

The Role of Recombination in Embryonic Aneuploidy Across Chromosomes

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Introduction

Recombination refers to the inherited pattern of DNA segment exchange between homologous chromosomes that occurred during parental meiosis, observable in the embryo's genome (Figure 1). Recombination during meiosis is essential for ensuring accurate chromosome segregation and generating genetic diversity. However, misplaced crossover events can disrupt segregation, leading to embryonic aneuploidy.

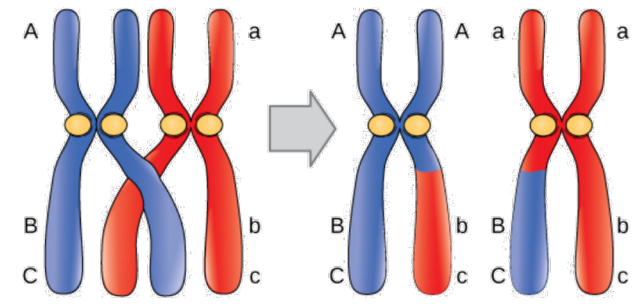


Figure 1. How recombination shuffles genetic material between homologous chromosomes, creating new allele combinations in the resulting gametes.

Aim

This is a meta-analysis that aims to investigate how recombination patterns (crossover frequency, location, and parental origin) correlate with the incidence of aneuploidy in human preimplantation embryos.

Methods

Meta-analysis registered in PROSPERO
CRD42024601316

Using databases from PubMed, Embase, and Cochrane Library from Jan 2000 to Oct 2024 (Fig 2)

- Inclusion:
- Studies using PGT-A, PGT-M, SNP genotyping, or karyomapping
 - Analysis of recombination patterns and chromosomal aneuploidy in human preimplantation embryos
 - English-language, peer-reviewed full-text articles

- Exclusion:
- Animal or non-human studies
 - Studies lacking recombination or aneuploidy analysis
 - Conference abstracts, reviews, non-English texts without translation

- Recombination events were inferred:
- SNP array-based haplotype reconstruction (Karyomapping) for detecting sudden swaps of parental homologue SNPs via parental-embryo trio data (Ottolini et al, 2015; Konstantinidis et al, 2020; Ma et al, 2022).
 - Low-coverage whole-genome sequencing data from IVF embryos were analysed through a method called LD-CHASE, which detects haplotype transitions by comparing related sibling embryos. (Ariad et al, 2024).

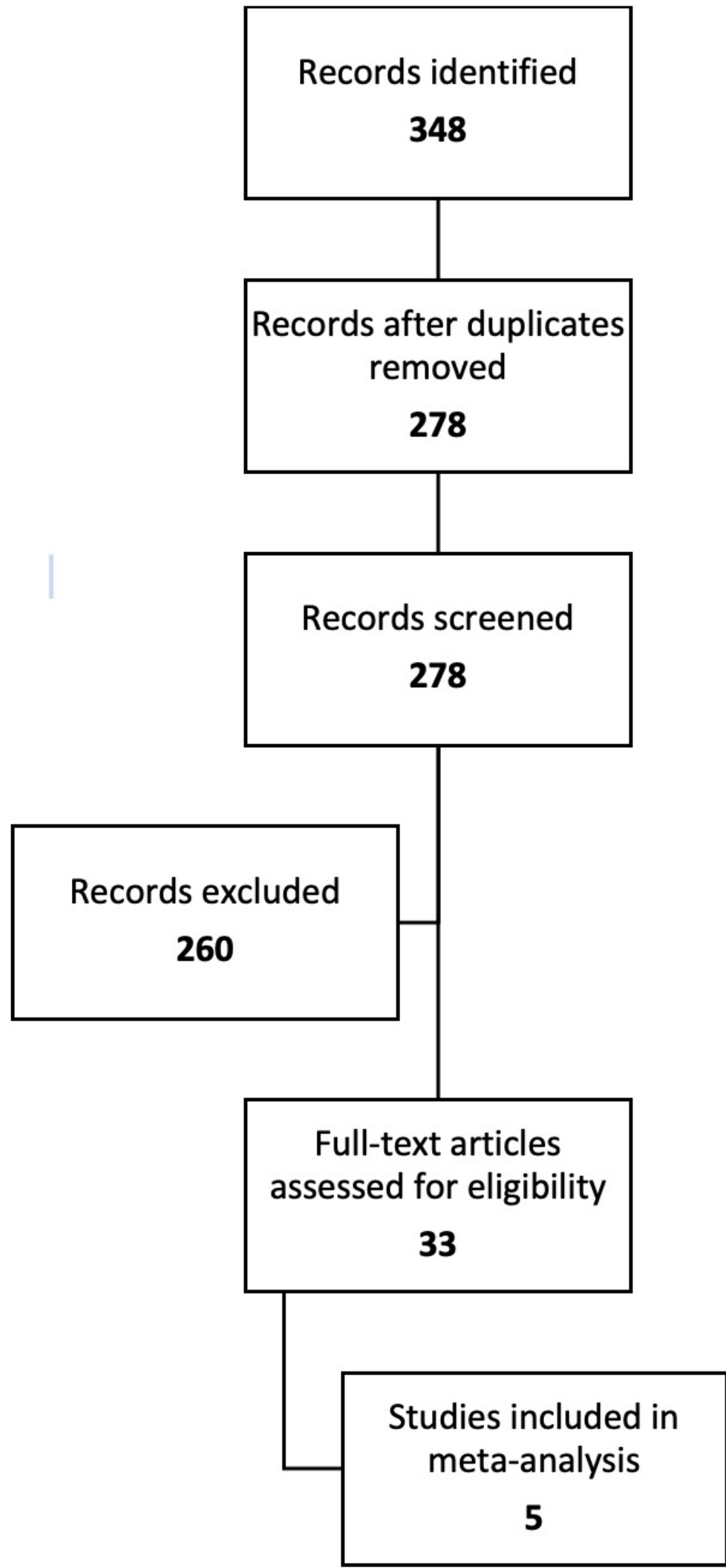


Figure 2. PRISMA Flow Diagram of Study Selection Process. This flowchart illustrates the systematic process of study selection for the meta-analysis.

Results

We analysed 101,616 recombination events, comprising 92,472 events in euploid embryos and 9,144 in aneuploid embryos:

- We defined the regions of pericentromeric (up to 2 Mb from the centromere), telomeric (5 Mb from each end of the chromosome arm), and subtelomeric (the area not classified as either of the first two regions).
- Aneuploid embryos had significantly more telomeric crossovers (29.7%, $p < 0.001$) compared to euploid embryos (3.5%), while subtelomeric recombination dominated in euploid embryos (94.3%) (Figure 3).
- Maternal recombination events significantly exceeded paternal events across nearly all chromosomes (Figure 4A).
- Larger chromosomes (1–8) showed the highest recombination rates (Figure 4A and B).
- Aneuploid embryos showed a modest but significant increase in paternal recombination (Figure 4B).

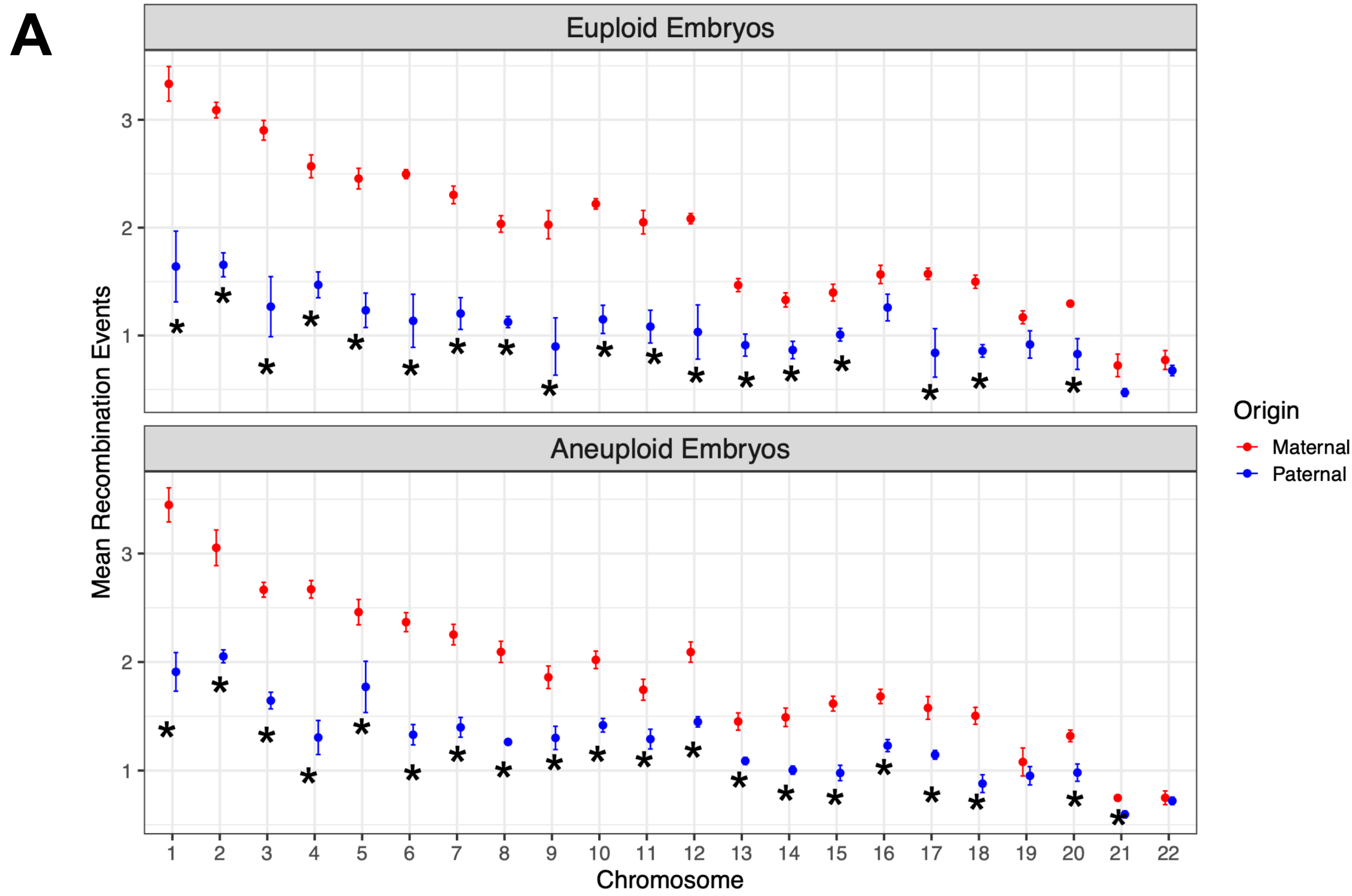


Figure 4. Mean recombination between maternal and paternal meiosis in euploid and aneuploid embryos across chromosomes. The bars represent standard error. Panel A shows maternal recombination rates consistently exceed paternal rates across most chromosomes, with the largest discrepancies observed on chromosomes 1 through 7. Panel B compares the recombination event between aneuploid and euploid embryos based on its origin. Statistically significant differences are marked with asterisks beneath each graph.

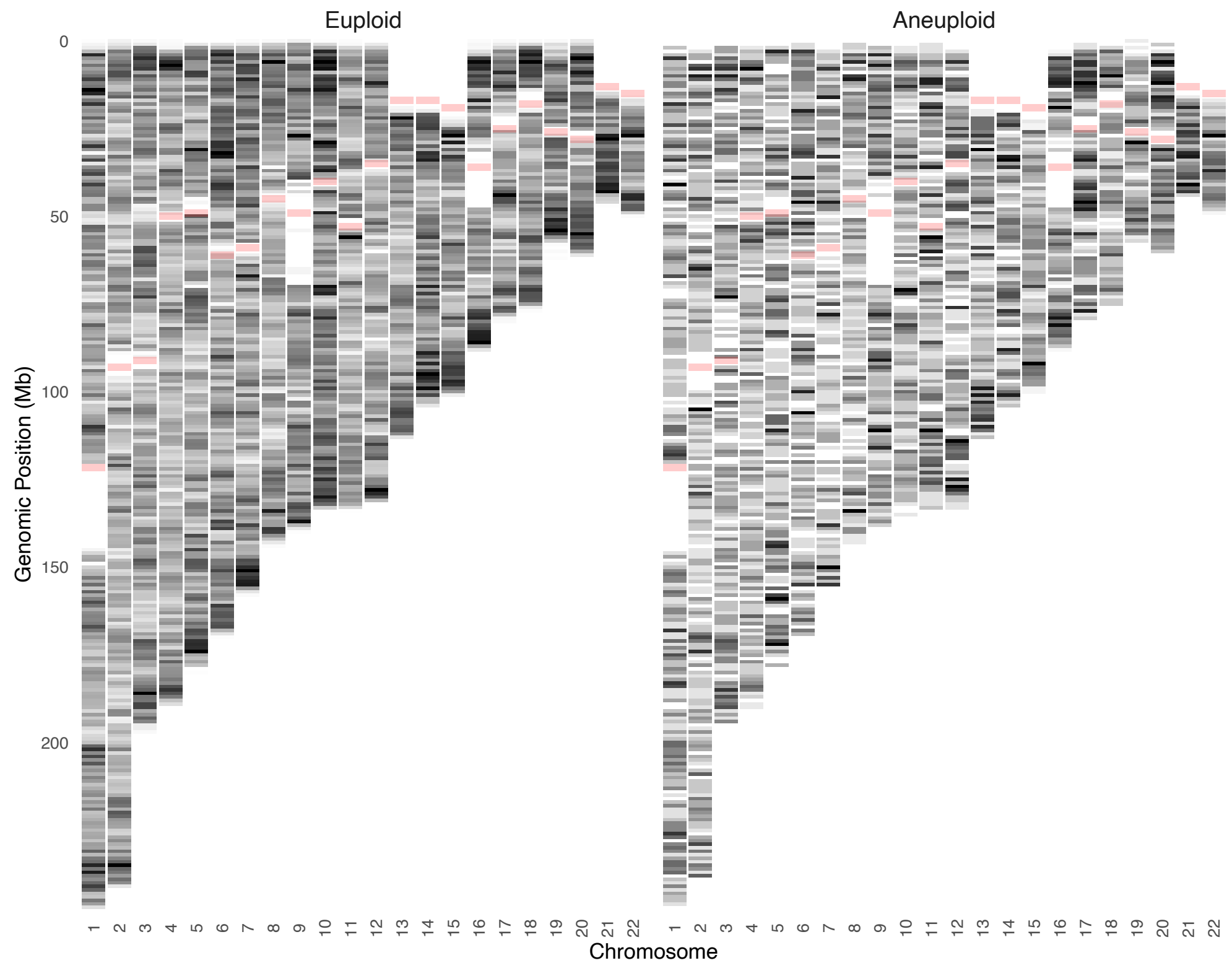
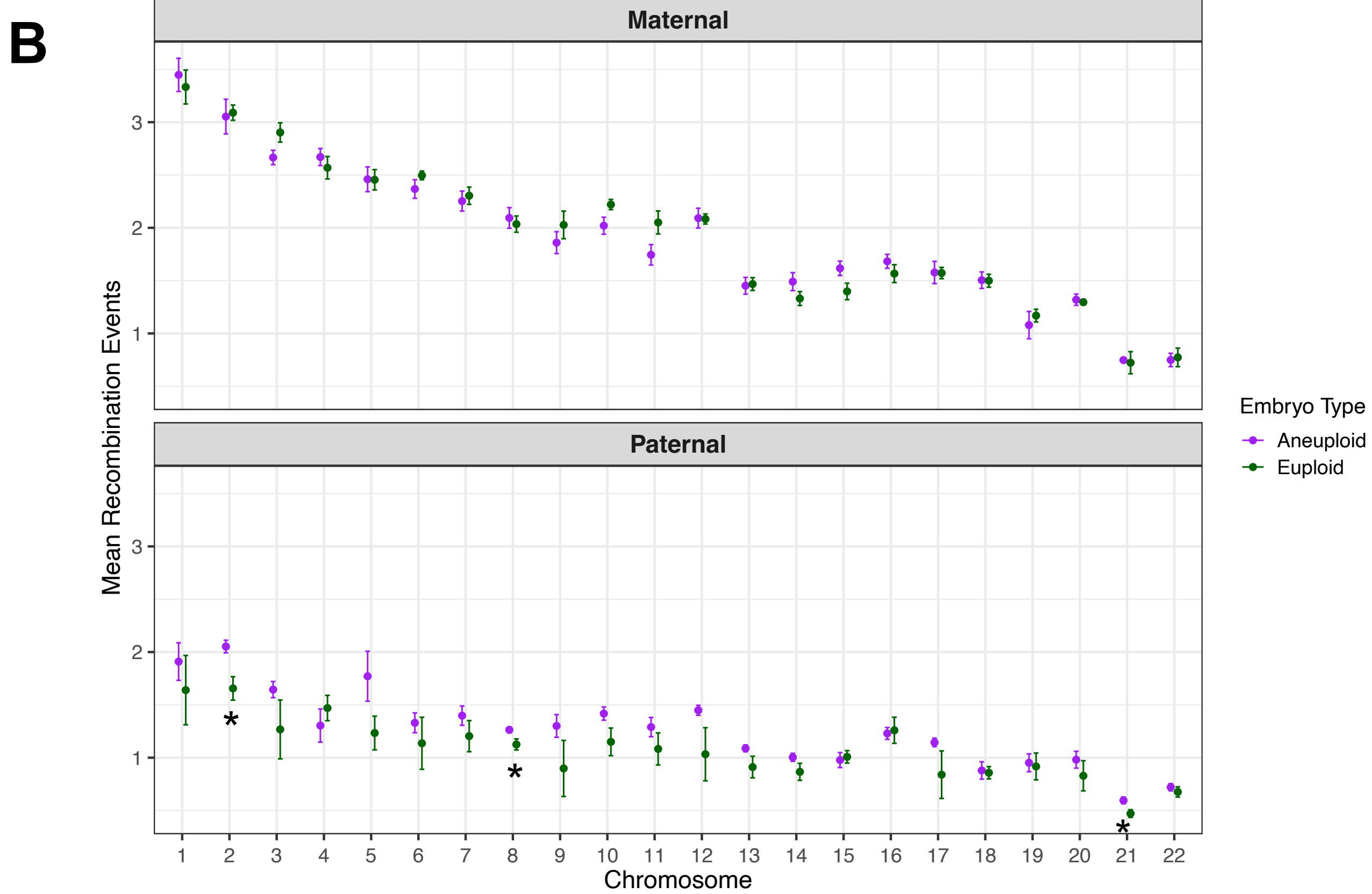


Figure 3. The spatial distribution of recombination events is visualised through recombination density heatmaps across all autosomes. The euploid panel demonstrates dispersed subtelomeric recombination, while the aneuploid panel reveals intense telomeric clustering ($p < 0.001$). Red blocks indicate centromere locations. A darker area means more recombination occurred.



Discussion

Maternal meiosis showed significantly more recombination events than paternal (mean: 1.92 vs. 1.06, $p < 0.001$). Crossovers near telomeres were more frequent and associated with aneuploidy ($p < 0.001$)

Recombination near telomeres (last 5 Mb) disrupts chromosome segregation, increasing aneuploidy risk. These misplaced events are more frequent in aneuploid embryos.

Paternal meiosis has fewer recombination events. However, slightly increased paternal recombination was observed in aneuploid embryos.

Recombination profiling can be indirectly obtained as a by product of PGT-M or PGT-A with parental haplotype information. By identifying aberrant recombination patterns, particularly those contributing to aneuploidy, these data may offer insights into oocyte or sperm chromosomal quality.

Conclusion

Recombination deviations, particularly their position and frequency, may play a role in embryonic aneuploidy.

References

