review

Playing for half the deck: the molecular biology of meiosis

Mia D. Champion and R. Scott Hawley*

Stowers Institute for Medical Research, 1000 East 50th Street, Kansas City, MO 64110, USA

*e-mail: rsh@stowers-institute.org

Meiosis reduces the number of chromosomes carried by a diploid organism by half, partitioning precisely one haploid genome into each gamete. The basic events of meiosis reflect three meiosis-specific processes: first, pairing and synapsis of homologous chromosomes; second, high-frequency, precisely controlled, reciprocal crossover; third, the regulation of sister-chromatid cohesion (SCC), such that during anaphase I, SCC is released along the chromosome arms, but not at the centromeres. The failure of any of these processes can result in aneuploidy or a failure of meiotic segregation.

Meiosis produces sperm and eggs with exactly half the chromosome number of the individual producing the gametes. To ensure that each gamete has one copy of each chromosome pair, the diploid cell employs three meiosis-specific processes. First, homologous chromosomes are 'matched' by homologue alignment, that is, physical association (pairing) and the formation of a structure referred to as the synaptonemal complex (SC), a process known as synapsis. Second, the homologue pairs are locked together through the process of reciprocal meiotic recombination (also referred to as crossing-over, exchange or chiasma formation) to form bivalent structures. Third, the orientation of the two centromeres of each bivalent to opposite poles of the developing spindle ensures the separation of the two homologues at the first meiotic division[1]. After meiosis I, the chromosomes undergo a mitosis-like division without an intervening DNA replication step (see Fig. 1).

A function-based summary of meiosis

On the basis of the early cytogenetic studies, it seemed reasonable to assume that synapsis proceeds, and indeed was a requisite for, exchange initiation. Such a view was supported by the finding of a mutant in *Drosophila melanogaster*, (*c(3)G*), that blocked both SC formation and the occurrence of any meiotic recombination[2]. However, in the 1990s, genetic studies in *Saccharomyces cerevisiae* indicated that mutational ablation of the SC had surprisingly mild consequences for exchange and segregation[3]. Indeed, in *S. cerevisiae*, initiation of recombination is essential for SC formation (see Fig. 2). Similar observations have also been made in *Arabidopsis thaliana* and in mammals[4,5]. An attempt to revise the classical view of meiosis by reversing the order of recombination initiation and synapsis[6] was frustrated by the observation that exchange is not required for synapsis in *Drosophila* oocytes or in the nematode *Caenorhabditis elegans* (refs 7–9).

Although simple (and perhaps overly polarized) answers to this dilemma have been proposed in the past[6,10], it now seems likely that both processes can occur quite independently. In most meiotic systems, they are coupled by one or more regulatory links of varying strength. It may be that yeast and *Drosophila* simply occupy one extreme of a continuum in which there is a strong functional inter-dependence between processes. This model is consistent with the existence of organisms like *Schizosaccharomyces pombe*, which recombine without building a SC, and with *Bombyx mori* females, which build a SC without apparent exchange[11,12]. This view echoes the proposal of Zickler and Kleckner[13], who suggested that the meiotic programmes of various organisms may "differ only in respect to the potency of secondary SC nucleation mechanisms".

If there is a universal 'truth' in meiosis, it is that recombination is initiated by double strand DNA breaks (DSBs) created by the Spo11 protein in yeast and its homologues in other organisms[5,8,9,14,15]. These breaks are repaired by some permutation of a mechanism, first described by Szostak *et al.*[16], that creates a double Holliday junction intermediate. This double Holliday structure has been isolated from meiotic cells[17,18]. In most organisms, many more DSBs occur than there are eventual crossover events. Most DSBs are resolved by a separate pathway that results in gene conversion (a non-reciprocal recombination process that transfers information between homologues without an associated crossover event) rather than exchange[19]. Recently, important molecular clues regarding the mechanisms by which such intermediates are processed to produce either crossover or non-crossover products have been found[20].
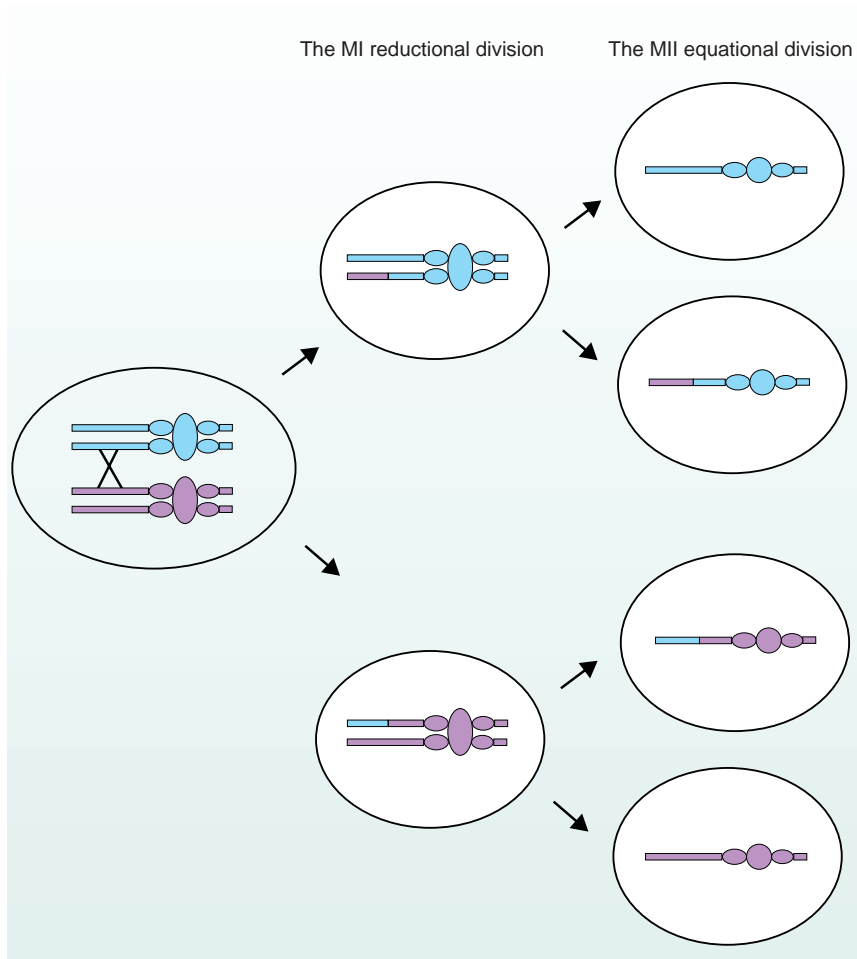
Figure 1 **Meiosis. a**, During prophase, homologous chromosomes pair, synapse and recombine. Chiasmata, the physical consequences of recombination, stabilize bivalents on the metaphase plate (see Fig. 3) **b**, During reductional division, the homologues segregate to opposite poles, but the sister chromatids remain adhered **c**, During the equational division, the sister chromatids separate and segregate to opposite poles.

The distribution of meiotic exchange along chromosome arms is not proportional to physical length. First, the number of exchanges per bivalent does not fit a Poisson distribution, as there are very few nonexchange bivalents and too few with high numbers of exchange[21]. Thus, recombination events are not distributed randomly between the paired chromosomes. Second, exchange occurs only in euchromatin, and not in heterochromatin, demonstrating that map length is not proportional to DNA content. Third, the frequency of exchange within the euchromatin is lowest near the telomeres and highest in the medial regions of the euchromatic arms[22–24]. Fourth, specific sites along chromosomes function as hotspots for exchange initiation[25]. Exchange positioning can be very precise, as demonstrated by the fact that exchange between the sex chromosomes in human males is restricted to the XpYp pseudoautosomal region[26]. A large number of meiotic mutants that disrupt the proper positioning of exchanges have been isolated[27,28]. Many of these have no direct or obvious role in synapsis or DNA metabolism, and thus may function indirectly to regulate other processes related to

exchange initiation and distribution. The large number and variety of mutants affecting the number and position of exchanges suggests that exchange distribution is controlled by a series of complex processes.

The consequences of a failure to undergo exchange are dependent on the meiotic system under examination. In many systems (such as many animal male meioses), the presence of unaligned chromosomes will trigger apoptotic arrest at or before metaphase (see below). In plants, achiasmate pairs of homologues simply fall apart during prometaphase and then move independently on the developing spindle. However, in many other meiotic systems, a back-up process exists that can ensure the segregation of those chromosomes that fail to undergo exchange (see below).

During prometaphase, the chromosomes are organized with respect to the developing spindle[29]. As the chromosomes condense in the later stages of prophase, chiasmata lock the bivalents into a structure in which the two homologous centromeres of each bivalent face in opposite directions (see Fig. 3). For meiotic divisions in which the spindle is organized by centrioles (that is, most male meioses), this property of oppositely oriented centromeres facilitates an initial attachment of the two centromeres to opposite poles of the spindle. To paraphrase Nicklas (1974)[1], "while the upper half-bivalents' centromeres almost face the upper pole, those of its partner almost face the lower pole, simply because bivalents are so constructed". The oppositely oriented centromeres then attach to microtubules emanating from the closest of the two spindle poles[1,30,31]. In rare cases where both centromeres are initially misdirected to the same pole, the bivalent moves briefly to one pole, releases its' spindle attachments and then reattempts to achieve a bipolar orientation.

By contrast, meiosis is acentriolar in most female animals (including humans)[32] and the bipolar spindle is assembled by the chromosome mass.

The opposite orientation of homologous centromeres is achieved by the initial back-to-back orientation of homologous centromeres. Groups of these half-spindles then coalesce to form the spindle poles[29,33]. In both sexes, all of the bivalents line up at the middle of the meiotic spindle at metaphase I. The chiasmata (or sites of reciprocal recombination) prevent the progression of centromeres to the poles by balancing the influence of poleward forces (Fig. 3).

Three lines of evidence argue that homologues are held together at the metaphase plate as a consequence of SCC[34–37]. First, studies demonstrated that mutants of the *desynaptic* gene in maize display a defect in both SCC and in the early separation of chiasmate bivalents[38–40]. Second, *Drosophila* exchanges fail to link homologous chromosomes in the presence of mutations that disrupt SCC along the chromosome arms during meiotic prophase[41]. Finally, chiasma resolution in yeast requires the cleavage of Rec8p, a protein required for meiotic SCC[42]. Proteins that regulate sister chromatid cohesion have been identified in both *Drosophila* and yeast[43–48]. At the onset of anaphase I, sister chromatid cohesion along the euchromatic arms of the chromosomes is released, allowing the resolution of chiasmata[49]. This allows the two homologues, each still comprised of two sister chromatids, to move to opposite poles.

The events that occur after meiosis I are often substantially different between the two sexes. In most males, each of the two products of meiosis I create a new 'mitotic-like' spindle on which the chromosomes align themselves, with their sister chromatids oriented towards opposite poles (metaphase II). The start of anaphase II is signalled by the separation of sister centromeres and the movement of the two sister chromatids to opposite poles. At telophase II, the sisters have reached opposite poles and nuclei begin to reform, each containing a single copy of each chromosome. Each of these four products of male meiosis will usually become a sperm. However, in the oocytes
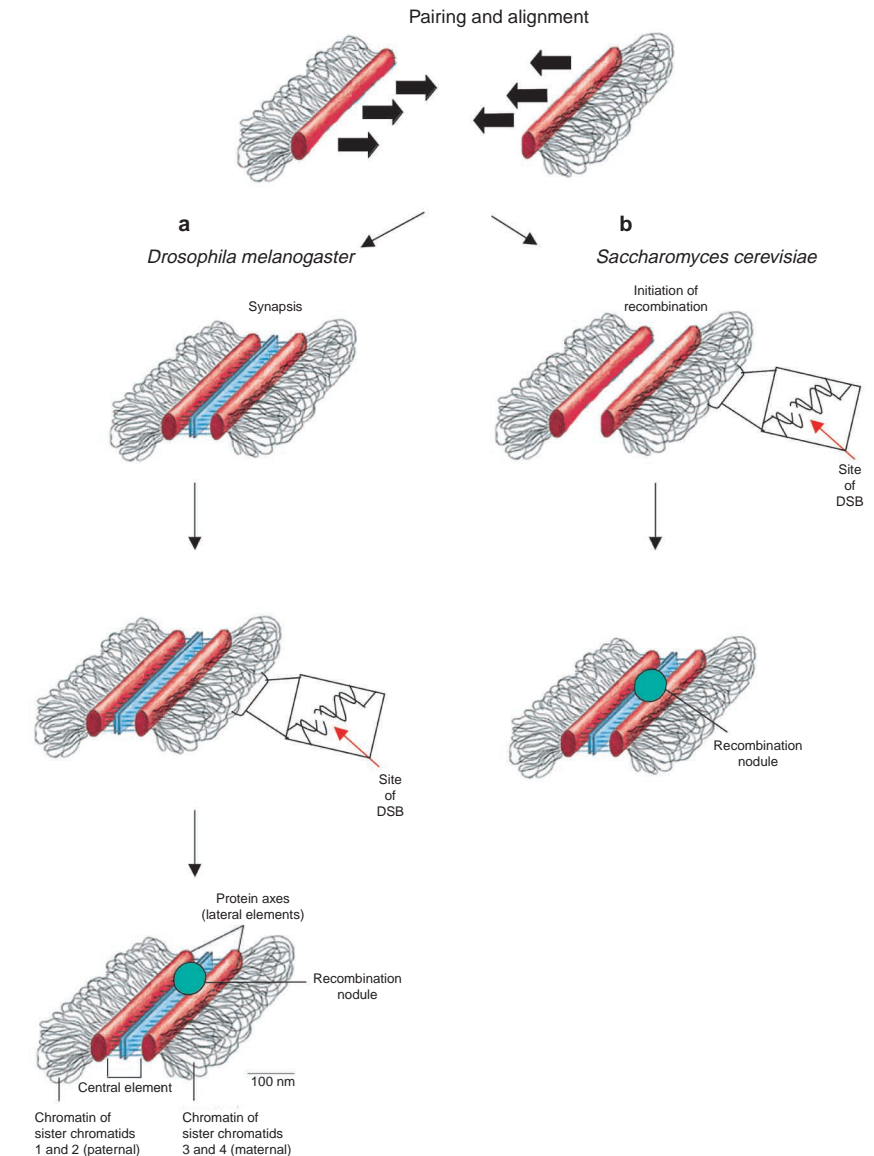
of most animals (including mammals), only one of the two products of meiosis I will always enter the second meiotic division. The other product of meiosis I is extruded as a polar body that may or may not undergo an meiosis II-like division. After the second meiotic division, only one of the products becomes the egg. The other product is relegated to become a polar body.

Figure 2 **Directionality of the meiotic process — *D. melanogaster* versus *S. cerevisiae*. a**, In *D. melanogaster*, synapsis of homologues is required for exchange to occur. **b**, Conversely, in *S. cerevisiae*, initial recombination events are required for synapsis. Copyright 2002 from *Molecular Biology of the Cell* by B. Alberts *et al*. Reproduced by permission of Routledge, Inc., part of the Talor Francis Group.

When meiotic segregation fails

Unfortunately, meiosis sometimes fails to accomplish this impressive dance. As a result, one or more pairs of homologous chromosomes fail to move to opposite poles. This failure, referred to a 'non-disjunction', occurs either because two homologues failed to pair and/or recombine, or because of a failure of the cell to
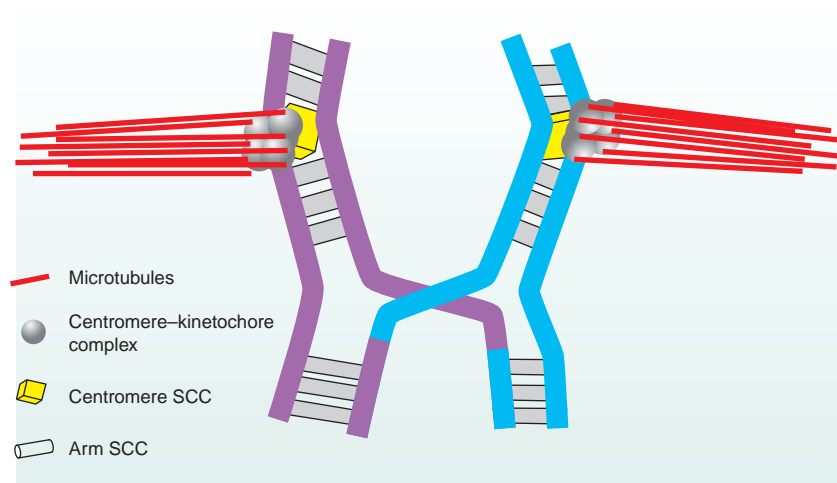
Figure 3 **Schematic representation of a bivalent at metaphase I arrest.** The homologues are attached to the meiotic spindle by the centromere–kinetochore protein complex, which creates significant tension. These poleward forces are balanced by the SCC distal to the exchange (see text).

properly move the segregating chromosomes to opposite poles on the meiotic spindle. Non-disjunction results in aneuploid gametes, which can create aneuploid embryos. Cases in which the embryo carries an extra copy of a given chromosome are said to be trisomic, whereas those that carry but one copy are said to be monosomic for that chromosome. There are no viable monosomies for the human autosomes. However, a few trisomic zygotes are capable of survival. These are trisomies for the sex chromosomes (XXX, XXY, XYY), trisomy 21 (Downs syndrome), trisomy 18 and trisomy 13.

The frequency of meiotic failure in human beings is difficult to estimate because most aneuploid zygotes spontaneously abort early during pregnancy. However, the best estimates suggest that at least 10–30% of fertilized human eggs are aneuploid[32] and that the frequency of error increases markedly with advancing maternal age. For the autosomes, these errors are usually caused by non-disjunction during female meiosis[32]. For example, in trisomy 16, virtually all cases are derived from maternal non-disjunction at meiosis I. Similarly, in trisomy 21, maternal errors account for 90% of the trisomies, and 75% of these are a result of

maternal errors at meiosis I. However, in trisomy 18, maternal meiosis II errors are the most common. Curiously enough, paternal non-disjunction contributes far more significantly to the origin of sex chromosome trisomies than it does to the generation of autosomal trisomies.

These observations leave us with far more questions than answers. Why is maternal non-disjunction a far more significant cause of human aneuploidy than paternal non-disjunction? What differences in the meiotic biology of the two sexes underlie this effect? Why, in female meiosis do some chromosomes non-disjoin preferentially (or entirely) during meiosis I, whereas in others, meiosis II events are far more common? Why is there an effect of maternal, but not paternal age? Some of the answers to these questions lie in some rather complex differences in the biology of meiosis between the two sexes.

In particular, there are differences in the ability of male and female germlines to detect errors in the meiotic process. Many meiotic systems possess checkpoint or surveillance mechanisms to monitor the fidelity of meiotic chromosome segregation. For example, in yeast, mutations in the spindle checkpoint genes result in

high frequencies of chromosome non-disjunction at anaphase I (ref. 50). The authors argue that a connection between homologues (for example, a chiasma) is insufficient to ensure proper segregation of chromosomes. In addition, centromere tension, which is monitored by spindle checkpoint proteins, may also be necessary for spindle elongation and chromosome segregation at anaphase I (ref. 50). We suggest that differences in the frequency of errors resulting from human male and human female meiosis largely reflect sex differences in such meiotic monitoring systems (see below).

There is a much more extensive system for error detection in male meiosis than in female meiosis. Male meiosis functions at two or more points in the meiotic cycle. First, male meiosis contains checkpoints that detects mis-aligned or unpaired chromosomes before the first meiotic division and then directs the cell towards apoptosis[51]. Oocytes seem to lack such a checkpoint[52]. Second, errors in early recombination and/or synapsis seem to trigger a pachytene arrest/apoptosis checkpoint in males that is not present in female meiosis. For example, during mammalian spermatogenesis, at least one mutant that disrupts early pairing and recombination events triggers death in mid-meiotic prophase[53]. However, in oogenesis, this mutant allows the progression of a meiosis that yields high frequencies of aneuploid gametes[53]. Similarly, mutants in the mouse equivalent of the yeast *spo11* gene also trigger apoptotic death of mammalian spermatocytes while allowing far more substantial progression of meiosis in oocyte[4]. Interestingly, the sex chromosomes are a rather odd exception to this story. At least some failures of sex chromosome recombination or metaphase alignment must be invisible to these male checkpoints. This is evidenced by the fact that non-disjunction in males accounts for some 50% of the cases of human XXY males and that most of these cases reflect a failure of the X and Y chromosomes to recombine[54].

However, it is not simply the absence of these checkpoints that makes female

meiosis a rather more error-prone process. Rather, it seems to be the interaction of errors in chiasma placement, a process that occurs before birth in human females with an age-dependent impairment of the segregational machinery. This combination of improperly positioned exchange events and an age-impaired spindle seems to yield high frequencies of meiotic errors. To explain this assertion, three points are particularly relevant: first, errors of meiotic chromosome segregation are often associated with reduced levels of exchange; second, the absence of exchange, or improperly placed exchanges make bivalents more susceptible to nondisjunction; third, the likelihood that bivalents without the proper number or placement of crossovers will non-disjoin increases on the spindles of older females.

Studies in both human and *Drosophila* oocytes demonstrate that the failed segregation of nonexchange chromosomes is a primary cause of non-disjunction. The vast majority of spontaneous meiosis I non-disjunction in *Drosophila* oocytes (76.6%,) results from a failure of the back-up system that ensures the segregation of nonexchange homologues[55]. Similar data were obtained after analysing the segregation of chromosomes 16 and 21 in human oocytes[56,57]. Furthermore, 40% of X chromosome non-disjunction cases in human females involved achiasmate bivalents[58,59]. Indeed, Hassold and Hunt[32] note that, "Significant reductions in recombination are a feature of all meiosis I-derived trisomies so far studied".

Those cases of spontaneous non-disjunction for the X chromosome in flies and chromosome 21 in human oocytes that did involve chiasmate bivalents, preferentially involved the mis-segregation of bivalents with very distal crossover events[55,56]. An example of this unusual distribution of exchanges is portrayed in Fig. 4. Clearly, exchanges differ in their ability to potentiate segregation, and distal exchanges are clearly at the weakest end of this spectrum. Nowhere is this effect shown more markedly than in an analysis of non-disjunction for chromosome 16 in

human oocytes[60]. In the cases of those chromosome 16 bivalents that undergo non-disjunction, proximal exchange frequencies are reduced some 20-fold. The reduced abilities of single distal crossovers to ensure segregation reflects their proximity to the telomere and not their distance from the centromere[61]. Thus, in terms of segregation, our best explanation for the weakness of distal exchange events is that they will have less SCC distal to the exchange, or in more formal terms 'a lesser amount of chiasma binder'.

It is our view that most cases of nondisjunction of distal exchange bivalents result from the premature release of the exchange, and the subsequent need of the cell to treat that pair of chromosomes as it would any other achiasmate bivalent, that is, by so-called 'distributive systems' (see below). This suggestion is consistent with the view that mutants that impair achiasmate segregation in *Drosophila* also greatly reduce the ability of bivalents with distal exchanges to disjoin properly[62–64].

Systems for distributive segregation have been described in many organisms[65–70]. In *Drosophila* (the best studied of these systems), achiasmate chromosomes still pair and remain associated with their homologue at the metaphase plate[71,72]. In this system, the Nod protein substitutes for chiasmata, in the sense that it holds pairs of achiasmate homologues together until they are properly segregated at anaphase I (ref. 73). The mechanisms underlying distributive (or achiasmate) segregation systems in other organisms are less well understood[66] and clearly vary from the *Drosophila* model[69,74]. Although virtually nothing is known about how such a mechanism might function in human oocytes, it is clear that one or more systems must exist. This conclusion is based on various studies of exchange distributions in humans, which reveal levels of non-exchange and distal exchange bivalents for chromosome 21 in oocytes that exceed the observed frequencies of non-disjunction in younger mothers[21,75,76].

It was also noted that apparent cases of meiosis II non-disjunction were usually associated with aberrant (usually far too

proximal) exchanges[55,56]. For example, all of the apparent meiosis II exceptions obtained in *Drosophila*[55] carry an exchange in the heterochromatin or in the very proximal euchromatin (Fig. 4). Similarly, other studies noted high frequencies of mis-segregation, including precocious sister chromatid separation in instances where gene conversion events had occurred in the pericentromeric regions[77]. One explanation for both of these observations is the so-called 'entanglement' model[55,56,78], in which these apparent meiosis II non-disjunctional progeny actually result from errors at meiosis I. According to this model, homologous chromosomes become entangled, either as a consequence of multiple exchanges, or, as we consider more likely, by an inability to release SCC near the centromeres, and thus to resolve pericentromeric exchanges before anaphase I.

The likelihood that bivalents without the proper number or placement of crossovers will non-disjoin increases for the spindles of older females: The observations described above create a paradox. Most of the observed non-disjunction in humans reflects reduced recombination and/or improperly placed recombination. Given that the actual recombination events themselves occur *in utero*, and that recombination maps stay relatively constant with maternal age[75], it becomes difficult to explain the well-known 'maternal age effect' in humans. Why then, if exchange occurs before birth, does the frequency of non-disjunction rise so steeply in the fourth and fifth decade of a woman's life? The best current model for explaining the correlation between the effect of recombination and maternal-age on chromosome disjunction is the 'two hit hypothesis'[56,78–80].

According to this model, the 'first hit' occurs during foetal meiosis and affects the process of recombination, resulting in a bivalent that is more susceptible to non-disjunction. By susceptible exchange-deficient bivalents, we mean those with no exchange or only a very distal exchange, the denizens of the distributive system.
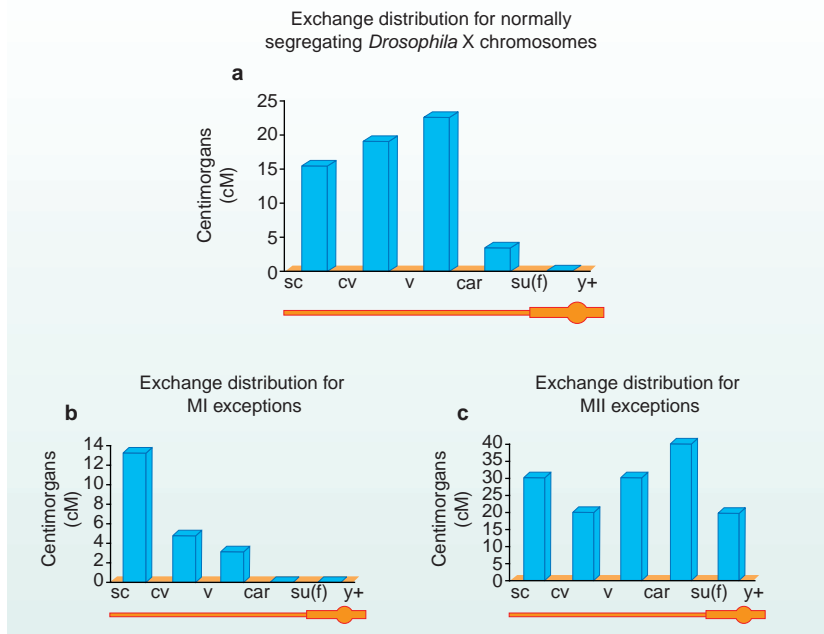
Figure 4 **Distribution of exchange along the X chromosome arm. a**, Normally, the frequency of exchange events is higher in the medial regions of the chromosome arm. **b**, X chromosome aneuploidy is most often caused by a failure to recombine or an increase of distal crossovers. **c**, Meiosis II exceptions exhibit an increase in exchange events located in the heterochromatin or very proximal euchromatin[80].

The 'second hit' occurs during metaphase arrest, when there is an age-related degradation of components necessary for chromosome segregation. This increases the likelihood that susceptible exchange-defective bivalents will non-disjoin. The meiotic spindle comprises a complex mechanical network that facilitates the proper segregation of chromosomes. This has been proposed to be the target of the 'second hit', resulting in chromosome non-disjunction.

The nature of such degradative mechanisms and their cellular targets remains a matter of enormous speculation. However, Eichenlaub-Ritter[81] has argued that "hormonal homeostasis and size of the follicle pool influence the quality, maturation competence and spindle size of the mammalian oocyte. Predisposition to errors in chromosome segregation are critically dependent on altered cell cycles". Similarly, Freeman et al.[82] have argued

that "the physiological status of the ovary is key to the maternal effect". Studies in model systems strengthen this view. In *Drosophila*, a distributive-system-specific meiotic mutant (*mei-P31*) was identified[83]. This mutant defines a gene encoding a small polypeptide hormone known to control oocyte maturation in mammals. On the basis of these findings, we suggest that changes in ovarian physiology impair the programmes of the first meiotic division and that nonexchange or distal exchange chromosomes are simply the 'canaries in the coal mine', that is, the first targets of impending difficulties. If one takes this view, then it is clear that the maternal age effect is less about how old a human female is, and more about how close she is to menopause[84].

As important as exchange failure is in the aetiology of non-disjunction, we would be remiss in not citing other possible influences. For example, several

studies suggest that the failure of proper sister chromatid cohesion at meiosis I or meiosis II may have a significant effect on the frequency of non-disjunction, at least for some chromosomes[32,85]. Similarly, there may well be effects that are caused by the accumulation of DNA damage[79]. Finally, we have ignored the effects of heterozygosity for aberrations or the possible effects of so-called environmental 'aneugens'. Such compounds do exist in fungi and it would not be surprising if one or more such compounds was reported in humans in the near future.

Summary

To quote Hassold and Hunt[32], "to err (meiotically) is human". We humans are simply not very good at meiosis. But our failures do not reflect an ability to pair our chromosomes or to recombine; rather weakness lies both in our ability to build and operate meiotic spindles in the oocytes of older (or pre-menopausal) women and in the absence of tension-sensitive spindle checkpoints in oocytes of any age. For the most part, these meiotic 'Achilles' heels' are blunted by the strong requirement for euploidy in human foetuses. Although meiosis fails frequently and aneuploid conceptions are common, the effect on the next generation is substantially mitigated by spontaneous abortion of aneuploid conceptions. Still, a substantial number of aneuploid children are born each year and the effects of these defects on their lives, and those of their families, are substantial. A more detailed understanding of the relationship between the processes that control oocyte maturation and meiosis I may provide us with better tools for identifying parents who maybe at risk, and perhaps someday may even suggest approaches to reduce that risk. ❑

1. Nicklas, R. B. Chromosome segregation mechanisms. *Genetics* **78**, 205–213 (1974).
2. Page, S. L. & Hawley, R. S. *c(3)G* encodes a *Drosophila* synaptonemal complex protein. *Genes Dev.* **15**, 3130–3143 (2001).
3. Rockmill, B. & Roeder, G. S. Meiosis in asynaptic yeast. *Genetics* **126**, 563–574 (1990).
4. Baudat, F. *et al.* Chromosome synapsis defects and sexually dimorphic meiotic progression in mice lacking Spo11. *Mol. Cell* **6**, 989–998 (2000).
5. Grelon, M. *et al.* AtSPO11-1 is necessary for efficient meiotic

recombination in plants. *EMBO J.* **20**, 589–600 (2001).

6. Hawley, R. S. & Arbel, T. Yeast genetics and the fall of the classical view of meiosis. *Cell* **72**, 301–303 (1993).

7. McKim, K. S. *et al.* Meiotic synapsis in the absence of recombination. *Science* **279**, 876–878 (1998).

8. McKim, K. S. & Hayashi-Hagihara, A. *mei-W68* in *Drosophila melanogaster* encodes a Spo11 homolog: evidence that the mechanism for initiating meiotic recombination is conserved. *Genes Dev.* **12**, 2932–2942 (1998).

9. Dernburg, A. F. *et al.* Meiotic recombination in *C. elegans* initiates by a conserved mechanism and is dispensable for homologous chromosome synapsis. *Cell* **94**, 387–398 (1998).

10. Walker, M. Y. & Hawley, R. S. Hanging on to your homolog: the roles of pairing, synapsis and recombination in the maintenance of homolog adhesion. *Chromosoma* **109**, 3–9 (2000).

11. Cervantes, M. D., Farah, J. A. & Smith G. R. Meiotic DNA breaks associated with recombination in *S. pombe. Mol. Cell* **5** 883–888 (2000).

12. Rasmusson, K. The transformation of the Synaptonemal Complex into the 'elimination chromatin' in *Bombyx mori* oocytes. *Chromosoma* **60**, 205–221 (1977).

13. Zickler, D. & Kleckner, N. Meiotic chromosomes: integrating structure and function. *Annu. Rev.Genet.* **33**, 603–754 (1999).

14. Keeney, S., Giroux, C. N. & Kleckner, N. Meiosis-specific DNA double-strand breaks are catalyzed by Spo11, a member of a widely conserved protein family. *Cell* **88**, 375–384 (1997).

15. Romanienko, P. J. & Camerini-Otero, R. D. The mouse *Spo11* gene is required for meiotic chromosome synapsis. *Mol. Cell* **6**, 975–987 (2000).

16. Szostak, J. W. *et al.* The double-strand-break repair model for recombination. *Cell* **33**, 25–35 (1983).

17. Schwacha, A. & Kleckner, N. Identification of joint molecules that form frequently between homologs but rarely between sister chromatids during yeast meiosis. *Cell* **76**, 51–63 (1994).

18. Schwacha, A. & Kleckner, N. Identification of double Holliday junctions as intermediates in meiotic recombination. *Cell* **83**, 783–791 (1995).

19. Allers, T. & Lichten, M. Intermediates of yeast meiotic recombination contain heteroduplex DNA. *Mol. Cell* **8** 225–231 (2001).

20. Cromie, G. A. & Leach, D. R. Control of crossing over. *Mol. Cell* **6**, 815–826 (2000).

21. Zwick, M. E., Cutler, D. J. & Langley, C. H. Classic Weinstein: tetrad analysis, genetic variation and achiasmate segregation in *Drosophila* and humans. *Genetics* **152**, 1615–1629 (1999).

22. Jones, G. H. The control of chiasma distribution. *Symp. Soc. Exp. Biol.* **38**, 293–320 (1984).

23. Carpenter, A. T. C. *Genetic Recombination* (ed. Kucherlapati, R.) 529–549 (ASM Press, Washington DC, 1988).

24. Hulten, M. Chiasma formation, crossing-over and recombination in meiosis. *Trends Genet.* **10**, 112–115 (1994).

25. Lichten, M. & Haber, J. E. Position effects in ectopic and allelic mitotic recombination in *Saccharomyces cerevisiae. Genetics* **123**, 261–268 (1989).

26. Burgoyne, P. S. Mammalian X and Y crossover. *Nature* **319**, 258–259 (1986).

27. Novak, J. E., Ross-Macdonald, P. B. & Roeder, G. S. The budding yeast Msh4 protein functions in chromosome synapsis and the regulation of crossover distribution. *Genetics* **158**, 1013–1025 (2001).

28. Page, S. L. *et al.* Genetic studies of *mei-P26* reveal a link between the processes that control germ cell proliferation in both sexes and those that control meiotic exchange in *Drosophila. Genetics* **155**, 1757–1772 (2000).

29. McKim, K. S. & Hawley, R. S. Chromosomal control of meiotic cell division. *Science* **270**, 1595–1601 (1995).

30. Nicklas, R. B. Chromosome distribution: experiments on cell hybrids and *in vitro. Philos. Trans. R. Soc. Lond. B* **277**, 267–276 (1977).

31. Nicklas, R. B.& Staehly, C. A. Chromosome micromanipulation. I. The mechanics of chromosome attachment to the spindle. *Chromosoma* **21**, 1–16 (1967).

32. Hassold, T. & Hunt, P. To err (meiotically) is human: the genesis of human aneuploidy. *Nature Rev. Genet.* **2**, 280–291 (2001).

33. Theurkauf, W. E. & Hawley, R. S. Meiotic spindle assembly in *Drosophila* females: behavior of nonexchange chromosomes and the effects of mutations in the nod kinesin-like protein. *J. Cell Biol.* **116**, 1167–1180 (1992).

34. Darlington, C. D. *Recent Advances in Cytology* (The Blakiston

35. Hawley, R. S. *Genetic Recombination* (ed. Kucherlapati, R.) 497–528 (ASM Press, Washington DC, 1988).

36. Lee, J. Y. & Orr-Weaver, T. L. The molecular basis of sister-chromatid cohesion. *Annu. Rev. Cell Dev. Biol.* **17**, 753–777 (2001).

37. Maguire, M. P., Paredes, A. M. & Riess, R. W. The desynaptic mutant of maize as a combined defect of synaptonemal complex and chiasma maintenance. *Genome* **34**, 879–887 (1991).

38. Maguire, M. Evidence for separate control of crossing over and chiasma maintenance in maize. *Chromosoma* **65**, 173–183 (1978).

39. Maguire, M. P. The need for a chiasma binder. *J. Theor. Biol.* **48**, 485–487 (1974).

40. Maguire, M. P. A possible role for the synaptonemal complex in chiasma maintenance. *Exp. Cell Res.* **112**, 297–308 (1978).

41. Bickel, S. E. *et al.* Genetic interactions between mei-S332 and ord in the control of sister-chromatid cohesion. *Genetics* **150**, 1467–1476 (1998).

42. Buonomo, S. B. *et al.* Disjunction of homologous chromosomes in meiosis I depends on proteolytic cleavage of the meiotic cohesin Rec8 by separin. *Cell* **103**, 387–398 (2000).

43. Hartman, T. *et al.* Pds5p is an essential chromosomal protein required for both sister chromatid cohesion and condensation in *Saccharomyces cerevisiae. J. Cell Biol.* **151**, 613–626 (2000).

44. van Heemst, D. & Heyting, C. Sister chromatid cohesion and recombination in meiosis. *Chromosoma* **109**, 10–26 (2000).

45. Warren, W. D. *et al.* The *Drosophila* RAD21 cohesin persists at the centromere region in mitosis. *Curr. Biol.* **10**, 1463–1466 (2000).

46. Shonn, M. A., McCarroll, R. & Murray, A. W. Spo13 protects meiotic cohesin at centromeres in meiosis I. *Genes Dev.* **16**, 1659–1671 (2002).

47. Toth, A. *et al.* Functional genomics identifies monopolin: a kinetochore protein required for segregation of homologs during meiosis I. *Cell* **103**, 1155–1168 (2000).

48. Watanabe, Y. & Nurse, P. Cohesin Rec8 is required for reductional chromosome segregation at meiosis. *Nature* **400**, 461–464 (1999).

49. Orr-Weaver, T. L. Meiosis in *Drosophila*: seeing is believing. *Proc. Natl Acad. Sci. USA* **92**, 10443–10449 (1995).

50. Shonn, M. A., McCarroll, R. & Murray, A. W. Requirement of the spindle checkpoint for proper chromosome segregation in budding yeast meiosis. *Science* **289**, 300–303 (2000).

51. Nicklas, R. B., Ward, S. C. & Gorbsky, G. J. Kinetochore chemistry is sensitive to tension and may link mitotic forces to a cell cycle checkpoint. *J. Cell Biol.* **130**, 929–939 (1995).

52. LeMaire-Adkins, R., Radke, K. & Hunt, P. A. Lack of checkpoint control at the metaphase/anaphase transition: a mechanism of meiotic nondisjunction in mammalian females. *J. Cell Biol.* **139**, 1611–1619 (1997).

53. Pelttari, J. *et al.* A meiotic chromosomal core consisting of cohesin complex proteins recruits DNA recombination proteins and promotes synapsis in the absence of an axial element in mammalian meiotic cells. *Mol. Cell Biol.* **21**, 5667–5677 (2001).

54. Hassold, T. J. *et al.* XY chromosome nondisjunction in man is associated with diminished recombination in the pseudoautosomal region. *Am. J. Hum. Genet.* **49**, 253–260 (1991).

55. Koehler, K. E. *et al.* Spontaneous X chromosome MI and MII nondisjunction events in *Drosophila melanogaster* oocytes have different recombinational histories. *Nature Genet.* **14**, 406–414 (1996).

56. Lamb, N. E. *et al.* Susceptible chiasmate configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. *Nature Genet.* **14**, 400–405 (1996).

57. Hassold, T., S. Sherman, & P. A. Hunt, The origin of trisomy in humans. *Prog. Clin. Biol. Res.* **393**, 1–12 (1995).

58. MacDonald, M. *et al.* The origin of 47,XXY and 47,XXX aneuploidy: heterogeneous mechanisms and role of aberrant recombination. *Hum. Mol. Genet.* **3**, 1365–1371 (1994).

59. Lorda-Sanchez, I. *et al.* Molecular study of 45,X conceptuses: correlation with clinical findings. *Am. J. Med. Genet.* **42**, 487–490 (1992).

60. Hassold, T. *et al.* Recombination and maternal age-dependent nondisjunction: molecular studies of trisomy 16. *Am. J. Hum. Genet.* **57**, 867–874 (1995).

61. Ross, L. O., Maxfield, R. & Dawson, D. Exchanges are not

equally able to enhance meiotic chromosome segregation in yeast. *Proc. Natl Acad. Sci. USA* **93**, 4979–4983 (1996).

62. Carpenter, A. T. A meiotic mutant defective in distributive disjunction in *Drosophila melanogaster. Genetics* **73**, 393–428 (1973).

63. Zitron, A. E. & Hawley, R. S. The genetic analysis of distributive segregation in *Drosophila melanogaster.* I. Isolation and characterization of Aberrant X segregation (Axs), a mutation defective in chromosome partner choice. *Genetics* **122**, 801–821 (1989).

64. Rasooly, R. S. *et al.* The lethal(1)*TW-6cs* mutation of *Drosophila melanogaster* is a dominant antimorphic allele of nod and is associated with a single base change in the putative ATP-binding domain. *Genetics* **129**, 409–422 (1991).

65. Hawley, R. S. & Theurkauf, W. E. Requiem for the distributive system: Achiasmate segregation in *Drosophila* females. *Trends Genet.* **9**, 310–317 (1993).

66. Wolf, K. W. How meiotic cells deal with non-exchange chromosomes. *Bioessays* **16**, 107–114 (1994).

67. McKim, K. S. & Rose, A. M. Chromosome I duplications in *Caenorhabditis elegans. Genetics* **124**, 115–132 (1990).

68. Dawson, D. S., Murray, A. W. & Szostak, J. W. An alternative pathway for meiotic chromosome segregation in yeast. *Science* **234**, 713–717 (1986).

69. Molnar, M. *et al.* Live observation of fission yeast meiosis in recombination-deficient mutants: a study on achiasmate chromosome segregation. *J. Cell Sci.* **114**, 2843–2853 (2001).

70. Green-Marroquin, B. L. *et al.* Orientation of nonrandomly segregating sex chromosomes in spermatocytes of the flea beetle, *Alagoasa bicolor* L. Chromosoma. **110**, 32–38 (2001).

71. Dernburg, A. F., Sedat, J. W. & Hawley, R. S. Direct evidence of a role for heterochromatin in meiotic chromosome segregation. *Cell* **86**, 135–146 (1996).

72. Hawley, R. S. *et al.* There are two mechanisms of achiasmate segregation in *Drosophila* females, one of which requires heterochromatic homology. *Dev. Genet.* **13**, 440–467 (1992).

73. Matthies, H. J., Baskin, R. J. & Hawley, R. S. Orphan Kinesin NOD Lacks Motile Properties But Does Possess a Microtubule-stimulated ATPase Activity. *Mol. Biol. Cell* **12**, 4000–4012 (2001).

74. Loidl, J., Scherthan, H. & Kaback, D. B. Physical association between nonhomologous chromosomes precedes distributive disjunction in yeast. *Proc. Natl Acad. Sci. USA* **91**, 331–334 (1994).

75. Lynn, A. *et al.* Patterns of meiotic recombination on the long arm of human chromosome 21. *Genome Res.* **10**, 1319–1332 (2000).

76. Tease, C., Hartshorne, G. M. & Hulten, M. A. Patterns of meiotic recombination in human fetal oocytes. *Am. J. Hum. Genet.* **70**, 1469–1479 (2002).

77. Sears, E. R. Misdivision of univalents in common wheat. *Chromosoma* **4**, 535–550 (1952).

78. Orr-Weaver, T. Meiotic nondisjunction does the two-step. *Nature Genet.* **14**, 374–376 (1996).

79. Hawley, R. S., Frazier, J. A. & Rasooly, R. Separation anxiety: the etiology of nondisjunction in flies and people. *Hum. Mol. Genet.* **3**, 1521–1528 (1994).

80. Koehler, K. E. *et al.* Recombination and nondisjunction in humans and flies. *Hum. Mol. Genet.* **5**, 1495–1504 (1996).

81. Eichenlaub-Ritter, U. Genetics of oocyte ageing. *Maturitas* **30**, 143–169 (1998).

82. Freeman, S. B. *et al.* Women with a reduced ovarian complement may have an increased risk for a child with Down syndrome. *Am. J. Hum. Genet.* **66**, 1680–1683 (2000).

83. Sekelsky, J. J. *et al.* Identification of novel *Drosophila* meiotic genes recovered in a P- element screen. *Genetics* **152**, 529–542 (1999).

84. Kline, J. *et al.* Trisomic pregnancy and earlier age at menopause. *Am. J. Hum. Genet.* **67**, 395–404 (2000).

85. Angell, R. First-meiotic-division nondisjunction in human oocytes. *Am. J. Hum. Genet.* **61**, 23–32 (1997).