Chromosome errors in human eggs shape natural fertility over reproductive life span

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45th Scientific Meeting

Publication

Chromosome errors in human eggs shape natural fertility over reproductive life span

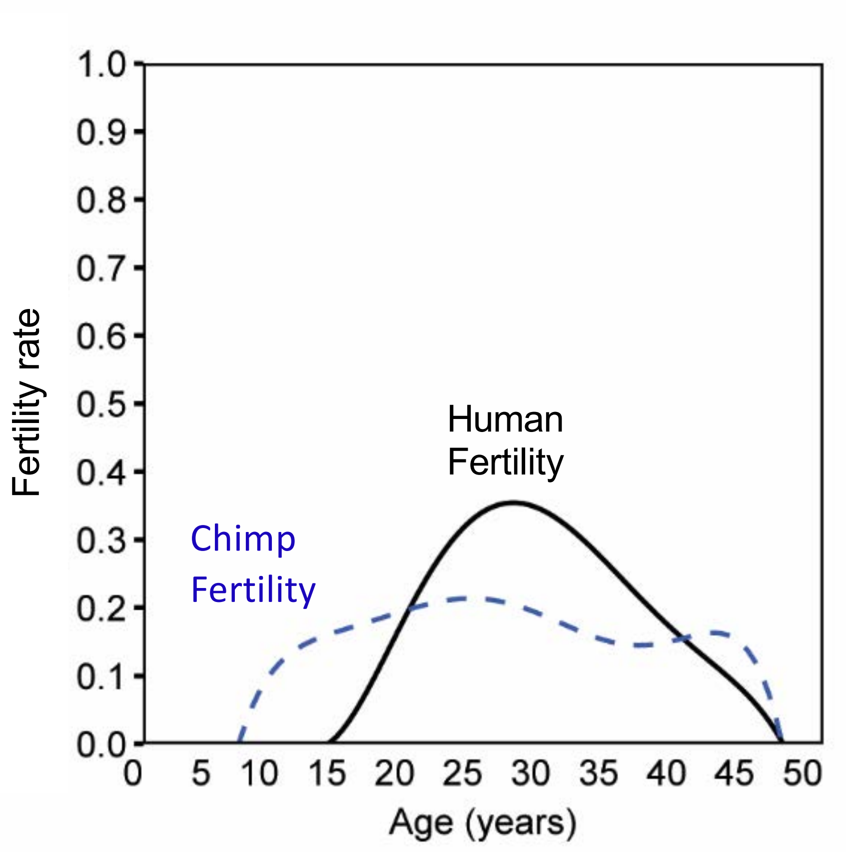
By Jennifer R. Gruhn, Agata P. Zielinska, Vallari Shukla, Robert Blanshard, Antonio Capalbo, Danilo Cimadomo, Dmitry Nikiforov, Andrew Chi-Ho Chan, Louise J. Newnham, Ivan Vogel, Catello Scarica, Marta Krapchev, Deborah Taylor, Stine Gry Kristensen, Junping Cheng, Erik Ernst, Anne-Mette Bay Bjørn, Lotte Berdiin Colmorn, Martyn Blayney, Kay Elder, Joanna Liss, Geraldine Hartshorne, Marie Louise Grøndahl, Laura Rienzi, Filippo Ubaldi, Rajiv McCoy, Krzysztof Lukaszuk, Claus Yding Andersen, Melina Schuh, Eva R. Hoffmann

Distinct types of chromosomal errors drive aneuploidy in human oocytes in an age-dependent manner.

Science 27 Sep 2019: Vol. 365, Issue 6460, pp. 1466-1469, DOI: 10.1126/science.aav7321

https://science.sciencemag.org/content/365/6460/1466

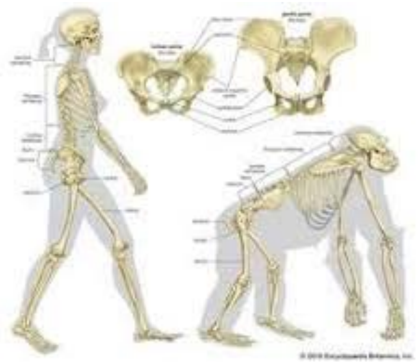
Unique natural fertility curve in humans



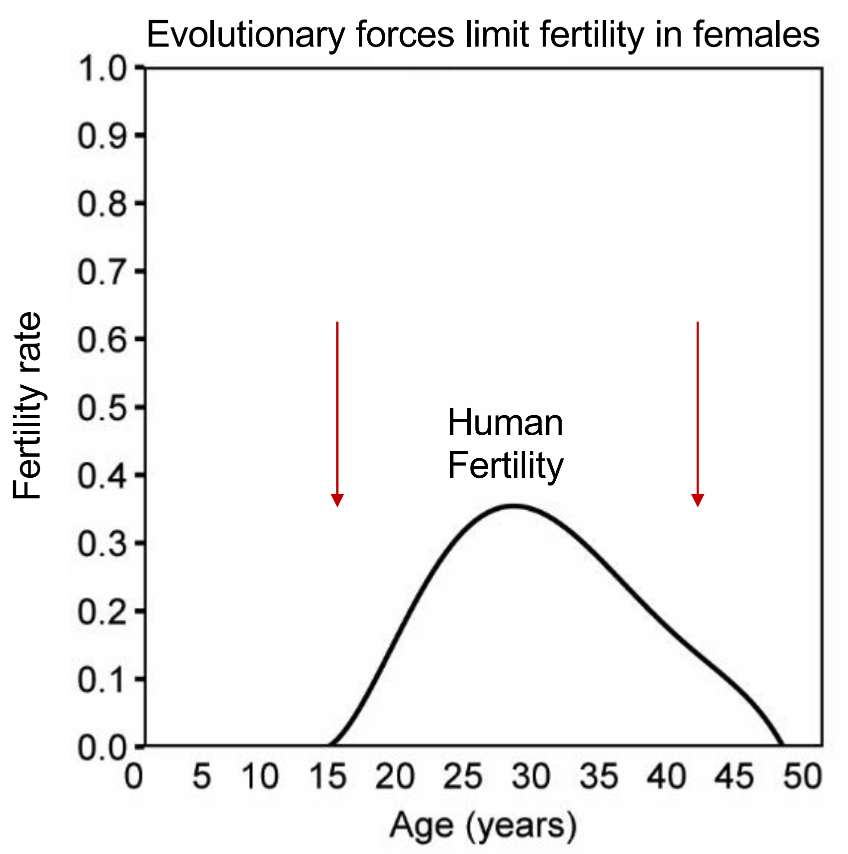
(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

Limited fertility at both younger and advanced ages

Young- hip development



Increased risk during childbirth



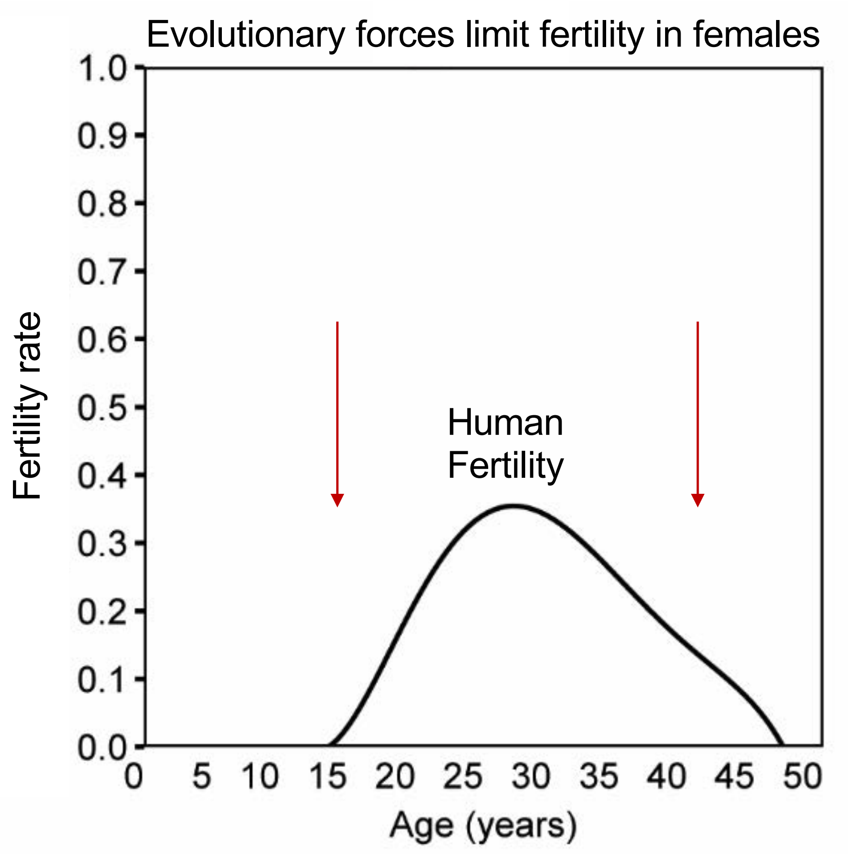
Grandmother hypothesis

High cost of reproducing better spent on younger generation's reproductive efforts

Hadza (Tanzania); Science, 2015

(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

What mechanisms may shape this fertility curve?



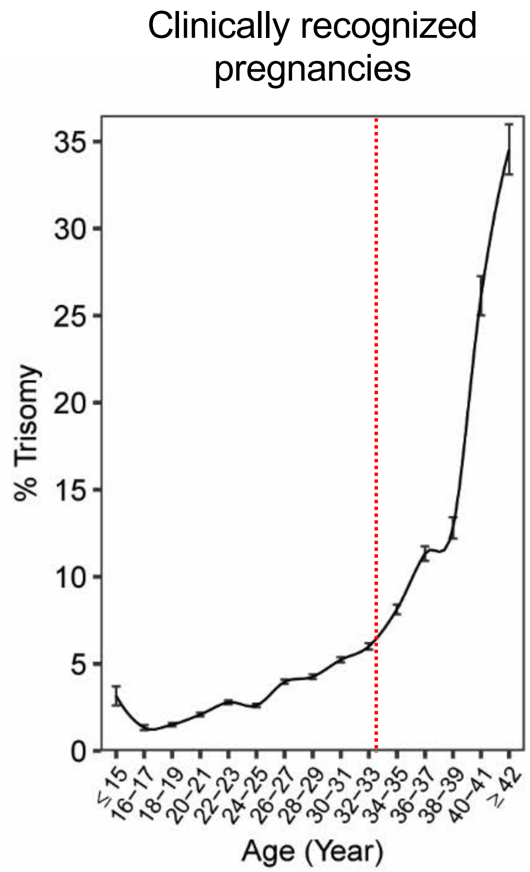
(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

Our candidate: Chromosomal errors (aneuploidy)

- Leading cause of pregnancy loss in humans
- 10-30% of all pregnancies are aneuploid

http://worms.zoology.wisc.edu/zooweb/Phelps/47XY_16.html

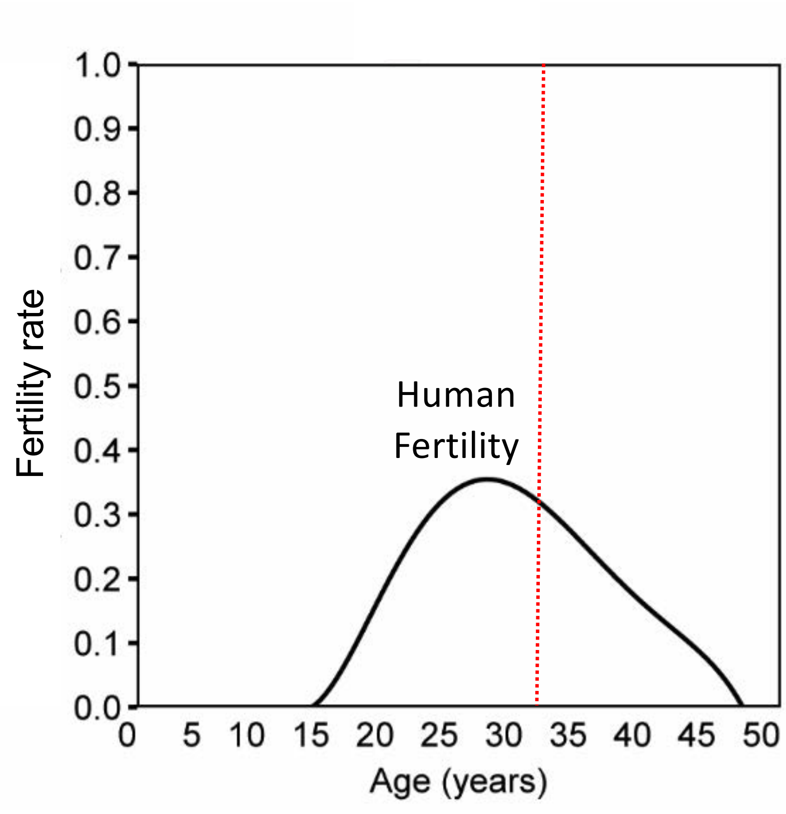
Our candidate: Chromosomal errors (aneuploidy)

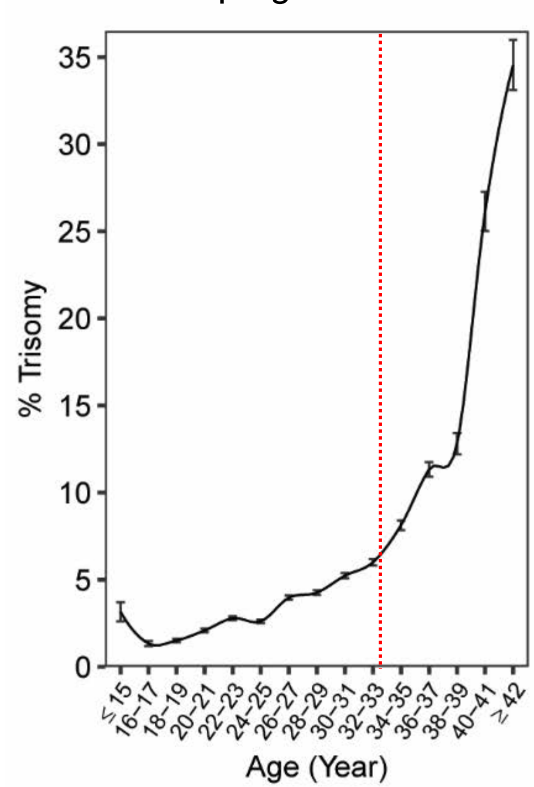


http://worms.zoology.wisc.edu/zooweb/Phelps/47XY_16.html

(Hassold *et al, Human Genetics*, 1985)

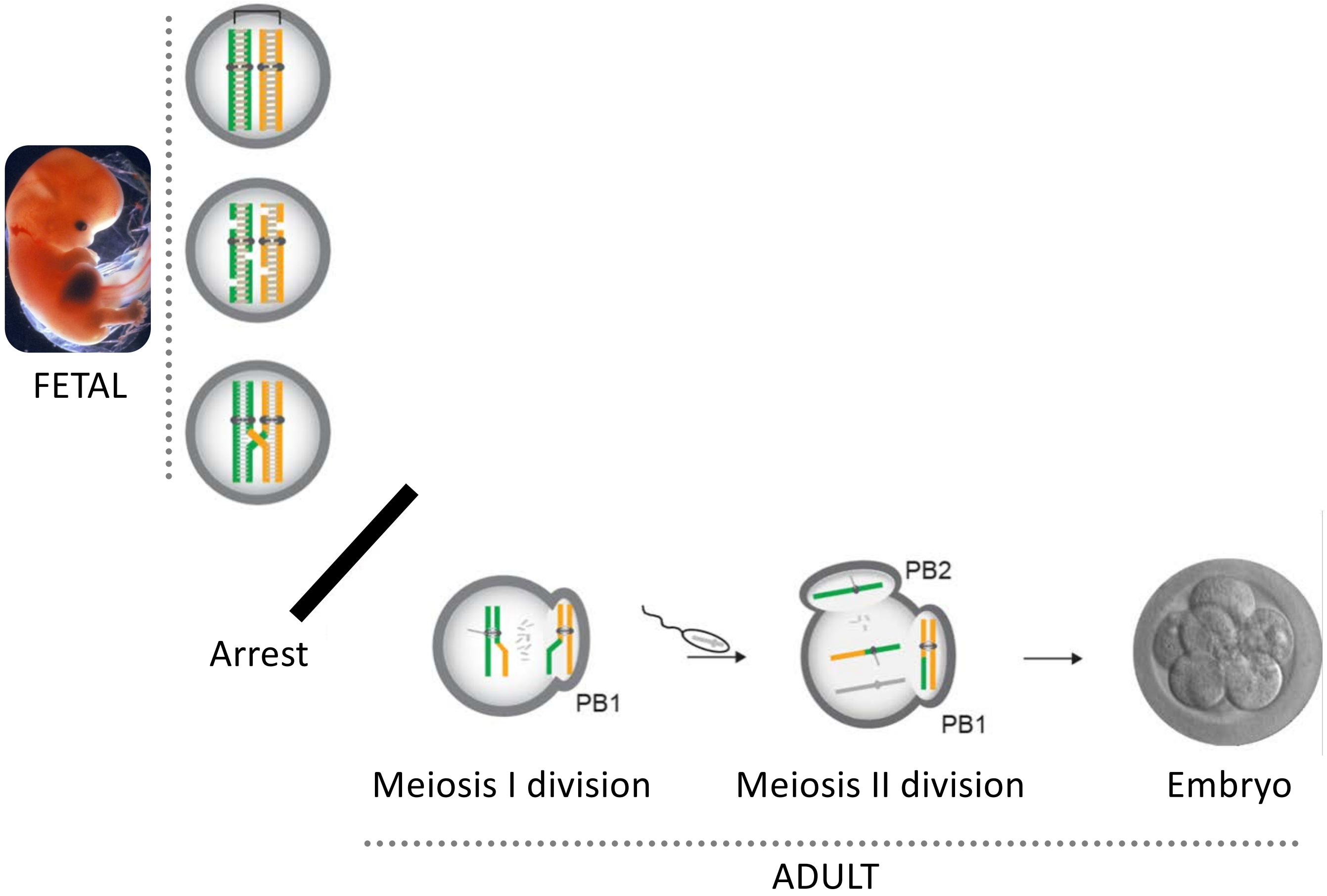
Chromosomal errors (aneuploidy) shape natural fertility in humans



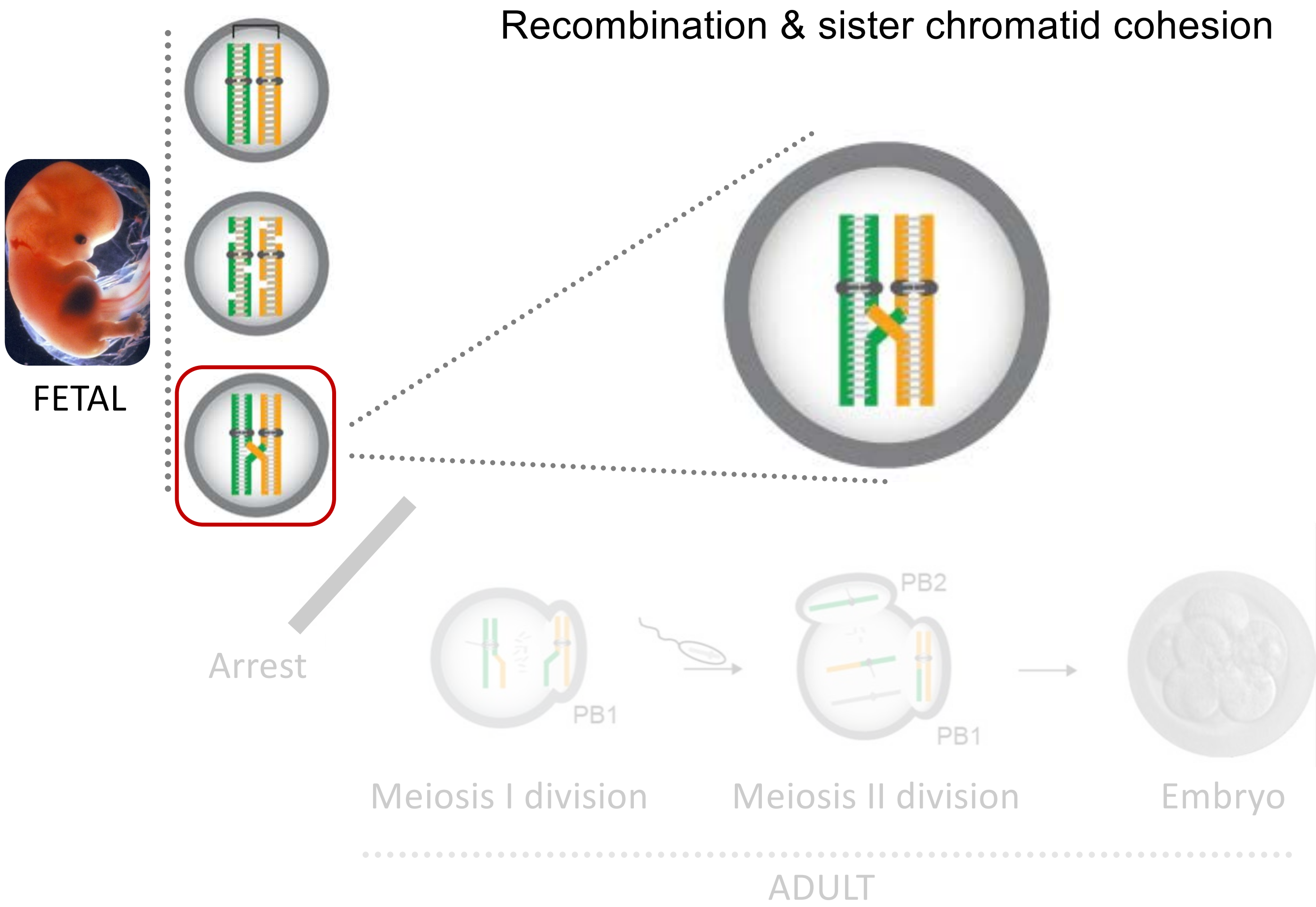


(Hassold *et al, Human Genetics*, 1985;Gruhn, Zielinska, Shukla, Blanchard *et al*, *Science*, 2019)

Current leading hypothesis on aneuploidy formation
Two-hit model: Vulnerable COs and cohesion weakening

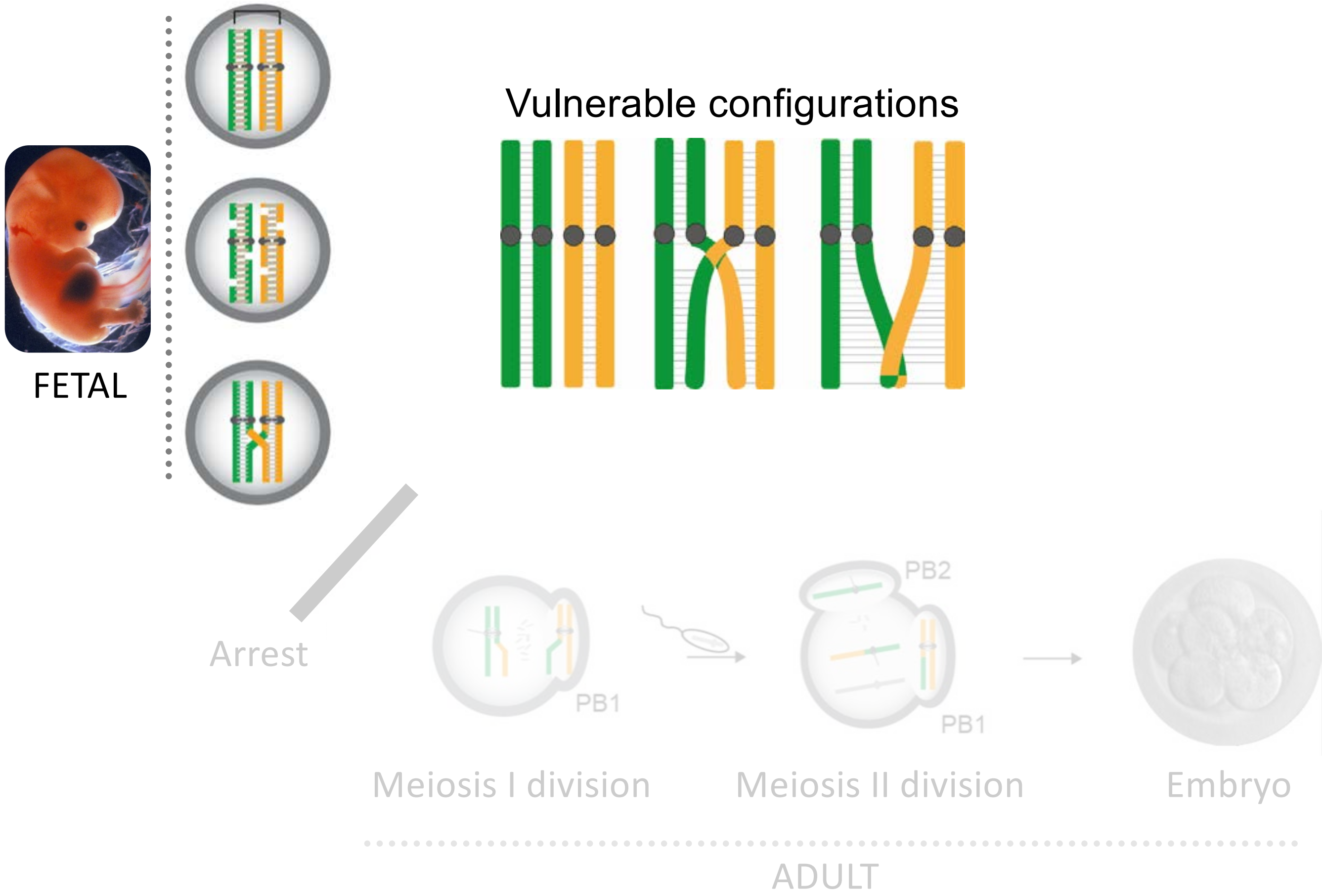


First Hit: Establishment of bivalent configuration



(Hassold *et al*, *Nature Genetics*, 1996)

First hit: Weakened connections lead to vulnerable chromosome structures



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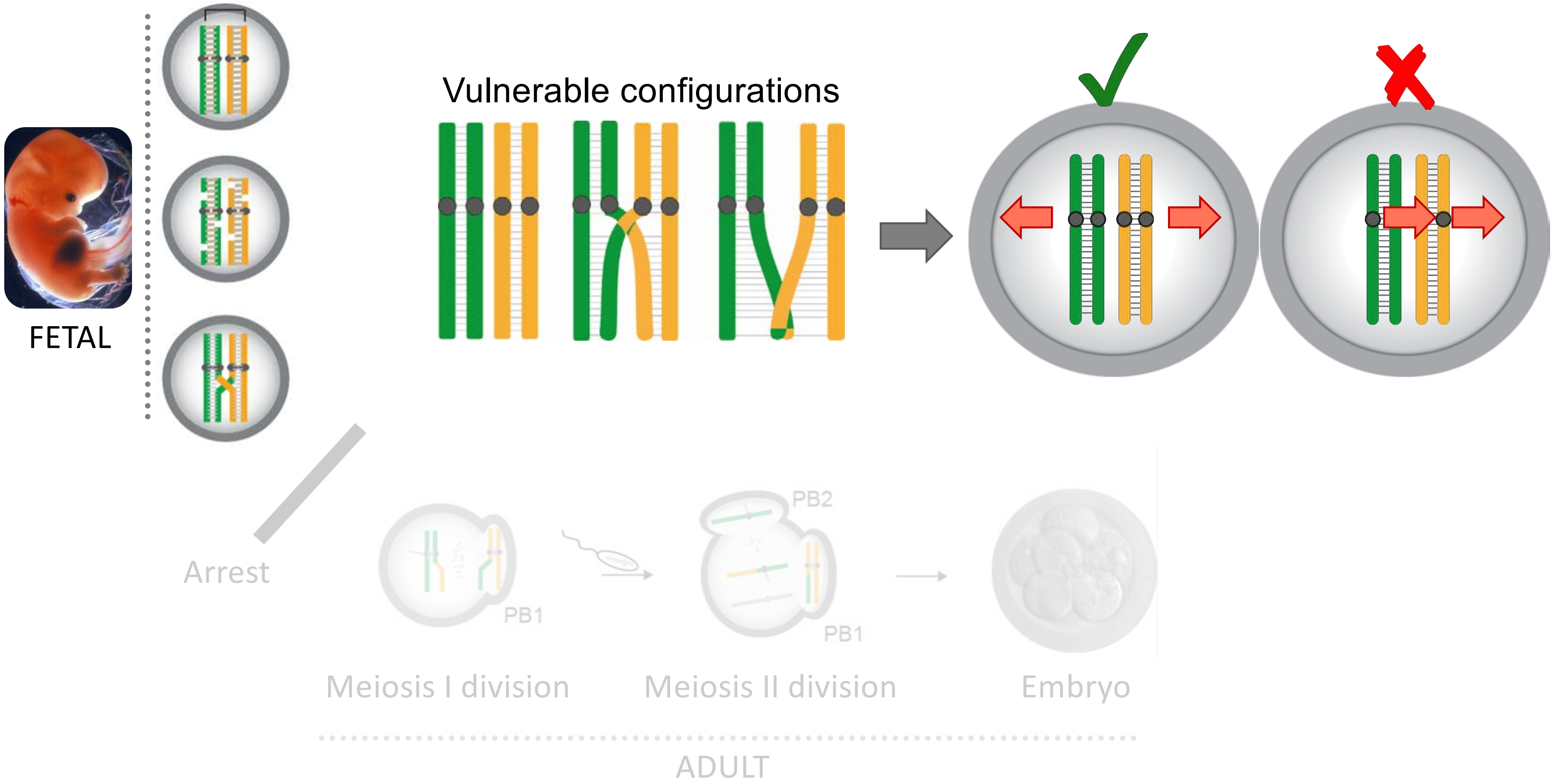
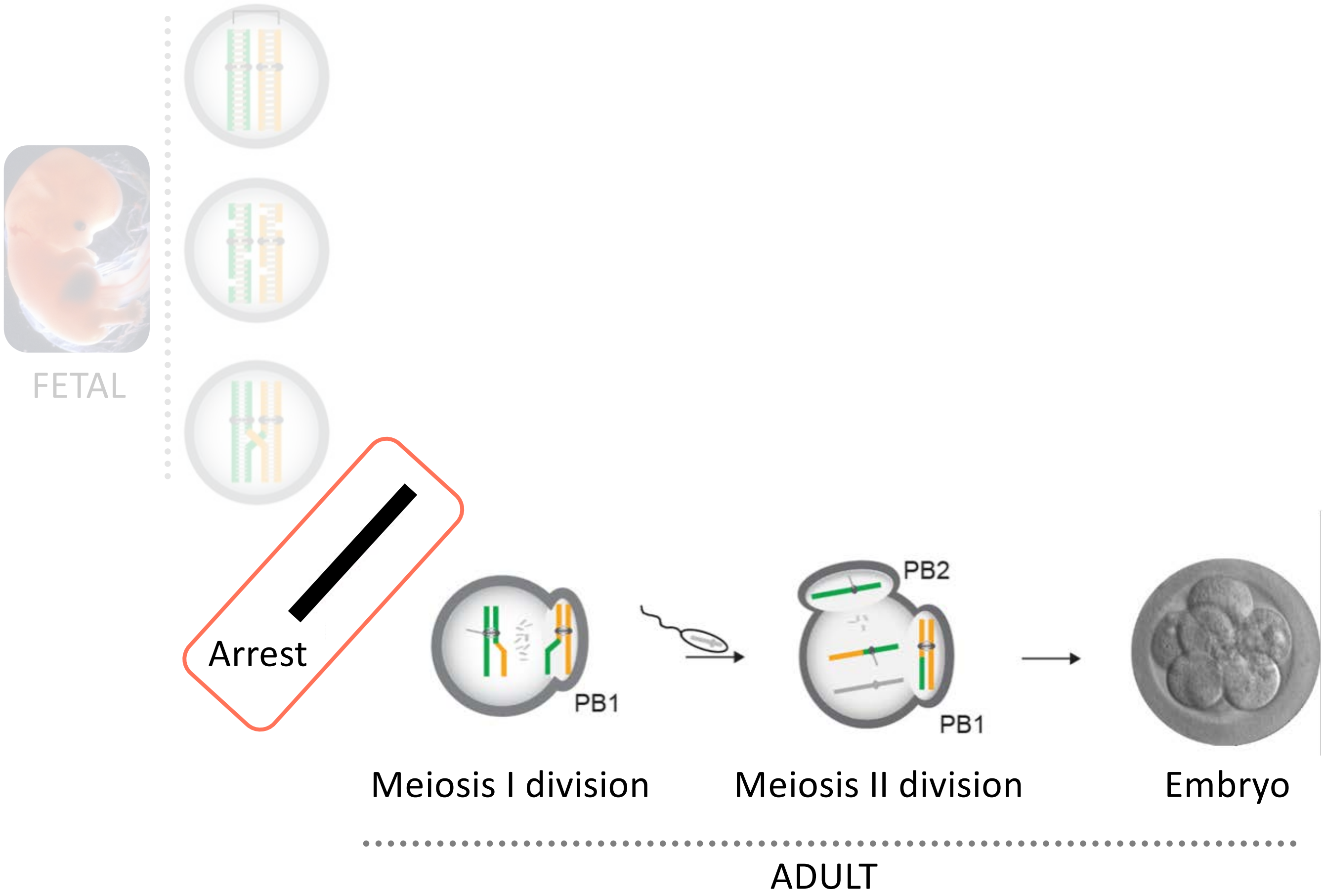


(Hassold *et al*, *Nature Genetics,* 1996)

Second Hit: Cohesion deterioration during prolonged arrest stage



(Duncan *et al*, *Aging Cell,* 2012; Zielinska *et al*, *eLife Sciences,* 2015; Patel *et al*, *Hum. Reprod. Update,* 2015; Lagirand-Cantaloube *et al*, *Sci Rep*, 2017)

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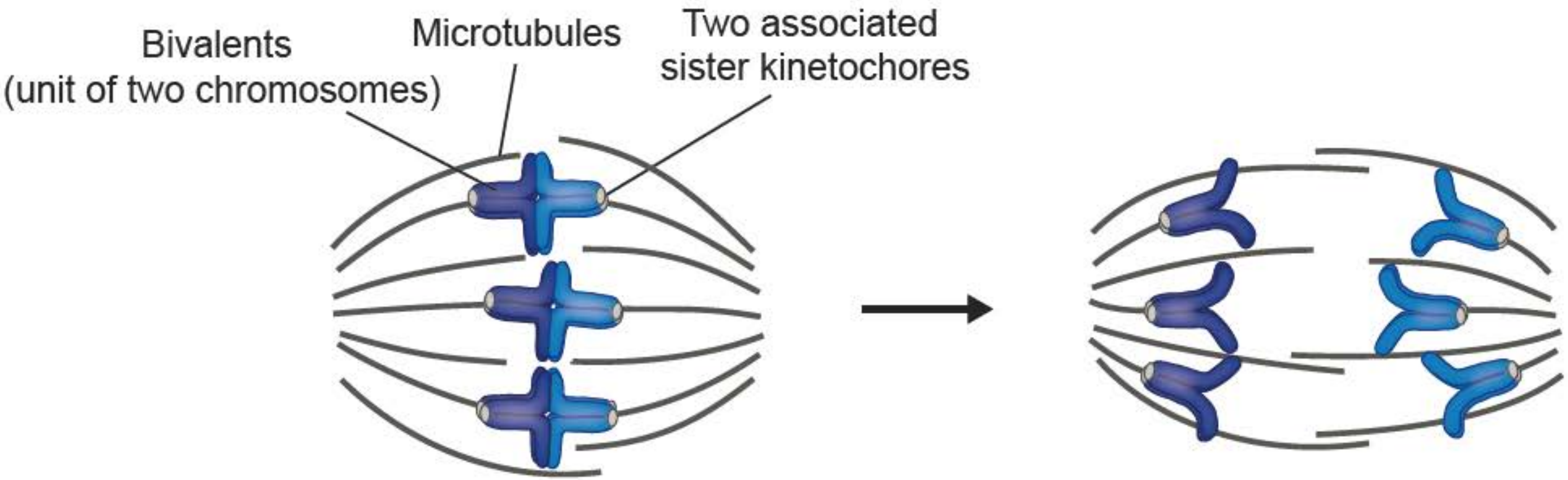

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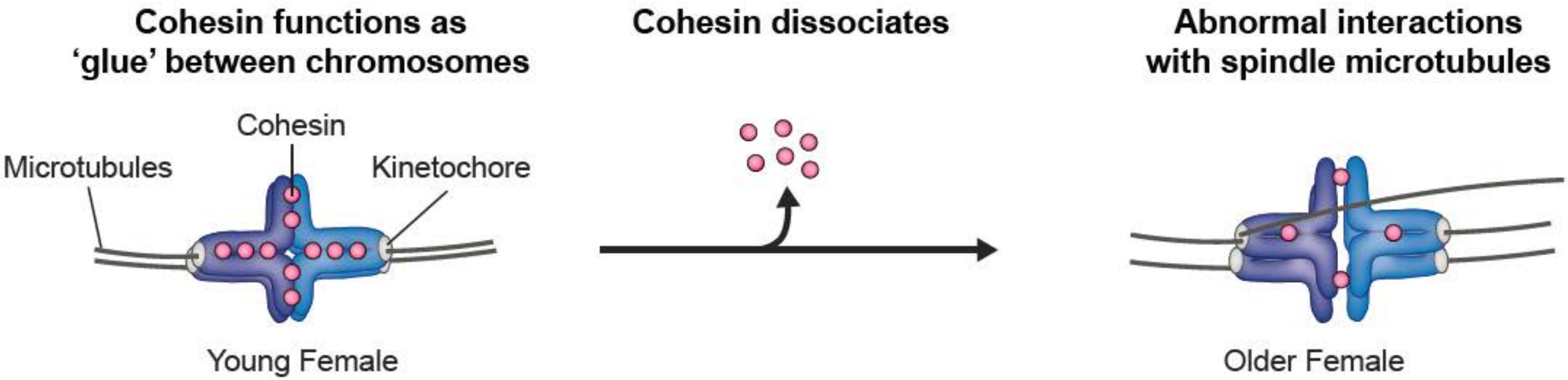
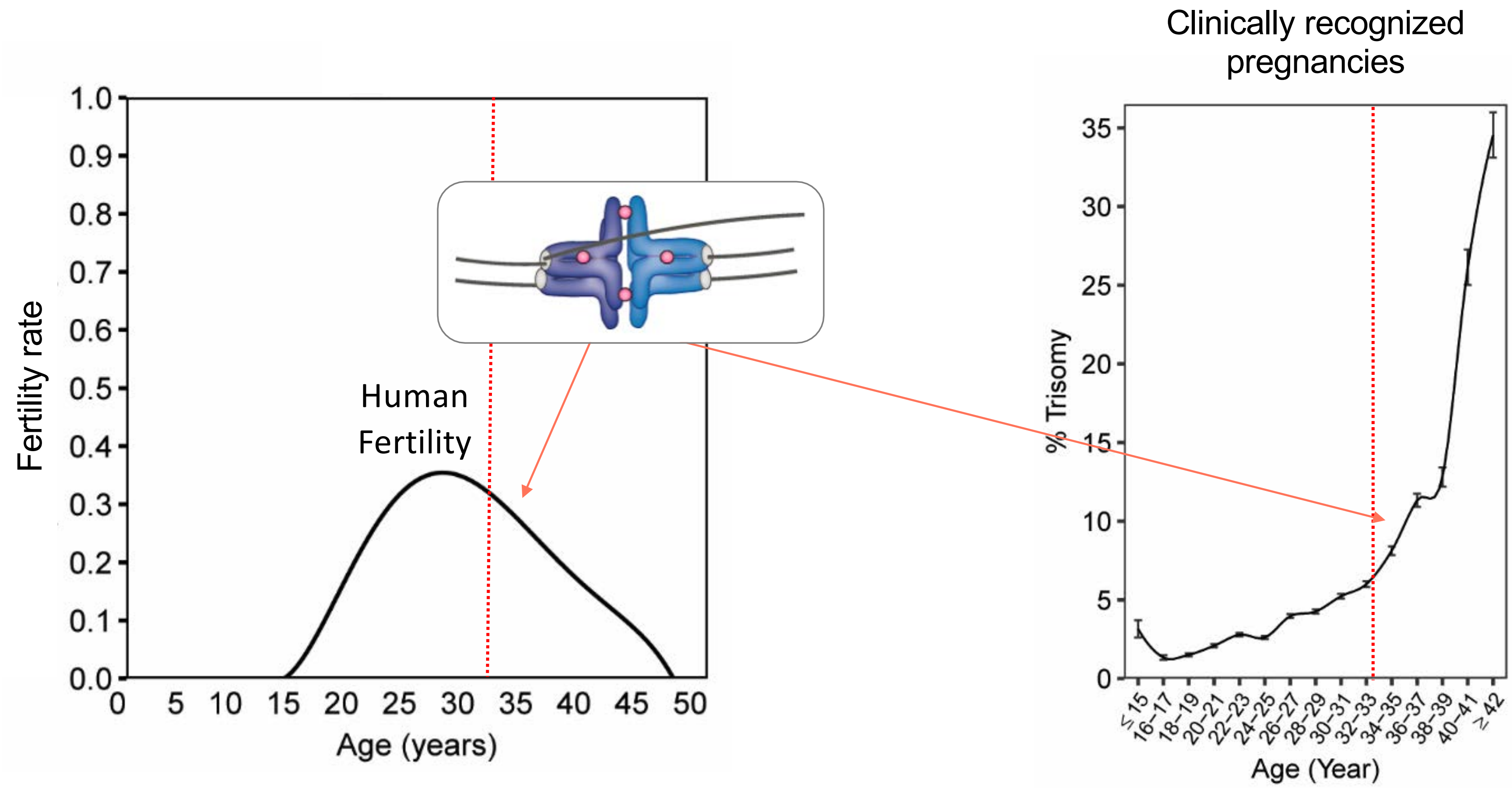
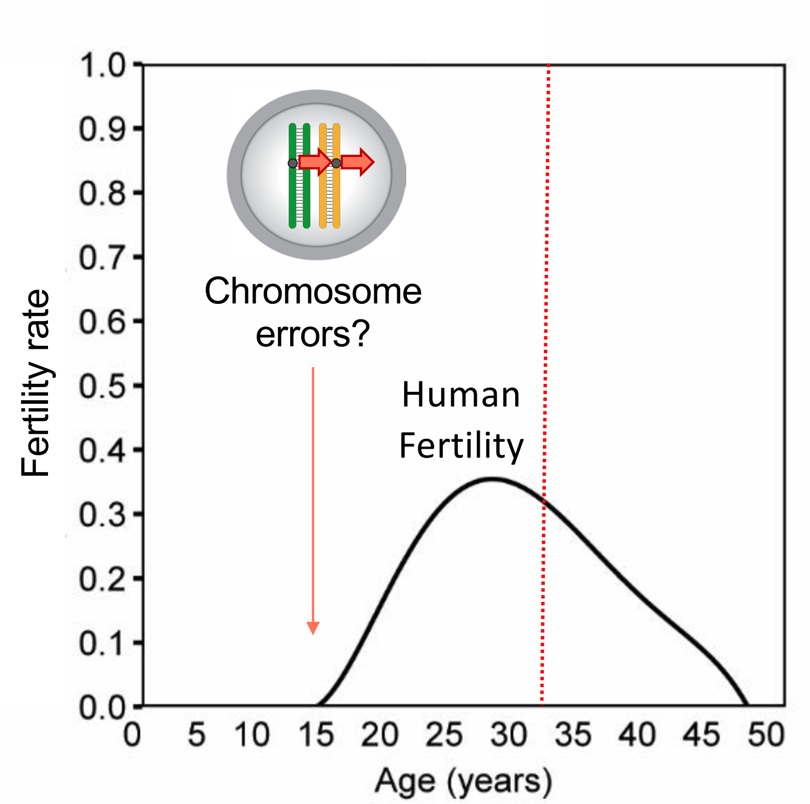


Cohesion deterioration speculated but not known: Indirect connection to segregation patterns

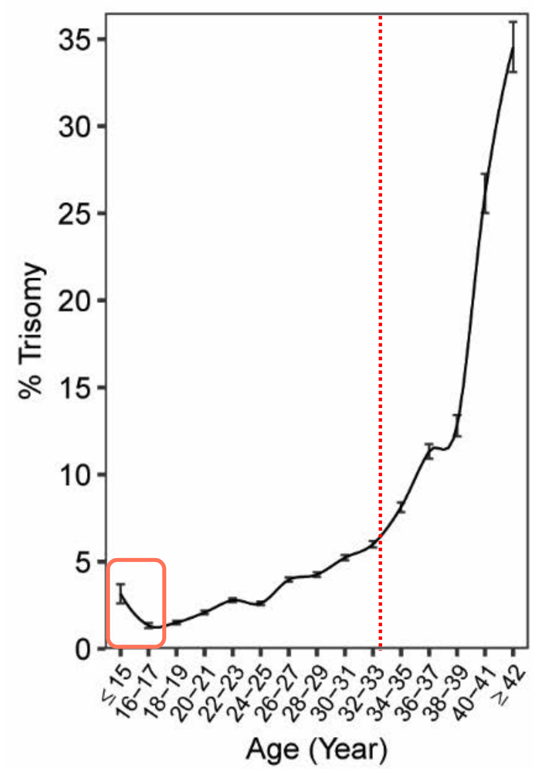


(Hassold *et al*, *Human Genetics,* 1985; Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019; Duncan *et al*, *Aging Cell,* 2012; Zielinska *et al*, *eLife Sciences,* 2015; Patel *et al*, *Hum. Reprod. Update,* 2015; Lagirand-Cantaloube *et al*, *Sci Rep*, 2017)

Chromosome-centric origin in young oocytes?

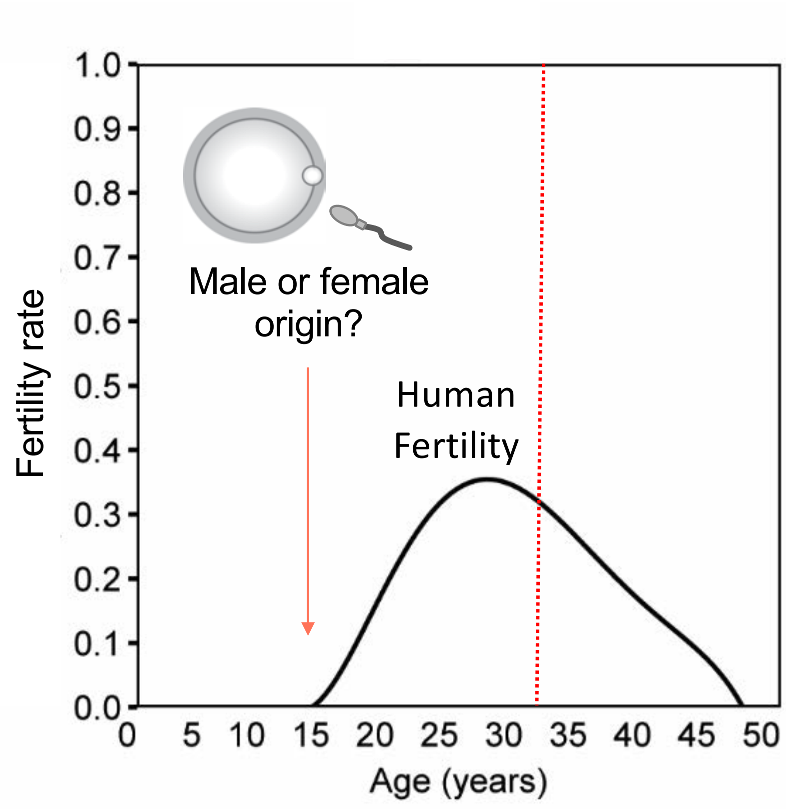


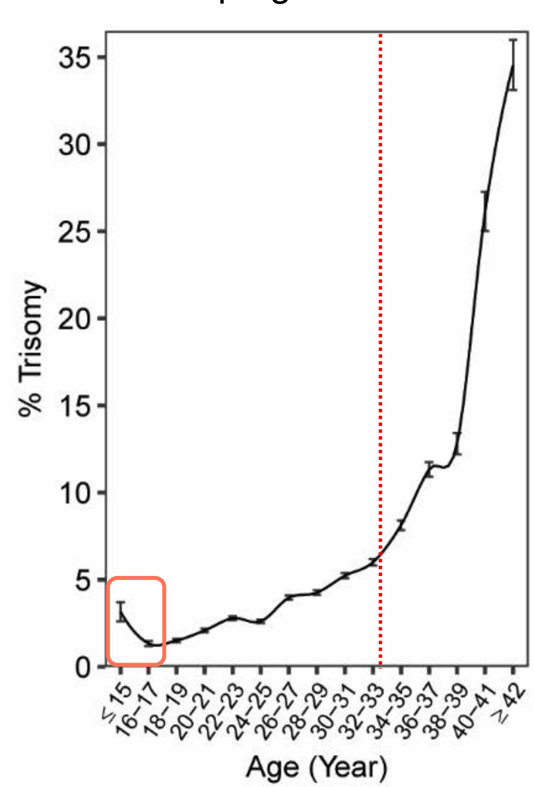
Clinically recognized pregnancies



(Hassold *et al, Human Genetics*, 1985; Zelazowski *et al, Cell*, 2017; Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

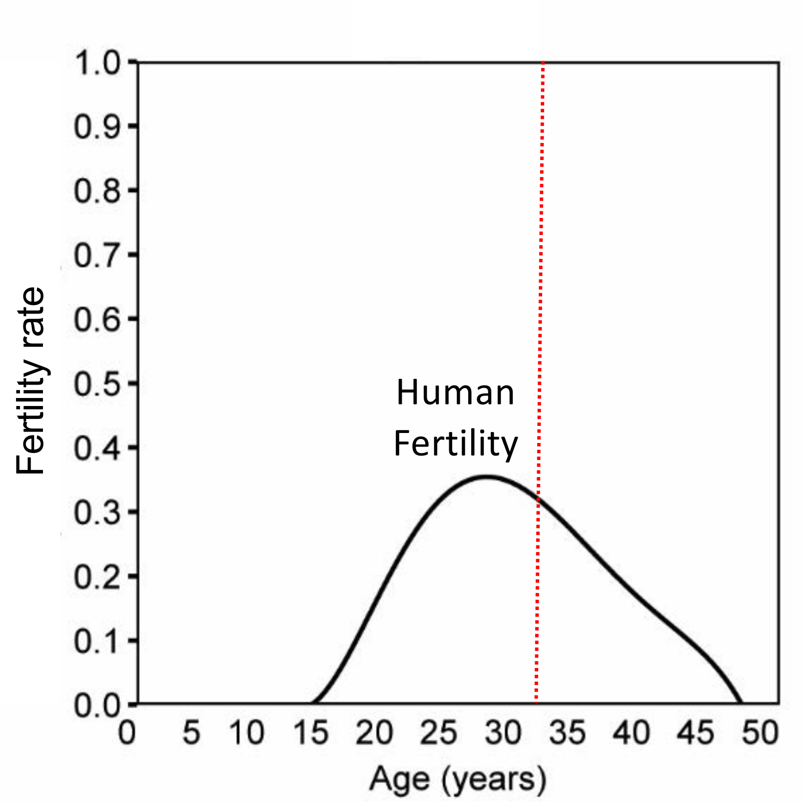
Female origin in young oocytes?





(Hassold *et al, Human Genetics*, 1985; Zelazowski *et al, Cell*, 2017; Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

Shaping natural fertility across the whole age spectrum

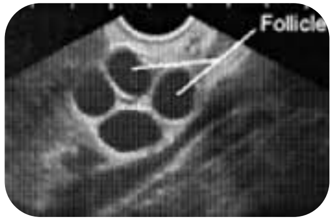


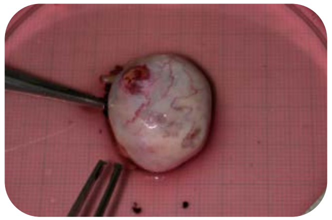
- Chromosome errors in oocytes
- Age-dependent changes
- Impact on fertility

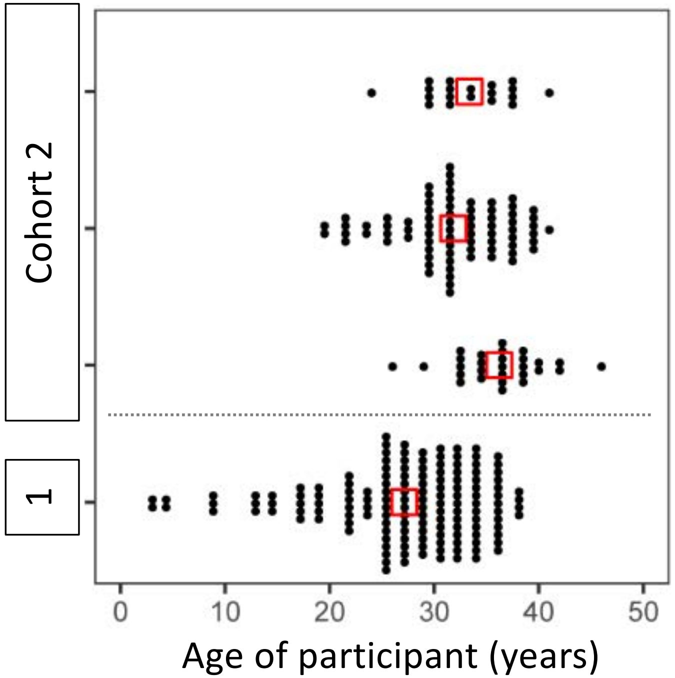
(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

Population age range (2.5 – 42)

>3,000 oocytes, 256 women, 218 aneuploidy analysis



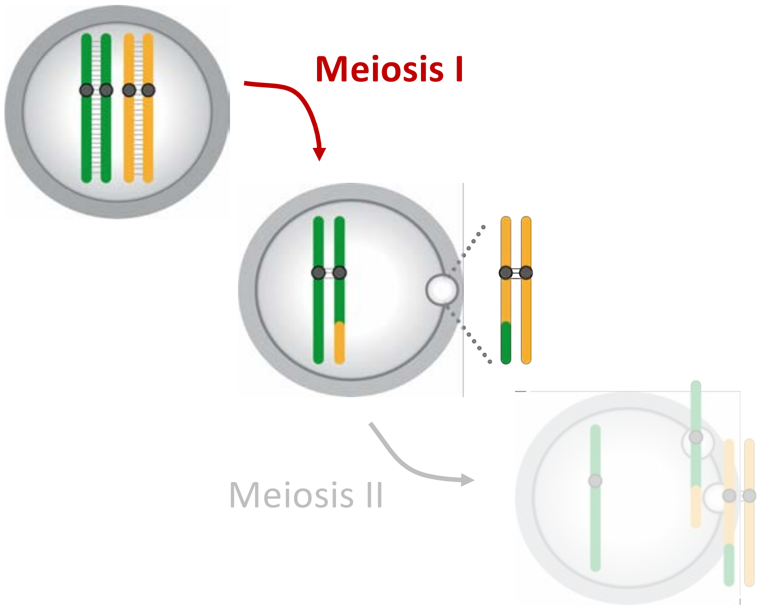


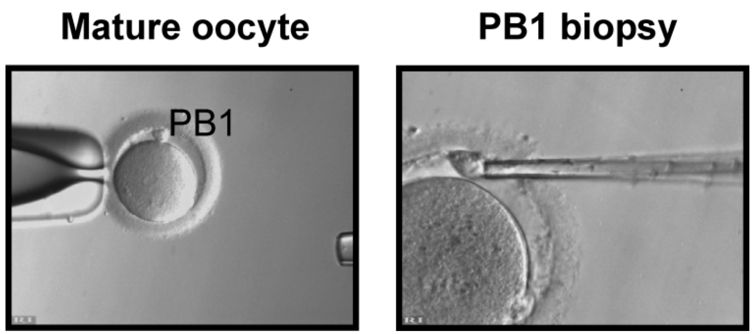


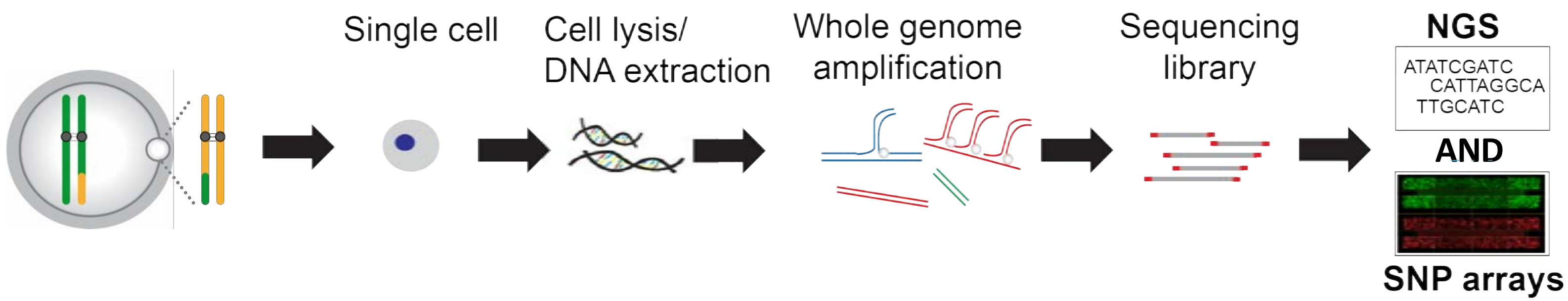
*GLM analysis shows no effect of cohort

(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

Single cell technologies to explore aneuploidy

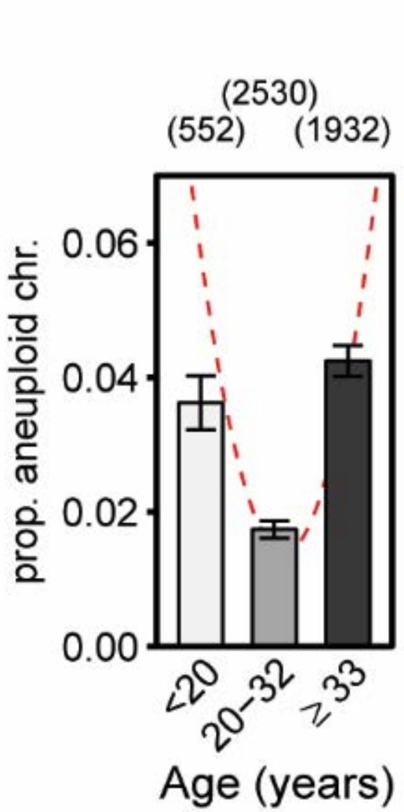






(Blanshard *et al*, *Methods in Cell Biology*, 2018)

U-shaped curve of aneuploidy in oocytes



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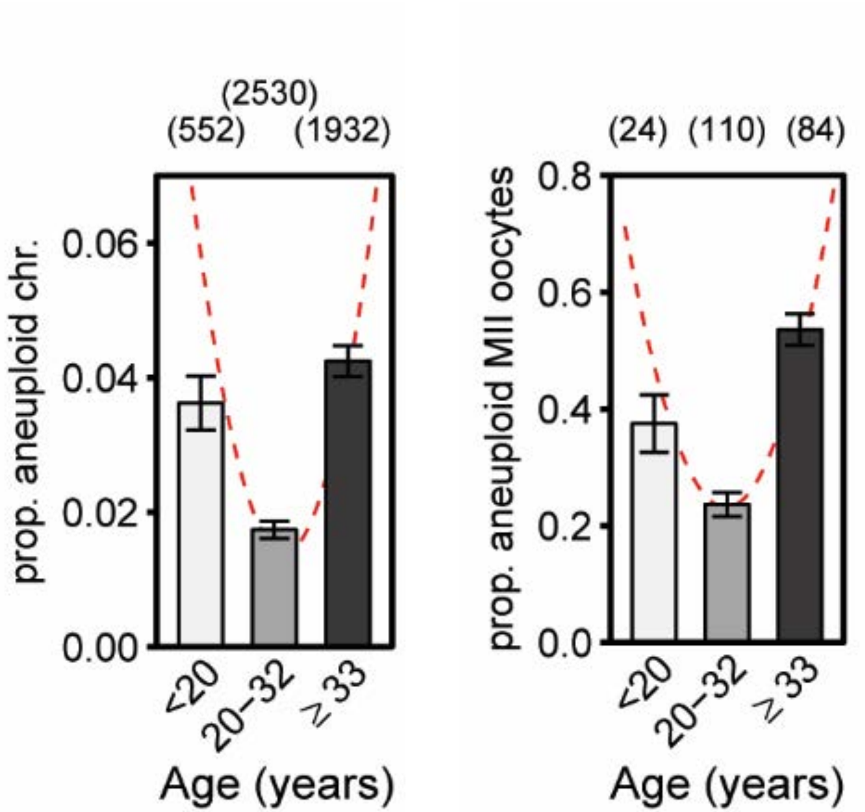

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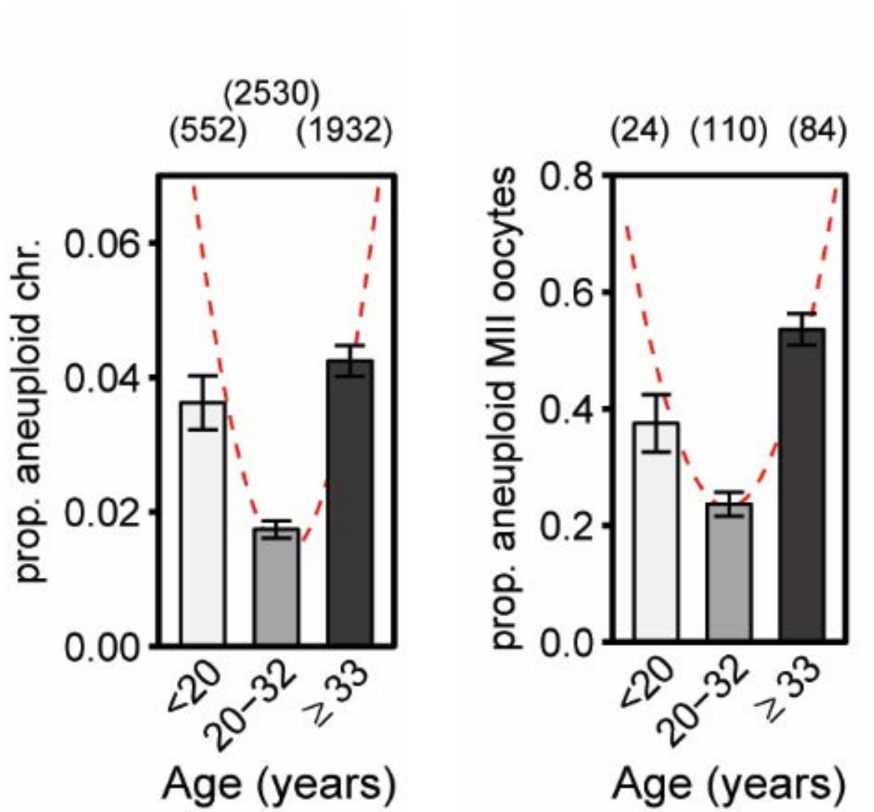
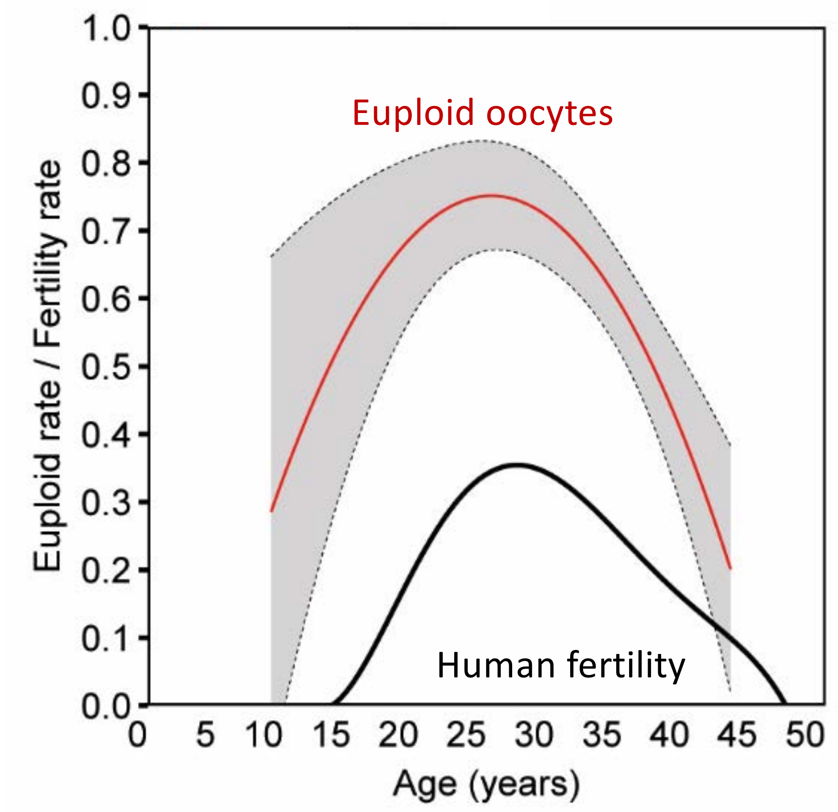


** All autosomal monosomies, and a majority of trisomies are not viable, and only a single chromosome error is needed to lead to failed implantation and/or pregnancy loss.

*glm analysis showed no effect of cohort

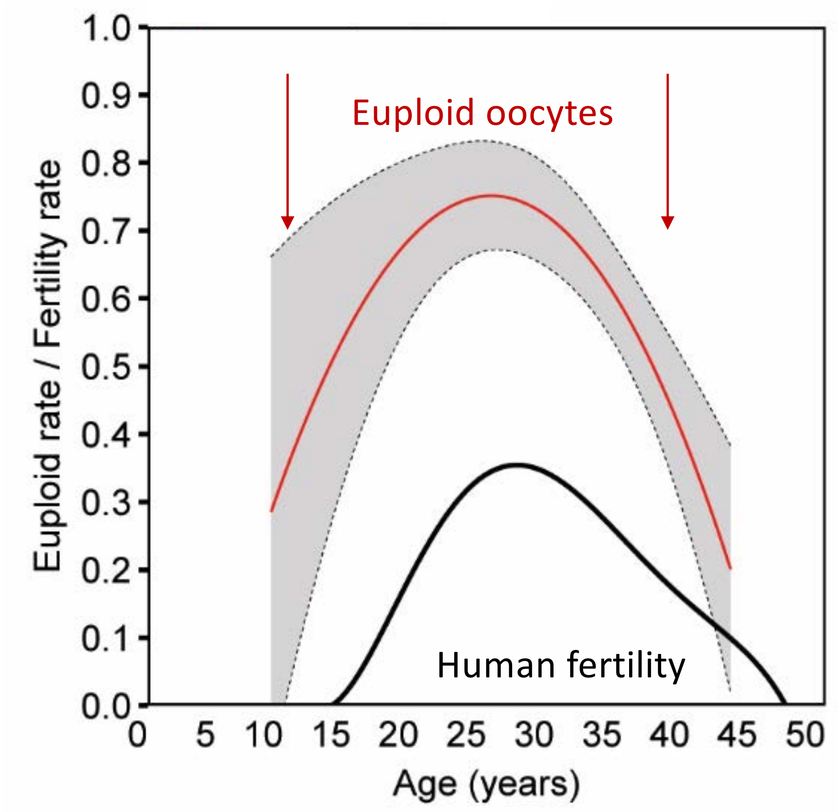
(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

Tapered fertility in both young and older women mediated by aneuploidy



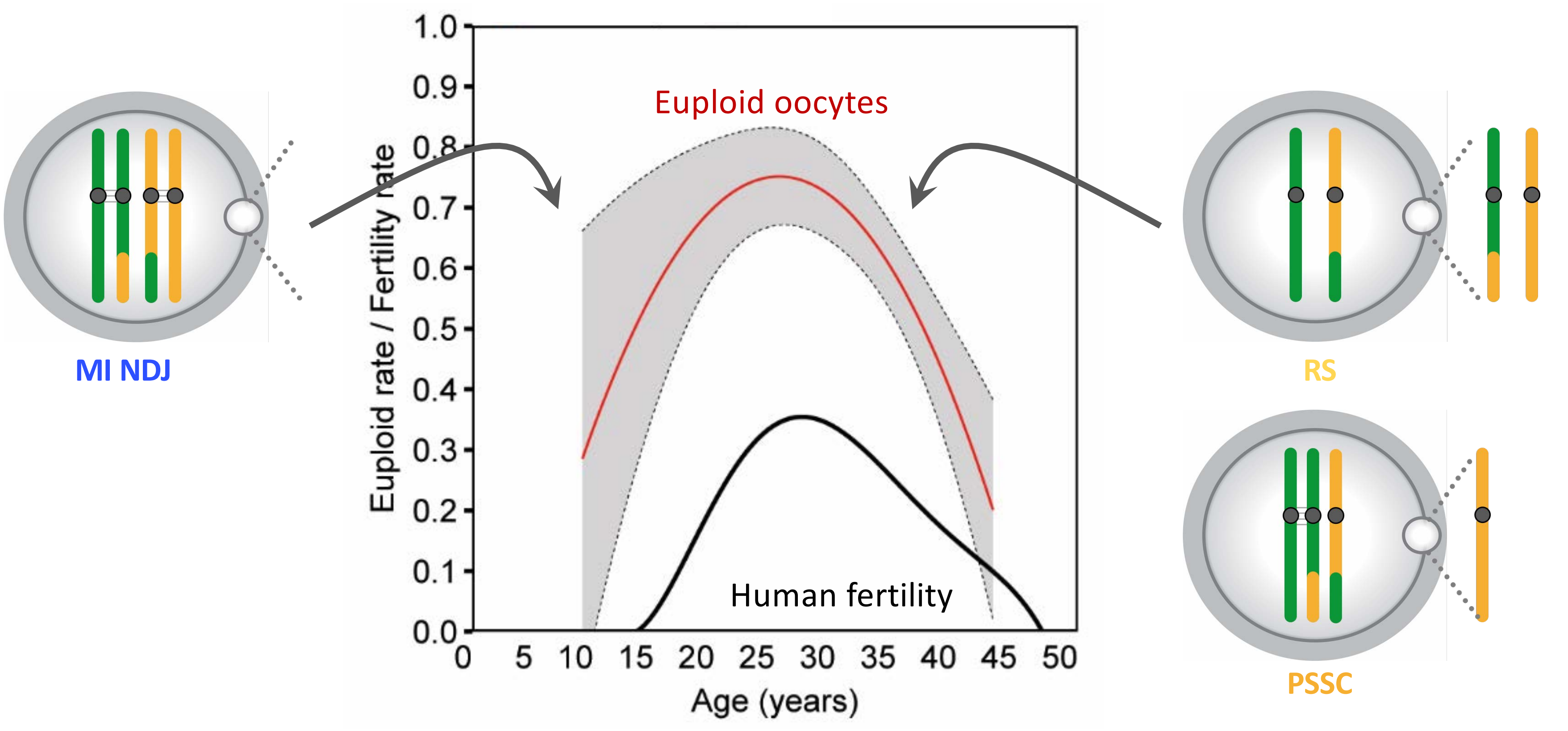
(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

What chromosome-centric mechanism could shape both ends of the aneuploidy curve?

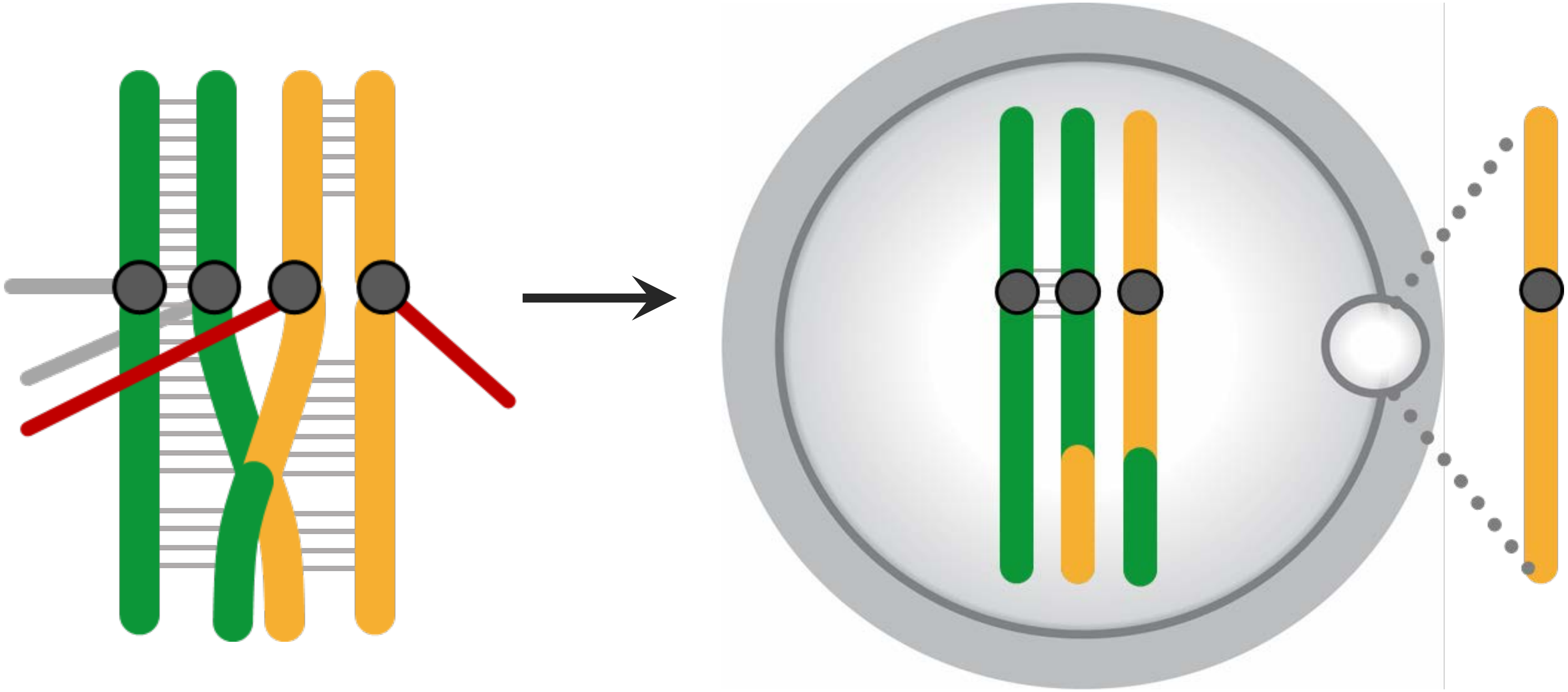


(Gruhn, Zielinska, Shukla, Blanchard, *et al.*, *Science*, 2019)

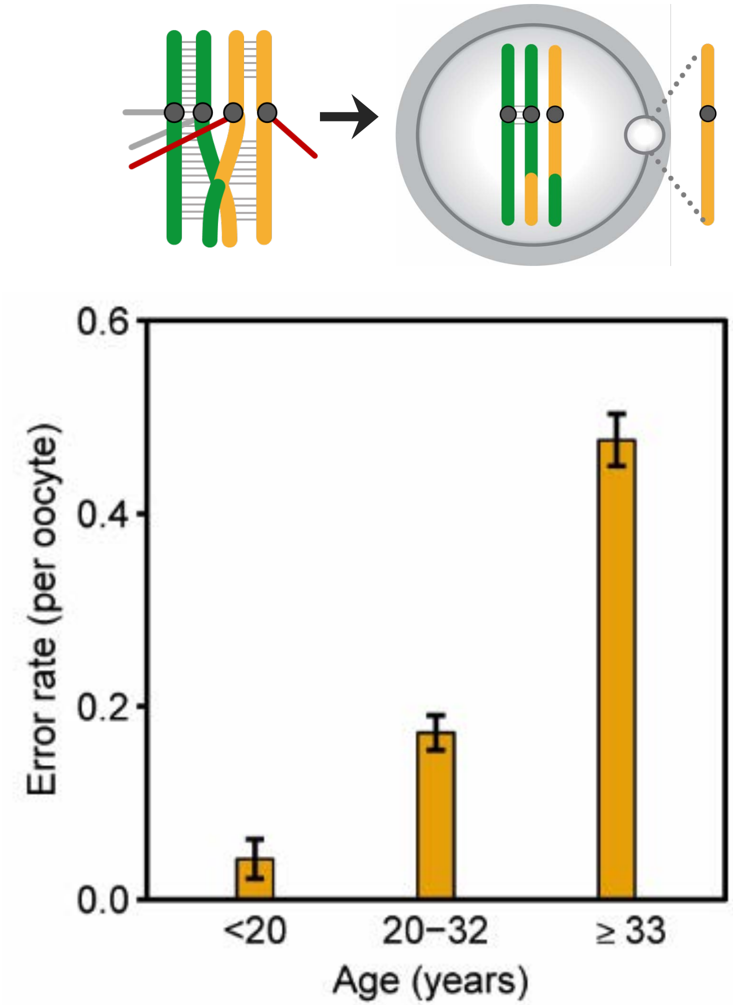
Chromosome error types drive aneuploidy in an age-dependent manner



Loss of centromeric cohesion & PSSC



Loss of centromeric cohesion & PSSC: Linear with age



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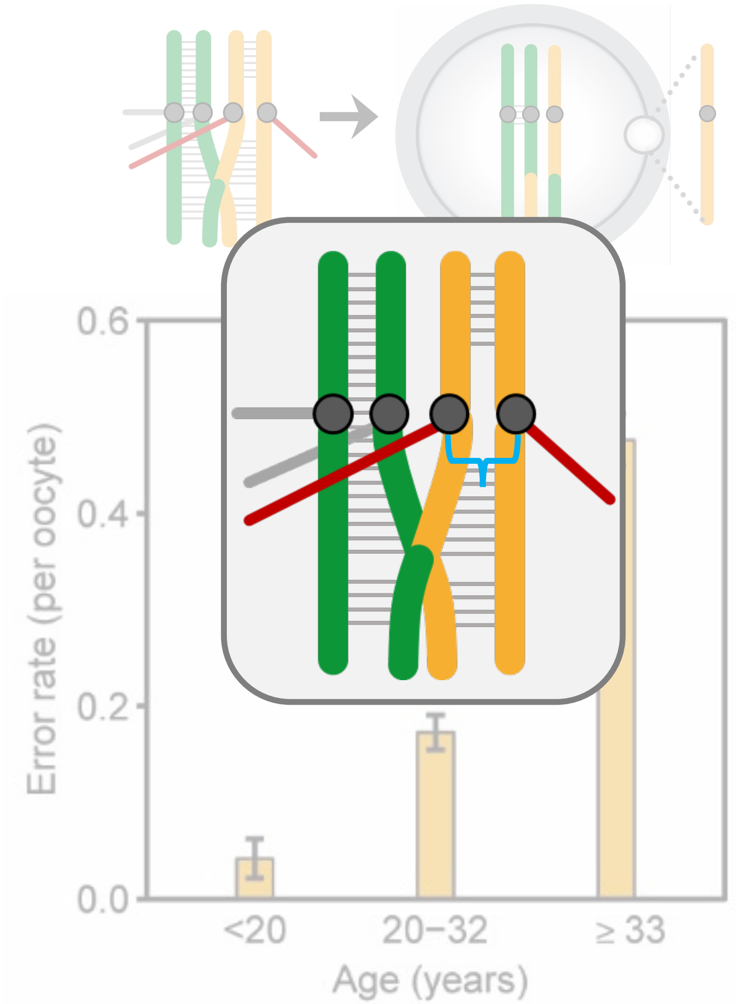

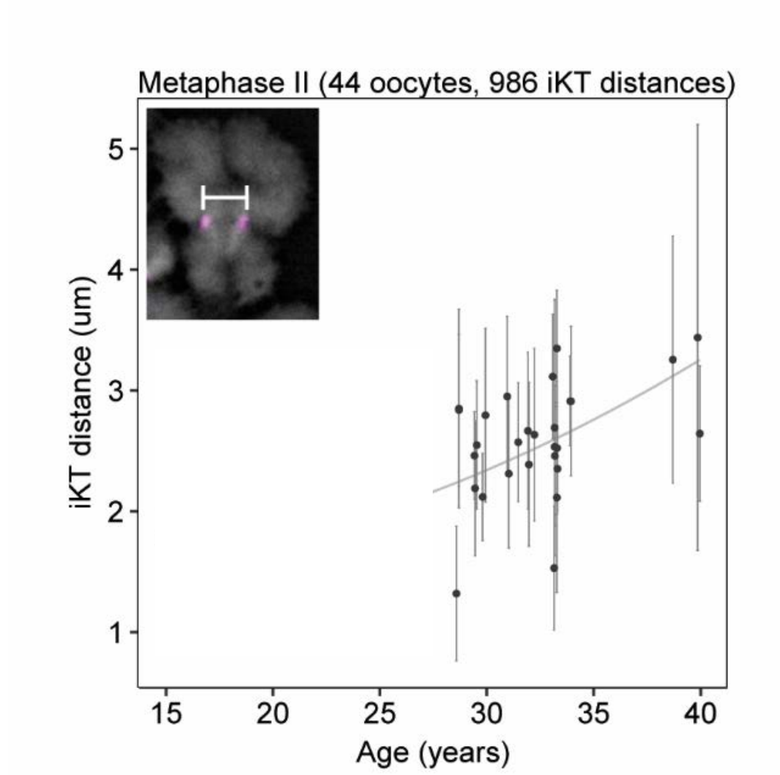

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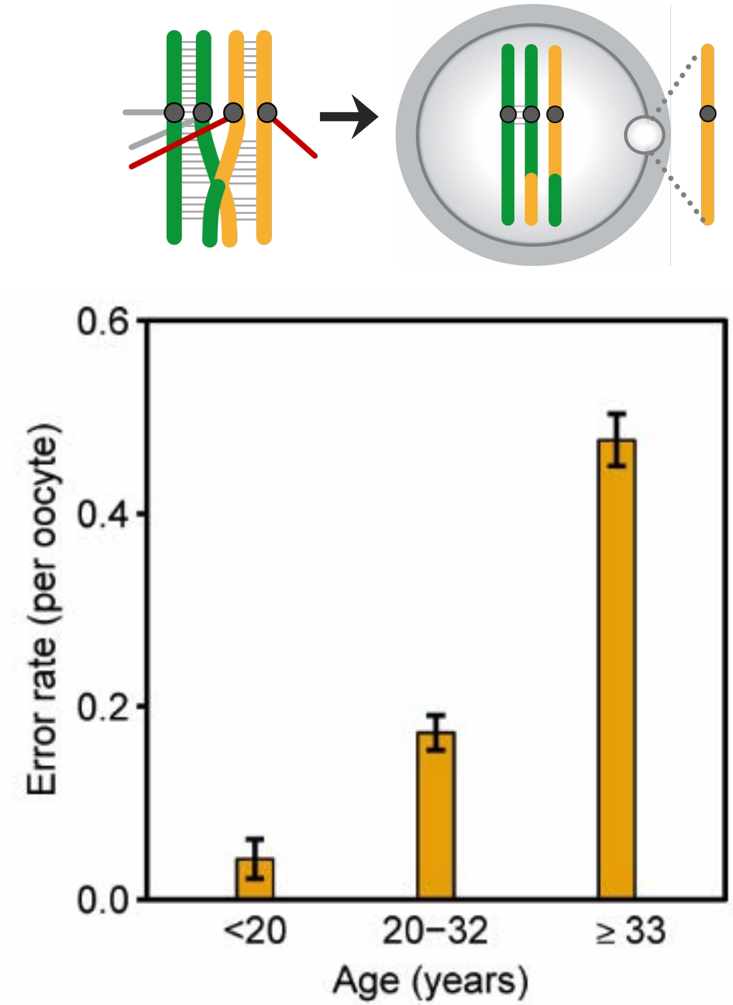
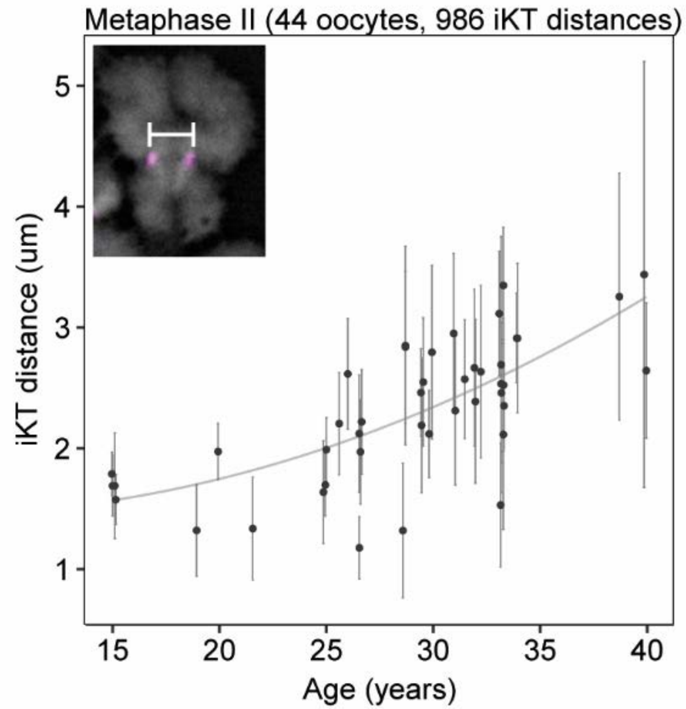
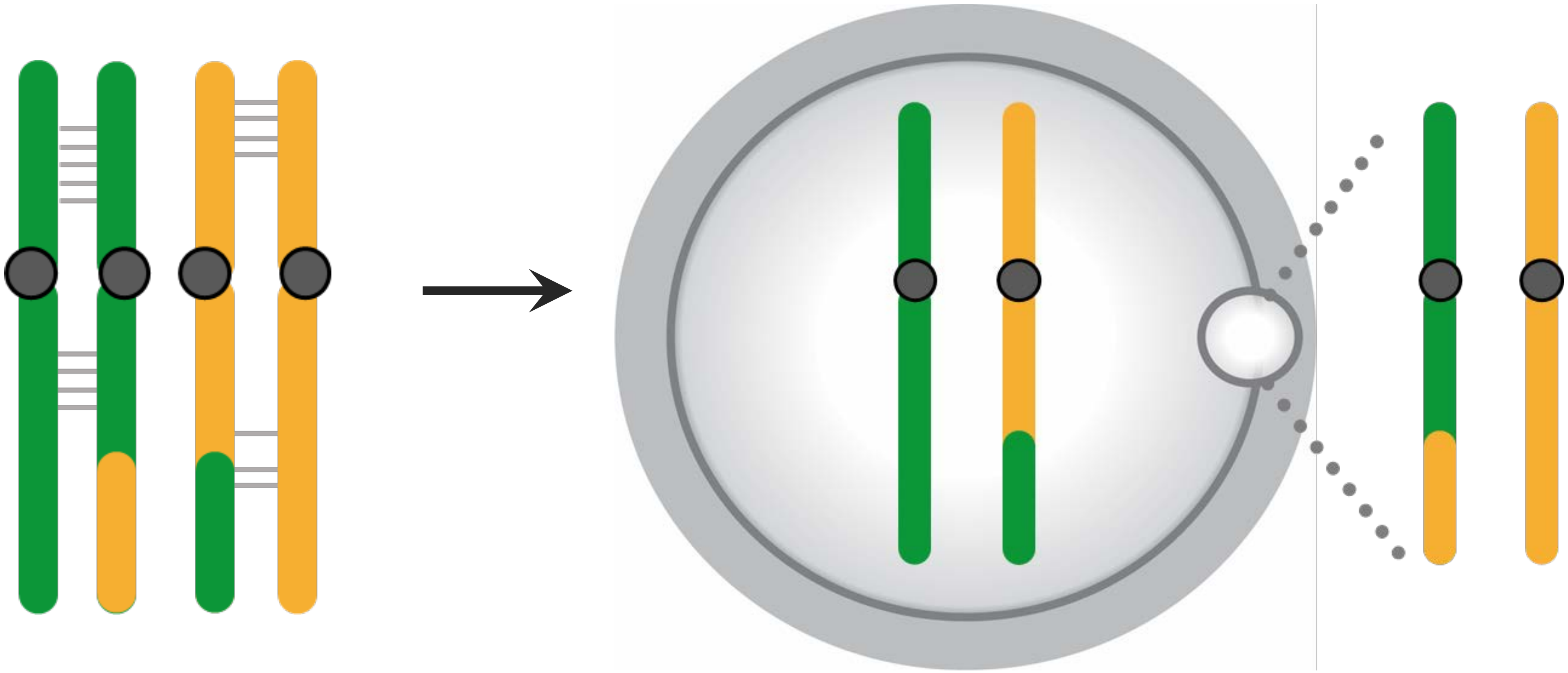




More extreme cohesion loss (centromere & arm) & Reverse Segregation



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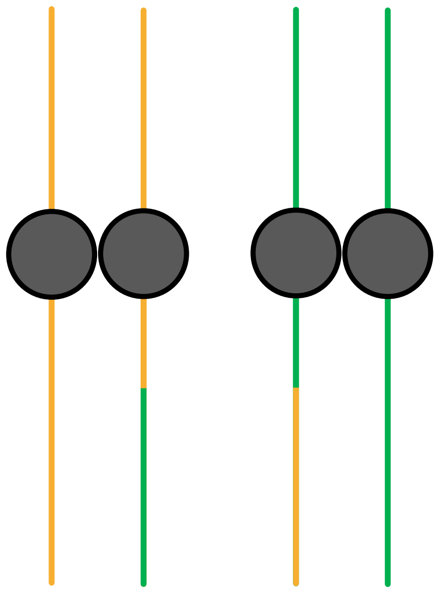

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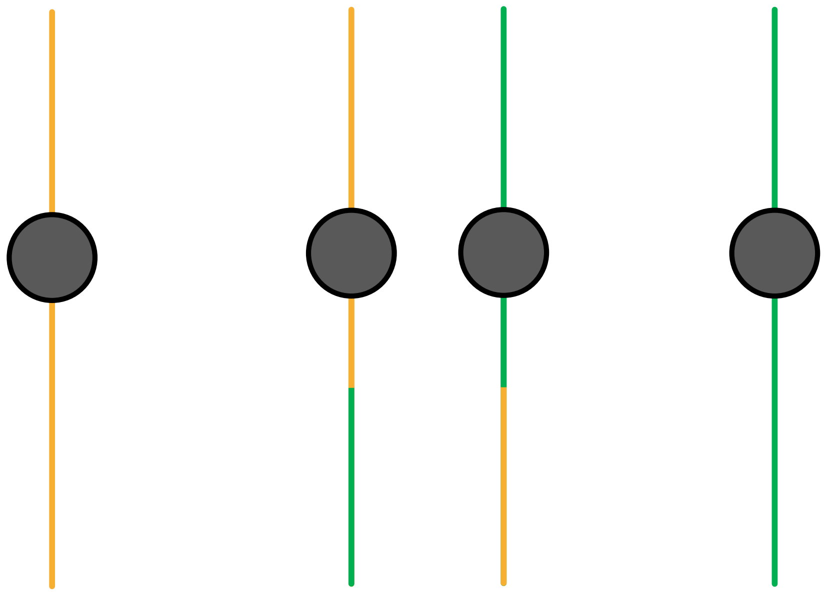

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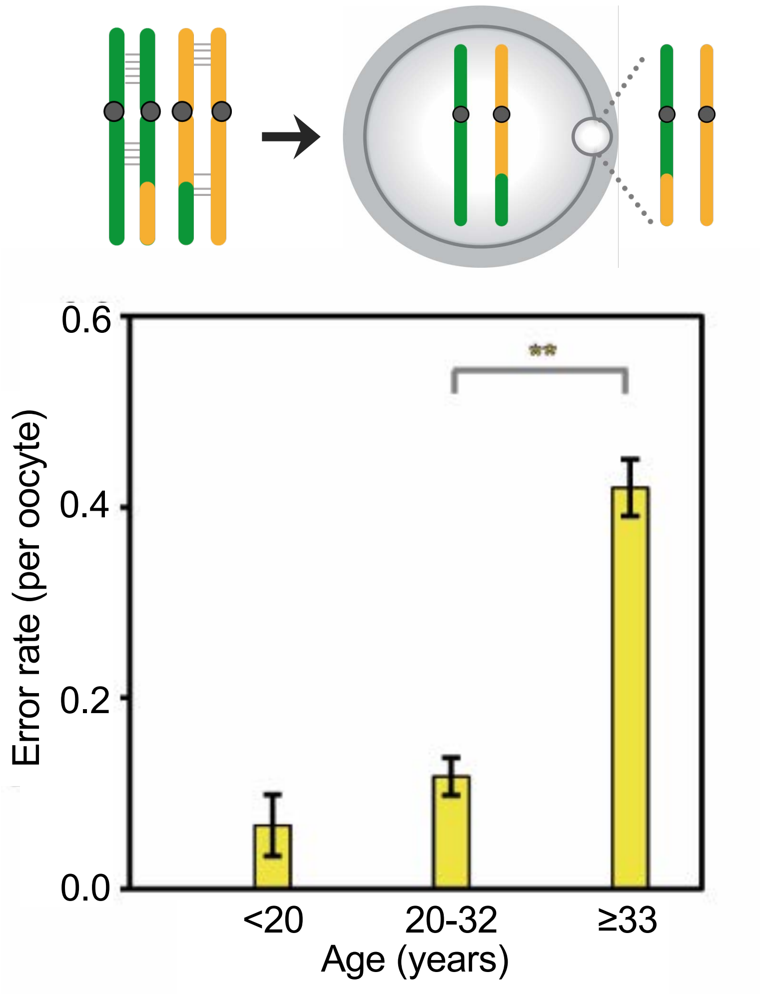
More extreme cohesion loss (centromere & arm) & Reverse Segregation: AMA



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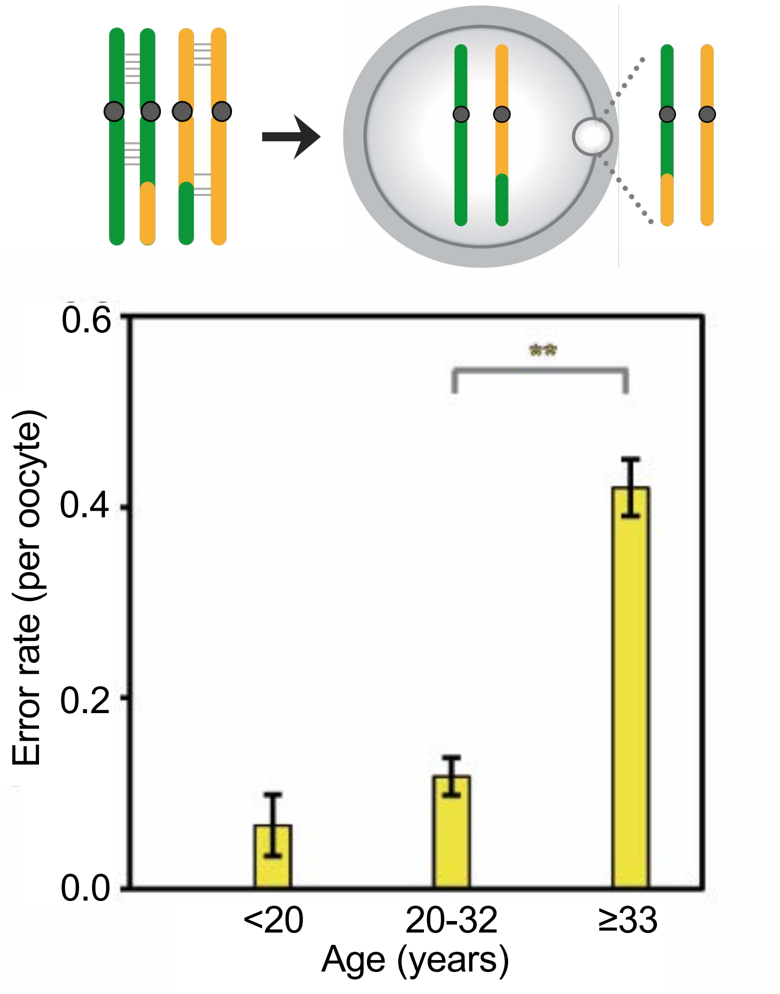

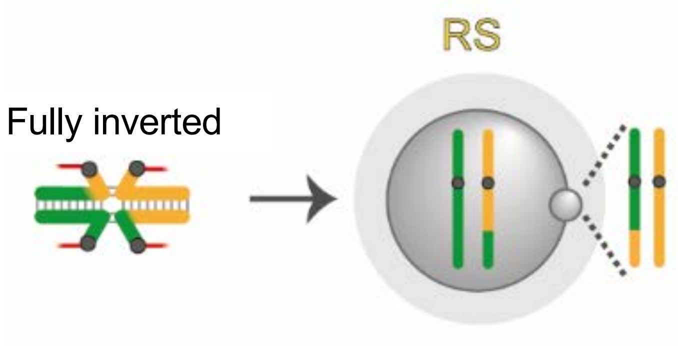

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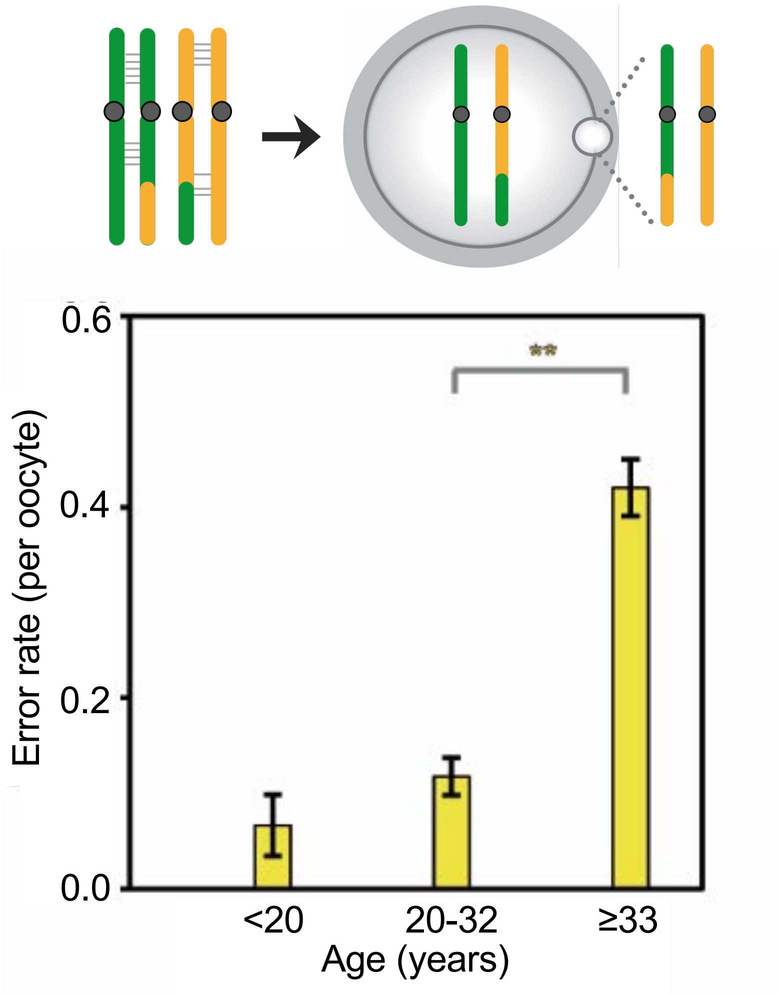

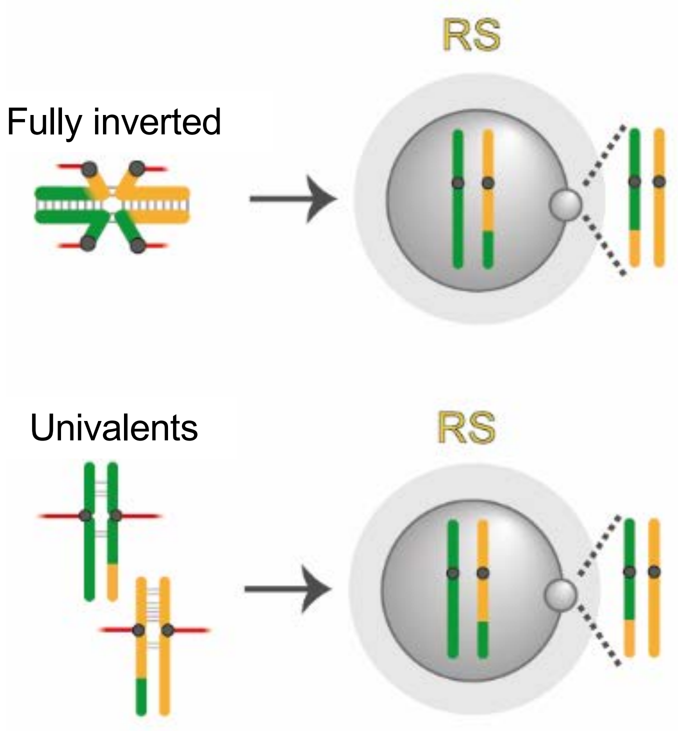

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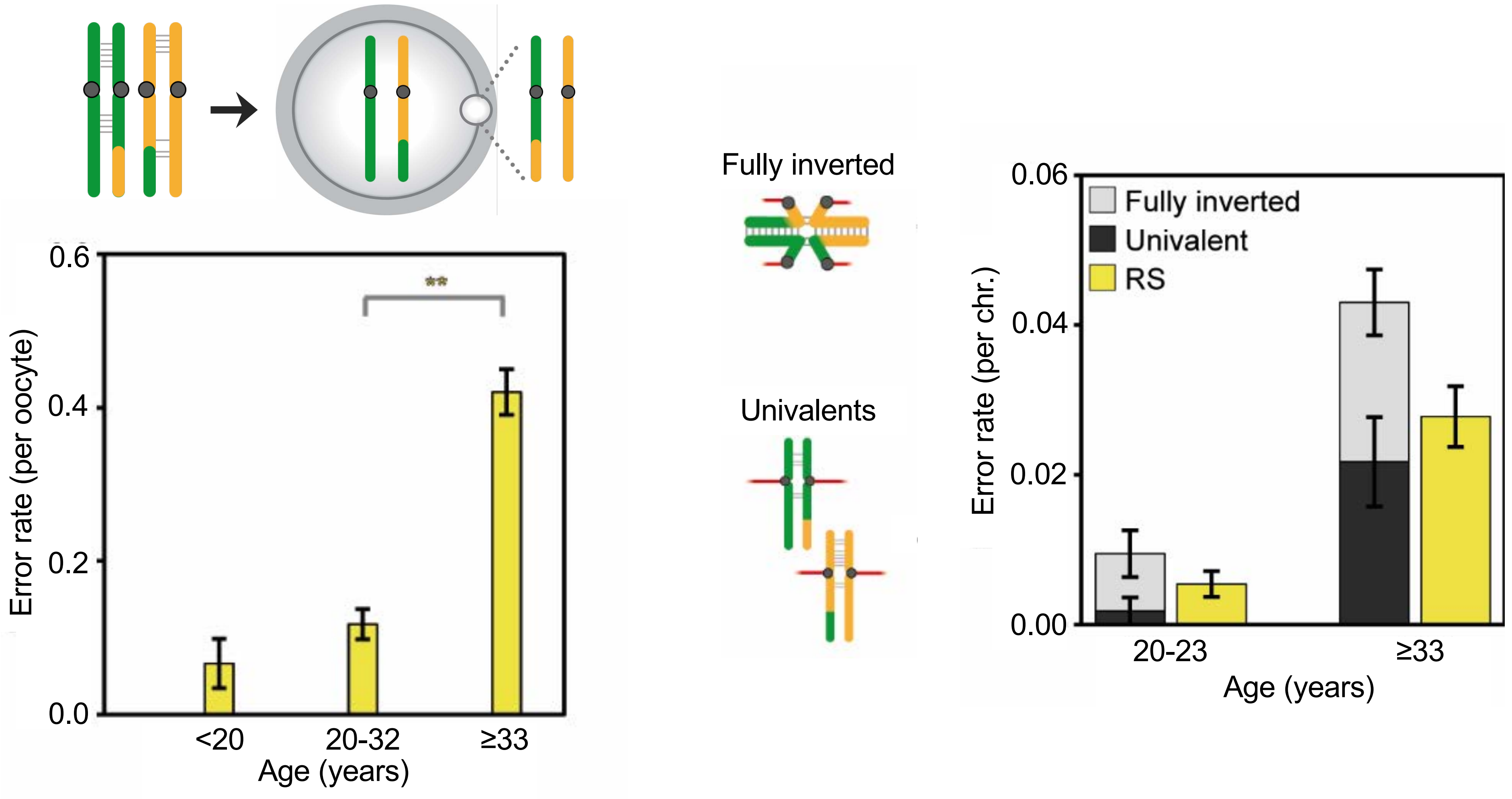

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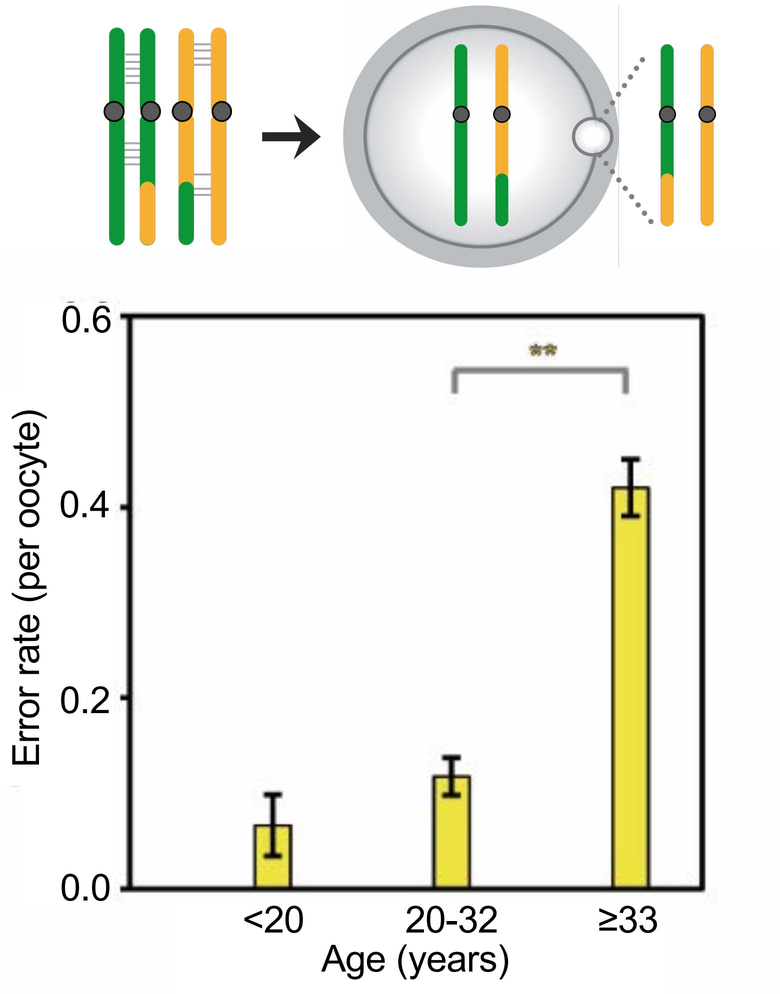
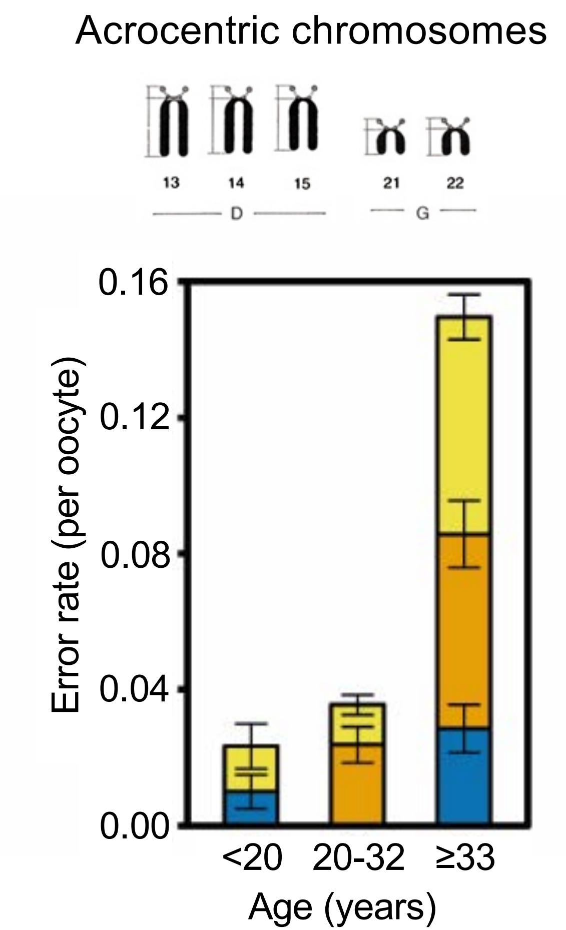
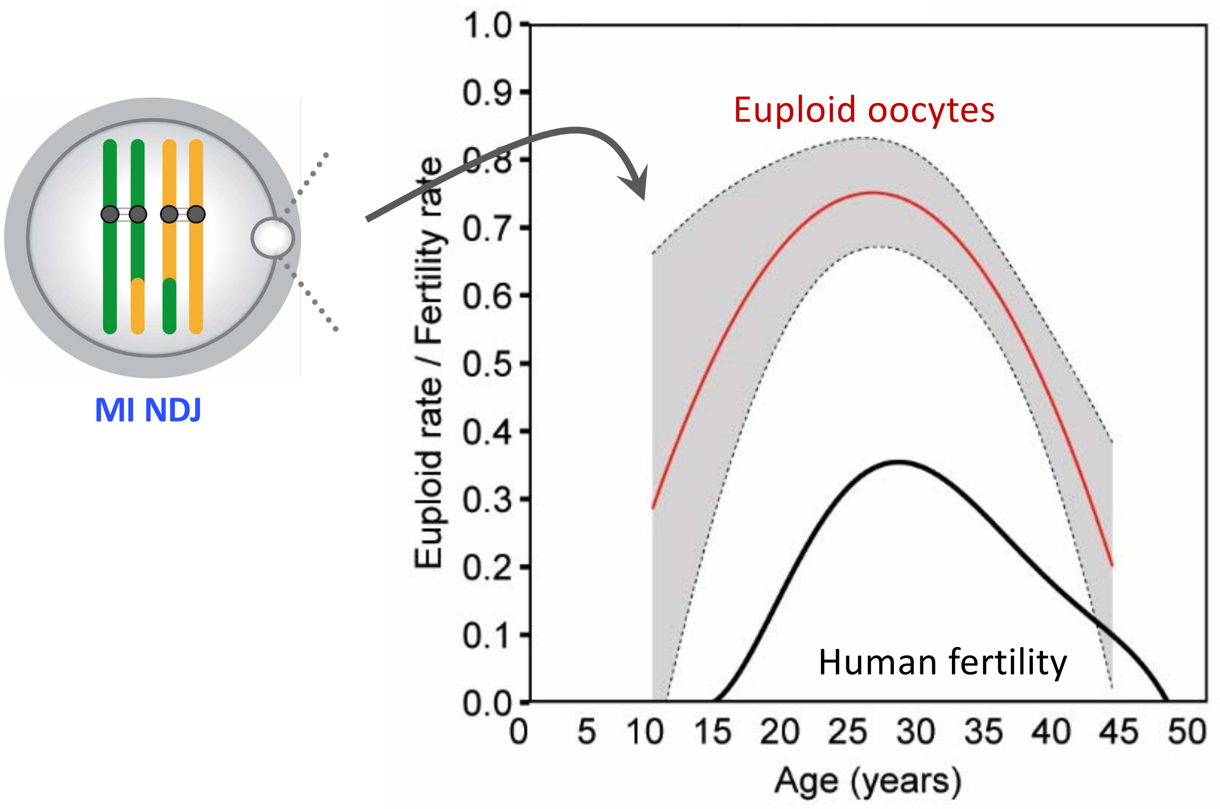
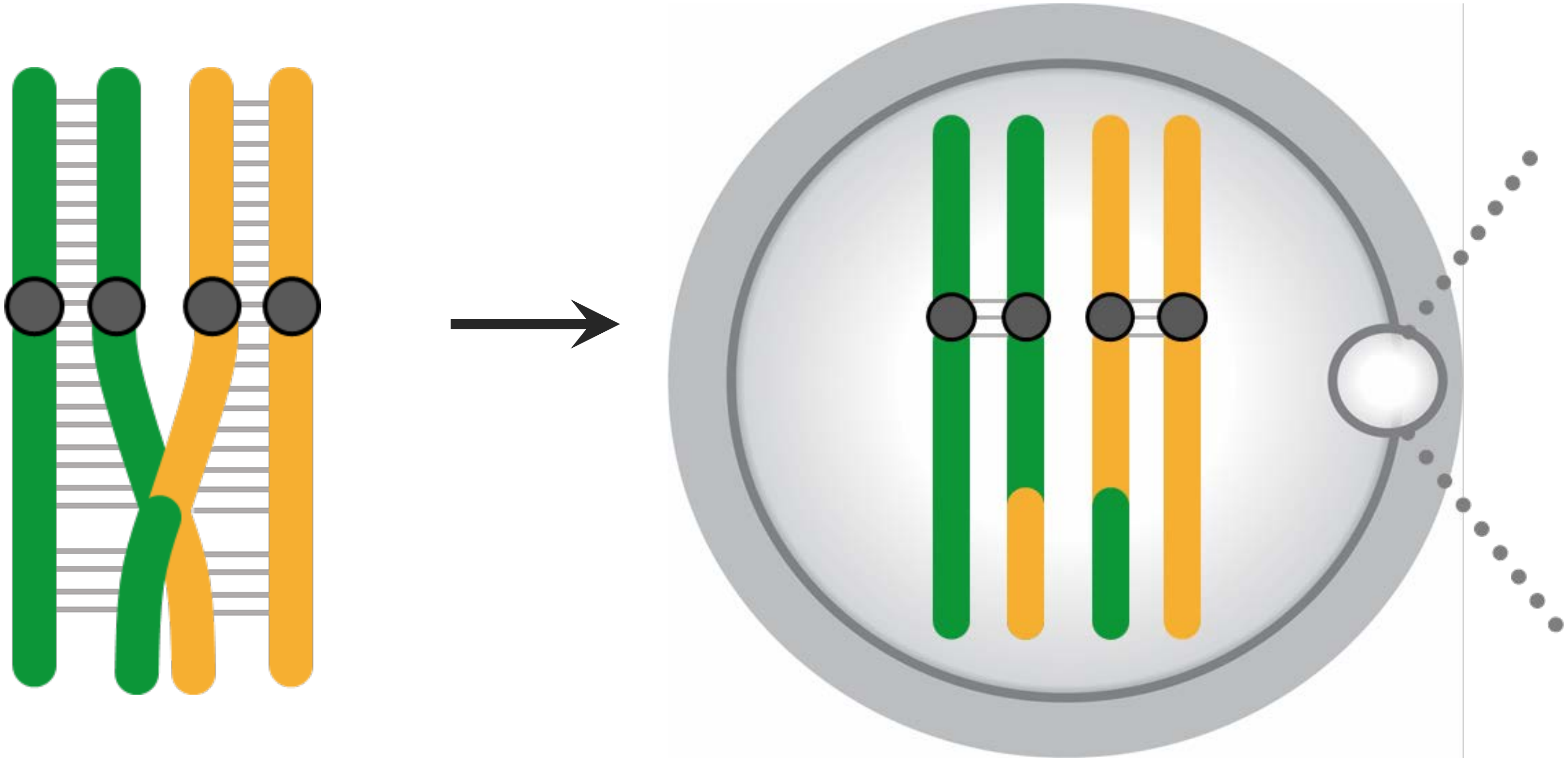




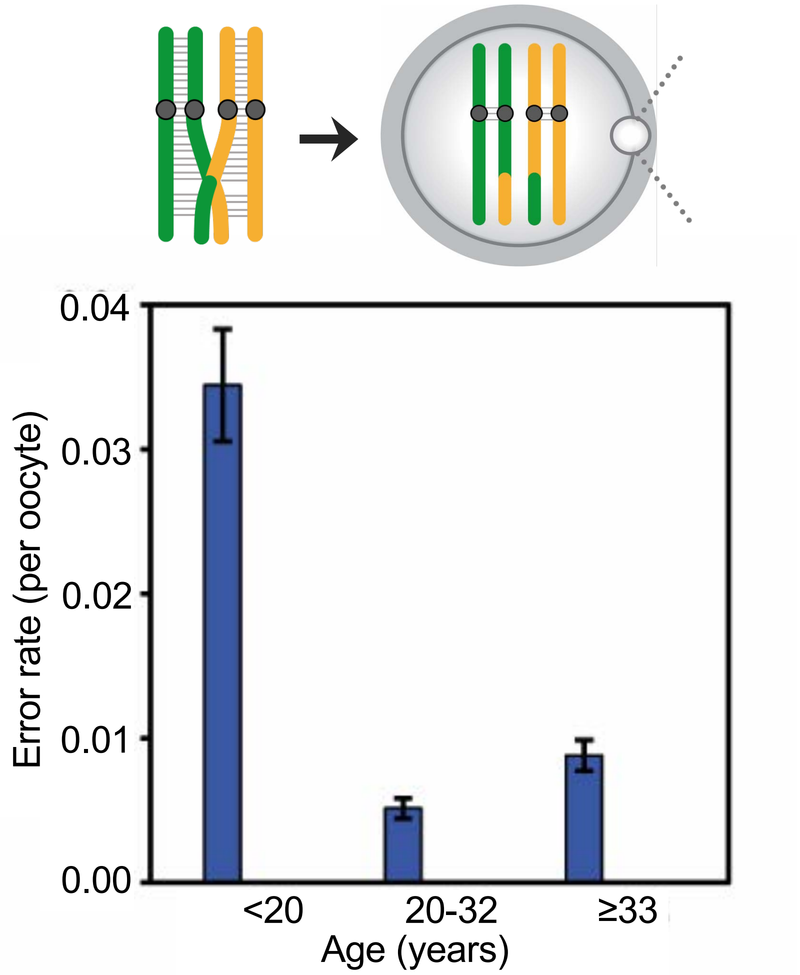
Chromosome errors in 'young' oocytes



Youngest oocytes & Meiosis I non-disjunction (MI NDJ)



Largest chromosomes & MI NDJ: ‘young’



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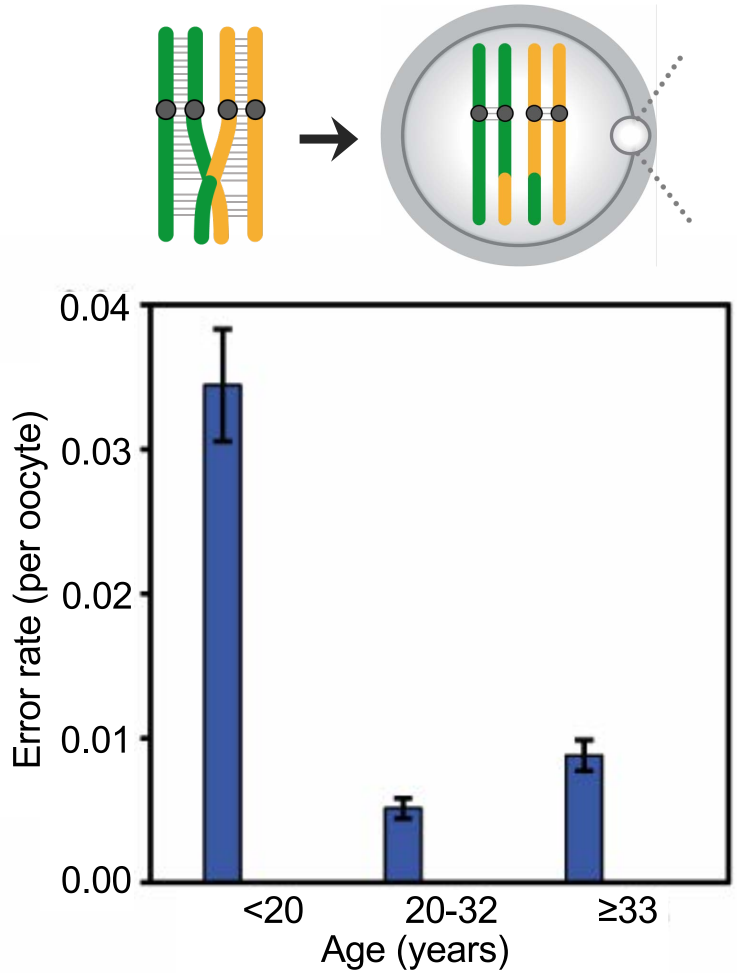
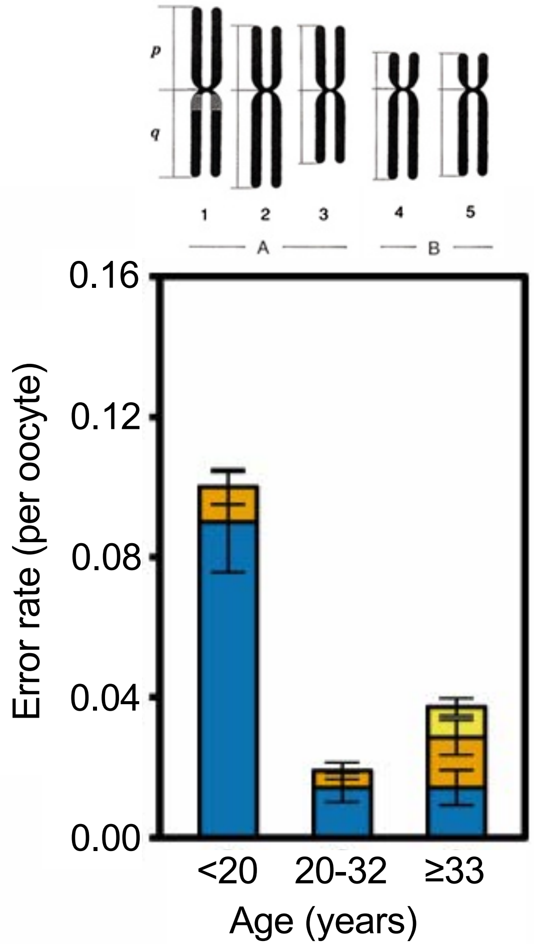
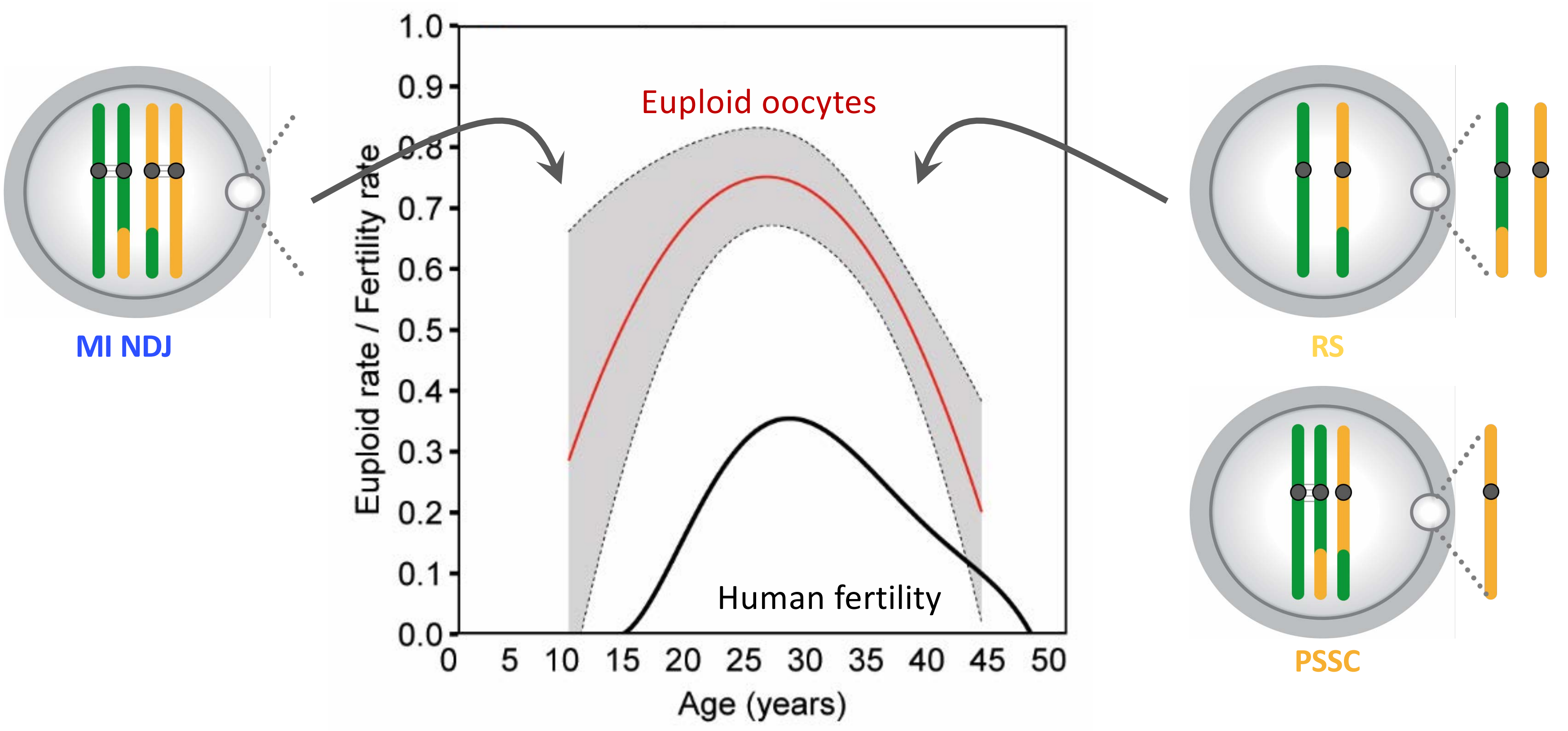


Chromosomes 1-5



Chromosome regulated suppression of natural fertility at both ends of the female age spectrum



Thanks to all our clinical collaborators, funders, & participants

All the girls and women who participated

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