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► **To cite this version:**

Wayne Crismani, Chloé Girard, Andrew Lloyd. Crossover interference: just ZYP it.. Proceedings of the National Academy of Sciences of the United States of America, 2021, 118 (17), pp.e2103433118. 10.1073/pnas.2103433118 . hal-03852697

HAL Id: hal-03852697

<https://hal.science/hal-03852697v1>

Submitted on 15 Nov 2022

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Crossover interference: just ZYP it.

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Main text

More than a century ago, research in *Drosophila* discovered fundamental mechanisms of inheritance that apply to sexually reproducing organisms (1). One key observation was that in meiosis, the cell division that generates sex cells, homologous chromosomes make large-scale reciprocal exchanges of genetic material called crossovers. A second observation was that these crossovers are not randomly distributed, with the presence of one crossover reducing the likelihood of another crossover nearby. This phenomenon, termed interference, results in crossover spacing that is more uniform. To this day, the mechanism of crossover interference remains largely unexplained. In this issue of PNAS, Capilla-Perez *et al* (2) and France *et al* (3) make a leap forward in our understanding of this puzzling phenomenon.

Meiotic crossovers are formed during prophase I within a highly organized chromosome structure. First, the two sister chromatids of each chromosome are tethered to a proteinaceous axis (Figure 1). Second, homologous chromosome axes are "zipped" together by a highly ordered and evolutionarily conserved structure: the synaptonemal complex. A repeating unit of the synaptonemal complex, which is analogous to the teeth of a zipper, is the ZYP1 protein, also called the transverse filament. In this issue Capilla-Perez *et al* (2) and France *et al* (3) leveraged the genetic tools available for the plant *Arabidopsis thaliana* to elucidate the role of the transverse filament in crossover interference. Genetic studies of the transverse filament had been largely precluded in *Arabidopsis* because it is encoded by an inverted duplication of the *ZYP1* gene separated by 2 kb, which was near impossible to knock out in the pre-CRISPR/Cas9 era.

Previous studies in multiple organisms have shown that the synaptonemal complex, and its transverse filament, are required for crossover formation: in the complete absence of the transverse filament in *Drosophila* (4), mouse (5), worm (6) and yeast (7) crossover formation is severely reduced. Capilla-Perez *et al* and France *et al* generated CRISPR/Cas9 lines deleting both *ZYP1* copies in *Arabidopsis* and reported that the transverse filament is not required for crossover formation in this species. Importantly, the fact that crossovers still

occurred provided the authors an opportunity to investigate other roles of the transverse filament not directly related to crossover formation, and found that: 1) meiotic progression can proceed relatively normally without the transverse filament: homologous chromosomes co-align but fail to synapse, and normal chromosome axis remodeling is abrogated; 2) the synaptonemal complex limits crossovers and imposes crossover interference; 3) male and female crossover rates, that are normally different, become identical without the transverse filament.

In many organisms, including *Arabidopsis*, two crossover pathways with differing genetic requirements exist (8). Crossovers formed by the major pathway require an evolutionarily conserved set of genes collectively referred to as ZMMs and are sensitive to interference. The second class of crossovers is insensitive to interference. As one class of crossover is sensitive to interference and the other not, changing the balance of crossovers contributed by the two pathways can alter genetic measurements of interference, without necessarily changing the underlying interference mechanism. Only loss of the interference mechanism, however, should result in random placement of ZMM crossovers and a possible increase in their number. This is exactly the outcome reported by Capilla-Perez *et al* and Francis *et al* with loss of the transverse filament in *Arabidopsis*. Both groups report an abolition of interference measured genetically, and an increase in ZMM-dependent crossovers (Figure 1). Thus, the loss of the transverse filament has resulted in either an inability for the interference signal to be transmitted or for it to be perceived.

Another common observation in many organisms is a difference in crossover rates between the sexes, termed heterochiasmy, correlating with differences in the length of the synaptonemal complex (Figure 1) (9, 10). In *Arabidopsis*, the synaptonemal complex around 40% longer in male meiosis and has around 40% more crossovers compared to identical chromosome pairs in female meiosis. Despite this long-known correlation, the directionality of any causal relationship had been hard to pin down. The observation that yeast condensin mutants with longer synaptonemal complexes have more crossovers has, to date, provided some of the strongest evidence that synaptonemal complex length (and/or chromosome axis length) dictates crossover number, rather than the other way around (11). One proposed explanation is that the suppressive interference signal propagates a set physical distance along the synaptonemal complex and chromosome axis (12). According to this model, a longer synaptonemal complex would tend to generate more crossovers. Capilla-Perez *et al* show that in the absence of the transverse filament and interference, heterochiasmy is abolished: both male and female meiosis show the same number of crossovers. These findings 1) strengthen the hypothesis that differences in synaptonemal complex length impose differences in crossover number, 2) supports the idea that interference propagates a set distance along the synaptonemal complex or chromosome axis, and 3) suggests that in *Arabidopsis* the transverse filament of the synaptonemal complex is required for the interference signal to be propagated or perceived.

One interesting observation from both studies is that, while interference appears to be completely lost and the number of crossovers is elevated compared to wild type, the increase is relatively modest compared to the hundreds of double-strand breaks introduced early in meiosis (13); the average number of crossovers increases to 14, from 6 and 10 in male and female respectively. The relatively small increase in crossovers is particularly striking when compared to the massive ~8-fold increase in total recombination that has been achieved by mutating genes that suppress the alternative, interference insensitive, crossover pathway (14). Why are crossover numbers still low in the absence of interference? One possible explanation is that the transverse filament in *Arabidopsis*, like in other organisms, also has a pro-crossover role and that a large number of sites initially designated as crossovers fail to mature.

An alternative explanation is that the non-crossover fate of the vast majority of potential crossover sites is settled independently of interference, for example, if a trans-acting factor

limited crossover formation. In many organisms, sites of interference-sensitive ZMM-dependent crossovers accumulate pro-crossover proteins, forming intense foci at the end of meiotic prophase (15–18). It would be possible to cap the number of ZMM-dependent crossovers if one or more of these proteins is operating under limiting conditions. A possible candidate for such a role is HEI10 which, when over-expressed in *Arabidopsis*, can increase the number of interfering crossovers (19). A trans-acting factor limiting crossovers could also explain the observation that formation of the obligate crossover, required for accurate chromosome segregation, is lost in the absence of interference. Interference would normally prevent large amounts of this factor being sequestered by any one chromosome, ensuring that each chromosome had sufficient resources to form at least one crossover. Intriguingly, Capilla-Perez *et al* see fewer crossovers and more univalents in *zyp1* mutants of the *Arabidopsis* ecotype with the less active *HEI10* allele, Landsberg erecta. It will be very interesting to test the combined effect of HEI10 over-expression with the mutation of the transverse filament.

A number of important questions still remain for the field, and the nature of the interference signal or mechanism remains unclear. However, these studies provide important new insights about the role of the synaptonemal complex in mediating crossover interference. How much does what is seen in *Arabidopsis* reflect what occurs in other organisms? There is evidence that the involvement of the synaptonemal complex in the interference mechanism is conserved in at least some other systems: in the nematode *C. elegans*, partial depletion of the transverse element proteins leads to an increase in crossover number and a decrease in interference strength (20). The lack of equivalent data from other species might stem from the fact that it seems difficult to disentangle the pro-crossover role of the synaptonemal complex from any potential role in mediating interference. This new set of results will certainly prompt the field to revisit this interesting concept.

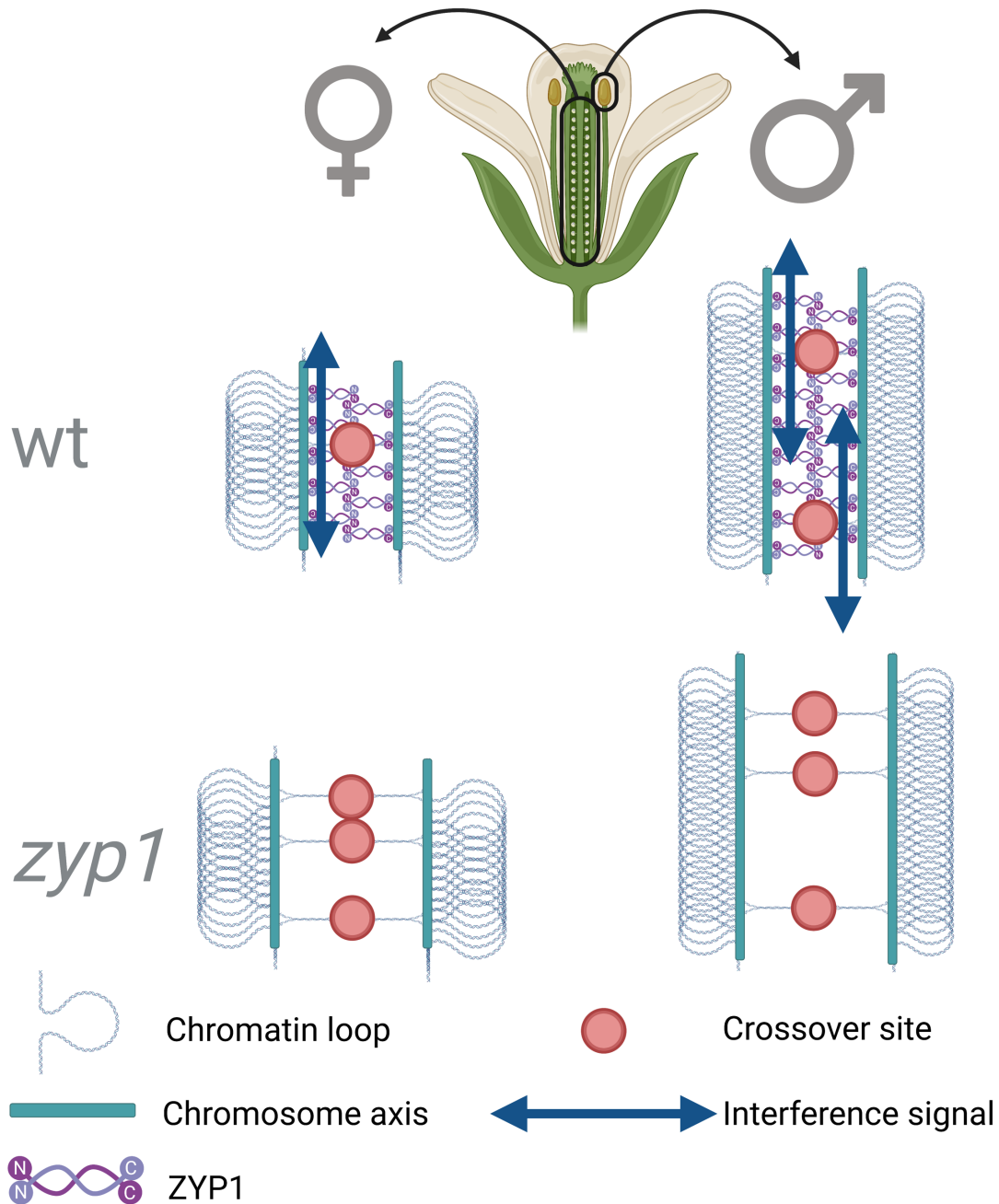


Figure 1. A model of interference. In wild type (wt), ZYP1 enables transmission or perception of the interference signal, preventing closely spaced crossovers. As the interference signal propagates a fixed physical distance, the longer chromosome axes in male permit more crossovers per chromosome than in female. In *zyp1* mutants, homologous chromosomes co-align at a distance of ~400 nm, compared to ~200 nm in wild type, but do not synapse due to lack of the transverse filament. In the absence of interference, crossovers: 1) increase in number; 2) become randomly distributed along and among chromosomes; and 3) the difference in crossover rates between male and female meiosis is abolished.

Acknowledgements

Thank you to Scott Hawley for helpful comments on the manuscript. WC receives funding from the Australian National Health and Medical Research Council (GNT1185387, GNT1156343).

CG receives funding from the French Agence Nationale de la Recherche ANR-20-CE20-0007. AL is funded through a UKRI Future Leaders Fellowship (MR/T043253/1). Figure created with BioRender.com.

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