

Effect of meiotic recombination on the production of aneuploid gametes in humans

N.E. Lamb,^a S.L. Sherman,^a T.J. Hassold^b

^aDepartment of Human Genetics, Emory University School of Medicine, Atlanta, GA;

^bSchool of Molecular Biosciences, Washington State University, Pullman, WA (USA)

Manuscript received 19 January 2005; accepted in revised form for publication by R. Martin, 4 March 2005.

Abstract. Within the last decade, aberrant meiotic recombination has been confirmed as a molecular risk factor for chromosome nondisjunction in humans. Recombination tethers homologous chromosomes, linking and guiding them through proper segregation at meiosis I. In model organisms, mutations that disturb the recombination pathway increase the frequency of chromosome malsegregation and alterations in both the amount and placement of meiotic recombination are associated with nondisjunction. This association has been established for humans as well. Significant alterations in recombination have been found for all meiosis I-derived trisomies studied to date and a subset of so called “meiosis II” trisomy. Often exchange levels are reduced in a subset of cases where the non-disjoining chromosome fails to undergo recombination. For other trisomies, the placement of meiotic recombination has been altered. It appears that recombination too near the cen-

tromere or too far from the centromere imparts an increased risk for nondisjunction. Recent evidence from trisomy 21 also suggests an association may exist between recombination and maternal age, the most widely identified risk factor for aneuploidy. Among cases of maternal meiosis I-derived trisomy 21, increasing maternal age is associated with a decreasing frequency of recombination in the susceptible pericentromeric and telomeric regions. It is likely that multiple risk factors lead to nondisjunction, some age dependent and others age independent, some that act globally and others that are chromosome specific. Future studies are expected to shed new light on the timing and placement of recombination, providing additional clues to the link between altered recombination and chromosome nondisjunction.

Copyright © 2005 S. Karger AG, Basel

Improper chromosome segregation during meiosis leads to genetically unbalanced eggs or sperm. If these gametes participate in fertilization, the resulting embryo will be aneuploid, with either one chromosome too many (trisomy) or too few (monosomy). In humans, aneuploidy is identified in at least 5% of all clinically recognized pregnancies, making it the leading

known cause of fetal wastage. Over the past fifteen years, more than 1,000 trisomic or monosomic conceptions have been examined to determine the parental origin and meiotic stage of the nondisjunction error (Hassold and Hunt, 2001). Since monosomies are almost always early embryonic lethals, most of the available data derive from trisomies; not surprisingly, the largest data set involves trisomy 21, the condition responsible for Down syndrome. These studies indicate remarkable inter-chromosomal variation in nondisjunction. However, regardless of the chromosome involved, most human trisomies originate from errors in maternal meiosis I. Given the biology of the human egg, this is not entirely unexpected: The first stage of female meiosis is initiated in the fetal ovary, and is followed by a long “arrest” phase that lasts until the time of ovulation. Thus, the first meiotic division is amazingly pro-

Supported by NIH grants P01 HD32111 and R01 HD38979.

Request reprints from Neil Lamb

Department of Human Genetics, Emory University School of Medicine
615 Michael Street, Atlanta, GA 30322 (USA)
telephone: 404-712-1564; fax: 404-727-3949
e-mail: nlamb@genetics.emory.edu

tracted, taking at least 10–15 years and as many as 45–50 years to complete.

While the association between maternal age and trisomy has long been recognized, other predisposing factors have been elusive. Common themes, however, are at last beginning to emerge. Within the last decade numerous studies have identified aberrant meiotic recombination as an important molecular correlate of nondisjunction. Under normal conditions, meiotic recombination serves two key roles. It separates allelic combinations along the chromosome, generating genetic diversity from generation to generation. Additionally, and more relevant to this discussion, recombination tethers homologous chromosomes, linking them with physical structures known as chiasmata and guiding them through proper segregation during the first meiotic stage (Smith and Nicolas, 1998).

In this review, we first discuss the essential features of the meiotic recombination pathway, and then summarize the recent data demonstrating that alterations in either the number or placement of meiotic recombination events can contribute to chromosome nondisjunction.

Recombination: the basics

A detailed description of meiotic recombination is beyond the scope of this article. There is some degree of variation in the order and timing of early recombination events among different organisms. Even so, the basic components of recombination are conserved among species and can be summarized along the following lines. After pre-meiotic DNA replication, germ cells enter prophase of meiosis I (MI), a protracted period that can be divided into five sub-stages (leptotene, zygotene, pachytene, diplotene and diakinesis). Concomitant with replication, sister chromatids become held in close proximity by the sister chromatid cohesion complex, a three-part proteinaceous structure that forms during leptotene of prophase I (Petronczki et al., 2003). Upon entry into the early stages of prophase, homologous chromosomes initiate a process of meiotic pairing initiated by double strand breaks, followed by the rejoining of broken ends (Allers and Lichten, 2001). A subset of the broken ends from one chromatid is joined to the corresponding sequence on the homologous chromosome, leading to the formation of a crossover. Evidence in budding yeast suggests that initial components of the synaptonemal complex are assembled at those double strand break sites destined to mature as crossovers (Bishop and Zickler, 2004). Other sequences are utilized in the homology check but are not destined to mature as crossovers; these non-crossover recombinants are processed by a different pathway.

The crossover products form chiasmata, the physical evidence of recombination. The distribution of crossovers/chiasmata along a chromosome can be directly observed by visually counting chiasmata at diakinesis (Hulten, 1974; Laurie and Hulten, 1985) or by immunostaining pachytene cells for some component of the recombination complex, such as MLH1 (Baker et al., 1996; Barlow and Hulten, 1998; Anderson et al., 1999; Lynn et al., 2002). While the positions of crossovers/chiasmata vary somewhat along the chromosomes, their distri-

bution is notably nonrandom. Across meiotic nuclei, there is virtually always at least one crossover/chiasma per arm for each pair of homologs (the so called “obligatory chiasma”). When two or more crossovers occur along the same chromosome arm, they exhibit “interference”, tending not to occur close together but instead spacing themselves evenly along the chromosome arm.

Although it is possible to directly measure recombination in human diakinesis or pachytene stage spermatocytes or oocytes, considerable hurdles are involved in obtaining the necessary cells, especially oocytes. Instead, most analyses of human recombination rely on an indirect approach; i.e., genetic linkage analysis of human pedigrees. This involves tracking the inheritance of alleles at multiple polymorphic markers along the chromosomes across generations. Recombination can be identified when the alleles at neighboring loci on a chromosome are initially present in different grandparents. While this indirect method only assays recombination events that are detectable in the progeny, it is capable of positioning recombination on the chromosome with a high degree of resolution – at least an order of magnitude greater than possible with direct approaches.

Key differences exist between males and females with respect to the timing of meiosis. Initiated at puberty, spermatogenesis is an ongoing process that requires approximately two months from beginning to end and continues throughout the male’s lifetime. In contrast, meiosis proceeds fitfully in the female: it is initiated prenatally but arrested before the first division until the oocyte is ovulated, at which point it arrests again at the second division until fertilized. Not surprisingly, gender differences are observed in the amount and placement of meiotic recombination (reviewed in Lynn et al., 2004). Recombination rates are approximately 1.6–1.7 fold higher in female meiosis than in male meiosis and across individual chromosomes, female recombination rates are higher than males with the exception of distal regions, where male rates of recombination are higher. The biological basis of this difference between the genders is largely unknown, although it may be controlled in part by sex-specific differences in the formation of the synaptonemal complex (Lynn et al., 2002).

Lessons from model organisms

Disturbances in the recombination pathway have been linked to abnormalities in chromosome segregation in numerous model systems. The most obvious effects involve mutations that reduce, or abolish, recombination: almost invariably, these mutations are associated with meiotic arrest, gross abnormalities in chromosome segregation or, at the very least, with increased levels of nondisjunction (Roeder, 1997). Additionally, the location of the exchanges also seems to be important. For example, meiotic studies using yeast artificial chromosomes (YACs) or derivatives of budding-yeast natural chromosomes indicate that exchanges in different chromosomal intervals have varying abilities to properly segregate chromosomes (Ross et al., 1996). Specifically, chromosomes with a single distally located exchange appear more likely to nondisjoin than those

Table 1. A summary of studies examining nondisjunction, recombination and maternal age in humans

Origin of error	Chromosome	Stage of error	No. of cases	Reference	Amount of recombination relative to controls	Placement of recombination relative to controls	Association between recombination and parental age?
Paternal	21	MI	22	Savage et al., 1998	Reduced due to achiasmate tetrads	Too few exchanges to analyze	Not assessed
		MII	28	Savage et al., 1998	Normal	Slight increase in proximal exchange	Not assessed
	XXY	MI	64	Thomas et al., 2000	Reduced due to achiasmate tetrads	Normal	Too few cases to assess
Maternal	21	MI	178 (1996) 400 (2005)	Sherman et al., 1994; Lamb et al., 1996, 1997, 2005	Reduced due to achiasmate tetrads (40% estimated as achiasmate)	Altered – shift towards telomere among single exchanges	No trend for achiasmate tetrads; younger mothers more likely to have altered placement
		MII	78 (1996) 129 (2005)	Lamb et al., 1996, 1997, 2005	Increased	Altered – shift towards centromere among all exchange classes	Older mothers more likely to have altered placement
	16	MI	62	Hassold et al., 1995	Reduced, but no achiasmate tetrads identified	Shift towards telomere for all exchange classes	Not assessed
	15	MI	97	Robinson et al., 1998	Reduced due to achiasmate tetrads (21% estimated as achiasmate)	Normal	Maternal age increases with number of exchanges
		MI	19	Robinson et al., 1998	Small numbers, but not significantly different	Small numbers, but not significantly different	Not assessed
	18	MI	50	Bugge et al., 1998	Reduced due to achiasmate tetrads (30% estimated as achiasmate)	Normal	Re-analyzed by Jacobs, found non-significant increase in maternal age for achiasmate vs. other exchange class
		MII	88	Bugge et al., 1998	Normal	Normal	
	XXX XXY	MI	68	Thomas et al., 2001	Reduced due to achiasmate tetrads (47% estimated as achiasmate)	Normal	Significant increase in maternal age among MI transitional class (1+ recombinants) compared to MI nulitransitional class
		MII	40	Thomas et al., 2001	Normal	Normal	No change

with more proximally positioned exchanges. Other studies indicate a high frequency of segregation errors in YACs where pericentromeric events have occurred (Sears et al., 1995). Taken together, these results suggest that exchanges can either be too near the centromere or too far from the centromere, and that both situations impart a risk for nondisjunction.

Similar results have also been observed among flies. In an analysis of spontaneous X chromosome nondisjunction in *Drosophila* females, bivalents with a single distally located exchange were associated with MI errors (Koehler et al., 1996). At the same time, extremely proximal exchanges were observed frequently among errors arising at meiosis II (MII). So, as in yeast, exchanges too close to or too far from the centromere seem to increase the risk of nondisjunction. Mutation studies also support the link between distal crossovers and mal-segregation. Mutations that cause nondisjunction of nonexchange bivalents in *Drosophila* females also increase nondisjunction of exchange chromosomes. In virtually all these cases, single crossovers are distally positioned (Rasooly et al., 1991; Moore et al., 1994), suggesting these exchange patterns are more susceptible to nondisjunction than bivalents with more proximally located chiasmata. Similarly, absence or the inappropriate location of meiotic exchange has also been associated with nondisjunction in *C. elegans* (Zetka and Rose, 1995) and mouse (Yuan et al., 2000).

Studies of human nondisjunction

In 1968, it was suggested that declining levels of recombination were associated with the maternal age effect on trisomy, providing the first proposed link between recombination and human nondisjunction (Henderson and Edwards, 1968). At the time however, techniques to study recombination in humans were still in development and this hypothesis could not be easily tested. It was not until polymorphic DNA markers came into widespread use that the association of aberrant recombination and nondisjunction could be examined. A modification of the indirect genetic mapping technique discussed above makes possible the reconstruction of the recombination events occurring in meioses that lead to aneuploidy. Reduced levels of chromosome 21 recombination among Down syndrome conceptuses were first reported in 1987 (Warren et al., 1987). Since then, several laboratories have studied the relationship between recombination and human nondisjunction, comparing exchange frequency and distribution in trisomy-generating meioses with those from chromosomally normal meioses. These studies make it clear that the association between altered meiotic recombination and trisomy first identified among model systems pertains to humans as well. Although the magnitude of the effect is variable, significant reductions in recombination have been found for all MI-derived trisomies studied to date, including trisomies 15, 16, 18, 21, Klinefelter syndrome (47,XXY) and 47,XXX of maternal origin as well as trisomy 21 and Klinefelter syndrome of paternal origin (Hassold et al.,

1991, 1995; Lamb et al., 1996, 1997; Bugge et al., 1998; Robinson et al., 1998; Savage et al., 1998; Thomas et al., 2001). These findings are summarized in Table 1. For many of these trisomies, the reduction in recombination is due to a subset of cases where the nondisjoining bivalent is “achiasmate” and never engages in genetic recombination. Consequently, the homologs are left to drift independently across the metaphase plate. If they drift to the same pole (as will occur half the time), aneuploidy will result. It is worth noting that in *Drosophila*, many such achiasmate bivalents would be properly positioned via a “backup” segregation pathway. To date however, no such mechanism has been identified in humans.

In addition to an effect of reduced recombination, altered placement of meiotic recombination has been identified for another subset of maternally derived trisomy 21 and all cases of trisomy 16. Among these cases, the exchange events are placed more distally along the chromosome arm than expected. These “distal only” exchange events appear to be less efficient at proper chromosome segregation, possibly because they are unable to lock homologs together, allowing independent movement.

A non-trivial proportion of trisomy also appears to result from errors at meiosis II (MII). As recombination takes place during MI, there was initially little reason to believe it would be altered among the MII cases. Surprisingly, aberrant patterns of meiotic recombination are associated with maternal meiosis II trisomy for chromosome 21 (Lamb et al., 1997). Specifically, there is an increase in exchange, which is most pronounced in the pericentromeric region of the chromosome. So, as reported for yeast and flies (Sears et al., 1995; Koehler et al., 1996) exchanges that occur too close to the centromere appear to be a risk for human nondisjunction as well. The connection between recombination (a meiosis I event) and the meiosis II nondisjunction may be explained if the meiosis II errors actually originated in meiosis I with the establishment of a susceptible exchange pattern. Possibly, crossovers that occur too close to the centromere lock homologs too tightly. This may lead to either chromosome entanglement or premature separation of sister chromatids at meiosis I followed by co-migration of the sister chromatids due to chance at meiosis II. As a result, the nondisjoined chromosomes would have identical centromeres, leading to the “meiosis II” classification even though the event initiated during meiosis I.

Subsequent studies of trisomy 18 or sex chromosome trisomy arising at maternal meiosis II have not identified a significant effect for recombination. For these conditions, nondisjunction truly appears to occur as a result of errors in the second meiotic stage. Consequently, it appears that the liability posed by altered recombination varies from chromosome to chromosome.

Although the majority of trisomy occurs as a result of meiotic nondisjunction, a small percentage can also arise as a consequence of mitotic nondisjunction and/or trisomy rescue leading to mosaicism. If the gonads are involved, a proportion of gametes may be chromosomally unbalanced, placing the individual at increased risk to have offspring with trisomy. Although the incidence of gonadal mosaicism is unknown, it has been documented at both the gamete and liveborn levels (e.g., James et al., 1998; Bruyere et al., 2000; Cupisti et al., 2003;

Warburton et al., 2004). Due to the pairing mechanisms involved in the trisomic oocyte, some portion of the resulting meiotic products will contain chromatids that did not participate in recombination. However, this lack of recombination among chromatids is a function of the pairing mechanism rather than a lack of recombination in the oocyte itself. Unfortunately current techniques do not allow these cases to be identified. By all accounts, however, such cases appear to be a very small fraction of the overall trisomic population.

Recombination and maternal age

A key unanswered question concerns the possible association between maternal age and altered recombination patterns. It is widely recognized that most, if not all, human trisomies are affected by increasing maternal age, although the magnitude of the effect varies among trisomies (Risch et al., 1986; Morton et al., 1988). Among women under the age of 25 years, ~ 2% of all clinically recognized pregnancies are trisomic but this frequency approaches 35% for women over the age of 40. Recent studies have hinted at a possible connection between maternal age and recombination. Among cases involving nondisjunction of chromosome 15, Robinson et al. (1998) found that the age of the mother was significantly increased among maternal MI-derived errors with multiple recombinants compared with those with zero or only a single detectable recombinant. This finding suggested that cases with multiple recombinants might be more resistant to nondisjunction due to an increase in bivalent stability. Similarly, an analysis of maternal nondisjunction of the X chromosome showed the mean maternal age of cases with recombination was significantly older than that of cases with no recombination (Thomas et al., 2001). This same pattern was observed for trisomy 18, although the difference was not statistically significant (Bugge et al., 1998). There was no maternal age association with the position of exchanges along the nondisjoined chromosome for either trisomy 18 or trisomy of the maternal sex chromosome.

Recently, a large-scale study of trisomy 21 was undertaken in a search for links between maternal age and recombination (Lamb et al., 2005). Four hundred cases of maternal MI-derived trisomy 21 were subdivided into three roughly equal groups based upon the age of the mother at time of conception: mothers younger than 29 years of age, mothers between 29 and 34 years of age, and mothers 35 years of age or older. Unlike the findings of nondisjoined chromosomes 15, 18 and X, the overall amount of meiotic exchange did not significantly differ with respect to age. There were, however, significant differences in the locations of the exchange, both among the groups and when compared to a normally disjoining population. Among the youngest nondisjoining age group, meiotic exchange was located most often in the susceptible pericentromeric and telomeric intervals of chromosome 21. With increasing age however, the overall exchange distributions began to approximate that found among the normally disjoining sample.

The authors suggested that multiple risk factors, some age dependent and others age independent, lead to nondisjunction. In a young woman, the machinery of meiosis (e.g., spindle func-

tion, sister chromatid cohesion proteins, microtubule motor proteins) functions optimally and correctly segregates all but the most susceptible exchange configurations (achiasmatic bivalents and exchanges close to either the centromere or telomere). The greatest risk factor for nondisjunction among women of this age group is the presence of a susceptible exchange pattern in the oocyte. As a woman ages, her meiotic machinery accumulates the effects of years of environmental and age-related insults, becoming less efficient and/or more error-prone. Suboptimal exchange bivalents are still susceptible to nondisjunction, but even correctly placed bivalents are now at risk. The proportion of nondisjunction occurring among oocytes with normal exchange configurations increases over time as age-dependent risk factors exert their influence. As a result, the most prevalent exchange profile of nondisjoined oocytes shifts from susceptible to nonsusceptible patterns.

An association between maternal age and recombination has also been recently identified among a normally disjoining population (Kong et al., 2004). Based on genome-wide microsatellite data compiled for over 23,000 individuals, a positive correlation was identified between maternal age and the level of maternal recombination, determined from their livebirth offspring. The authors believe the apparent increase is a consequence of selection i.e., high recombination counts decrease the likelihood of nondisjunction and thereby increase the chance of a gamete to become a liveborn. This maternal age effect is very slight, estimated as an additional two recombinants across the entire genome over a 25-year period, and is several orders of magnitude lower than that observed among trisomic cases.

Future studies

The studies of recombination and nondisjunction have provided important insights into the etiology of human trisomies. However, additional studies now need to be undertaken to identify the mechanisms controlling meiotic recombination, and to address a number of important unanswered basic questions. For example, how are sites for double strand breaks chosen; and is this process influenced by *cis*-acting factors such as higher-order chromatin structure, or by *trans*-acting factors independent of DNA sequence? Additionally, as initial work in mice has shown that recombination rates correlate and co-vary with the length of the synaptonemal complex (Lynn et al., 2002), will identification of the factors governing synaptonemal complex assembly shed light on proteins that drive recombination as well?

As studies progress in model organisms, the details of the pathway controlling meiotic recombination will be uncovered. As each new player is discovered, human homologs will likely be elucidated, making it possible to search for alleles that may alter or modify the action of the gene in humans. Further, several laboratories are now attempting to generate appropriate mouse models that link altered recombination and maternal age, either by knocking out recombination-related genes or by experimentally shifting the placement of recombination. These findings are eagerly awaited, as they will undoubtedly provide additional clues that move us closer to understanding the connection between altered recombination and chromosome mal-segregation in our species.

References

- Allers T, Lichten M: Differential timing and control of noncrossover and crossover recombination during meiosis. *Cell* 106:47–57 (2001).
- Anderson LK, Reeves A, Webb LM, Ashley T: Distribution of crossing over on mouse synaptonemal complexes using immunofluorescent localization of MLH1 protein. *Genetics* 151:1569–1579 (1999).
- Baker SM, Plug AW, Prolla TA, Bronner CE, Harris AC: Involvement of mouse Mlh1 in DNA mismatch repair and meiotic crossing over. *Nat Genet* 12:336–342 (1996).
- Barlow AL, Hulten MA: Crossing over analysis at pachytene in man. *Eur J Hum Genet* 6:350–358 (1998).
- Bishop DK, Zickler D: Early decision: meiotic crossover interference prior to stable strand exchange and synapsis. *Cell* 117:9–15 (2004).
- Bruyere H, Rupps R, Kuchinka BD, Freidman JM, Robinson WP: Recurrent trisomy 21 in a couple with a child presenting trisomy 21 mosaicism and maternal uniparental disomy for chromosome 21 in the euploid cell line. *Am J Med Genet* 94:35–41 (2000).
- Bugge M, Collins A, Petersen MB, Fisher J, Brandt C, Hertz JM, et al: Non-disjunction of chromosome 18. *Hum Mol Genet* 7:661–669 (1998).
- Cupisti S, Conn CM, Fragouli E, Whalley K, Mills JA, Faed MJW, Delhanty JDA: Sequential FISH analysis of oocytes and polar bodies reveals aneuploidy mechanisms. *Prenat Diagn* 23:663–668 (2003).
- Hassold T, Hunt P: To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet* 2:280–291 (2001).
- Hassold TJ, Sherman SL, Pettay D, Page DC, Jacobs PA: XY chromosome nondisjunction in man is associated with diminished recombination in the pseudoautosomal region. *Am J Hum Genet* 49:253–260 (1991).
- Hassold T, Merrill M, Adkins K, Freeman S, Sherman S: Recombination and maternal age-dependent non-disjunction: molecular studies of trisomy 16. *Am J Hum Genet* 57:867–874 (1995).
- Henderson SA, Edwards RG: Chiasma frequency and maternal age in mammals. *Nature* 217:22–28 (1968).
- Hulten M: Chiasma distribution at diakinesis in the normal human male. *Hereditas* 76:55–78 (1974).
- James RS, Ellis K, Pettay D, Jacobs PA: Cytogenetic and molecular studies of four couples with multiple trisomy 21 pregnancies. *Eur J Hum Genet* 6:207–212 (1998).
- Koehler KE, Boulton CL, Collins HE, French RL, Herman KC, Laceyfield SM, et al: Spontaneous X chromosome MI and MII nondisjunction events in *Drosophila melanogaster* oocytes have different recombinational histories. *Nat Genet* 14:406–414 (1996).
- Kong A, Barnard J, Gudbjartsson D, Thorleifsson G, Jonsdottir G, Sigurdardottir S, et al: Recombination rate and reproductive success in humans. *Nat Genet* 36:1203–1206 (2004).
- Lamb NE, Freeman SB, Savage-Austin A, Pettay D, Taft L, Hersey J, et al: Susceptible chiasmate configurations of chromosome 21 predispose to nondisjunction in both maternal meiosis I and meiosis II. *Nat Genet* 14:400–405 (1996).
- Lamb NE, Feingold E, Savage A, Avramopoulos D, Freeman S, Gu Y, et al: Characterization of susceptible chiasma configurations that increase the risk for maternal nondisjunction of chromosome 21. *Hum Mol Genet* 6:1391–1399 (1997).
- Lamb NE, Yu K, Shaffer J, Feingold E, Sherman SL: An association between maternal age and meiotic recombination for trisomy 21. *Am J Hum Genet* 76:91–99 (2005).
- Laurie DA, Hulten MA: Further studies on bivalent chiasma frequency in human males with normal karyotypes. *Ann Hum Genet* 49:203–214 (1985).
- Lynn A, Koehler KE, Judis L, Chan ER, Cherry JP, Schwartz S, et al: Covariation of synaptonemal complex length and mammalian meiotic exchange rates. *Science* 296:2222–2225 (2002).
- Lynn A, Ashley T, Hassold T: Variation in human meiotic recombination. *Ann Rev Genomic Hum Genet* 5:317–349 (2004).
- Moore DP, Miyazaki WY, Tomkiel JE, Orr-Weaver TL: Double or nothing: a *Drosophila* mutation affecting meiotic chromosome segregation in both females and males. *Genetics* 136:953–964 (1994).
- Morton NE, Jacobs PA, Hassold T, Wu D: Maternal age in trisomy. *Ann Hum Genet* 52:227–235 (1988).

- Petronczki M, Siomos MF, Nasmyth K: Un ménage à quatre: the molecular biology of chromosome segregation in meiosis. *Cell* 112:423–440 (2003).
- Rasooly RS, New CM, Zhang P, Hawley RS, Baker BS: 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).
- Risch N, Stein Z, Kline J, Warburton D: The relationship between maternal age and chromosome size in autosomal trisomy. *Am J Hum Genet* 39:68–78 (1986).
- Robinson WP, Kuchinka BD, Bernasconi F, Petersen MB, Schulze A, Brondum-Nielsen K, et al: Maternal meiosis I nondisjunction of chromosome 15: dependence of the maternal age effect on the level of recombination. *Hum Mol Genet* 7:1011–1109 (1998).
- Roeder GS: Meiotic chromosomes: it takes two to tango. *Genes Dev* 11:2600–2621 (1997).
- Ross LO, 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).
- Savage AR, Petersen MB, Pettay D, Taft L, Allran K, Freeman SB, et al: Elucidating the mechanisms of paternal non-disjunction of chromosome 21 in humans. *Hum Mol Genet* 7:1221–1227 (1998).
- Sears DD, Hegemann JH, Shero JH, Hieter P: *Cis*-acting determinants affecting centromere function, sister-chromatid cohesion and reciprocal recombination during meiosis in *Saccharomyces cerevisiae*. *Genetics* 139:1159–1173 (1995).
- Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, et al: Non-disjunction of chromosome 21 in maternal meiosis I: evidence for a maternal age-dependent mechanism involving reduced recombination. *Hum Mol Genet* 3:1529–1535 (1994).
- Smith KN, Nicholas A: Recombination at work for meiosis. *Curr Opin Genet Dev* 8:200–211 (1998).
- Thomas NS, Collins AR, Hassold TJ, Jacobs PA: A reinvestigation of non-disjunction resulting in 47,XXY males of paternal origin. *Eur J Hum Genet* 8:805–808 (2000).
- Thomas NS, Ennis S, Sharp AJ, Durkie M, Hassold TJ, Collins AR, Jacobs PA: Maternal sex chromosome non-disjunction: evidence for X chromosome-specific risk factors. *Hum Mol Genet* 10:243–250 (2001).
- Warburton D, Dallaire L, Thangavelu M, Ross L, Levin B, Kline J: Trisomy recurrence: a reconsideration based on North American data. *Am J Hum Genet* 75:376–384 (2004).
- Warren AC, Charkravarti A, Wong C, Slaugenhaupt SA, Halloran SL, Watkins PC, Metazotou C: Evidence for reduced recombination on the nondisjoined chromosome 21 in Down syndrome. *Science* 237:652–654 (1987).
- Yuan L, Liu JG, Zhao J, Brundell E, Daneholt B, Hoog C: The murine SCP3 gene is required for synaptonemal complex assembly, chromosome synapsis, and male fertility. *Mol Cell* 5:73–83 (2000).
- Zetka MC, Rose AM: Mutant rec-1 eliminates the meiotic pattern of crossing over in *Caenorhabditis elegans*. *Genetics* 141:1339–1349 (1995).