A direct measurement of crossing over in human prophase oocytes

R Scott Hawley¹,²

Addresses: ¹Stowers Institute for Medical Research, Kansas City, MO 64110, USA; ²Department of Physiology, University of Kansas Medical Center, Kansas City, KS 66160, USA

Email: rsh@stowers.org

F1000 Biology Reports 2009, 1:86 (doi:10.3410/B1-86)

The electronic version of this article is the complete one and can be found at: http://F1000.com/Reports/Biology/content/1/86

Abstract

The nature of the relationship between crossing over and failed segregation in human oocytes is of obvious interest. A recent paper by Cheng and colleagues provides important insights into the distribution of crossover events (as marked by MLH1 foci) in human oocytes and raises complex questions regarding discrepancies between direct cytological assessment of exchange and measurement of crossing over by linkage analysis.

Introduction and context

In meiosis, reciprocal recombination, also known as crossing over or chiasma formation, plays the vital role of holding homologous chromosomes together until their proper segregation at the first meiotic division [1]. In human females it has long been known that either the failure of a pair of homologs to recombine, or an unusual distribution of recombination events, is associated with meiotic nondisjunction [2]. These observations have led to a two-step model of meiotic nondisjunction in which the creation of so-called ‘vulnerable’ crossover configurations during meiotic prophase (a process that occurs during mid-to-late-fetal development in human beings) predisposes homologs to nondisjoin at either the first or second meiotic division events (events that occur one to five decades later) [2-4]. Given that crossovers function by virtue of using sister-chromatid cohesion on both sides of the crossover to link the homologs together [1], it makes sense that either the failure of crossing over per se or a crossover that occurred too distally between a pair of homologs might have insufficient cohesion to ensure proper homolog segregation. One prediction of this model is that these vulnerable crossover configurations do exist in fetal oocytes. This proposal has recently been directly tested and the results are described in a paper by Cheng et al. that recently appeared in PLoS Genetics [5].

Major recent advances

Cheng et al. studied the localization of the crossover associated protein MLH1 (for a review, see [6]) in more than 1000 prophase oocytes derived from 31 fetal ovarian samples. Although their studies did indeed confirm the existence of the predicted vulnerable crossover configurations (i.e., either a pair of homologs with no detectable MLH1 foci or bivalents with only a very distal or proximal focus), there were several unexpected observations. First, their observations confirm those of others [7,8] in suggesting that crossing over occurs over a wider temporal window in human females (from zygotene to pachytene) than it does in either human males or mouse females (where MLH1 foci appear to be tightly restricted to pachytene). Second, the number of MLH1 foci observed predicts a total genome genetic length of only 3465 cM, some 80% of the value of 4300-4600 cM obtained from direct measurement by linkage studies (for a review, see [5]).

As pointed out by the authors, the most reasonable explanation for this discrepancy is because crossover formation occurs over a wide temporal window, and some events may, therefore, be completed before others are initiated and it may thus not be possible to visualize all MLH1 foci that occur in a given oocyte at a single time. In addition, Holloway et al. [9] have provided strong evidence in mouse oocytes for a set of
MLH1-independent crossovers mediated via the MUS81 pathway. Moreover, using high-resolution linkage analysis in humans, Fledel-Alon et al. [10] have demonstrated the existence of double crossovers that occur in surprisingly close proximity, and suggested that one or both of these crossovers might be mediated by an MLH1-independent second pathway. Thus, the deficit of MLH1 foci, with respect to the length of the genetic map, may well be explained both by the fact that not all MLH1 foci are seen at any one time and by the existence of a second MLH1-independent pathway for crossing over.

However, there is a more serious discrepancy with respect to vulnerable crossover configurations. For example, using conventional linkage analysis, Bugge et al. [11] have estimated that the frequency of oocytes lacking a crossover on chromosome 13 is close to 12% and Oliver et al. [12] have determined that the frequency of oocytes that are non-exchange for chromosome 21 is approximately 20%. Similar data for chromosome 21 derived from high-resolution recombination mapping have been recently published by Fledel-Alon et al. [10]. These values are substantially higher than the values of 1% (chromosome 13) and 4.9% (chromosome 21) obtained by Cheng et al. [5]. Thus, the frequency of non-crossover oocytes for both chromosome 21 and chromosome 13, as estimated by linkage analysis, significantly exceeds the fraction of nonexchange chromosomes as measured by the absence of MLH1 foci.

As Cheng et al. point out, these discrepancies are extremely hard to understand. One component of the difference may be methodological—it is standard practice in these types of cytological studies to ignore oocytes with obvious failures in pairing and synapsis. Perhaps some of these oocytes contribute to the pool of functional oocytes on which linkage studies are based. The authors’ best attempt to reconcile these disparate observations is to note that their estimates of non-exchange bivalents provide a better fit for the frequency of aneuploid embryos, assuming that all non-exchange bivalents segregate their homologs at random. Unfortunately, this assumption ignores the possibility that, like many other organisms [13-15], human females may indeed possess an exchange-independent back-up system for ensuring the segregation of those chromosomes that fail to recombine.

Future directions
The study by Cheng et al. offers intriguing insights into the distribution of MLH1 foci, and their temporal control in human fetal oocytes. Of even greater interest are the authors’ observations regarding the nature of interference in human oocytes and differences in the types of unusual (and presumably vulnerable) crossover distributions observed for different human chromosomes. There will clearly be no ‘one size fits all’ model for explaining the effects of abnormalities in recombination distribution on proper segregation. That said, the dilemma of just how many non-crossover bivalents there really are, and to what degree various classes of crossover and non-crossover bivalents might be selected for or against during oocyte development, remains open—as does the issue of whether or not human females may indeed have a system for ensuring the segregation of non-crossover bivalents (a possibility that would, quite honestly, not surprise this author). But perhaps most importantly, the observations of Cheng et al. and those of others (for example, see [6]) need to be viewed as a starting point—one in which prophase human oocytes become accessible to the types of analysis of crossover events, as defined by location of the proteins such as MLH1, which are routinely applied to human male meiotic cells and mouse oocytes. Surely, further study of the recombination process in human oocytes will address the questions asked above.

Competing interests
The author declares that he has no competing interests.

Acknowledgements
RSH is grateful to the American Cancer Society for their support with a Research Professor Award.

References
1. Nicklas RB: Chromosome segregation mechanisms. Genetics 1974, 78:205-13.
2. Hassold T, Hall H, Hunt P: The origin of human aneuploidy: where we have been, where we are going. Hum Mol Genet 2007, 16(Spec No.2):R203-8.
3. Hassold T, Hunt P: To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2001, 2:280-91.
4. Orr-Weaver T: Meiotic nondisjunction does the two-step. Nat Genet 1996, 14:374-6.
5. Cheng EY, Hunt PA, Nalau-Cecchini TA, Fligner CL, Fujimoto VY, Pasternak TL, Steinauer JE, Woodruff TJ, Cherry SM, Hansen TA, Vallentine RU, Broman KW, Hassold TJ: Meiotic recombination in human oocytes. PLoS Genet 2009, 5:e1000661.
6. Lynn A, Ashley T, Hassold TJ: Variation in human meiotic recombination. Annu Rev Genomics Hum Genet 2004, 5:317-49.
7. Lenzi ML, Smith J, Snowden T, Kim M, Fishel R, Poulos BK, Cohen PE: Extreme heterogeneity in the molecular events leading to the establishment of chiasmata during meiosis I in human oocytes. Am J Hum Genet 2003, 76:112-27.
8. Teas C, Hartshorne G, Hulten M: Altered patterns of meiotic recombination in human fetal oocytes with asynapsis and/or synaptonemal complex fragmentation at pachytene. Reprod Biomed Online 2006, 13:88-95.
9. Holloway JK, Booth J, Edelmann W, McGowan CH, Cohen PE: MUS81 generates a subset of MLH1-MLH3-independent crossovers in mammalian meiosis. PLoS Genet 2008, 4:e1000186.
10. Fledel-Alon A, Wilson DJ, Broman K, Wen X, Ober C, Coop G, Przeworski M: Broad-scale recombination patterns underlying proper disjunction in humans. PLoS Genet 2009, 5:e1000658.
11. Bugge M, Collins A, Hertz JM, Elberg H, Lundsteen C, Brandt CA, Bak M, Hansen C, Delozier CD, Lespinasse J, Tranebjaerg L, Hahnemann JM, Rasmussen K, Bruun-Petersen G, Duprez L, Tommerup N, Petersen MB: Non-disjunction of chromosome 13. *Hum Mol Genet* 2007, 16:2004-10.

12. Oliver TR, Feingold E, Yu K, Cheung V, Tinker S, Yadav-Shah M, Masse N, Sherman SL: New insights into human nondisjunction of chromosome 21 in oocytes. *PLoS Genet* 2008, 4: e100033.

13. Hawley RS, Irick H, Haddox DA, Whitley MD, Arbel T, Jang J, McKim K, Zitron AE, New C, Childs G, Lohe A: There are two mechanisms of achiasmate segregation in *Drosophila* females, one of which requires heterochromatic homology. *Dev Genet* 1992, 13:440-67.

14. Hughes SE, Gilliland WD, Cotitta JL, Takeo S, Collins KA, Hawley RS: Heterochromatic threads connect oscillating chromosomes during prometaphase I in *Drosophila* oocytes. *PLoS Genet* 2009, 5:e1000348.

15. Stewart MN, Dawson DS: Changing partners: moving from non-homologous to homologous centromere pairing in meiosis. *Trends Genet* 2008, 11:564-73.