Common variation in meiosis genes shapes human recombination and aneuploidy

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JC | Mingyu Suo | 2026/9/11

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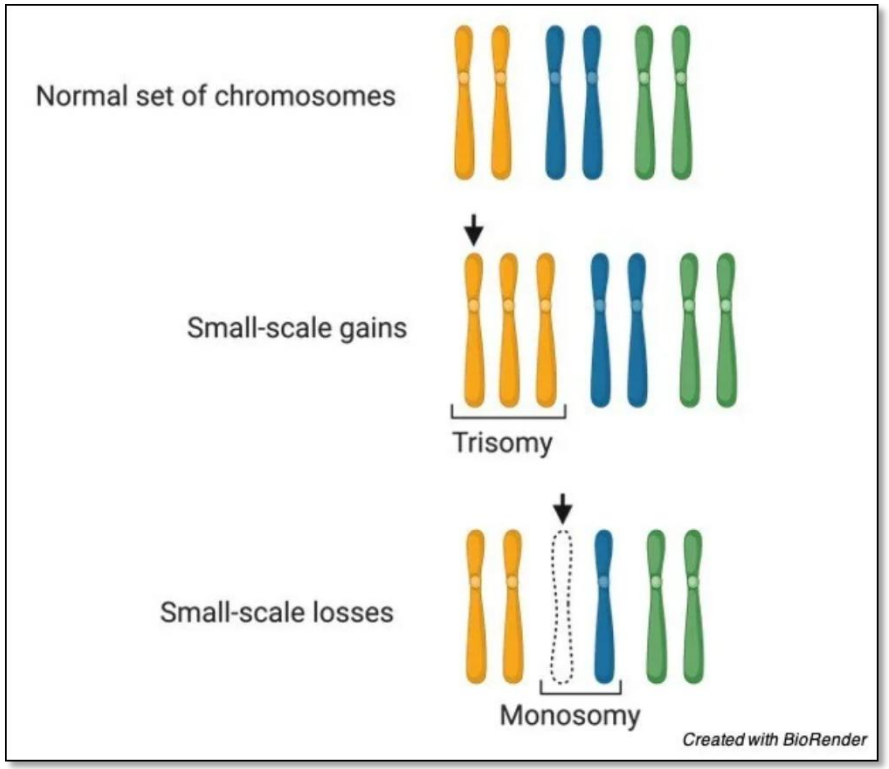
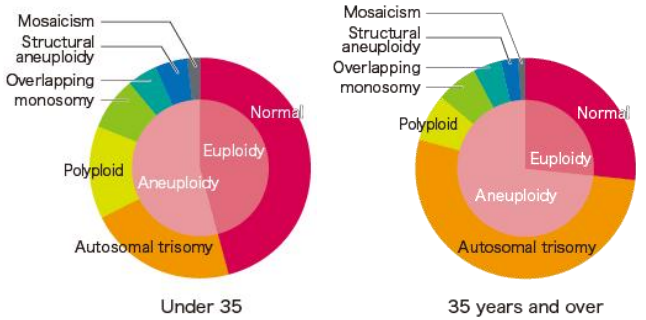
- He received his PhD from Stanford University and completed his postdoctoral work at Princeton University and the University of Washington.
- The McCoy lab seeks to **understand the genomic basis** of functional and fitness-altering variation through the development and **application of computational methods**.
- Their work combines diverse datasets and concepts from **population genetics** and statistics to achieve quantitative perspectives on **human evolution and reproduction**.

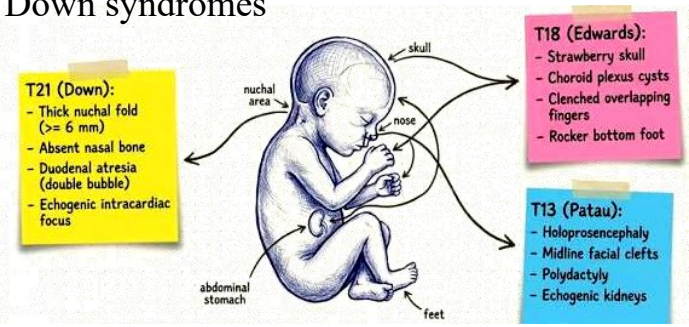
Aneuploidy
非整倍体



- leading cause of human **pregnancy loss**

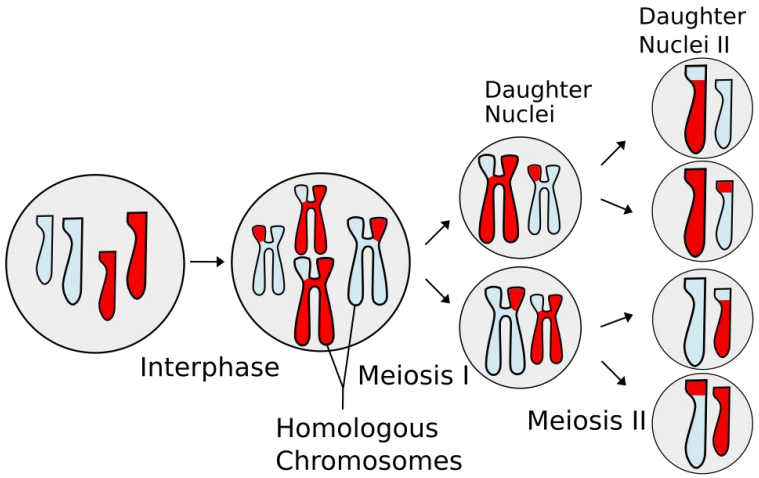


- cause of genetic conditions such as Klinefelter, Turner and Down syndromes



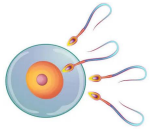
Female meiosis

减数分裂



start: fetal development

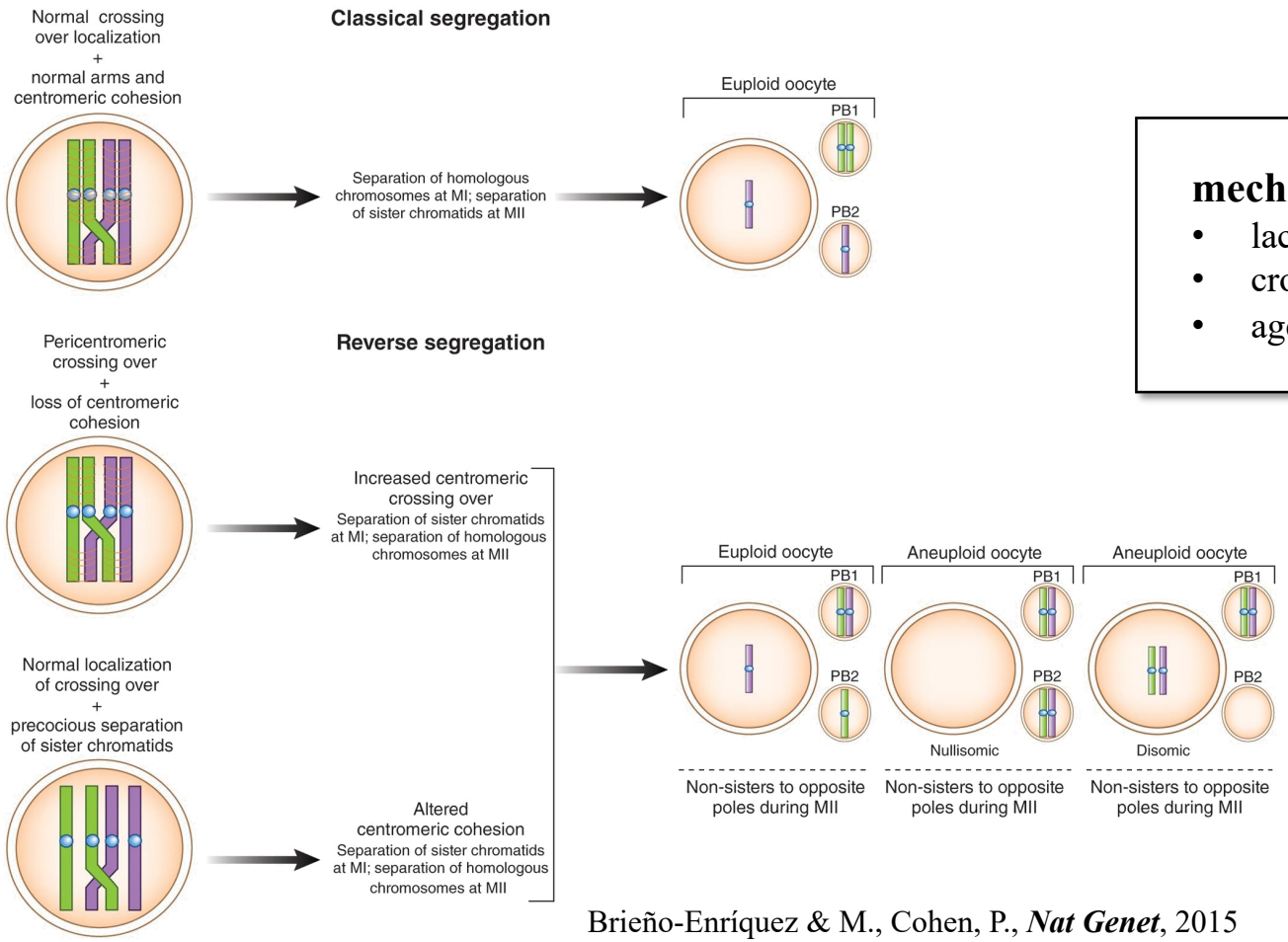
MI: onset of puberty [青春期]



MII: after fertilization

The physical linkages formed by meiotic **crossovers help stabilize paired chromosomes** during this prolonged period of female meiotic arrest

Meiosis -> Aneuploidy



mechanisms of maternal meiotic aneuploidy

- lack of crossovers
- crossover suboptimal placement
- age-related cohesin [黏连蛋白] deterioration

Brieño-Enríquez & M., Cohen, P., ***Nat Genet***, 2015

Current limitation

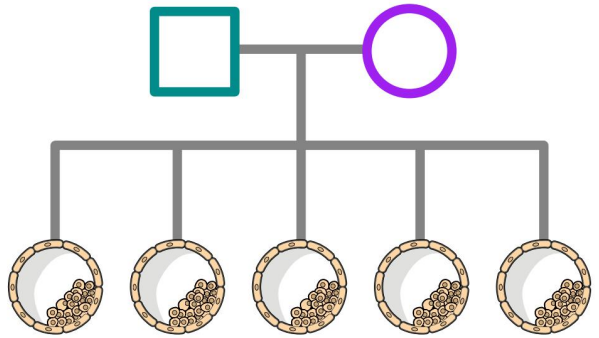
- largest studies of crossovers in living human families **lacked aneuploid participants**
- Much of current knowledge about the connection between human recombination and aneuploidy, as well as their genetic bases, thus **comes from smaller samples of people living with survivable aneuploidies**

Research design

pre-implantation genetic testing (**PGT, 胚胎植入前遗传学检测**) of in vitro fertilized (**IVF, 体外受精**) embryos

$n_{\text{parental pairs}} = 22{,}850$

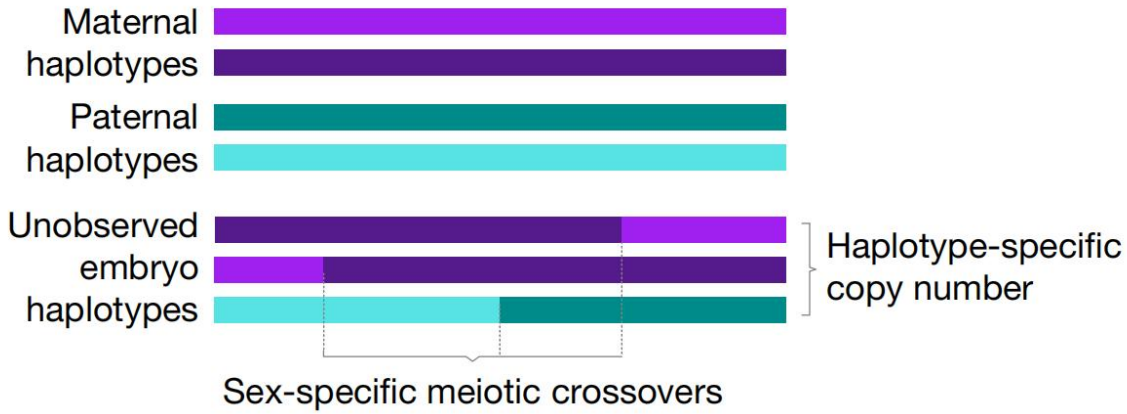
$n_{\text{embryos}} = 139{,}416$



Research goal

1. map recombination and aneuploidy
2. quantitatively test their relationship
3. discover genetic factors influencing these phenotypes

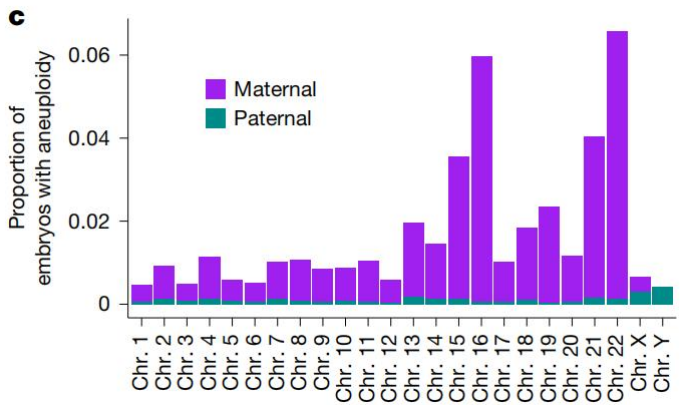
Method | karyoHMM



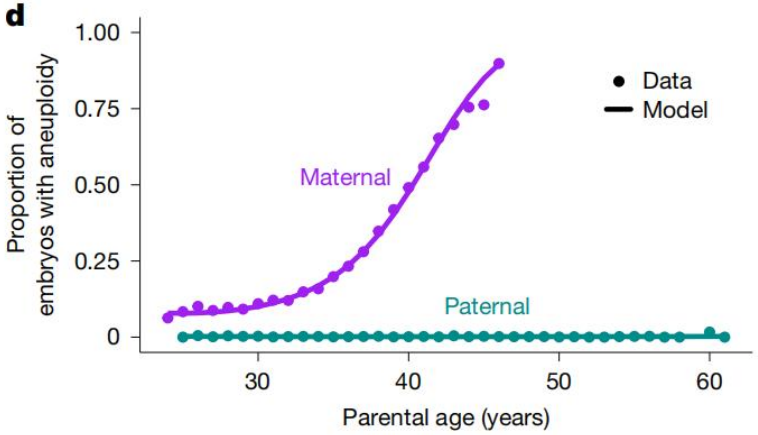
haplotype transmission + crossover + chromosome copy number

Meiotic aneuploidy is common in embryos

- identified 41,480 (**29.8%**) embryos with **at least one aneuploid chromosome**
- **trisomies [三体] exceeded monosomies [单体]** -> selection before blastocyst formation



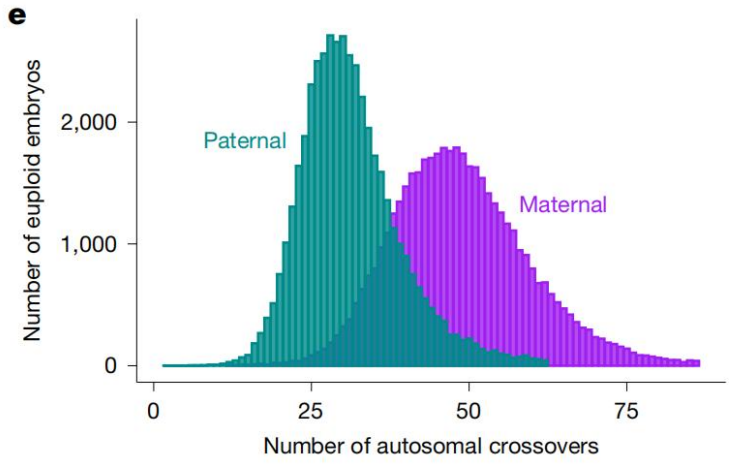
Aneuploidies primarily involve gain or loss of **maternal homologues** and are enriched on **particular chromosomes**

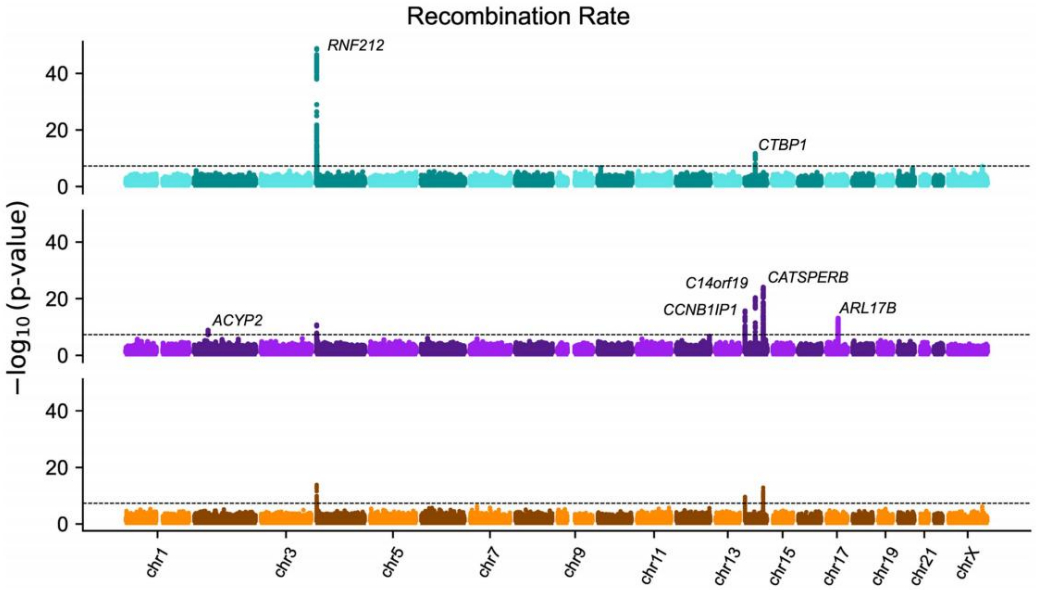


Aneuploidies affecting maternal homologues increase with maternal age, whereas aneuploidies affecting paternal homologues exhibit no significant relationship with paternal age

Relationship between crossovers and aneuploidies?

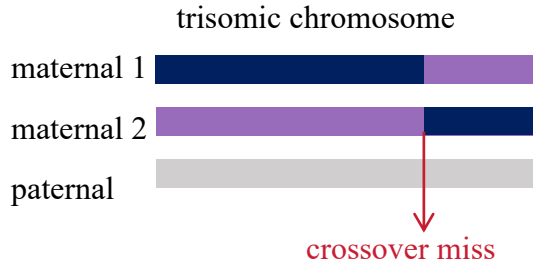
Euploid [整倍体] embryo:
maternal crossovers exceed paternal crossovers





Relationship between crossovers and aneuploidies?

Technical limitation



Solution

aneuploid embryo
(e.g., Trisomy 21)

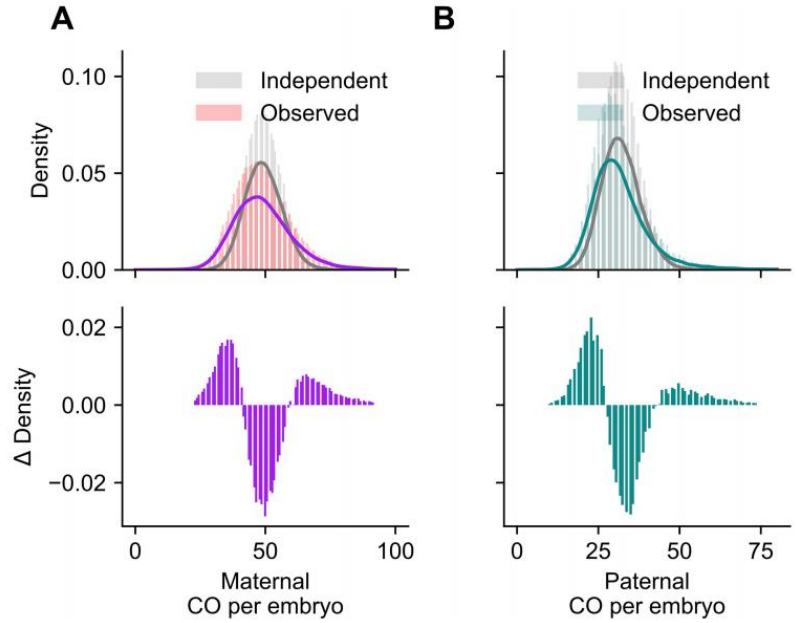
✕ chr.21
√ chrs. 1-20, 22

euploid embryo

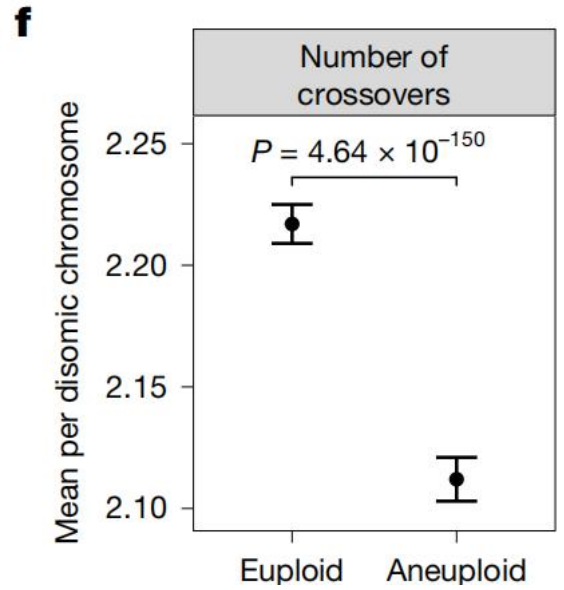
√ chrs. 1-22

Underlying principle

Cross-chromosomal covariance in crossover counts per embryo

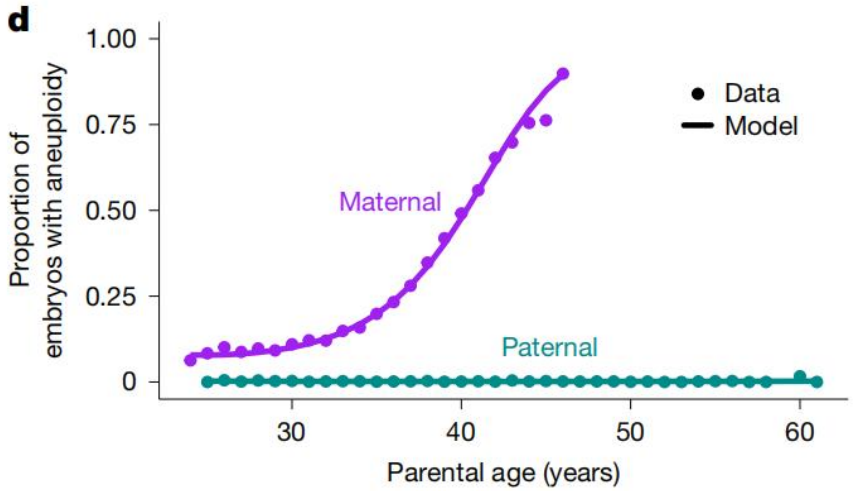


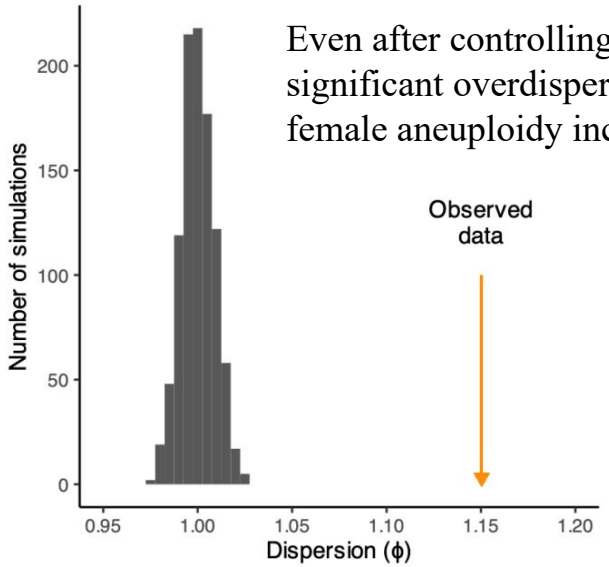
Aneuploid embryos possess fewer crossovers



low crossover tendency -> increased meiotic aneuploidy risk

Beyond maternal age?





Even after controlling maternal age, significant overdispersion exists in female aneuploidy incidence

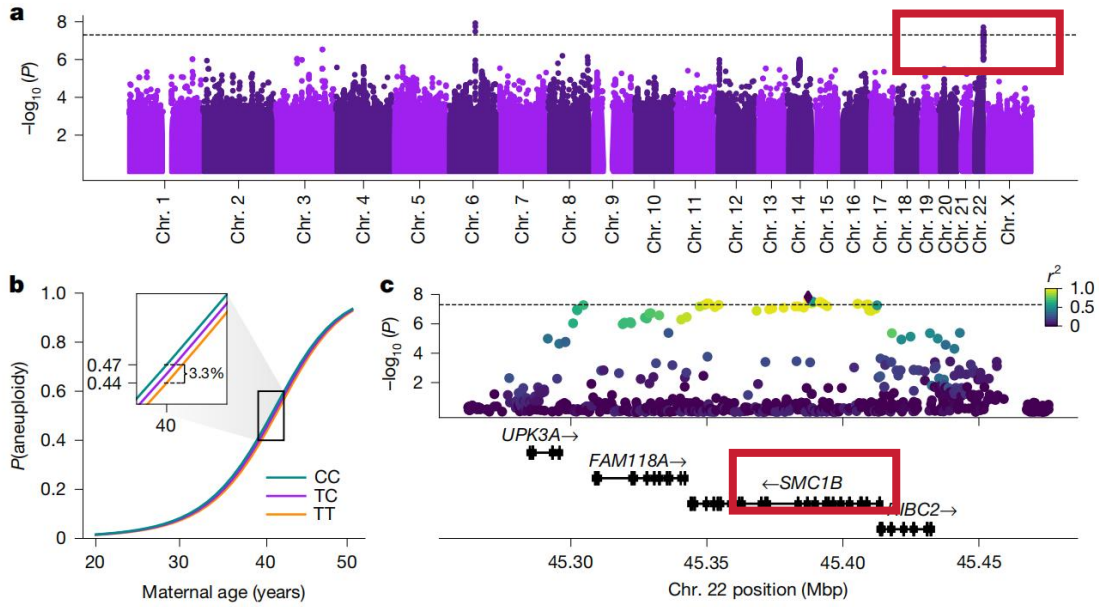
age + genetics/environment -> aneuploidy

Research goal

1. map recombination and aneuploidy
2. quantitatively test their relationship
3. discover genetic factors influencing these phenotypes

SMC1B variants associate with aneuploidy

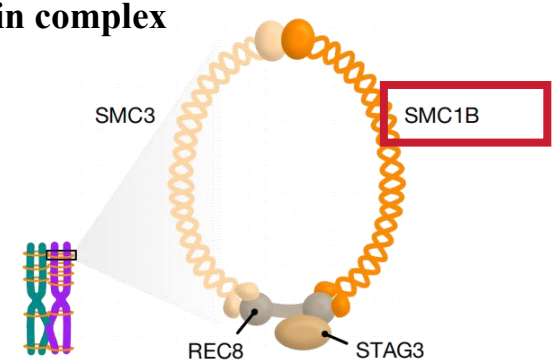
GWAS tests of maternal meiotic aneuploidy and maternal genotype



aneuploidy-associated lead SNP rs6006737

for a 40-year-old patient, each copy of the risk allele confers an estimated 1.65% additional average risk of aneuploidy

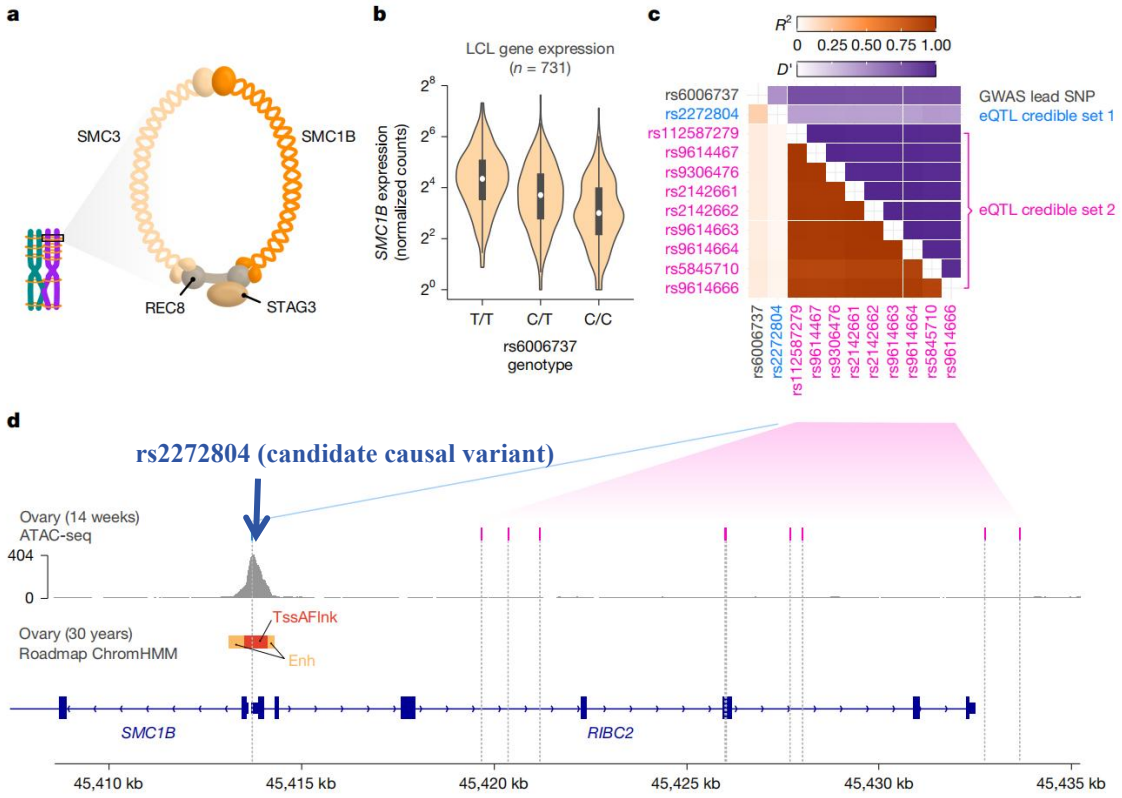
encodes a component of the ring-shaped cohesin complex



Smc1b-deficient mice:

- reduced crossover
- defective synapsis
- premature loss of cohesion
- chromosome mis-segregation
- infertility

Associated haplotype is an *SMC1B* expression quantitative trait locus

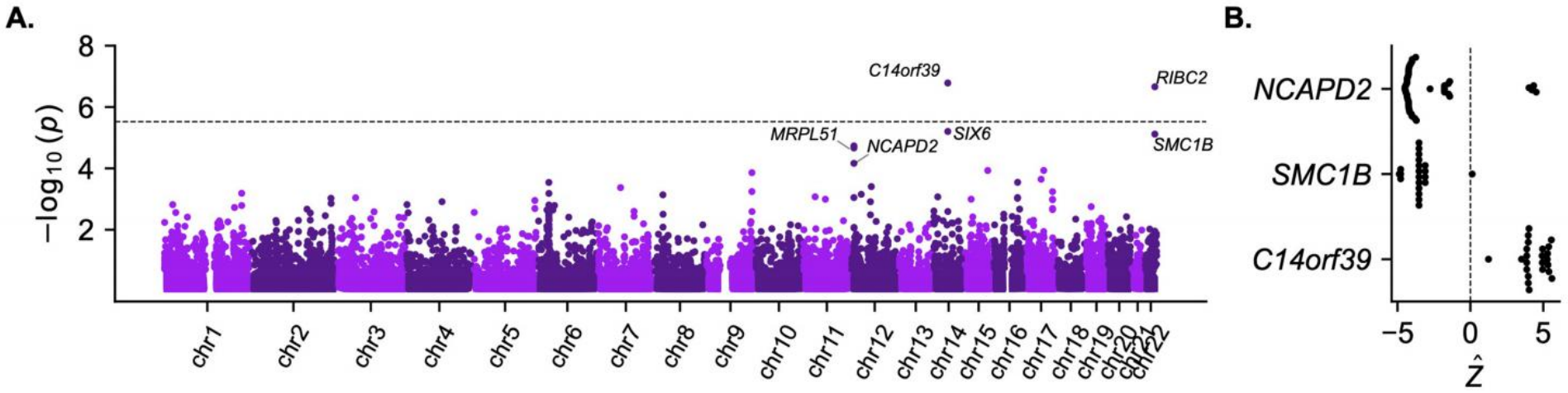


- Each copy of the aneuploidy risk allele is associated with **reduced expression of *SMC1B***
- Pairwise LD between a set of SNPs including GWAS **lead SNP rs6006737** and variants defining **fine-mapped eQTL credible sets for *SMC1B***
  - **credible set 1: rs2272804 (causal SNP)**
    - lies within a putative **promoter sequence** within open chromatin
    - lies within a predicted **binding motif of ATF1** (expressed in female germ cells)
  - credible set 2: distributed throughout the upstream region of *SMC1B*

rs2272804 -> ATF1 binding ↓ -> *SMC1B* ↓ -> recombination/cohesion ↓ -> aneuploidy ↑

TWAS reveals new links to meiosis genes

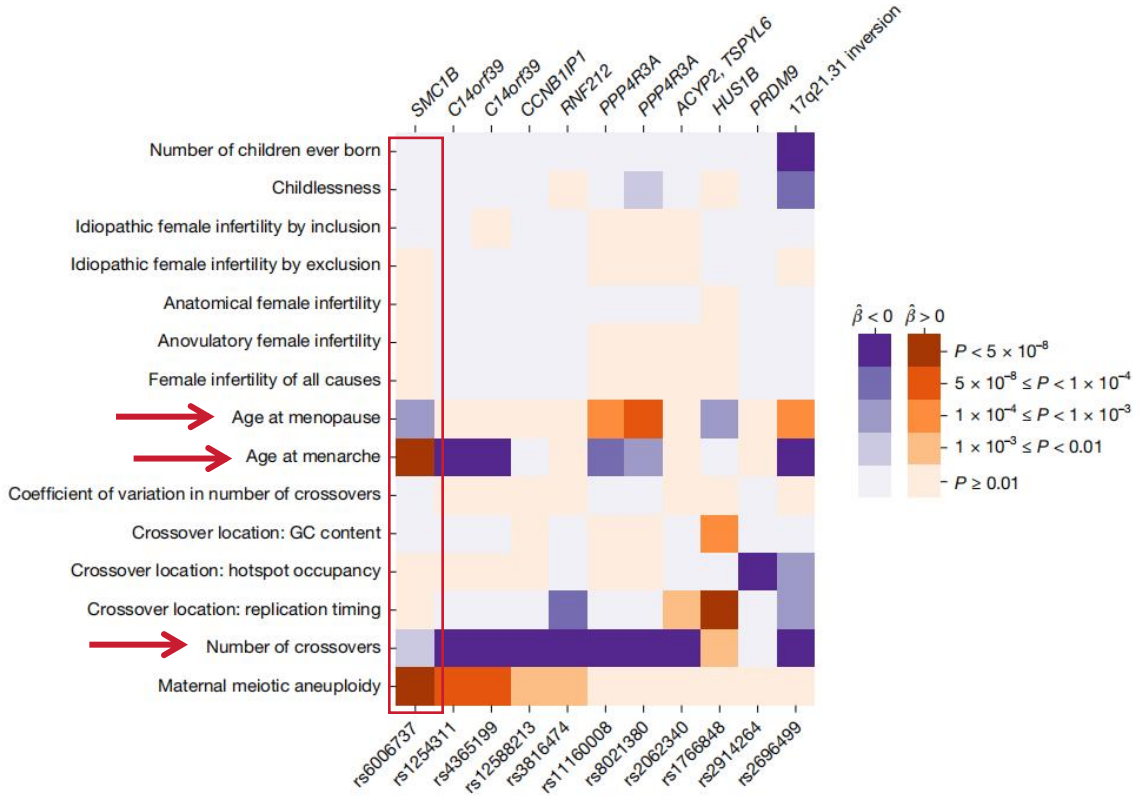
Transcriptome-wide association study (**TWAS**) for maternal meiotic aneuploidy



- *RIBC2:* secondary/noncuasal association (same haplotype co-regulates expression of both *RIBC2 & SMC1B*)
- ***C14orf39 [new signal]:*** encodes a component of the synaptonemal complex [联会复合体]
- ***NCAPD2 [new signal]***: encodes a regulatory subunit of the condensin I complex

common cis-regulatory variation in multiple core meiosis genes collectively influences maternal aneuploidy risk

Pleiotropic effects [多效性] on fertility traits

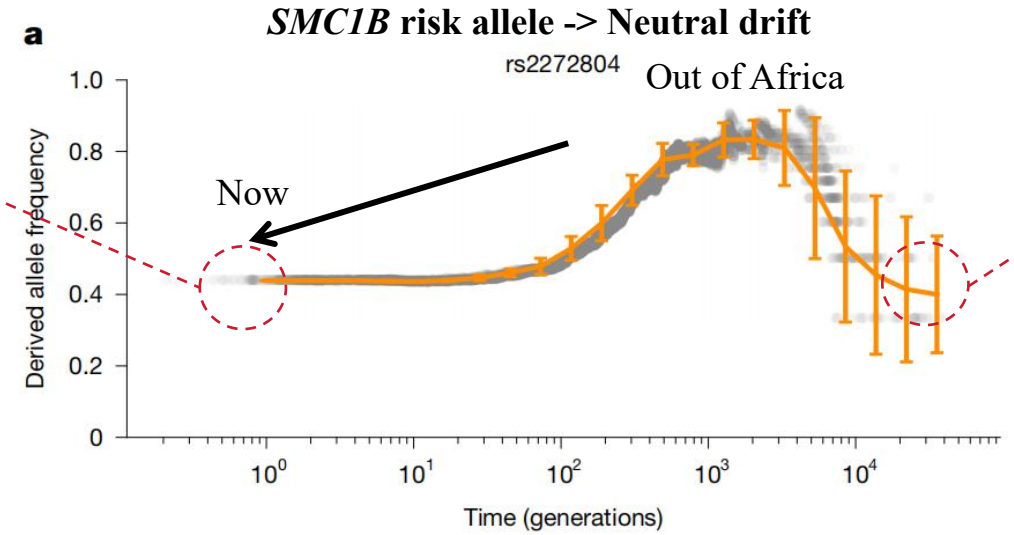


Example: the **risk allele of the aneuploidy-associated lead SNP** rs6006737 associated with

- lower rates of female **recombination** within our data
- greater **age at menarche [月经初潮]** and lesser **age at menopause [绝经]** and thus a shorter female **reproductive timespan**

Evolution of the *SMC1B* risk allele

The Conflict: Deleterious variants should be purged by negative natural selection, yet the **causal eQTL variant** rs2272804 (A allele) maintains **a global allele frequency of 44%** (reaching 71% in African populations)



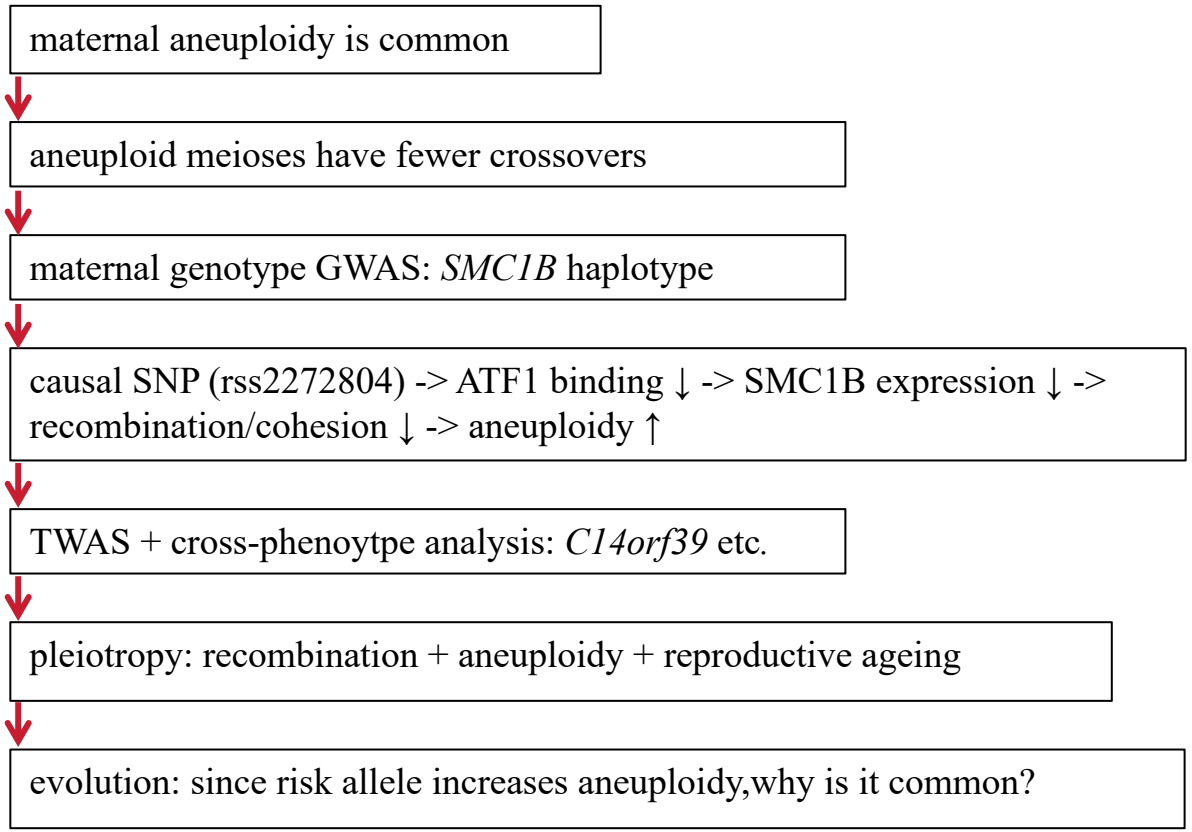
a higher frequency within an ancestral human population, modestly declining outside of Africa within the last 1,000 generations

Ancient Ancestry: The derived risk allele **originated ~910,000 years ago** (predating the Neanderthal-modern human split).

embryonic euploidy does not directly map to realized reproductive fitness

Summary

1. map **recombination and aneuploidy**
2. quantitatively test their **relationship**
3. discover **genetic factors** influencing these phenotypes



common regulatory variation in core meiotic genes shapes recombination -> chromosome segregation fidelity -> aneuploidy -> human reproductive phenotypes

Thanks!

JC | Mingyu Suo | 2026/9/11