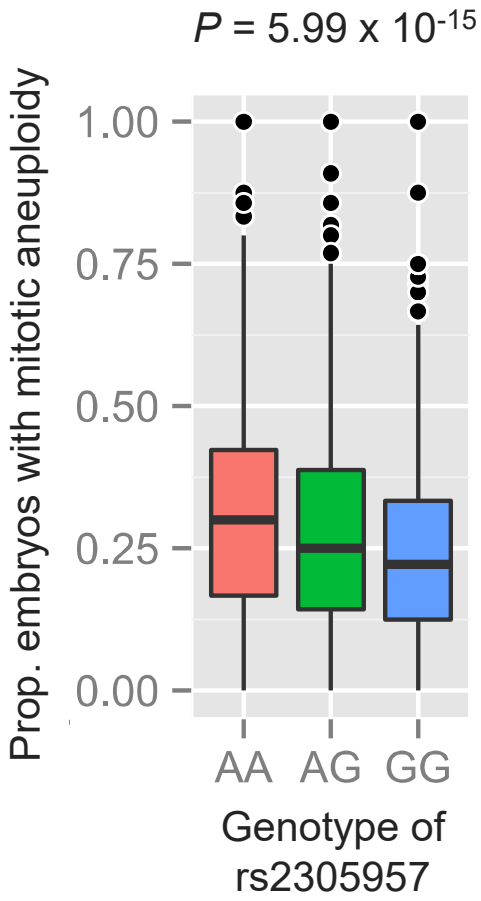
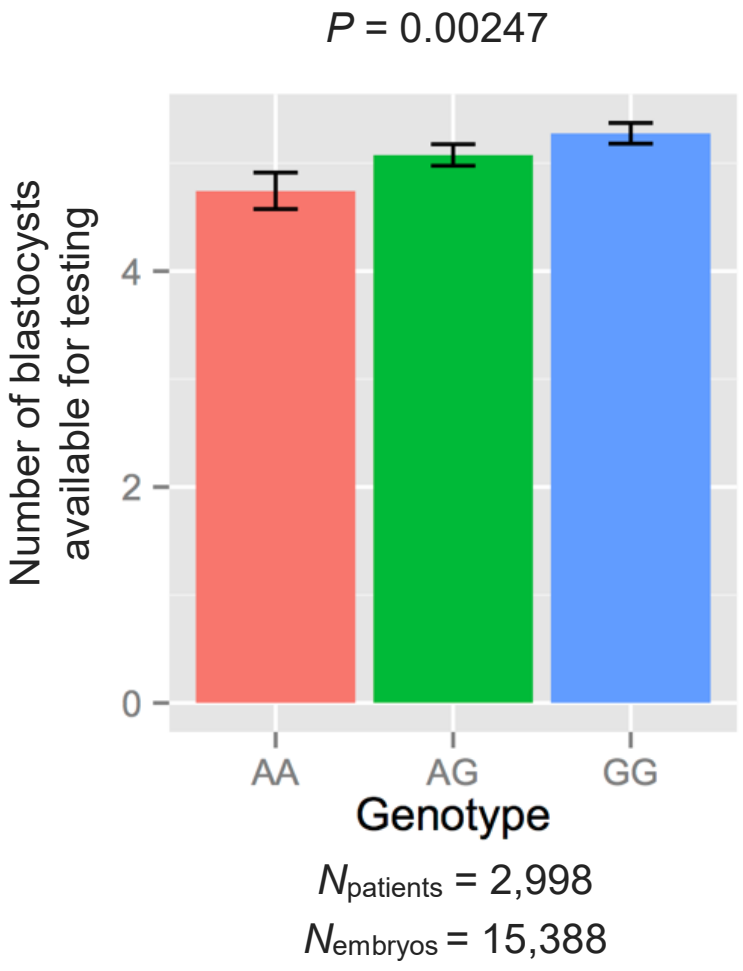


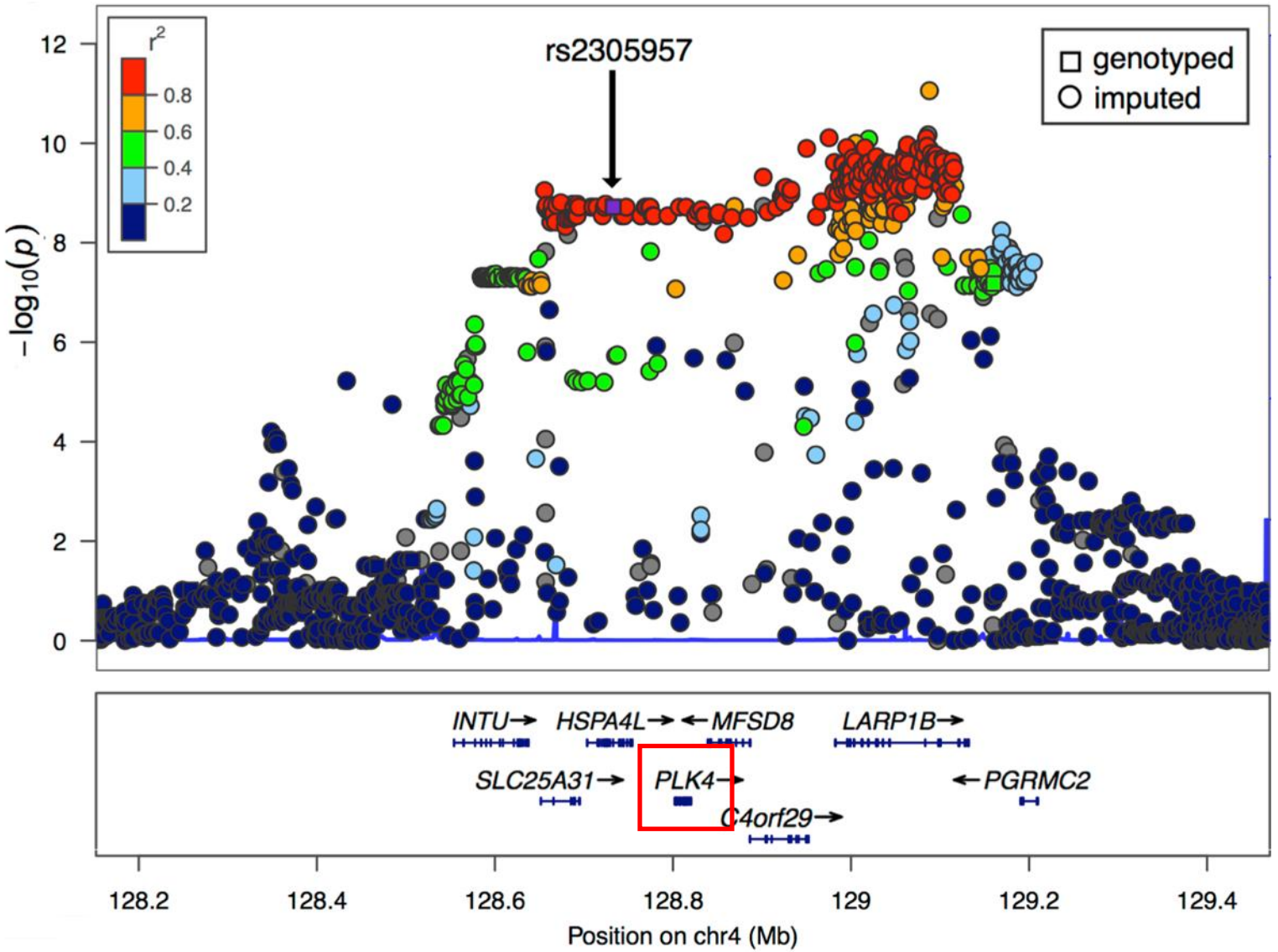




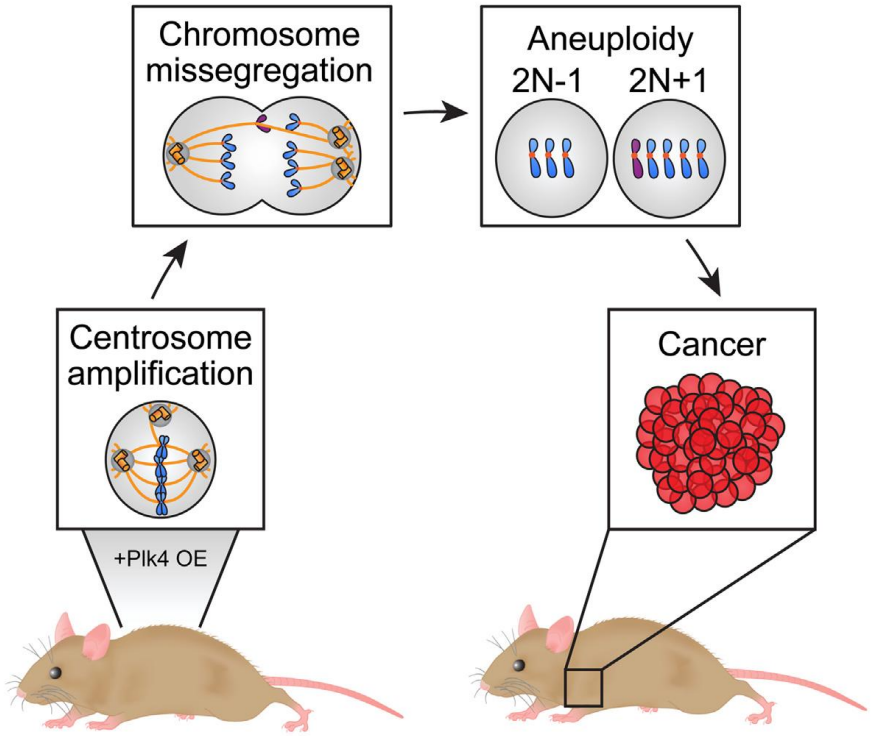
$N_{patients}$ = 2,998

$N_{embryos}$ = 15,388

Associated haplotype spans the mitotic regulator *PLK4*



Patterns of chromosome loss are suggestive of tripolar mitosis



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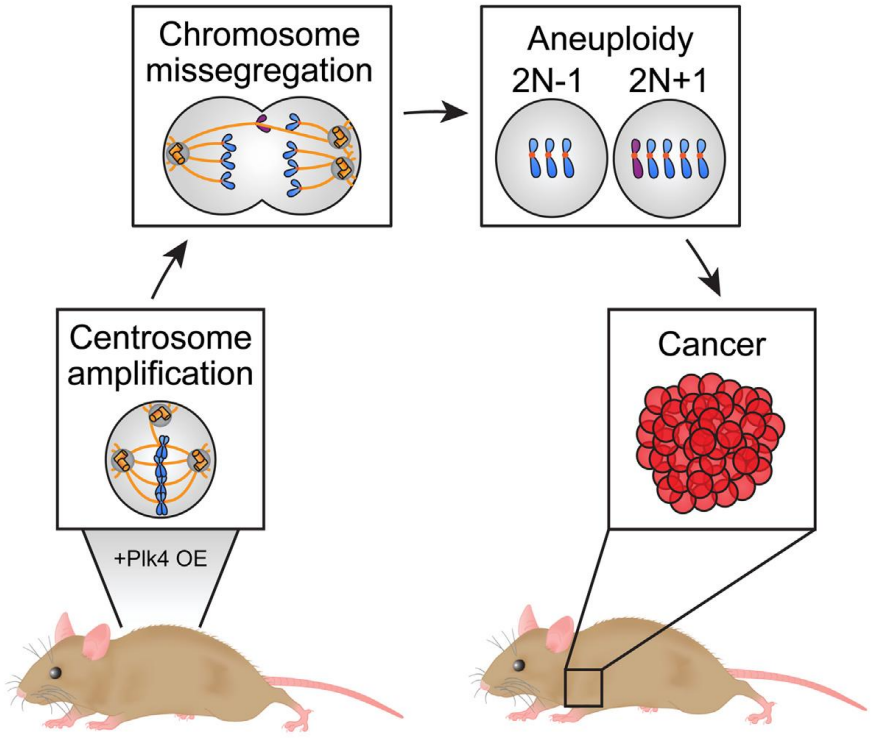

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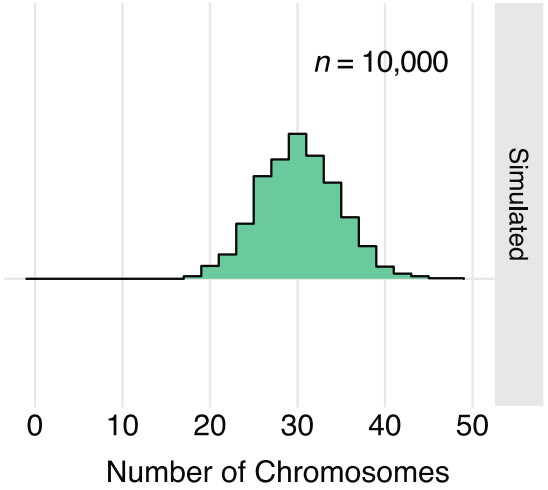

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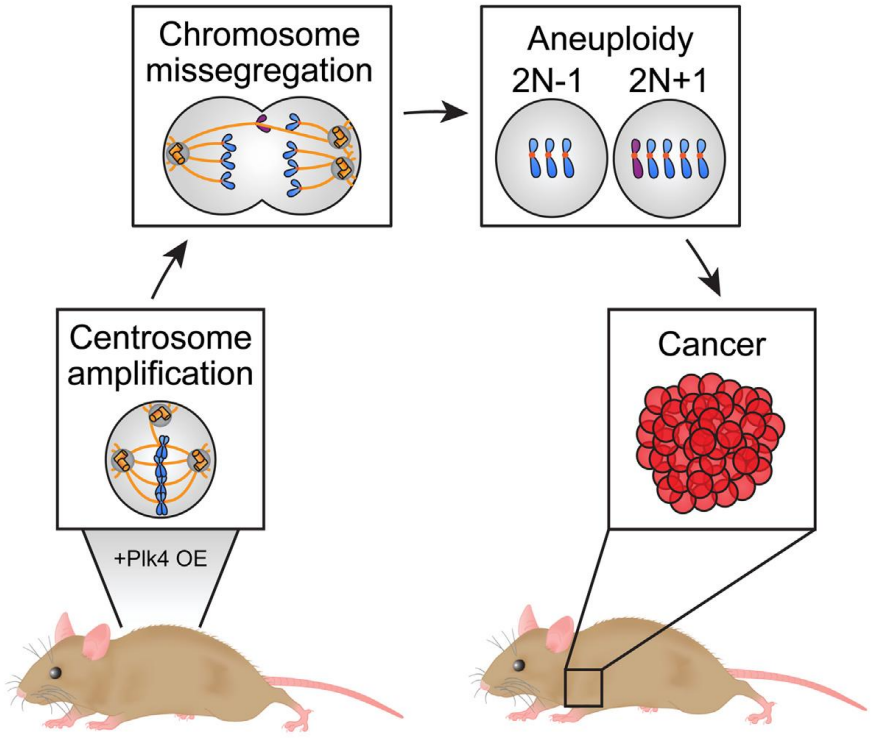

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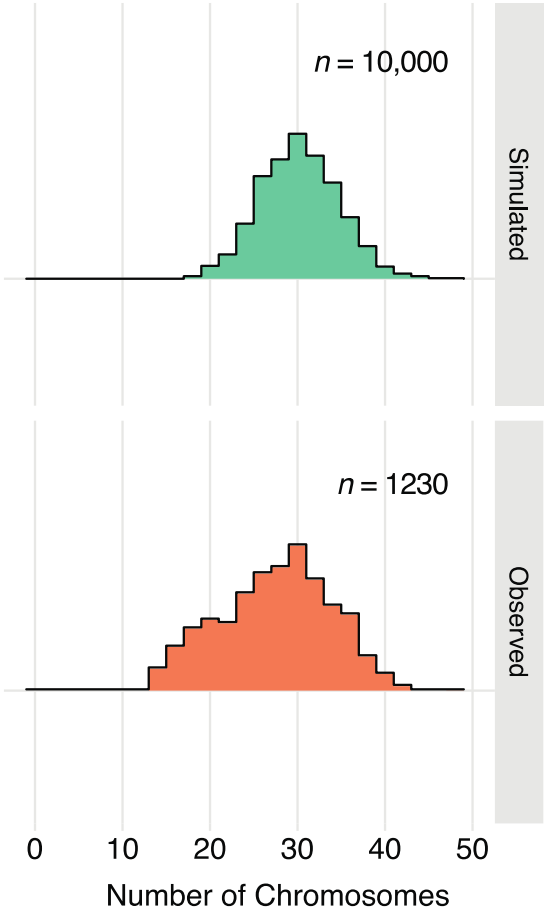

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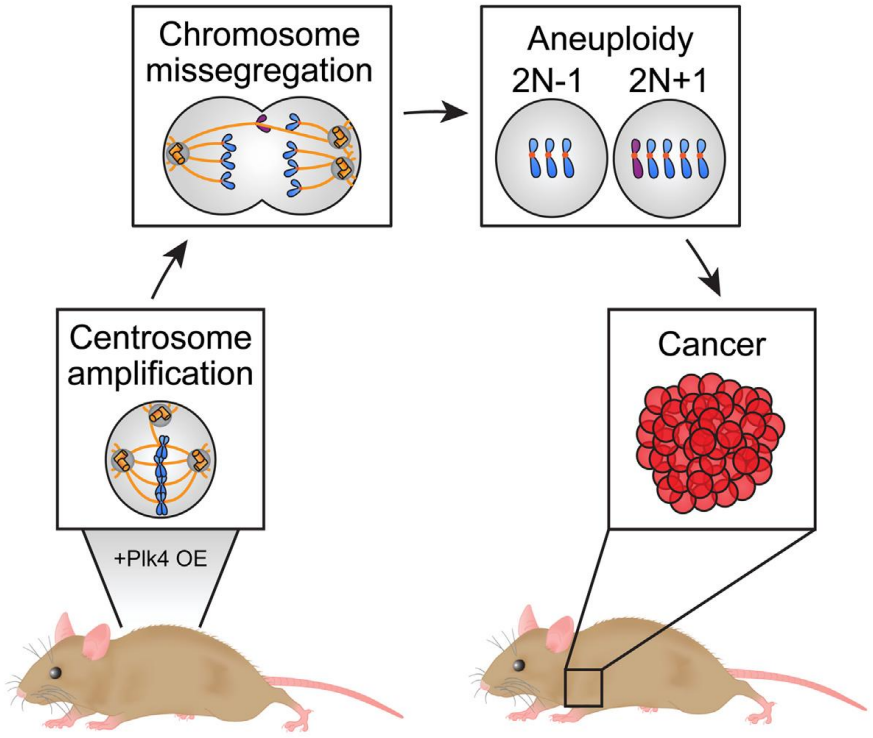

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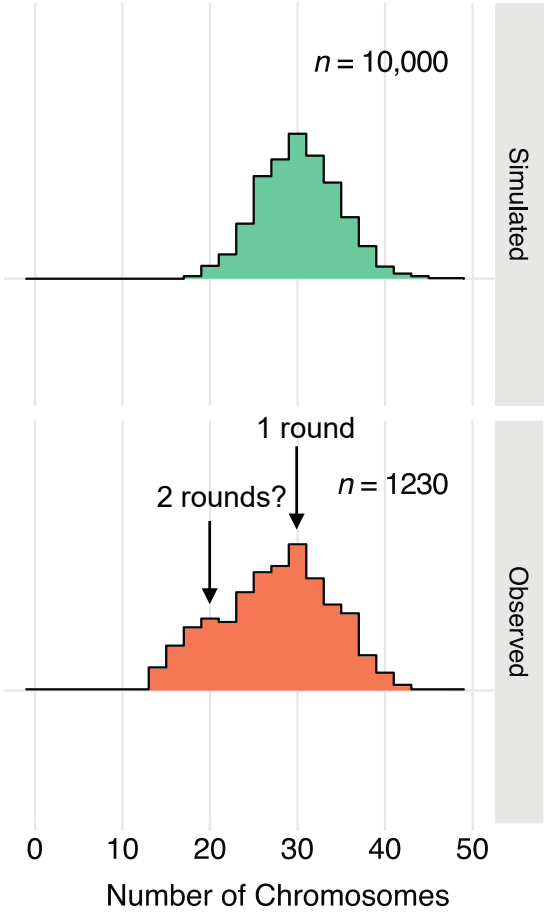

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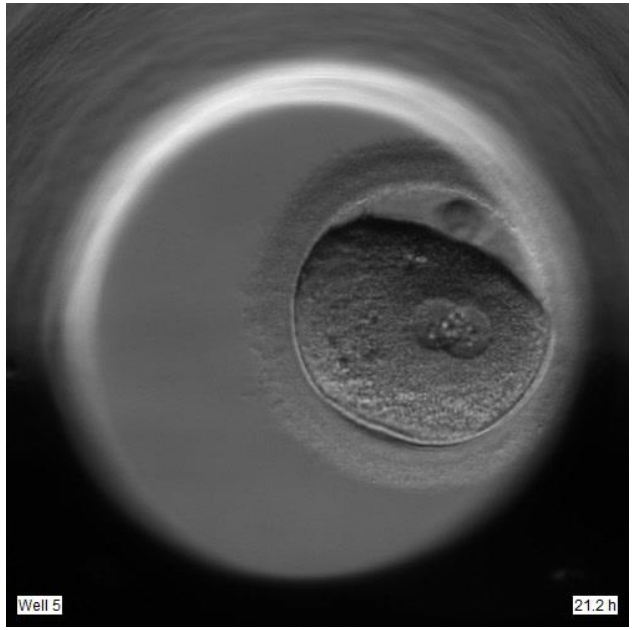
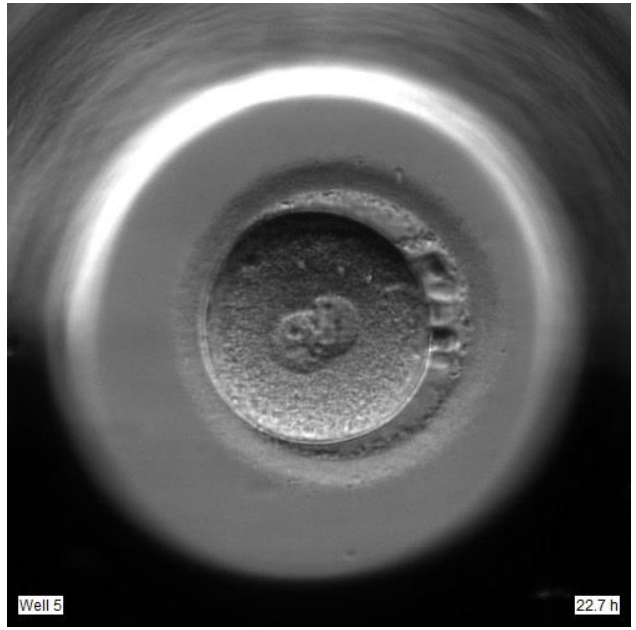
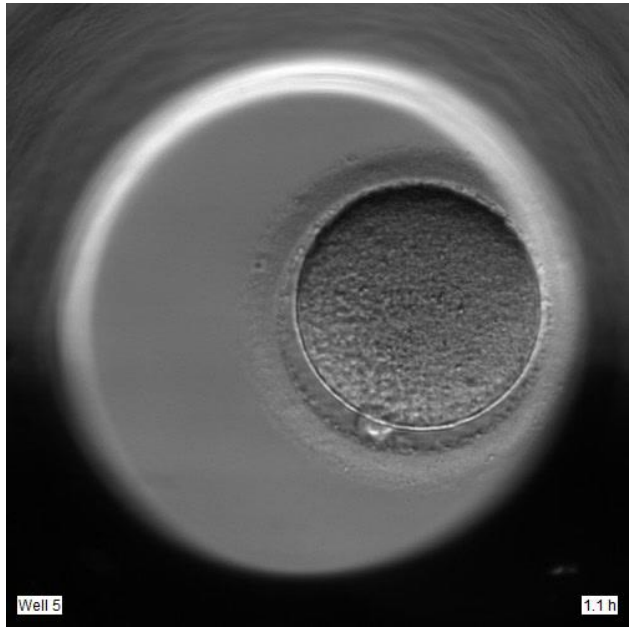
Time-lapse data support tripolar mitosis as mechanism driving the association







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