evolution (Gondo et al., 1998). Concerted evolution must have occurred to homogenize the copies of RS447 megasatellite DNA within the human genome. (See Concerted Evolution; Gene Duplication: Evolution; Mutational Change in Evolution.)

See also
Microsatellites
Minisatellites

References

Further Reading

Meiosis

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Meiosis is a specialized type of cell division that occurs only in the testis and ovary. The principal function of meiosis is to produce gametes (eggs and sperm) that have the haploid number of chromosomes. In humans, this represents a reduction from 46 (23 pairs) to 23 chromosomes (one complete set). Meiosis is also important for producing genetic variation in gametes.

Introduction

Meiosis consists of one round of deoxyribonucleic acid (DNA) replication followed by two nuclear divisions. The two divisions (meiosis I and II) are divided into the same stages (prophase, metaphase, anaphase and telophase) as mitosis (Table 1; Figures 1 and 2). The most complex part of meiosis occurs during prophase of the first meiotic division (prophase I). Prophase I is conventionally subdivided into five stages (leptotene, zygotene, pachytene, diplotene, diakinesis) that reflect variations in chromosome behavior during this period (Table 1; Figure 1).

Meiosis I has three crucial features that distinguish it from mitosis: homologous chromosome pairing; reciprocal recombination (also called crossing-over or chiasma formation); and chromosome (as opposed to chromatid) segregation. For ease of description, these aspects of chromosome behavior are presented separately. However, it is important to remember that they are interdependent events. Thus, chromosome pairing and recombination are very intimately connected; and correct chromosome segregation at the first meiotic division can only be accomplished after normal completion of pairing and crossing-over.

Chromosome Pairing

Homologous chromosomes are usually located in separate regions of the premeiotic nucleus. Chromosomes, therefore, need to move actively around the
Table 1  Prophase I: stages and landmark events of chromosome behavior

Leptotene Chromatin condensation begins and the chromosomes first become visible as long, extended thread-like structures. As part of this condensation process, the chromosomes form a proteinaceous core (axial element) composed of cohesion proteins and two synaptonemal complex proteins, SCP2 and SCP3. The telomeres (the DNA–protein complexes that cap the ends of all chromosomes) bind to the nuclear membrane and begin to localize within a limited area of the membrane (‘bouquet’ formation; Scherthan, 2001) (see Figures 1a and 3a)

Pachytene By convention, zygotene ends and pachytene commences at the point when maximal synapsis is achieved (Figure 1). Intermediate recombination structures mature into crossovers in this stage. The positions of exchange are marked by foci of the mismatch repair protein MLH1 (see Figure 7)

Diplotene Transition to the diplotene stage is signaled by the lapping of homologous chromosome pairing (Figure 1f), a process termed desynapsis. Human fetal oocytes arrest in diplotene and remain in this stage until shortly before ovulation

Diakinesis Desynapsis is complete and the bivalents are held together only at the points of crossing-over (chiasmata). The chromosomes continue to condense

Zygotene The transition from leptotene to zygotene is marked by the start of chromosome pairing. The central core of the synaptonemal complex is formed by the protein SCP1. In oocytes, synapsis generally initiates from chromosome ends (Figures 1b–d and 3b). DNA repair proteins, such as RAD51 and DMC1, decorate unpaired axes until synapsis is complete.

Figure 1  [Figure is also reproduced in color section.] Human fetal oocytes at leptotene to diplotene of prophase I (see Table 1). The cells have been stained using antibodies against the protein SCP3 (green) and, in (a–e), against the kinetochoore (red); the chromatin is stained blue. (a) Leptotene. Thin, thread-like axes are visible in the nucleus. (b) Early zygotene. Homologous chromosomes have commenced synapsis; generally, synapsis is initiated from chromosome ends (arrows). (c) Mid-zygotene. Synapsis is more extensive (arrow), unpaired axes are still visible centrally (arrowheads). (d) Late zygotene. Synapsis is complete over the lengths of most chromosome pairs, although a few unpaired axes are still present (arrowheads). (e) Pachytene. Homologous chromosome synapsis is complete. (f) Early diplotene. Synapsis begins to break down (desynapise) and the axes of the homologous chromosomes separate; desynapsis occurs from the chromosome ends (arrows) and interstitially (arrowheads).

nucleus to search for and identify their homologous partner. Meiotic chromosome pairing is generally considered to be a two-phase process. First, homologous chromosomes (or chromosomal segments) become aligned. Currently, it is not clear how distance recognition of homology is achieved to enable this alignment. Second, once alignment of homologous chromosomes (or chromosomal segments) is present, the chromosomes associate intimately in a process termed synapsis. Synapsis is mediated by a meiosis-specific proteinaceous structure, the synaptonemal complex (SC). There is some evidence that the initial phase of synapsis is limited to regions of chromosome homology (homosynapsis) but that this restriction may ease later to allow some nonhomologous synapsis (heterosynapsis). This change in synaptic behavior
is most easily identified in cases where there are heterozygositites for chromosome rearrangements, such as in translocations and inversions.

Synapsis requires the formation of double-strand breaks (DSBs) in the chromatin; these DSBs are formed by the topoisomerase II-related protein Spo11 in concert with a number of other proteins (Bishop, 2001). Laboratory mice in which the Spo11 gene has been knocked out do not form DSBs and do not show normal synapsis. DSBs appear to be an essential prerequisite to homology testing which involves a recombination-like process between closely aligned chromosomes. Where homology is established, then SC formation proceeds.

**Synaptonemal complex**

The SC was first identified by electron microscope analysis of pachytene spermatocytes. It appears as a tripartite ribbon running along the axes of paired chromosomes (Figure 4). The ribbon is approximately 200 nm in width. SC lengths at pachytene vary considerably between human spermatocytes and oocytes: in spermatocytes, the total length per cell is approximately 260 μm, whereas in oocytes, it exceeds 520 μm. In both sexes, a limited part of each chromosome is associated with the SC and, therefore, in intimate contact with the homologous regions on its partner chromosome. Most of the chromosome is instead present as a chromatin cloud surrounding the SC and is not involved in homologous interactions. As far as is known, there are no specific DNA sequences associated with the SC, although on the whole this DNA tends to be more AT-rich than the genome as a whole.

Three SC proteins have been identified to date. Two of these, SCP (synaptonemal complex protein) 2 and 3, are located at the axes of chromosomes as they condense during early prophase I. SCP2 and 3 appear to associate with (or are loaded on to) the cohesion protein complex that binds together sister chromatids.

**Figure 2** Chromosome behavior in the later stages of meiosis. After diakinesis, the bivalents attach to spindle microtubules and orient in a bipolar fashion at metaphase I. When orientation is complete, the cohesion complex proteins that bind sister chromatids are removed (except at the kinetochores), releasing the chiasmata and allowing the chromosomes to be pulled to the spindle poles at anaphase I. The chromosomes reorient on the metaphase II spindle, and the chromatids separate and move to opposite spindle poles. The net result is the formation of cells containing a haploid, unreplicated genome.

**Figure 3** [Figure is also reproduced in color section.] Human fetal oocytes stained with antibodies against SCP3 (green) and the telomere protein, TRF1 (red). (a) Leptotene cell in which most telomeres are present in a restricted part of the nucleus, forming a bouquet configuration. (b) Mid-zygotene cell in which the telomeres show a scattered distribution; synaptic initiation is clearly from the telomeres in most cases.
following DNA replication (Figure 4b). The third protein, SCP1, is present in the central region of the SC. SCP1 is a long filamentous protein. Its C-terminal end binds to the lateral element, with the N-terminal region pointing into the central region. N-terminal regions from opposite lateral elements associate centrally to hold the SC together (Figure 4b).

Recombination nodules

Electron microscope investigations identified small structures, termed nodules, associated with SC formation. These nodules are categorized as either ‘early’ or ‘late’. This discrimination is based upon the time of appearance of the nodules and a presumption regarding function. Early nodules are associated with synapsing chromosomal axes. They are generally small and ellipsoid and are assumed to be involved in homology testing between aligned chromosomal segments. Ultrastructural and immunocytochemical studies have indicated the presence of DNA repair proteins, such as RAD51 and DMC1, in these early nodules as would be anticipated if DNA–DNA interactions were occurring (Moens et al., 2002). Late nodules are present following synapsis (Figure 4c). They can vary in appearance from round structures to bar-like objects straddling the SC and are believed to be involved in crossing-over. The DNA mismatch repair protein, MLH1, has been shown to be present in late nodules. Early nodules occur in larger numbers than late nodules. It is not clear if late nodules evolve from a subset of early nodules or whether the two types form independently. (See Mismatch Repair Genes.)

DNA repair proteins

An expanding array of DNA repair proteins has been identified as playing some role in chromosome pairing and recombination, as adjudged by the colocalization of the proteins with unpaired axial elements of leptotene/zygotene chromosomes or the SCs of paired chromosomes (Table 2). However, much remains to be discovered regarding the detailed interactions of these various proteins both with each other and with meiotic chromosomes. (See DNA Repair.)

XY pairing

In human spermatocytes, the heteromorphic sex chromosomes undergo a different schedule of synapsis from the autosomes. This pattern of behavior may be predicated on the need to maintain the X in a genetically inactive state during meiosis. The X and Y chromosomes share a small region of homology (approximately 2.6 Mb in length) at the distal ends of their short arms (the so-called ‘pseudoautosomal’ region or ‘PAR’). They also have a much smaller (approximately 0.23 Mb) region of homology at the ends of the long arms. Synapsis initiates at the short arm PAR in early pachytene (Figure 5a) and goes beyond the region of homology occasionally to include the entire short arm. However, this synapsis is not long lasting and the chromosomes begin to separate (desynapse). By mid-pachytene, the chromosomes are associated only at their very distal tips. In approximately half of early pachytene cells, the regions of homology of the long arms also associate (Figure 5c).
Table 2 Timing and possible functions of some DNA repair proteins that associate with chromosome cores during leptotene, zygotene and pachytene of prophase I

<table>
<thead>
<tr>
<th>Protein</th>
<th>Stages present</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPO11 (sporulation)</td>
<td>Leptotene to zygotene</td>
<td>Produces double-strand breaks, essential for synapsis</td>
</tr>
<tr>
<td>RAD 51</td>
<td>Leptotene to pachytene</td>
<td>RecA homolog that binds to single-stranded DNA; possible role in early steps of recombination by mediating single end invasion</td>
</tr>
<tr>
<td>DMC1 (disrupted meiotic cDNA)</td>
<td>Leptotene to pachytene</td>
<td>RecA homolog that binds to single-stranded DNA; colocalizes with Rad51</td>
</tr>
<tr>
<td>RPA (replication protein A)</td>
<td>Zygote to pachytene</td>
<td>Binds to single-stranded DNA, possibly involved in early steps of recombination</td>
</tr>
<tr>
<td>BLM (Bloom syndrome mutated helicase)</td>
<td>Leptotene to pachytene</td>
<td>Helicase, colocalizes with RPA, possibly functions in recombination</td>
</tr>
<tr>
<td>MSH 4/5 (MutS homolog)</td>
<td>Zygote to pachytene</td>
<td>Required for chromosome pairing; in yeast, interacts with MLH1 to control crossing-over</td>
</tr>
<tr>
<td>MLH1 (MutL homolog)</td>
<td>Zygote to diplotene</td>
<td>Required for crossing-over</td>
</tr>
<tr>
<td>MLH3</td>
<td>Pachytene</td>
<td>Involved in DNA mismatch repair</td>
</tr>
</tbody>
</table>

**Figure 5** [Figure is also reproduced in color section.] Morphological changes in the XY chromosome pair during pachytene (b–f) as seen after staining with antibodies against SCP3 (white) and the kinetochore (red). The kinetochores of the X and Y are indicated by a small and large pointer respectively. (a) Interpretative drawing of the sex chromosomes shown in (b). (b) Early pachytene. The X and Y chromosomes are long and thin, and show association at the short arm telomere (small pointer). (c) Early pachytene. The X and Y chromosomes are associated at both the short arm (small pointer) and long arm telomeres to form a ring-like configuration. (d) Mid-pachytene. The X and Y chromosomes are thickened and have begun to split. (e,f) Late pachytene. The X and Y chromosomes show progressively more splitting as pachytene progresses, until eventually the two axes become indistinguishable.

The sex chromosomes undergo very considerable morphological changes during pachytene, eventually forming a highly differentiated ‘sex vesicle’ in late pachytene (Figure 5d–f). This unusual pattern of synopsis and chromosome differentiation provides a reliable means to subdivide pachytene in the human male, and thereby can be exploited to distinguish early to late pachytene cells when examining meiotic behavior of autosomes. The X chromosome pair in human prophase I oocytes does not show any difference in behavior from the autosomes.

**Crossing-over**

The currently accepted model of crossing-over (outlined in Figure 6) proposes that reciprocal exchanges originate from the DSBs put in place during leptotene as part of the chromosome pairing process. It is generally believed that crossing-over is not completed until pachytene. The sites of crossing-over can be identified at pachytene by staining for the presence of the DNA mismatch repair protein, MLH1 (Mut L
Meiosis

Figure 6 Double-strand break (DSB) model of recombination (see Kirkpatrick, 1999). The resolution of the double Holliday junction by cutting in opposite sense results in the formation of a crossover. Same-sense cutting results in noncrossover duplexes. Both outcomes carry mismatch heteroduplex DNA that may be resolved as gene conversion events (nonreciprocal recombination). (a) DNA duplexes of nonsister chromatids. (b) DSB formation (SPO11, etc.). (c) 5’ to 3’ resection leaving a 3’ overhang. (d) Single end invasion, displacement of one DNA strand to form a D loop (RAD51, DMC1, RPA). DNA repair synthesis from the 3’ ends. (e) Formation of double Holliday junction. Cutting of strands in opposite orientation at each junction (arrow) produces a crossover (MLH1, MSH 4/5) as indicated in (f).

homolog 1). MLH1 is present as discrete foci along the SC (Figure 7) and these foci mimic the numbers and distributions of chiasmata (see below). (See Mismatch Repair Genes.)

Figure 7 [Figure is also reproduced in color section.] Detecting the positions of crossovers at pachytene using the DNA mismatch repair protein, MLH1. The cells have been stained using antibodies against SCP3 (red), MLH1 (yellow) and, in the spermatocyte, the kinetochore (blue). (a) Pachytene spermatocyte. (b) Normal pachytene oocyte. There are obvious differences between the spermatocyte and oocyte: the SCs are much longer in the oocyte; there are more MLH1 foci in the oocyte; MLH1 foci tend to be positioned closer to the telomeres in the spermatocyte. (c) Pachytene oocyte showing failure of pairing affecting some chromosomes (arrows). MLH1 foci are present on synapsed chromosome pairs (arrowheads).
**Chiasma(ta)**

The position of a crossover becomes apparent as a bivalent condenses during diplotene and diakinesis (Figure 8a). Sister chromatids remain tightly associated proximally and distally to the crossover giving rise to a cytogenetically visible structure called a chiasma (plural chiasmata). This association is mediated by sister chromatid adhesion along the chromosomal axes following the dissolution of the SC at diplotene. Chiasma numbers and positions can be analyzed in metaphase I spermatocytes (Figure 8b); for technical reasons this has proved impractical in oocytes. Chiasmata provide a reliable means of determining the rate of meiotic chromosome recombination, at both the genomic and chromosomal level (Laurie and Hultén, 1985; Hultén, 1994).

Chiasmata (crossovers) are nonrandomly distributed with regard both to numbers per chromosome pair and to positions along chromosome arms. Each bivalent receives at least one exchange (the so-called obligate chiasma). Thereafter, chiasmata are distributed roughly in proportion to bivalent length. The positions of the chiasmata along chromosome arms reflect at least two factors: preferential formation in certain chromosomal segments and chiasma (crossover) interference. The former is exemplified by the high rate of chiasma formation close to chromosome ends in human spermatocytes (Figure 8b). The influence of interference is most easily seen when two or more chiasmata are present along a chromosome arm. Adjacent chiasmata rarely form close to one another but are more usually separated by a comparatively large chromosome length. The exclusion of a second exchange close to a first is termed chiasma (crossover) interference. Currently, the mechanism of interference is unclear.

**Sex differences in recombination**

Human males with normal fertility show remarkably little interindividual variation in numbers of chiasmata, with an average of approximately 50 per spermatocyte (range 40–60 per cell) (Laurie and Hultén, 1985).

![Figure 8](image-url)  
**Figure 8** (a) Cartoon illustrating how the configurations in (b) are achieved by bivalents with one or two chiasmata. Two chromosome pairs are shown, in each case one homolog is colored gray, the other black. A crossover between a gray and black chromatid generates an exchange that is visible in the metaphase I bivalent. The acrocentric chromosome pair has a single crossover and produces a ring bivalent, the metacentric has two crossovers and produces a ring bivalent. (b) Metaphase I spermatocyte. Pairs of homologous chromosomes are held together by variable numbers of chiasmata. Bivalents with 1, 2 or 3 chiasmata are indicated, as is the XY chromosome pair. (c) Metaphase II spermatocyte. The chromatids of each chromosome (arrowheads) are held together only at the centromeres (arrow). (d) Metaphase I spermatocyte from a man with an abnormally low number of chiasmata. In contrast to (a), bivalents (arrows) have only one or two chiasmata; additionally, a number of chromosome pairs have failed to form crossovers and are present as univalents (arrowheads).
Analysis of MLH1 foci at pachytene has produced a similar estimate of crossover frequency in spermatocytes (Barlow and Hultén, 1998; Lynn et al., 2002). Interestingly, the recombination rate is higher in oocytes. Initial MLH1 analysis has suggested an average of approximately 70 crossovers per oocyte at pachytene, with a larger intercell variability (range 40–100) than in spermatocytes. The higher rate of recombination in oocytes is most probably related to the considerable difference in pachytene chromosome length described above. The female genome has a longer physical platform for formation of crossovers than the male. Not only do the two sexes show a significant variation in recombination frequency, but they also display differences in distribution (Tease et al., 2002). In spermatocytes, the foci are often located close to the ends of the chromatids. In oocytes, foci are located more interstitially (away from chromosome ends) and only very rarely positioned close to telomeric segments (compare Figure 7a and 7b). Indirect genetic analyses have similarly identified this intersex variation in numbers and distributions of crossovers. (See Genetic Mapping: Comparison of Direct and Indirect Approaches; Genetic Maps: Direct Meiotic Analysis.)

**Chromosome Segregation**

At metaphase I, the pairs of homologous chromosomes (bivalents) attach to spindle microtubules and move to the spindle equator in preparation for nuclear division. At the first meiotic division, sister kinetochores (microtubule-attaching segments of the centromeres) act as a single unit and orient in a monopolar fashion. This is quite distinct from mitosis where the kinetochores of sister chromatids orient to opposite spindle poles. (See Chromosomes during Cell Division; Mitosis: Chromosome Segregation and Stability.)

The chiasmata in each bivalent act as anchors to hold the pairs of homologs together during the orientation process. Evidence from experimental organisms shows that incorrect orientation, or failure to attach to spindle microtubules, can switch on a signaling pathway that results in cell division arrest until the chromosomes successfully interact with the spindle (Nicklas, 1997). It is presumed that a similar mechanism exists in human spermatocytes, although there is some doubt as to whether it is as sensitive (or possibly even present) as in human oocytes.

The cohesin protein complex is present at the kinetochore of meiotic chromosomes (Nasmith, 2001). At the transition from metaphase I to anaphase I, sister chromatid cohesion lapses except at the kinetochores. It is not yet clear how the cohesion protein complex associated with the kinetochore is protected from lysis at this stage of meiosis. The presence and retention of cohesin proteins is crucial for monopolar orientation of sister kinetochores at metaphase I.

Lapsing of sister chromatid cohesin results in the loss of the chiasmate associations holding the homologous chromosomes together and the homologs are able to move freely to opposite spindle poles as the microtubules shorten. The resulting daughter nuclei, therefore, obtain only half of the chromosome complement (Figure 8c). Maternally and paternally inherited homologs assort at random at anaphase I. The resulting cells, therefore, contain a haploid chromosome set different from that contributed by maternal and paternal germl cell. It is also important to remember that the chromatids of each chromosome are now no longer identical because of crossing-over. These two processes of random assortment and meiotic recombination contribute to genetic variation in the human population.

In oocytes, the cytoplasmic division at anaphase I is highly unequal, producing a large secondary oocyte and a residual, minute cell termed the first polar body. The polar body ceases meiosis and the chromosomes begin to degenerate. Oocytes arrest at metaphase II and are ovulated at this stage. They are stimulated to complete meiosis only after fertilization. In spermatocytes, the products of the first meiotic division are equal in size and both go on to complete meiosis II. Chromosome condensation resumes very shortly after anaphase I and the chromosomes soon orient on the metaphase II spindle. Although the second meiotic division has much in common with a mitotic division, it should be noted that, unlike mitosis, the chromatids of each chromosome are separate except at the centromeres (Figure 8c). In addition, in contrast to mitosis, genetic segregation occurs at the second meiotic division to produce daughter nuclei that are not identical.

Once chromosome orientation is complete (and following fertilization in the case of oocytes), centromere adhesion lapses and the spindle microtubules pull each chromatid to the poles. Meiosis is now complete. The resulting cells in male meiosis are termed spermatids. They undergo very considerable morphological changes in the process of forming spermatozoa (spermiogenesis). In female meiosis, cytoplasmic division at anaphase II is again very unequal producing a second small polar body. The egg nucleus decondenses to form the female pronucleus of the zygote. (See Mitosis: Chromosome Segregation and Stability.)

**Consequences of Abnormal Meiosis**

Meiosis is a surprisingly error-prone process in humans and thereby has a significant adverse impact on human reproduction. Meiotic errors can result in
infertility and are also responsible for generating the genetically imbalanced gametes that produce aneuploid conceptions. Errors of meiotic chromosome behavior are the single largest contributor to genetically determined congenital abnormalities and mental impairment affecting live-born children.

**Chromosome pairing and recombination errors**

All aspects of meiotic chromosome behavior are open to error. For example, over 30% of human pachytene oocytes may show some form of chromosome pairing anomaly. Commonly, chromosome pairs fail to pair, a phenomenon termed asynapsis (Figure 7c). In yeast, anomalies of chromosome pairing can trigger cell checkpoints resulting in arrest of cell development and ultimately cell death. It is not yet clear if a similar phenomenon occurs in human germ cells. If this mechanism is present, then any increase in the already high proportion of fetal oocytes with pairing errors could result in depletion of the germ cell population and lead to the premature onset of menopause in women. Similarly, meiotic pairing errors in spermatocytes could result in an insufficiency of sperm production in men.

Incorrect alignment (unequal synapsis) of homologs in conjunction with crossing-over may generate a large variety of deletions and duplications that can cause genetic disease in offspring.

Failure of crossing-over in fully synapsed chromosome pairs results in the presence of unpaired chromosomes (univalents) at metaphase I (Figure 8d). This phenomenon is termed desynapsis. The lack of a chiasmate association means that homologous chromosomes may segregate at random with respect to one another, with a resulting marked increase in the rate of aneuploid (chromosomally imbalanced) gametes. In spermatocytes, there is evidence that crossover failure can result in the developmental arrest of the cells at metaphase I; these cells may then be lost through either necrotic or apoptotic pathways. Surveys of men attending infertility clinics have shown an increased likelihood of meiotic errors, such as a significantly reduced chiasma frequency.

**Nondisjunction**

Analyses of the chromosome complements of spermatogonia have shown that malsegregation (nondisjunction) of chromosomes is normally uncommon. Current estimates indicate a rate of approximately 2% aneuploid spermatogonia. Recent studies have indicated that infertile men attending reproductive clinics for collection of sperm for intracytoplasmic sperm injection (ICSI) tend to show increased rates of aneuploidy in their sperm.

The rate of aneuploid sperm is often elevated in men carrying structural chromosome rearrangements. For example, in men with reciprocal translocations, the proportion of genetically imbalanced sperm may reach 60–70%. In this case, malsegregation is elevated because of the presence in the first meiotic division of multivalents (associations of more than two homologous chromosomes) resulting from chiasma formation in the translocated chromosomal segments. Translocation heterozygosity is also associated with an altered pattern of chiasma distribution in the rearranged chromosomes; in turn, this can influence the orientation of the multivalent at metaphase I and thus the likelihood of chromosome malsegregation.

Human oocytes have a higher predisposition for chromosome segregation errors than spermatocytes. Approximately 10–30% of clinically recognized pregnancies have some form of chromosome abnormality. Over 90% of conceptions with autosomal aneuploidy are the result of chromosome nondisjunction in oocytes. Indirect genetic analysis has indicated that abnormal patterns of crossover distribution, such as failure of crossing-over or formation of exchanges very close to the centromere or telomere, may increase the risk of chromosome nondisjunction in oocytes (Hassold and Hunt, 2001). It is not yet clear why, for some chromosome pairs, bivalents with particular chiasma distributions should be at increased risk of malsegregation. The only factor that is known unequivocally to influence the rate of nondisjunction is maternal age. Although many hypotheses have been advanced to explain the increased risk on chromosome segregation errors with age, it is fair to say that our understanding of this phenomenon remains very incomplete. (See Meiosis and Mitosis: Molecular Control of Chromosome Separation.)

**Acknowledgement**

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**See also**

Meiosis and Mitosis: Molecular Control of Chromosome Separation

**References**


**Further Reading**


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**Meiosis and Mitosis: Molecular Control of Chromosome Separation**

*Jan-Michael Peters, Research Institute of Molecular Pathology, Vienna, Austria*  
*Silke Hauf, Research Institute of Molecular Pathology, Vienna, Austria*

Sister chromatid separation in anaphase is initiated by the anaphase-promoting complex, a ubiquitin ligase that activates the protease separase. This protease separates sister chromatids by cleaving cohesin, a protein complex that holds sister chromatids together.

**Sister Chromatid Cohesion**

In prokaryotes, replicated deoxyribonucleic acid (DNA) molecules are separated from each other while replication is ongoing. In contrast, in eukaryotes, sister chromatids remain attached to each other after replication has been completed. This cohesion serves several important functions:

1. Cohesion provides a ‘memory’ function that defines which chromatids represent identical copies and therefore have to be separated into the forming daughter cells during cell division; that is, cohesion is an essential prerequisite for the temporal separation of DNA replication and mitosis.
2. DNA damage can be repaired by using the other sister chromatid that is held in close proximity as a template.
3. Cohesion causes a bilateral symmetry of the chromosome, which facilitates bipolar attachment to the mitotic spindle. Bipolar attachment ensures that each daughter cell receives one chromatid.