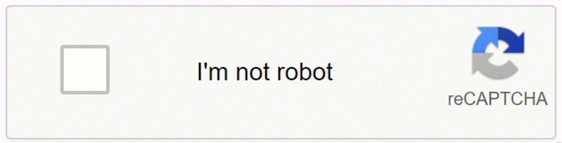

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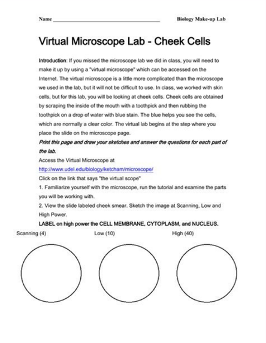
Virtual Microscope Lab - Cheek Cells

VIRTUAL LAB: U. of Arizona Karyotyping Activity

In this activity, you will use a computer model to look at chromosomes and prepare a karyotype. You will diagnose patients for abnormalities and learn the correct notation for characterizing karyotypes.

Go to: www.biology.arizona.edu - click on Karyotyping under human biology
OR
http://www.biology.arizona.edu/human_bio/activities/karyotyping/karyotyping.html

1. How are karyotype analyses conducted?

2. What are some uses of analyzing karyotypes?

3. What causes a dark band on the chromosome?

4. What is a centromere?

5. Which chromosome determines sex in humans? Is this an autosome or sex chromosome?

Patient Histories: *Click on Patient Histories. You will be completing a karyotype for Patient A, B & C

Patient A (Click on the link to "Complete Patient A's Karyotype")
***Match the chromosome to its homolog. After all the matches are complete you'll analyze your patient. (Scroll down to view your completed karyotype).**

6. What is patient A's history (summarize)

7. How many total chromosomes are in your karyotype - count them __________
The last set of chromosomes is the sex chromosomes, if you have two large chromosomes, your patient is XX (female), one large and one small indicates and XY (male) .
What sex chromosomes does your patient have _________
Which chromosome set has an extra + ________

8. What diagnosis would you give this patient (what disease)? _______________

Patient B - click on the link to go to Patient B and repeat the above process.
9. What is Patient B's history (summarize)

10. How many total chromosomes are in your karyotype - count them __________
What sex chromosomes does your patient have _________
Which chromosome set has an extra + ________
11. Finish the notation for this patient's karyotype : 47 X _____

12. What is the diagnosis? ____________________________________

6F 1/29/2013

Name ______________________________________ Date _________ Period ________

Worksheet: Dihybrid Crosses

UNIT 3: GENETICS

Directions: *Answer the following genetic cross problems. You can refer to the "Punnett Square Cheat Sheet" attached at the end of this worksheet to help you solve the different types of problems. It is essential that you know the all of the vocabulary inlcuded in the "cheat sheet" as well. Remember when you are doing a genetic cross to follow the steps below to complete!*

STEP 1: Determine what kind of problem you are trying to solve.
STEP 2: Determine letters you will use to specify traits.
STEP 3: Determine parent's genotypes.
STEP 4: Make your punnett square and make gametes
STEP 5: Complete cross and determine possible offspring.
STEP 6: Determine genotypic and phenotypic ratios.

Two-Factor Crosses (Di-hybrid)

1. In man, assume that spotted skin (S) is dominant over non-spotted skin (s) and that wooly hair (W) is dominant over non-wooly hair (w). Cross a marriage between a heterozygous spotted, non-wooly man with a wooly-haired, non-spotted woman. Give genotypic and phenotypic ratios of offspring.

2. In horses, black is dependent upon a dominant gene, B, and chestnut upon its recessive allele, b. The trotting gait is due to a dominant gene, T, the pacing gait to its recessive allele, t. If a homozygous black pacer is mated to a homozygous chestnut trotter, what will be the appearance of the F_1 generation?

3. In snapdragon flowers, red color is not completely dominant over white color and tall plants are dominant over short plants. What would expect to get from a genetic cross of a homozygous tall red snapdragon with a short white plant? Give genotypic and phenotypic ratios of the offspring.

Corn genetics worksheet. Corn genetics lab quizlet. Corn genetics lab report answers. Corn genetics lab answers. Corn genetics worksheet answers.

doi: 10.1038/268460a0 CrossRef Full Text | Google Scholar Varas, J., Sánchez-Morán, E., Copenhaver, G. For genetic crossovers, there is no polarity within Bz1. Recombination is the exchange of genetic information between chromosomes. The large block of repetitive sequence upstream of Bz1 is heavily methylated consistent with methylation suppressing recombination as has been seen in Arabidopsis (Melamed-Bessudo and Levy, 2012; Mirouze et al., 2012; Yelina et al., 2015). S., Gerlach, W. 318, 1347–1352. We have two goals for this review. doi: 10.1146/annurev-genet-120213-092304 PubMed Abstract | CrossRef Full Text | Google Scholar Kianian, P. M., Dennis, E. On average, DSBs have an increased tendency to peak at TSS and on both sides of TTS (He et al., 2017), agreeing with CO peaks close to TSS and TTS (Kianian et al., 2018). GM received funding from Endowed Chair in Molecular Genetics Applied to Crop Improvement. M., Shroyer, T., and Chandler, V. Thus the importance of a DSB hotspot flanking Bz1 for recombination is unclear. doi: 10.1101/gr.127522.111 PubMed Abstract | CrossRef Full Text | Google Scholar Mancera, E., Bourgon, R., Brozzi, A., Huber, W., and Steinmetz, L. A. L., and Peacock, W. 28, 99–111. U.S.A. 93, 5920–5924. genome. J., Elshire, R. R. E., Warthmann, N., Yant, L., et al. PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. Only four of the 101 COs mapped outside of the three hotspots (Yao et al., 2002). (2013). Google Scholar Nelson, O. C., Acharya, C. RILs, recombinant inbred lines; GBS, genotyping by sequencing. This pollen phenotype is readily scored under a microscope and allows screening of very large numbers of meiotic products. Trans. Nelson (1957) proposed testing intragenic recombination at the maize Waxy (Wx) locus. J., Hardcastle, T. TABLE 1. The Wx pollen system was also used to explore whether the distance of a locus from the centromere altered recombination frequency (Yu and Peterson, 1973). 29, 2183–2202. doi: 10.1007/s10709-011-9613-x PubMed Abstract | CrossRef Full Text | Google Scholar Wei, F., Zhang, J., Zhou, S., He, R., Schaeffer, M., Collura, K., et al. 7:e1002354. TABLE 3. Distribution of Maize Crossovers by High-Throughput Genotyping At the genome-wide scale, maize COs form a particular U-shape pattern, with COs increasing strongly toward chromosome ends (Anderson et al., 2003; Li et al., 2015; Rodgers-Melnick et al., 2015; Kianian et al., 2018). doi: 10.1139/g00-015 PubMed Abstract | CrossRef Full Text | Google Scholar Johns, M. Maize studies identified genes as recombination hotspots with crossovers distributed approximately evenly across many genes, which conflicts with the discrete hotspots and polarity found in S. What is reported in genome-wide studies is an accumulated pattern from 100s of genes. doi: 10.1073/pnas.1319032110 PubMed Abstract | CrossRef Full Text | Google Scholar Higgins, J. When both wx-C and wx-90 were on normal chromosomes crossover events accounted for approximately 65% of the Wx revertants based on the segregation of flanking markers. U.S.A. 114, 12231–12236. Meiotic recombination can refer to crossovers (COs) which are due to exchange of whole chromosome parts, to non-crossovers (NCOs) which are locally restricted, or to both. The recombination machinery has been extensively described and reviewed in general as well as in plants (Pradillo et al., 2014; Lambing et al., 2017). Deficiency in DNA methylation increases meiotic crossover rates in euchromatic but not in heterochromatic regions in Arabidopsis. R., et al. (1931). The WAXY locus in maize. There was crossing over between the flanking markers in 35% of the Wx revertants when wx-C was located within a pericentric inversion. (2006). If DSBs near the TSS contribute substantially to recombination, then more recombinants should be recovered between alleles with intact TSS regions than with alleles containing TSS region deletions. Polarity can also be seen in Arabidopsis genes where recombination peaks near TSS, then decreases toward the end of genes (Hellsten et al., 2013; Choi et al., 2016). J., Zhao, X., Santos, B., and Henderson, I. J., Li, T., et al. T., Springer, N. High marker density is critical for studying polarity and other questions. A recent maize genomic DSB study using a genome-wide approach similar to the one used in S. K., and Martínez-Férez, I. cerevisiae may not hold in maize (see section "The Role of Double-Strand Breaks in Maize and Other Model Organisms"). Genetics 206, 1373–1388. In spite of different genome architecture of Arabidopsis and maize, many commonalities of DSB and CO hotspots can indeed be found. B 312, 291–302. Google Scholar Civardi, L., Xia, Y., Edwards, K. doi: 10.1371/journal.pgen.1000732 PubMed Abstract | CrossRef Full Text | Google Scholar Baudat, R., Buard, J., Grey, C., Fledel-Alon, A., Ober, C., Przeworski, M., et al. Rev. thaliana The foundation for our understanding of recombination is built upon intragenic recombination studies in fungal systems, particularly the budding yeast, S. 12:e1006179. 50, 175–210. doi: 10.1073/pnas.022635499 PubMed Abstract | CrossRef Full Text | Google Scholar Giraut, L., Falque, M., Drouaud, J., Pereira, L., Martin, O. Local chromosome context is a major determinant of crossover pathway biochemistry during budding yeast meiosis. This is mirrored in other model systems, for example Arabidopsis, with highest DSB levels at TSS and TTS (Choi et al., 2018), and is in general a prerequisite for recombination polarity along a gene body. doi: 10.1016/j.cell.2016.09.035 PubMed Abstract | CrossRef Full Text | Google Scholar Liu, S., Schnable, J. The feasibility of investigating 'Genetic fine structure' in higher plants. (2005). Genome Res. Median gene conversion tract lengths in S. Most Wx revertant pollen will be from non-crossover events as double crossovers are rare in short genetic intervals. Later, this model was confirmed by genomic studies on the genome wide distribution of DSBs and meiotic recombination (Figure 1). Outside of Bz1 the most extensive intragenic recombination data comes from the Wx locus. G., Brigham, B., Carter, J., Hooker, K. 5:e324. The genome-wide maize DSB data identified 3126 high-confidence DSB hotspots, about one-fourth of them in genes. Non-crossover events may produce non-mutant Wx kernels. J., and Emmerling, M. At that time however, it was not clear. Instead, DSBs occur at other H3K4me3 sites on the chromosome; many of these are near the TSS (Brick et al., 2012). DSB hotspot widths are similar to S. Greater precision is necessary to minimize the misleading correlations possible with low-resolution mapping (Tischfield and Keeney, 2012). (C) Alternatively, a mix of genes having DSB hotspots at their 5′ ends, their 3′ ends, and genes that are diffuse hotspots give the same pattern of crossovers. J., Lambing, C., Underwood, C. Proc. Science 326, 1112–1115. Chromosome Res. Resection creates a 3′-overhang that invades a homologous DNA region and pairs with its complementary sequence, binding it as a repair template. Nature 338, 35–39. Data from the fourth study was reported in Alina Ott's Ph.D. dissertation, and a manuscript is in preparation (Ott, 2017). What the genomic maize DSB study shows clearly, however, is the concentration of DSBs around TSS and TTS of many genes (He et al., 2017). doi: 10.1146/annurev-genet-120215-035111 PubMed Abstract | CrossRef Full Text | Google Scholar Haberer, G., Young, S., Bharti, A. doi: 10.1073/pnas.1120742109 PubMed Abstract | CrossRef Full Text | Google Scholar Meyers, B. Hugo Dooner, studying the Bronze1 (Bz1) gene estimated that the ratio of genetic to physical distance within Bz1 was 100-fold higher than the genome average (Dooner, 1986). Recombination occurs uniformly within the bronze gene, a meiotic recombination hotspot in the maize genome. 22, 213–222. A., Strommer, J. Sequences required for paramutation of the maize b gene map to a region containing the promoter and upstream sequences. Homozygous deletions of DSB hotspots reduce recombination and eliminate polarity at the S. RO and SD-S: drafting of manuscript. In total, the maize DSB mapping effort identified 3126 hotspots (He et al., 2017), similar to the 3604 DSB hotspots in S. Genetics 141, 347–360. One possibility was that recombination was different in bacteriophage and eukaryotes. U.S.A. 99, 1082–1087. Reconciling polarity gradients as seen in high-throughput genotyping versus intragenic studies. U.S.A. 106, 8410–8416. But two of these studies determined that about one-fourth of the crossovers mapped within a gene were in the central region (Li et al., 2015; Ott, 2017). 200, 240–246. While underlying mechanisms and involved proteins overlap, there are profound differences between somatic and meiotic recombination. (B) Chromosome pairing during meiosis. In this study using the Bz1 region, crossing over was compared between a short genic region and a block of repetitive sequence flanking the genes. The H3K4me3 modification at mouse DSB hotspots is produced by the Prdm9 histone methyltransferase (Baudat et al., 2010). doi: 10.1073/pnas.87.22.8731 PubMed Abstract | CrossRef Full Text | Google Scholar Wijnker, E., James, G. However, in practice, COs are localized to intervals defined by available sequence polymorphisms which may not coincide with the defined 5′ and 3′ ends. Using a much larger population, Rodgers-Melnick's study found 410 hotspots (Rodgers-Melnick et al., 2015). In this region, at least, sequence differences cannot account for the lack of crossing over in repetitive sequence. Multiple branches of the meiotic recombination pathway contribute independently to homolog pairing and stable juxtaposition during meiosis in budding yeast. (2009). Cytol. A histone H3 methyltransferase controls epigenetic events required for meiotic prophase. Analysis of the relationships between DNA double-strand breaks, synaptonemal complex and crossovers using the Atfas1-4 mutant. P., and Szostak, J. Wx encodes a starch synthase required for amylose in the kernel endosperm and pollen. According to the original canonical DSB model, gene conversion tracts produced at NCOs and COs will flank or encompass the position of initiating DSBs, thus indirectly mapping DSBs (Szostak et al., 1983). (2003). Cell 70, 9–20.e6. Mol. It seems that hotspots are not the best means to describe crossovers in maize which could be better described as following a chromosome-wide polarity gradient toward the chromosome ends coupled with an avoidance of repetitive sequence in the case of COs. This wider perspective encompasses additional questions including the importance of trans-acting modifiers, frequently genes from recombination pathways (Pan et al., 2017). These studies established a picture of recombination initiating at DSB hotspots which were usually found near TSSs (Petes, 2001). (2008). Due to the underlying literature we have focused this review on hotspots for crossover and DSBs. This perspective may be problematic. thaliana," Supplementary Table 1). Z. G., Tischfield, S. Thus in a line where one allele contains a deletion of its DSB hotspot and the other allele retains its DSB hotspot, recombination preferentially deletes the previously non-mutant sequence (Nicolas et al., 1989). Conflict of Interest Statement The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Second, we describe characteristics in several model systems to illustrate the variation present in nature, and to argue that recombination in maize shares some, but not all, properties of each of these systems. Although there was no consensus target sequence for the SPO11 nuclease responsible for meiotic DSBs, the DNA sequence was non-random with preferred nucleotides at certain positions, and a central AT-rich sequence surrounded by modestly GC-rich sequence. M., Schott, J., Zhu, X., and Llorente, B. cerevisiae genes, emphasize polarity at the 5′ and 3′ ends of genes (Li et al., 2015; Ott, 2017; Kianian et al., 2018). U.S.A. 110, 19478–19482. cerevisiae and S. L., and Pradillo, M. Genetica 139, 1109–1118. Contrasting with the absence of polarity at the Wx locus is the strong polarity for COs at the maize A1, B1, and R1 genes. All authors approved the final version of the manuscript. High resolution mapping of COs and NCOs placed 84% of recombination hotpots overlapping promoters near TSSs (Mancera et al., 2008). Comparative characteristics of DSB hotspots. The two approaches give different snapshots and interpretations of crossing over and point to their relative strengths and weaknesses. doi: 10.1038/emboj.2008.257 PubMed Abstract | CrossRef Full Text | Google Scholar Brick, K., Smagulova, F., Khil, P., Camerini-Otero, R. 12, 1459–1466. doi: 10.1093/molbev/msy174 [Epub ahead of print]. Evol. Looking at recombination between pairs of alleles with a variety of genetic backgrounds and mutational lesions found no indication of polarity at Wx (Okagaki and Weil, 1997). A recombination event between two mutant alleles would create a non-mutant Wx allele giving a revertant Wx pollen grain. Recombination polarity at the 5′ and often 3′ ends of genes has been reported to be the common pattern in several plant species (reviewed in Choi and Henderson, 2015). cerevisiae HIS4 locus (Detloff et al., 1992). 3:e83. J., Glaubitz, J. doi: 10.1371/journal.pgen.1000715 PubMed Abstract | CrossRef Full Text | Google Scholar Wessler, S., Tarpley, A., Purugganan, M., Spell, M., and Okagaki, R. One possibility suggested at the time was that local structural differences between progenitor alleles inhibited synapsis and recombination. eLife 2:e01426. (2007). (2001). Maize has been a genetic model organism since the early 1900s, and there is an extensive history of intragenic recombination studies in maize. Fine-scale variation in meiotic recombination in Mimulus inferred from population shotgun sequencing. Pollen phenotyping procedures were developed for other genes to study intragenic recombination. 24, 1650–1664. Single-crossovers between these wx-C alleles on a rearranged chromosome and the wx-90 allele on a normal chromosome produce inviable gametes unless there was a second crossover within the inversion (Figure 2). Chromosome structure dynamics during the cell cycle: a structure to fit every phase. (2002). The zygotene foci are distributed across the chromosomes where single-stranded DNA ends produced by DSBs and resection promote chromosome alignment (Smithies and Powers, 1986; Peoples-Holst and Burgess, 2005). Plant Sci. The polarity found in these studies could be a result of a generalized polarity at most genes or the result of a mix of genes with and without CO polarity as seen in intragenic studies. It seems reasonable to conclude that a majority of maize DSBs promote chromosome alignment (Peoples-Holst and Burgess, 2005). However, the number of studies with adequate data is small and conclusions about relative frequency of genes showing polarity should not be drawn. cerevisiae (Lange et al., 2016). Google Scholar Dooner, H. doi: 10.1371/journal.pgen.1005301 PubMed Abstract | CrossRef Full Text | Google Scholar Wang, G., Xu, J., Tang, Y., Zhou, L., Wang, F., Xu, Z., et al. Self-organization of meiotic recombination initiation: general principles and molecular pathways. H., and Lichten, M. Unequal sister chromatid and homolog recombination at a tandem duplication of the a1 locus in maize. Analysis of recombination sites within the maize waxy locus. P., Zhang, L., Nikolau, B. EMBO J. A History of Maize Intragenic Recombination The classical conception of genes posited that genes were indivisible units and recombination occurs between genes (reviewed in Green, 1955; Portin, 1993). (2017). Variation in recombination frequency and distribution across eukaryotes: patterns and processes. The trimethylated histone H3 lysine 4 (H3K4me3) is a histone modification promoting an open chromatin structure that is found at DSB hotspots (Borde et al., 2009). Approximately, 85% of the maize genome is composed of families of repetitive elements widely distributed in the maize genome (Schnable et al., 2009). Acad. (1995). D., and Petukhova, G. L., Rothstein, R. doi: 10.1371/journal.pgen.0030083 PubMed Abstract | CrossRef Full Text | Google Scholar Choi, K., Reinhard, C., Serra, H., Ziolkowski, P. doi: 10.1098/rstb.1986.0008 CrossRef Full Text | Google Scholar Stack, S. Meiotic recombination break points resolve at high rates at the 5′ end of a maize coding sequence. DSB break maps, produced by capturing and sequencing SPO11-bound oligonucleotides released during initial DSB resection, confirmed that DSBs occur mainly near TSSs in S. Resolution of double Holliday structures into COs produces a gene conversion tract, as do pathways leading to NCOs. The latter is often used interchangeably with GC although it does not cover all GC instances. doi: 10.7554/eLife.19669 PubMed Abstract | CrossRef Full Text | Google Scholar Melamed-Bessudo, C., and Levy, A. cerevisiae that provide insight into maize. doi: 10.1073/pnas.1713225114 PubMed Abstract | CrossRef Full Text | Google Scholar Hellsten, U., Wright, K. K., Fang, C., Olson, M. U.S.A. 112, 3823–3828. I., and Ashley, T. When wx-C was within a complex rearrangement the few revertants arose through non-crossover events. Acknowledgments This paper is dedicated to Oliver E. Our purpose here is to review the maize intragenic recombination work, and place this work in context with results from genomic studies of maize recombination and work in fungal and animal model systems. H3K4me3 is present at other sites along mouse chromosomes including TSS. doi: 10.2307/3870816 PubMed Abstract | CrossRef Full Text | Google Scholar Freeling, M. Plant Cell 15, 1807–1816. doi: 10.1534/genetics.105.05271 PubMed Abstract | CrossRef Full Text | Google Scholar Yao, H., and Schnable, P. Can. DSBs were underrepresented in repetitive sequences with repetitive DNA comprising 14% of the genome while accounting for only 1.16% of DSB breaks defined by SPO11 reads (Pan et al., 2011). The landscape of mouse meiotic double-strand break formation, processing, and repair. doi: 10.1073/pnas.1120841109 PubMed Abstract | CrossRef Full Text | Google Scholar Nelson, O. (D) Crossovers between wx-C and wx-90 will produce inviable pollen unless there is a second crossover within the inversion. cerevisiae (Nicolas and Petes, 1994; Gray and Cohen, 2016). Genetics 170, 1929–1944. Maize chromosomes have rather big pericentromeric heterochromatin regions that cover more than half of them (Baucom et al., 2009; Wei et al., 2009). Enhancement of genetic exchange in maize: intragenic recombination. cerevisiae repetitive sequence disqualifies S. This conjecture was supported by subsequent molecular findings of little similarity between regions flanking most, but not all, parental Adh1 alleles (Johns et al., 1983; Sachs et al., 1986). doi: 10.1101/gr.172122.114 PubMed Abstract | CrossRef Full Text | Google Scholar Franklin, A. Intragenic recombination studies have also looked at recombination within small genetic intervals. Front. cerevisiae genes. Nature 472, 375–378. A correlation of cytological and genetical crossing-over in Zea mays. Loss of DNA methylation affects the recombination landscape in Arabidopsis. Alternatively, a double Holliday junction structure may form which can resolve into a crossover. Genetics 113, 1021–1036. Recovery of maize Wx recombinants from an inversion heterozygote. Two alleles of maize alcohol dehydrogenase 1 have 3′ structural and poly(A) addition polymorphisms. FIGURE 3. Non-crossover conversion tracts in the 5′, the central, and 3′ regions of maize genes were roughly equally distributed, with a slightly higher number in the middle region of genes (Ott, 2017). Genetics 123, 621–624. An alternative position was supported by several prominent geneticists who viewed genes as having multiple sites where crossing over could occur (Pontecorvo, 1955). Intragenic studies look at many recombination events at a few genes while genomic approaches average over many genes with few recombination events each. Although this differs at first glance from intragenic studies which reported genes with and without polarity, the data actually agrees. Cell 144, 719–731. K., Gundlach, H., Raymond, C., Fuks, G., et al. Crossover hotspots were identified in three studies (Rodgers-Melnick et al., 2015; Ott, 2017; Kianian et al., 2018). PubMed Abstract | Google Scholar Nelson, O. Though limited to only four alleles, results at the rice Wx locus are in agreement (Inukai et al., 2000). Saccharomyces cerevisiae DSBs map preferentially to nucleosome depleted regions (NDRs) around the TSS, a hallmark of open chromatin (Pan et al., 2011). E., White, M. Cell Res. Rather, chromosomal context and the relationship between the DSB and the synaptonemal complex are important (Medhi et al., 2016). (A) Histogram representing crossover polarity seen in high-throughput genotyping studies. Recombination within genes, intragenic recombination, was not believed to exist, especially since several apparent exceptions turned out to be recombination between duplicated gene copies in a complex locus. In general, crossovers in S. (1992). doi: 10.1101/gad.270876.115 PubMed Abstract | CrossRef Full Text | Google Scholar Fine structure of a genetic region in bacteriophage. In summary, the key results from intragenic recombination studies in maize are as follows: (1) both crossover and non-crossover events are detected; (2) many maize genes are recombination hotspots; (3) some but not all genes show polarity that may be punctate or have a gradient; (4) some recombination hotspots are in non-genic low-copy sequences; (5) sequence differences between parental chromosomes affect the distribution of recombination events. Meiotic DSBs can be visualized on chromosomes as RAD51 foci (Franklin et al., 1999). Mapping crossovers from maize tetrads determined an average of 19 crossovers per meiosis (Li et al., 2015), similar to the range of cytologically determined CO in maize inbreds (Sidhu et al., 2015). Genet. Less than 20% of S. (1994). A hierarchical combination of factors shapes the genome-wide topography of yeast meiotic recombination initiation. Genetics 105, 733–743. While high-throughput studies emphasize increased CO rates at 5′ and 3′ ends of genes, intragenic studies report on individual genes, exposing the mix of genes with large diffuse hotspots or localized hotspots (Figure 3). doi: 10.1023/A:1016575925934 PubMed Abstract | CrossRef Full Text | Google Scholar Stadler, L. On the other hand, high-throughput genotyping studies suffer from a lack of resolution or depth, and small sample sizes. (C) Chiasmata and recombination nodules are visible via microscopy. D., Xia, Y., Li, J., Neuffer, M. doi: 10.1016/j.yexcr.2012.03.025 PubMed Abstract | CrossRef Full Text | Google Scholar Sidhu, G. PubMed Abstract | Google Scholar Dietrich, W. • "Hotspots" are genomic regions with elevated levels of recombination-related events, and can refer to the meiotic double-strand breaks (DSBs) initiating recombination, COs or general recombination including both COs and NCOs. There is no standard definition of hotspots regarding their strength or size. Nature 438, 374–378. Polarity for recombination is seen in many S. Nucl. doi: 10.7554/eLife.01426 PubMed Abstract | CrossRef Full Text | Google Scholar Xu, X., Hsia, A. Mike Freeling described an odd situation where alcohol dehydrogenase1 (adh1) alleles derived from the same progenitor allele showed intragenic recombination, but adh1 alleles derived from different progenitor alleles did not recombine (Freeling, 1978). There is now an intense interest and effort in understanding the roles of chromatin features including the synaptonemal axis, loops, and cohesin proteins, which will help refine our views on meiotic recombination mechanisms and patterns (Barrington et al., 2017). Several explanations for the contrasting results from bacteriophage versus Drosophila melanogaster and other familiar genetic systems were proposed (Green, 1955). Three maize genome-wide studies reported polarity for crossovers, with COs most frequent in the 5′ region of genes and low in the central region of genes (Li et al., 2015; Ott, 2017; Kianian et al., 2018). Analysis of a gene conversion gradient at the HIS4 locus in Saccharomyces cerevisiae. Maize sequencing based CO studies. S., Stein, J. The B73 maize genome: complexity, diversity, and dynamics. Point mutations at both ends of Bz1 are converted more frequently than point mutations in the middle of the gene. Three studies have been published (Li et al., 2015; Rodgers-Melnick et al., 2015; Kianian et al., 2018). One mapped DSB hotspot was immediately upstream of Bz1. The maize wx-B allele is a 1 kb deletion around the TSS from -459 to +505, while wx-C4 has a smaller deletion within the transcribed region from +257 to +454 (Wessler et al., 1990; Okagaki and Weil, 1997). The number of defined maize DSB hotspots is conservative. In maize, the relative importance of polarity in recombination is one of the questions arising between intragenic recombination studies and high-throughput genotyping studies. Heredity 108, 447–455. cerevisiae (Table 2). K., Weck, E., Adams, S., Ralston, E., Favreau, M., and English, J. Distribution of Crossovers in Maize Intragenic Studies In a series of studies beginning in 1985, and continuing today, Hugo Dooner described a number of properties of maize recombination using the Bz1 locus (Table 1). Genes Dev. Genetic fine structure of the bronze locus in maize. Removing H3K4me3 at DSB hotspots using prdm9 mutant mice blocks DSBs from forming at these hotspots. Author's Note Results from Alina Ott's Ph.D. dissertation have now been published in Liu et al. doi: 10.1073/pnas.0902972106 PubMed Abstract | CrossRef Full Text | Google Scholar He, Y., Wang, M., Dukowic-Schulze, S., Zhou, A., Tiang, C.-L., Shilo, S., et al. Funding SD-S thanks Changbin Chen for all his support and the opportunity to work on maize meiosis, supported by the National Science Foundation (IOS-1025881 and IOS-1546792), and a grant-in-aid fund from the University of Minnesota. This illustration shows the second crossover occurring within V. R., Sasaki, M., Milman, N., Keeney, S., and Smith, G. Briefly, recombination initiates with a DSB. (1975). In summary, the correlation of DSBs and recombination in S. Landmark maize intragenic recombination studies. There are two types of COs, with interference-sensitive COs (type I) constituting the majority of COs, and a few additionally interspersed interference-insensitive COs (type II) in many species (Gray and Cohen, 2016). Recombination in diverse maize is stable, predictable, and associated with genetic load. Nat. Is recombination confined to structural genes on the eukaryotic genome? Nucleosomes and DNA methylation shape meiotic DSB frequency in Arabidopsis thaliana transposons and gene regulatory regions. Though only a fraction of DSBs is resolved into COs in Arabidopsis, DSB and CO levels were shown to correlate strongly at the chromosome scale, though varying along arms (Choi et al., 2018) (Table 2). A., Falque, M., Martin, O. These two studies relied on relatively small populations. V., Ding, J., Becker, F., Klasen, J. doi: 10.1105/tpc.107.057596 PubMed Abstract | CrossRef Full Text | Google Scholar Dooner, H. Arthur Chovnick's Perspectives article in Genetics provides a historical overview (Chovnick, 1989). Intragenic meiotic crossovers generate novel alleles with transgressive expression levels. Exp. J., Schnable, P. This result was consistent with the conjecture that recombination is restricted to genes (Thuriaux, 1977), and stands in complete contrast to the initial view of recombination occurring only between genes. MS thesis, Richmond, VA, Virginia Commonwealth University. Our interest in hotspots seems to be focusing our attention on local determinants of recombination as a functional unity and away from the larger and possibly more important chromosomal context (Pan et al., 2011). E., et al. Perhaps of greater interest is the close relationship between DSB hotspots and COs found in S. In general, maize intragenic studies focused on genes with an easily scored phenotype, and most genes studied proved to be hotspots. These loci or genes are often recombination hotspots. E., Pan, J., Kim, S., Zhu, X., et al. PubMed Abstract | Google Scholar Salomé, P. doi: 10.1038/s41467-018-04562-5 PubMed Abstract | CrossRef Full Text | Google Scholar Lange, J., Yamada, S., Tischfield, S. Noteworthy, however, is that not all NDRs are DSB hotspots and H3K4me3 is absent at some DSB hotspots (Pan et al., 2011; Tischfield and Keeney, 2012). doi: 10.1105/tpc.112.102483 PubMed Abstract | CrossRef Full Text | Google Scholar Inukai, T., Sako, A., Hirano, H. With the cloning and sequencing of maize genes, it became possible to compare the frequency of recombination within genes to the genome average. This absence of polarity extends beyond Bz1 into adjacent sequences. Studying recombination in the Al – Sh2 interval, Patrick Schnable's group identified three CO hotspots in the 130–140 kb interval (Yao et al., 2002; Yao and Schnable, 2005). N., and Cande, W. doi: 10.1126/science.1183439 PubMed Abstract | CrossRef Full Text | Google Scholar Benzer, S. Determination of Rates and Patterns of Recombination at the Maize Red Color (r1) Locus. DNA synthesis can then proceed from the exposed 3′-end. W., Orr-Weaver, T. The almost 73% of maize DSB hotspots in repetitive sequence contrasts with the under-representation of DSB hotspots in S. Exceptional diversity, non-random distribution, and rapid evolution of retroelements in the B73 maize genome. Contrasted patterns of crossover and non-crossover at Arabidopsis thaliana meiotic recombination hotspots. J., and Schnable, P. 11, 1660–1676. L. (D) Mapping recombinants. To summarize, the number of NCOs peak at the ends of Bz1, but COs are evenly distributed across the entire Bz1 coding region and are rare in upstream and downstream regions. Thirty-three of 35 crossovers in B1 mapped to a 620 bp interval overlapping the start codon (Patterson et al., 1995. 5′ flanking sequences are required for polarity at the 5′ end; the requirement for 3′ flanking sequences have not been tested (Dooner and He, 2014). Plant Cell 20, 249–258. Effect of structural heterozygosity on intragenic recombination and flanking marker assortment. 5:23. M. V. (2012). Genetics 134, 5–19. Sampling depth may be a limiting factor in detecting CO hotspots, but the variable number and locations of CO hotspots suggests we need to think carefully about the meaning of hotspots. Mapping meiotic single-strand DNA reveals a new landscape of DNA double-strand breaks in Saccharomyces cerevisiae. cerevisiae. Only when integrating information learned from different model organisms and different approaches do we have a chance of resolving the whole story on DSBs, recombination, polarity, and underlying genome features. In Arabidopsis, mapping of SPO11-oligonucleotides also revealed that DSBs are preferentially located in regions with high gene density, and underrepresented in TE dense regions (Choi et al., 2018). Figure 1 depicts the approaches for gene-scale and genomic-scale to illustrate their data origins and differences. cerevisiae counterparts and DSB hotspots from Arabidopsis and other model systems, there are some clear differences (Table 2). Of critical importance here is the observation that these mice are defective in DSB repair and chromosome pairing (Hayashi et al., 2005). PubMed Abstract | Google Scholar Fowler, K. R., Rawat, V., et al. doi: 10.1073/pnas.91.17.8268 PubMed Abstract | CrossRef Full Text | Google Scholar Creighton, H. U.S.A. 112, 15982–15987. This absence of sequence homology will strongly inhibit recombination. Cell 167, 695–708.e16. doi: 10.1105/tpc.9.9.1633 PubMed Abstract | CrossRef Full Text | Google Scholar Dooner, H. Beginning in the early 2000s, studies in the plant model system Arabidopsis thaliana have supported a similar picture of recombination (Wang and Copenhaver, 2018). WE: R1 recombination data. In another study, Arabidopsis NCO gene conversion ranged from mean tracts of 1 bp to ∼0.5 kb, the longest at ∼3.0 kb (Drouaud et al., 2013). A., Underwood, C. The genomic landscape of meiotic crossovers and gene conversions in Arabidopsis thaliana. PLoS Genet. (C) Gametes from meiosis with crossovers within a pericentric inversion are generally inviable because one centromere carries with it both short arms and the other centromere carries both long arms. On the role of AtDMC1, AtRAD51 and its paralogs during Arabidopsis meiosis. Heterochromatin is thus negatively correlated with COs at large scale, but we want to keep the focus on the gene-scale data to allow comparison between traditional intragenic studies in maize and the newer cohort of sequencing-technology-driven studies. Four studies based on next-generation sequencing have mapped recombination events in maize (Table 3). First, we hope to show how the study of individual genes may influence our interpretation of genomic studies of recombination. Since high recombination rates measured within genes suggests that little recombination happens in intergenic regions this work directly asks whether crossing over can take place outside of genes. Are plants as the mostly related species not the best system to compare with maize? Similarly, in Arabidopsis, it has been shown that the level of polarity-underlying DSBs at the TSS and TTS are independent from each other (Choi et al., 2018). FIGURE 2. With relaxed stringency and controls the number is considerably larger (He et al., 2017). Thus, less than 4% of maize DSBs resulted in COs versus 56% in S. Molecular organization and germinal instability of R-stippled maize. K., and He, L. There is, however, polarity for NCOs at both ends of the Bz1 gene. Crossing Over and Polarity Lessons From S. Not all of the genic hotspots described by intragenic recombination studies were identified in these studies. doi: 10.1534/genetics.104.034454 PubMed Abstract | CrossRef Full Text | Google Scholar Yao, H., Zhou, Q., Li, J., Smith, H., Yandeau, M., Nikolau, B. I. To facilitate a smooth and easy understanding of the information in this review, we first clarify the following terms which are frequently used: FIGURE 1. Alternatively, detecting intragenic recombination might require screening very large populations. The agreement of recombination distribution is even better when comparing other large-genome crops with each other, as for example maize, wheat, and barley (Higgins et al., 2012; Darrier et al., 2017). High-throughput genotyping studies, drawing parallels with the polarity found in S. (1978). Non-mutant Wx pollen contains a mixture of amylose and amylopectin starches and is stained a dark black by potassium iodine, while mutant wx pollen contains only amylose and stains reddish. Conclusions drawn from high-throughput genotyping studies emphasized polarity with COs concentrated at 5′ and 3′ ends of genes (Li et al., 2015; Ott, 2017; Kianian et al., 2018). Genetics 41, 124–137. doi: 10.1038/nature07135 PubMed Abstract | CrossRef Full Text | Google Scholar Marsolier-Kergoat, M.-C., Khan, M. Nelson's studies provided early evidence for a non-crossover recombination pathway, by using lines where the wx-C allele was located inside a chromosome inversion or a complex chromosomal rearrangement (Nelson, 1975). Science 327, 836–840. (A) Locations of the Wx locus and the flanking markers Bronze1 (Bz1) and Virescent (V) on the normal chromosome 9, and their locations on the pericentric inversion chromosome 9. cerevisiae, the tight connection between DSB hotspots and recombination is well-established (Pan et al., 2011; Marsolier-Kergoat et al., 2018), but there are large differences between eukaryotes (Fowler et al., 2014; Stapley et al., 2017). Genetics 113, 449–467. • "Polarity" exists when there is a gradient of recombination, e.g., higher recombination rates at the 5′ or 3′ end of a gene. doi: 10.1101/gr.225599.117 PubMed Abstract | CrossRef Full Text | Google Scholar Chovnick, A. Haplotype structure strongly affects recombination in a maize genetic interval polymorphic for Helitron and retrotransposon insertions. doi: 10.1016/0092-8674(83)90331-8 CrossRef Full Text | Google Scholar Thuriaux, P. The active chromatin mark H3K4me3 for example can be found near DSBs, but overlaps COs even more, arguing that it promotes recombination downstream of DSBs, in yeast and Arabidopsis, while DSB association is merely due to location to promoters (Tischfield and Keeney, 2012; Choi et al., 2018). However, polarity for CO is not seen at Bz1 despite the adjacent DSB hotspot (Dooner and Martínez-Férez, 1997; He et al., 2017). Recombination rate heterogeneity within Arabidopsis disease resistance genes. DSB data derives from SPO11-oligos or RAD51-bound fragments via ChIP-seq. A., Wang, M., Simons, K., Ghavami, F., He, Y., Dukowic-Schulze, S., et al. To fully comprehend what intragenic as well as large-scale genomics studies can tell us about recombination, we recapitulate and reconcile knowledge from historic and more recent studies. Gene conversions and their relation to homologous chromosome pairing. Lond. S., Ware, D., Fulton, R. Recombination rates between adjacent genic and retrotransposon regions in maize vary by 2 orders of magnitude. Acids Res. The marker resolution underlies the precision at which gene conversion tracts can be defined, and might explain the even shorter estimates of CO-associated tracts of ∼0.3–0.4 kb and NCO-associated tracts of 25–50 bp (Wijnker et al., 2013). doi: 10.1002/j.1460-2075.1993.tb05789.x PubMed Abstract | CrossRef Full Text | Google Scholar Detloff, P., White, M. Genome 43, 589–596. B., Alleman, M., and Kermicle, J. cerevisiae and A. Maize genome structure variation: interplay between retrotransposon polymorphisms and genic recombination. Allelic variation at the level of intragenic recombination. doi: 10.1038/nature04112 PubMed Abstract | CrossRef Full Text | Google Scholar He, L., and Dooner, H. doi: 10.1073/pnas.41.6.344 CrossRef Full Text | Google Scholar Borde, V., Robine, N., Lin, W., Bonfils, S., Géli, V., and Nicolas, A. PubMed Abstract | Google Scholar Barrington, C., Pezic, D., and Hadjur, S. doi: 10.1098/rstb.2016.0455 PubMed Abstract | CrossRef Full Text | Google Scholar Sukhapinda, K., and Peterson, P. S., Estill, J. A., Bomblies, K., Fitz, J., Laitinen, R. Analysis of intragenic recombination at wx in rice: correlation between the molecular and genetic maps within the locus. Sci. M., Jenkins, J., Shu, S., Yuan, Y., Wessler, S. V., and Morgante, M. The 410 CO hotspots defined by Rodgers-Melnick accounted for 30.6% crossovers defined to a narrow interval (Rodgers-Melnick et al., 2015). Upstream, the genetic distance from a marker within Bz1 to the upstream gene Mkk1 100 kb away was less than the genetic length of Bz1 (Dooner, 1986; Fu et al., 2002). Mouse provides the valuable lesson that open chromatin in promoters is not necessarily a target for DSBs. On the other hand, mouse DSB hotspots are mediated by PRDM9 which does not seem to exist in plants. doi: 10.1073/pnas.1514265112 PubMed Abstract | CrossRef Full Text | Google Scholar Smagulova, F., Gregoretti, I. B 372:20160455. D., Johnston, S. cerevisiae repetitive sequences. (2010). I., Kubo, K. (1998). 5′-polarity was seen at A1 and B1. cerevisiae is clear as almost all DSBs lead to recombination and both the initiating DSBs and resolving recombination hotspots are mainly found near TSSs. The picture is different in other systems, including Arabidopsis, where a few 100 DSBs get resolved into only ∼6–12 COs (Giraut et al., 2011; Lu et al., 2012; Salomé et al., 2012; see Table 2). An initiation site for meiotic gene conversion in the yeast Saccharomyces cerevisiae. Kianian's study defined hotspots as 5 kb regions with CO rates fivefold higher than the genome average; there were 282 and 257 hotspots in the male and female parents of the population respectively (Kianian et al., 2018). doi: 10.1086/281997 CrossRef Full Text | Google Scholar Nelson, O. U.S.A. 91, 8268–8272. Genomic features shaping the landscape of meiotic double-strand-break hotspots in maize. AT-rich motifs were also found at Arabidopsis DSB sites (Choi et al., 2018), likely due to those motifs generally excluding nucleosomes (Segal and Widom, 2009). cerevisiae? High-resolution mapping of meiotic crossovers and non-crossovers in yeast. In the third study, 50% of the crossovers did not map to either the 5′ or 3′ regions (Kianian et al., 2018). Google Scholar Stapley, J., Feulner, P. doi: 10.1038/nature11089 PubMed Abstract | CrossRef Full Text | Google Scholar Buhler, C., Borde, V., and Lichten, M. cerevisiae tetrads. Intragenic recombination in Drosophila: the rosy locus. On the other hand, S. RO, SD-S, WBE, and GM: editing of manuscript. pombe, DSBs in hotspots contribute far less to COs than expected – most DSBs in hotspots do not resolve as COs. Might this be similar to maize where three-fourths of DSB hotspots are in repetitive sequence? (1993). K. Similarly, at the maize Stc1 locus, COs are found across the length of the gene with similar numbers of crossovers at the 5′ and 3′ ends of the gene (Dooner and He, 2008; He and Dooner, 2009). Compared with S. Gen. H. Both COs and NCOs can result in local genetic changes via gene conversion. E. cerevisiae are located close to the position of initiating DSBs. Gene conversion tracts in Arabidopsis wild type have been far more difficult to detect and characterize, and are in general fewer and shorter than in budding yeast. E., Santure, A. The spatial regulation of meiotic recombination hotspots: are all DSB hotspots crossover hotspots? A single recombination nodule on a chromosome is illustrated. Analysis of Arabidopsis genome-wide variations before and after meiosis and meiotic recombination by resequencing Landsberg erecta and all four products of a single meiosis. In S. doi: 10.1038/hdy.2011.95 PubMed Abstract | CrossRef Full Text | Google Scholar Schnable, P. Structure and Architecture of the Maize Genome. W. pombe) present a very different picture (Table 2). doi: 10.3389/fpls.2014.00023 PubMed Abstract | CrossRef Full Text | Google Scholar Rodgers-Melnick, E., Bradbury, P. Intragenic studies directly score recombination via visible kernel markers. C., Wei, F., Pasternak, S., et al. Though their mechanisms are distinct, their outcomes are treated equally in intragenic as well as whole genome studies. P., Santos, J. (1989). A large share of our current understanding of recombination is based on work studying intragenic recombination (recombination within genes) in model fungal species, especially the budding yeast (Saccharomyces cerevisiae). (1996). 91, 331–332. The location of the controlling element alleles. cerevisiae versus the lower resolution possible with the RAD51 based approach used in maize, or it could represent physical differences in their DSB hotspots. (1956). Precise mapping of DSB hotspots via SPO11-bound nucleotides released at resection revealed that almost 90% of DSBs occurred in a described hotspot (Pan et al., 2011) (Table 2). The waxy locus in maize III. V., Brick, K., Khil, P., Camerini-Otero, R. Deleting the promoter region in a yeast gene strongly reduces recombination at the gene (De Massy and Nicolas, 1993; Porter et al., 1993). Overall, 95% of DSBs identified by SPO11 oligonucleotides were confined to just 15% of the yeast genome (Marsolier-Kergoat et al., 2018). Both COs and NCOs give rise to a short region with non-reciprocal transfer of genetic information known as a gene conversion tract. Both DNA methylation and sequence polymorphisms are suggested mechanisms for suppressing COs in maize repetitive sequences (Fu et al., 2002; Yao and Schnable, 2005). The relationship between genetic and physical distances in the cloned a1-sh2 interval of the Zea mays L. However, there is a chasm between what we know based on extensive data, what we think we know, and what is known in other model systems used for studying recombination. Mapping crossovers using S. W., and Smadja, C. Crossing over as assessed by late recombination nodules is related to the pattern of synapsis and the distribution of early recombination nodules in maize. Plant Physiol. A high-throughput recombination study via the maize transcriptome mapped 2634 NCO conversion tracts in a maize RIL population (Ott, 2017). This difference might be a consequence of the precision of the SPO11 based approach used in S. (1957). Genome-wide analysis reveals novel molecular features of mouse recombination hotspots. pombe DSB hotspots are not strongly correlated with NDRs (Fowler et al., 2014). Am. Nat. Evolutionarily diverse determinants of meiotic DNA break and recombination landscapes across the genome. A., and Petes, T. U.S.A. 109, E981–E988. Genetics 173, 2211–2226. Sequencing approaches rely on isolated microspores from tetrads or progeny lines. Haplotype structure and local sequence differences locally suppressing recombination provides an additional mechanism for modifying crossover frequencies (Yao and Schnable, 2005; Dooner and He, 2008). cerevisiae, these hotspots are over-represented within the genic region defined by the start and stop codons, and only 3% are located near the TSS (Smagulova et al., 2011; Brick et al., 2012). PubMed Abstract | Google Scholar Pan, J., Sasaki, M., Kniewel, R., Murakami, H., Blitzblau, H. In S. doi: 10.1073/pnas.082562199 PubMed Abstract | CrossRef Full Text | Google Scholar Yelina, N. Other studies by Peterson examined the effects of chemical treatments on recombination and noted the effect of environment on recombination at the Wx locus (Sukhapinda and Peterson, 1980). pombe versus the tight association in S. Genetics 140, 1389–1406. U.S.A. 87, 8731–8735. doi: 10.1371/journal.pbio.0050324 PubMed Abstract | CrossRef Full Text | Google Scholar Chelysheva, L., Gendrot, G., Vezon, D., Doutriaux, M.-P., Mercier, R., and Grelon, M. For example, in S. PubMed Abstract | Google Scholar Pawlowski, W. Where do crossovers occur in maize? Genetic evidence that the meiotic recombination hotspot at the HIS4 locus of Saccharomyces cerevisiae does not represent a site for a symmetrically-processed double-strand break. The even distribution of NCO conversion tracts across maize genes argues against the concentration of DSBs at the ends of maize genes. The A1 gene has a 377 bp hotspot beginning in exon 1 and spanning exon 2 (Xu et al., 1995). doi: 10.1073/pnas.1413864112 PubMed Abstract | CrossRef Full Text | Google Scholar Sachs, M. F. The length of gene conversion tracts depends on DSB resection, synthesis from the exposed 3′-end, and migration of Holliday junctions. doi: 10.1016/j.molcel.2018.02.032 PubMed Abstract | CrossRef Full Text | Google Scholar Medhi, D., Goldman, A. eLife 5:e19669. A second study incorporated genetic markers flanking the Wx locus to connect recombination within the Wx locus with the exchange of flanking markers (Nelson, 1962). II. Using the 793 COs mapped within a gene, Ott identified 158 genes with more than one CO event in her population; many of these genes are statistically likely to be CO hotspots (Ott, 2017). Nature 268, 460–462. PLoS Biol. Results from similar studies in the fission yeast Schizosaccharomyces pombe (S. Cell 33, 25–35. Though the concept is enticing, enrichment of maize DSB hotspots around the TSS and TTS of genes may not exist at all genes, with or without producing polarity. cerevisiae and other model species captured and sequenced single-stranded DNA bound to RAD51 (He et al., 2017). The wx-B1 allele has a deletion from -655 to +299 (Wessler et al., 1990). The recombination landscape in Arabidopsis thaliana F2 populations. Because the haplotypes used in this experiment were derived from the same progenitor, there was little if any sequence difference in the region except for the genetic markers. • "Intragenic recombination" refers to both NCOs and COs within genes. At the chromosomal level, intragenic and genome-wide studies identified an association between gene-density and elevated crossover rates (Yao et al., 2002; Wang et al., 2011; Pan et al., 2017). Supplementary Material The Supplementary Material for this article can be found online at: References Anderson, L. Genes appear to fall into two categories with crossovers either concentrated at one end of the gene, either 5′ or 3′ polarity, or distributed evenly across the gene (Eggleston et al., 1995; Patterson et al., 1995; Dooner and Martínez-Férez, 1997; Okagaki and Weil, 1997; Yao and Schnable, 2005). In addition, the fraction of crossovers attributed to recombination hotspots is not high. Deleting the promoter region in maize Bz1 and Wx does not strongly reduce recombination at the gene (see section "Lessons From S. 22, 508–518. The physical and genetic framework of the maize B73 genome. Soc. High-resolution mapping of crossover events in the hexaploid wheat genome suggests a universal recombination mechanism. doi: 10.1139/g80-026 CrossRef Full Text | Google Scholar Szostak, J. J., and Weil, C. Ann. 11:e1005301. The amount of events distinguishing hotspots from cold regions is arbitrary, and the definition and identification depends strongly on the respective study. Genetics 132, 113–123. (1977). Unlike S. Exceptionally high levels of restriction site polymorphism in DNA near the maize Adh1 gene. Intragenic studies reporting on individual genes found a mix of genes showing polarity and others that do not. Here too there is no evidence for polarity of COs. Nelson fine-mapped 29 wx alleles, and a number of these mutations were sequenced in Sue Wessler's lab. After the initial observation of intragenic recombination in maize, the Wx locus was used for further studies focusing on exploring the recombination process. doi: 10.1534/genetics.116.196014 PubMed Abstract | CrossRef Full Text | Google Scholar De Massy, B., and Nicolas, A. D., Perry, R. Histone H3 lysine 4 trimethylation marks meiotic recombination initiation sites. doi: 10.1126/science.1178534 PubMed Abstract | CrossRef Full Text | Google Scholar Serrentino, M.-E., and Borde, V. C., Chaparro, C., Upshaw, N., Jogi, A., Deragon, J.-M., et al. Second, there is directionality to the repair of meiotic DSBs since DSBs are repaired using sequences on the homologous chromosome. Indirect evidence against a yeast-like concentration of DSBs near TSSs in maize comes from one whole genome study. doi: 10.1038/nature09869 PubMed Abstract | CrossRef Full Text | Google Scholar Smithies, O., and Powers, P. Two of the four genes in the region were CO hotspots, and the third hotspot was in a unique non-genic sequence. cerevisiae shows that NCO conversion tracts can be located a short distance from the DSB (Marsolier-Kergoat et al., 2018). The orientation of V is not known. Some species lack the type I interference-sensitive pathway (Gray and Cohen, 2016). (1999). The Role

of Double-Strand Breaks in Maize and Other Model Organisms Meiotic DSBs serve two functions, first to promote chromosome pairing and second to produce the crossovers necessary to ensure proper segregation of chromosomes at anaphase (Page and Hawley, 2003). Is there a clear reason why class I versus class II COs are a more important criteria for choosing a reference model system than the weak association between DSB hotspots and COs in maize and S. G., and Schnable, P. A DSB hotspot at the 5′ end of a gene can give polarity near the 3′ end of a neighboring gene. cerevisiae (Pan et al., 2011). Recombination patterns in maize reveal limits to crossover homeostasis. Conclusions from genetic fungal studies have been supported by recent molecular and genomic approaches, providing a relatively detailed, although still incomplete, picture of recombination (reviewed in Keeney et al., 2014; Gray and Cohen, 2016). Genome-wide crossover distribution in Arabidopsis thaliana meiosis reveals sex-specific patterns along chromosomes. (A) DSB generation by SPO11 with subsequent binding of RAD51 and DMC1. Genetics 60, 507–524. The double-strand-break repair model for recombination. C., Ott, A., Yeh, C. cerevisiae, most meiotic DSBs resolve into COs and NCOs. The 140–170 DSBs observed per yeast meiosis (Buhler et al., 2007) closely match the 90.5 COs and 46.5 NCOs counted per meiosis (Mancera et al., 2008). This, however, was not seen when Oliver Nelson measured recombination between wx-B and wx-C4 with downstream alleles (Supplementary Table 1). Some intragenic recombination studies look at short regions containing several genes, albeit mostly with emphasis on the outcome within genes. Spatiotemporal asymmetry of the meiotic program underlies the predominantly distal distribution of meiotic crossovers in barley. E., Lambing, C., Hardcastle, T. 9:2370. doi: 10.1105/tpc.7.12.2151 PubMed Abstract | CrossRef Full Text | Google Scholar Yamada, S., Ohta, K., and Yamada, T. C., Tingey, S. Meiotic recombination is a major contributor to genetic diversity and facilitates selection by nature and breeders. G. doi: 10.15252/embj.201798014 PubMed Abstract | CrossRef Full Text | Google Scholar Baucom, R. Intragenic studies on small genetic regions have characterized most genes as recombination hotspots, but some genes are coldspots and some non-genic regions are recombination hotspots (Yao et al., 2002; He and Dooner, 2009; Wang et al., 2011). The small discrete DSB hotspots located near TSSs concentrate recombination events at the 5′ end of many genes. Google Scholar Fu, H., Zheng, Z., and Dooner, H. For COs, gene conversion tracts were detected first at a maximal median length of ~1.1 kb, for NCOs in the range of 1 bp to ~6.6 kb (Lu et al., 2012). The resolution of one study was generally not sufficient to address this question (Rodgers-Melnick et al., 2015). Even when the overall structure of a repetitive block is preserved, nucleotide polymorphisms could locally inhibit crossing over, as seen in the a1-sh2 region (Yao and Schnable, 2005). S., and Nikolau, B. J. Plant Cell 11, 809–824. M., and Anderson, L. Acetylated Histone H3K9 is associated with meiotic recombination hotspots, and plays a role in recombination redundantly with other factors including the H3K4 methylase Set1 in fission yeast. L., and Burgess, S. (1955). Genetics 79, 31–44. U.S.A. 41, 344–354. (1985). Philos. pombe (Fowler et al., 2014). cerevisiae as a model for maize where three-fourths of DSB hotspots are in repetitive sequence? Biol. 5:e1000715. B., Mitchell, S. The ratio of physical distance to genetic distance (kb/cM) at the 5′ and 3′ ends of Bz1 are similar (Dooner and Martínez-Férez, 1997). 41, 3504–3517. 9:e1003922. 48, 187–214. doi: 10.1371/journal.pgen.1002354 PubMed Abstract | CrossRef Full Text | Google Scholar Gray, S., and Cohen, P. (2014). Location and Distribution of Maize Double-Strand Breaks Double-strand breaks cannot be directly mapped by intragenic studies, but their possible positions may be deduced by examining recombination in deletion mutations. High-resolution crossover maps for each bivalent of Zea mays using recombination nodules. E., McElver, J., Sunjevaric, I., Rothstein, R., Bowen, B., and Cande, W. Terms in bold indicate data source options. Variation in gene conversion tract length and mismatch repair both contribute to polarity (Nicolas and Petes, 1994). PubMed Abstract | Google Scholar Nicolas, A., Treco, D., Schultes, N. doi: 10.1093/nar/gkt049 PubMed Abstract | CrossRef Full Text | Google Scholar Yandeau-Nelson, M. (1968). NCO conversion tracts reached up to 40.8 kb in length, but 97% were less than 5 kb in length. • “Recombination” is a term used for mechanisms of somatic DNA repair as well as for exchange of genetic information during meiosis. Crossovers were mapped with sufficient precision to identify polarity for approximately 50% (Kianian et al., 2018) and approximately 10% of crossovers placed (Li et al., 2015; Ott, 2017). J., Zhao, X., et al. Author Contributions RO: conception of this project. Maize DSB hotspots were also wider than S. 28, 532–546. W., Xu, J., Reddy, G., Golub, E. High-resolution crossover mapping reveals similarities and differences of male and female recombination in maize. doi: 10.1371/journal.pgen.1006179 PubMed Abstract | CrossRef Full Text | Google Scholar Choi, K., Zhao, X., Tock, A. More recent data in S. The 5′ end is defined here as the transcription start site (TSS), and the 3′ end as the transcription termination site (TTS). (B) DSB hotspots at both ends of genes could produce this distribution. Issues may arise when extrapolating results from the handful of maize genes where intragenic recombination has been studied in depth. Recombination at R1 showed a polarity gradient with highest levels of recombination at the 3′-end of R1 that declined to low levels in the middle of the gene, a distance of approximately 3.5 kb (Eggleston et al., 1995; Dietrich, 1998; Kermicle, personal communication). The DSBs in this experiment most likely were in the region between wx-B1 and wx-I rather than in the 5′ region. D., Lai, A., et al. This picture of open chromatin being favored by the DSB machinery is also true in Arabidopsis: here, DSBs were shown to correlate with H3K4me3 and low nucleosome density (Choi et al., 2018). Natl. pombe as a model system for maize recombination, any more than the under-representation of DSB hotspots in S. Recombination between wx-B1 and the wx-I allele, containing a large insertion in the 3′ region, also argued against a single DSB hotspot near the TSS (Okagaki and Weil, 1997). (B) CO generation via double Holliday junction. The waxy locus in maize. Similarly, no crossovers were detected in the downstream interval between Bz1 and the adjacent gene, Stc1 (He and Dooner, 2009). N., and Freeling, M. 5:e1000732. Control of the number of COs and which DSBs are channeled into the crossover pathway is tightly regulated (Lake and Hawley, 2016). Plant Cell 9, 1633–1646. Although maize DSB hotspots shared some characteristics with their S. doi: 10.1038/338035a0 PubMed Abstract | CrossRef Full Text | Google Scholar Okagaki, R. Control of meiotic crossovers: from double-strand break formation to designation. The control in cis of the position and amount of the ARG4 meiotic double-strand break of Saccharomyces cerevisiae. cerevisiae tetrads gave an average of 90.5 crossovers per meiosis, with an estimated 160 DSBs per meiosis (Mancera et al., 2008; Pan et al., 2011). C., and Pawlowski, W. M., Yu, J., et al. Molecular characterization of a genomic interval with highly uneven recombination distribution on maize chromosome 10 L. Today, Seymour Benzer’s papers demonstrating intragenic recombination in bacteriophage are often seen as the experimental work changing our understanding of recombination and genes (Benzer, 1955). U.S.A. 17, 492–497. Y., and Sano, Y. J., and Stahl, F. Over 50% of maize DSB hotspots are in gypsy-like elements (He et al., 2017). (2016). Furthermore, DSBs in S. Intralocus recombination frequency estimates by pollen and conventional analysis. PubMed Abstract | Google Scholar Keeney, S., Lange, J., and Mohibullah, N. In fact, the majority of DSB hotspots appear unlikely to contribute much to crossing over as almost 73% of hotspots are in repetitive sequence where crossovers are believed to be suppressed (He et al., 2017). Here, 28 of 29 recombinants were crossovers between wx-B1 and wx-I. Filler DNA is associated with spontaneous deletions in maize. Genetics 89, 211–224. doi: 10.1105/tpc.012898 PubMed Abstract | CrossRef Full Text | Google Scholar Peoples-Holst, T. However, results from one intragenic recombination study argues against sequence polymorphism as the primary mechanism suppressing crossing over in repetitive sequences (Fu et al., 2002). doi: 10.1073/pnas.17.8.492 CrossRef Full Text | Google Scholar Darrier, B., Rimbert, H., Balfourier, F., Pingault, L., Josselin, A.-A., Servin, B., et al. cerevisiae have been measured at 2.0 kb for COs and 1.8 kb for NCOs (Mancera et al., 2008). doi: 10.1101/gr.188201 PubMed Abstract | CrossRef Full Text | Google Scholar Mirouze, M., Lieberman-Lazarovich, M., Aversano, R., Bucher, E., Nicolet, J., Reinders, J., et al. J., et al. doi: 10.1016/j.cell.2011.02.009 PubMed Abstract | CrossRef Full Text | Google Scholar Patterson, G. A partial list of key results from intragenic studies is presented in Table 1. Nature 485, 642–645. Repetitive elements are commonly found in blocks separating individual genes or small clusters of genes (Haberer et al., 2005). pombe disqualify S. cerevisiae, Arabidopsis and maize. Cis-effect on meiotic recombination across distinct a1-sh2 intervals in a common Zea genetic genetic background. Other definitions have been used such as the promoter region for the 5′ end. S. From here, the invading strand plus newly synthesized sequence may dissociate from the complementary strand giving non-crossover events through SDSA (synthesis-dependent strand annealing). The genic region surrounding Bz1 presents a similar pattern with a majority of the genes in the region functioning as CO hotspots (Fu et al., 2002; He and Dooner, 2009). Some CO and NCO conversion tracts had complex tracts arising via template switching between the parental alleles (Marsolier-Kergoat et al., 2018). 19, 863–874. The pachytene foci, also known as late recombination nodules when viewed with electron microscopy, represent the sites of crossing-over (Stack and Anderson, 2002). Genetics 47, 737–742. doi: 10.1101/gad.1293605 PubMed Abstract | CrossRef Full Text | Google Scholar Plug, A. No Model System Explains All As described here, there are aspects of systems other than S. (2015). Relation of unequal crossing over to the interdependence of Rr elements (P) and (S). (1997). In contrast, only a fraction (~5–10%) of DSBs get resolved into COs in Arabidopsis (Giraut et al., 2011; Lu et al., 2012; Salomé et al., 2012; also see Table 2). (2000). Plant Cell 24, 4096–4109. Ty1-gypsy-like elements are the most abundant families (Meyers et al., 2001). doi: 10.1371/journal.pgen.1003922 PubMed Abstract | CrossRef Full Text | Google Scholar Eggleston, W. U.S.A. 109, 5880–5885. PubMed Abstract | CrossRef Full Text | Google Scholar Lu, P., Han, X., Qi, J., Yang, J., Wijeratne, A. C., and Mézard, C. These blocks are not conserved between maize lines, and two genes may be separated by a short stretch of low-copy sequence in one line and by significant stretches of repetitive sequence resulting from multiple repetitive elements in another line (He and Dooner, 2009). TABLE 2. DNA methylation epigenetically silences crossover hot spots and controls chromosomal domains of meiotic recombination in Arabidopsis. Genetic recombination is directed away from functional genomic elements in mice. doi: 10.1007/BF00425430 CrossRef Full Text | Google Scholar Drouaud, J., Khademian, H., Giraut, L., Zanni, V., Bellalou, S., Henderson, I. DNA methylation is yet another component underlying the structure of the chromosome, but details on its association with DSB and COs are beyond the scope of this review, which focused on intragenic recombination. Mouse DSB hotspots share characteristics of both S. A molecular genetic analysis of insertions in the bronze locus in maize. Molecular characterization of meiotic recombination across the 140-Kb multigenic a1-sh2 interval of maize. The median interval defining crossovers in three of the four studies was over 100 kb (Li et al., 2015; Rodgers-Melnick et al., 2015; Ott, 2017). Acquisition of DSB and CO data by gene-scale and genome-scale approaches. (1980). Two of the studies reported evidence for high crossover frequency at the 3′ end of the gene (Li et al., 2015; Kianian et al., 2018). 36, 2661–2663. Looking at single genes or small genetic intervals, intragenic studies conclude that most crossovers take place within genes. However, as we have seen from intragenic studies, COs at Bz1 do not show polarity, although NCOs show polarity at the 5′ and 3′ ends of Bz1 (Dooner and Martínez-Férez, 1997; Dooner and He, 2014). • “Gene conversion” (GC) is the non-reciprocal transfer of information. K., Doyle, G. cerevisiae, the fraction of maize DSBs resolving as crossovers is small. Three-dimensional microscopy of the Rad51 recombination protein during meiotic prophase. doi: 10.1073/pnas.93.12.5920 PubMed Abstract | CrossRef Full Text | Google Scholar Porter, S. PubMed Abstract | Google Scholar Pradillo, M., Varas, J., Oliver, C., and Santos, J. Where a DSB occurs along a chromosome may be just as important in determining the DSB fate as local hotspot features (Serrentino and Borde, 2012). (1986). In Arabidopsis, DSB hotspots also localize to gene promoters, additionally to terminators, as well as introns (Choi et al., 2018). Abundance, distribution, and transcriptional activity of repetitive elements in the maize genome. In mid-zygotene when chromosomes are pairing, there are approximately 500 RAD51 foci decreasing to about 12 RAD51 foci in pachytene (Franklin et al., 1999; Pawlowski et al., 2003). pombe DSB hotspots are near the TSS. The agreement of genome-wide DSB maps and high-resolution recombination maps provides a clear picture of the general recombination pattern in S. pombe hotspots are preferentially repaired from the sister chromatid; these events do not contribute to crossing-over. Summary Maize has been a genetic model genetic system for almost 100 years, and has been used to address questions regarding recombination as fundamental as the connection between cytological crossing over and genetic crossing over (Creighton and McClintock, 1931). (2011). U.S.A. 99, 6157–6162. (1990). SD-S: re-analyzing recombination data. Altered nuclear distribution of recombination protein RAD51 in maize mutants suggests the involvement of RAD51 in meiotic homology recognition. Nature 454, 479–485. This contrasts with S. Double-strand breaks are necessary for recombination, but the importance of DSB hotspots for genetic crossovers is less clear. Presynaptic association of Rad51 protein with selected sites in meiotic chromatin. P., Golubovskaya, I. pombe and hint at the complexities underlying hotspots. 139, 1612–1624. Zip4/Spo22 is required for Class I CO formation but not for synapsis completion in Arabidopsis thaliana. P. 10, 329–345. M., Barakate, A., Ramsay, L., Waugh, R., Halpin, C., et al. cerevisiae DSB hotspots, 1.2 kb versus 189 bp. B., and McClintock, B. D. Genetics 165, 849–865. (1983). (2018). (1962). Commun. Plant Cell 7, 2151–2161. This is a conservative estimate of the number of hotspots based on very stringent criteria (He et al., 2017). Genetics 147, 815–821. Mechanistic view and genetic control of DNA recombination during meiosis. Open chromatin is so far the only universal criteria for DSBs and CO locations across different model systems, though caution is needed regarding the scale (Tischfield and Keeney, 2012). Using chromosome translocation lines with wx alleles at different distances from the centromere they showed that distance of a locus from the centromere is correlated with recombination frequency. A portion of these crossovers occurred outside of the inversion and accompanied a NCO event between the wx alleles. A large fraction of COs are initiated at non-hotspot DSBs in S. Using this pollen assay, Nelson was able to detect intragenic recombination in a higher eukaryote (Nelson, 1959). Nelson in recognition for his many contributions to the study of genetics. doi: 10.1104/pp.105.068718 PubMed Abstract | CrossRef Full Text | Google Scholar Hayashi, K., Yoshida, K., and Matsui, Y. Does the absence of class I COs in S.

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