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# Discussion Draft v2

Despite quantifying a similar number of wild derived inbred strains from *M. m. domesticus* and *M. m. musculus*, we only observed rapid male specific evolution for the genome wide recombination rate for *M. m. musculus.* Estimates of effective population size for the three main subspecies of the house mouse found *M. m. musculus* had the lowest (Geraldes et al. 2011). Selection becomes less efficient at removing deleterious mutations in small populations outside of mutation-drift balance. In such populations, modifiers for increased recombination rates will be selected for as they increase the efficiency of selection.

An additional possibility is that the different rates in recombination rate variation across subspecies is related to history of hybridization across the populations sampled in this panel of inbred strains. Theoretical work as connected recombination that rate of purging deleterious introgressed DNA in populations after hybridization (Caballero et al 2019, Schumer 2018). The three high-recombining strains identified in this study have connections to hybridization. Both *MusculusPWD* and *musculusSKIVE* strains were established from samples from the european house mouse hybrid zone. Notably *musculusSKIVE* comes from a yonger section of the hybrid zone with a nuclear genome from *M. m. musculus* and a mitochondria genome from *M. m. domesticus* (Gyllensten and Wilson 1987). The subspecies *M. m. molossinus* is a natural hybrid of *M. m. musculus* and *M. m. cataneus* (Geraldes et al 2008, (Geraldes et al. 2011)). Models for the aggregate recombination metics, suggest that the location of recombination events and the total rate influence the dynamics of purging of deleterious introgress DNA (Veller et al 2019) – motivating increased study of recombination rates and natural populations. 4

To place our results in the broader context of recombination rate evolution we compare our main resuts to expectionat under three modifier models and two functional and cell physiology models (table X). While there are challenges to fitting models built under different assumptions, we feel it’s a useful exercise to highlight any unifying patterns for our specific traits across exsisting models. The three modifier models were built to explain variation in genome wide recombination rates between sexes (heterochiasmy), while the chromosome ocillatory movement (COM) model was built to describe positive interference. This spindle based selection model was developed to explain the results resented in this manuscript. In cases where the models can’t be extended to predicting results, we list a ‘NA’ for the prediction.

### Evolution of reversed heterochiasmy direction

In our results and more generally in the literature, female biased heterochiasmy is the most common pattern, however male biased heterochiasmy is not especially rare (Brandvain and Coop 2012). Our results extend previous reports of male biased heterochiasmy (Dumont and Payseur 2011) to new subspecies of house mouse (*molossinus*) and emphasize the short evolutionary period. Whether these instances of evolution of genome-wide recombination rates are due to independent events or segregating genetic variation within house mouse subspecies requires further study. Regardless, the faster male evolution in genome-wide recombination rates suggests that even for species in female biased heterochiasmy species, selecting for higher male specific genome wide recombination rates may be the most effective way to increase the sex-averaged recombination rate for a genetic background. This insight could be important for animal breeding programs (Battagin et al. 2016).

Under the spindle based model, faster male evolution of the genome wide recombination rate, is primarily driven by a more efficient spindle assembly checkpoint (SAC) acting on chromosome structures at metaphase I alignment. <We refer the reader to (Lane and Kauppi 2019) for more details on the SAC pathway.> The SAC prevents anueploidy by ensuring all bivalents are correctly attached to the microtubulue spindle (bi-orientated) before starting the metaphase-to-anaphase transition (Lane and Kauppi 2019, @subramanian2014, @dumontDesai2012).

A stable chromosome structure requires, i) kinetochores attached to opposite poles of the cells and ii) at least one crossover to create tension across a proportion of sister cohesion ((Lane and Kauppi 2019)). Genetic variants will be selected in a manner to optimize the process of bi-orientation and prevent SAC from delaying cell cycle or triggering apoptosis. Multiple lines of evidence indicate that the effectiveness of SAC in spermatogenesis is greater compared to oogenesis (Lane and Kauppi 2019, @subramanian2014)), which are connected to conserved features of gametogenesis; centrosome spindle (So et al. (2019), Dumont and Desai (2012)) and cell volume (Kyogoku and Kitajima 2017). The more stringent SAC in spermatogenesis will be more effective at removing genetic variants which interfere with bi-orientation compared to females. This dynamic can give rise to sex-specific genetic variants which in turn can result in context of meiosis between males and females as the primary source of distinct evolutionary trajectories in genome wide recombination rates.

### Conservation in sexual dimorphism in between cell variation in crossover number

Regardless of whether these hypotheses are true, Our observations of between cell variation fail to support a basic prediction of (the relationship between mean and variance) a higher mean will be associated with a higher variance. Across all strains, including the high-recombining strains, muscPWD, muscSKIVE and molMSM, females consistently have higher between cell variance for crossover count. These results add to previous findings in mice and humans that oogenesis has increased variance for crossovers (Lynn et al. 2002, @gruhn2013) and precursors to crossovers (Lenzi et al. 2005)?, compared to spermatocytes. This feature of heterochiasmy supports evolutionary theories predicting distinct reproductive strategies between females (diversifying offspring) and males (maintain successful haplotypes) (Trivers and others 2002).

In the spindle based selection model, the less efficient SAC in oocytes leads to relaxed selection on the metaphase I chromosome structure. This will result in increased variance in chromosome structure and crossover number per cell, not just across strains, but across cells within individuals. Oocytes at metaphase I, have an acentriolar spindle comprised of diffuse network of microtubules with multiple microtubule organizing centers (Schuh and Ellenberg 2007). Centrosomes spindles are in spermatogensis and mature sperm cells delivers centrioles (most mammals) or centrosome material (rodents and rabbits) to the egg during fertilization (Manandhar, Schatten, and Sutovsky (2005)). This is another way the spindle based selection model is linked to conserved sex differences in gametogenesis (Ross and Normark 2015).

Regardless of whether these hypotheses are true, our results further support the results of females having greater variation in the number of crossovers across cells in mice and humans (Lynn et al. 2002, @gruhn2013). This feature of heterochiasmy supports evolutionary theories predicting distinct reproductive strategies between females (diversifying offspring) and males (maintain successful haplotypes) (Trivers and others 2002).

<stabilization – bi-oriented, robust SAC response, SAC acts to correctly time metaphase to anaphase transition – only after correct alignment and bi-orientation of bivalents in the metaphase cell, – spindle dynamics much different due to asymmetrical division Mogessie et al 2018, Mogessie Schuh –actin and MT are apart of oocyte spindle> <Bennabi et al 2016 –spindle assembly in oocytes, sun and kim 2011 – SAC and regulators, Kolano et al 2012 –error prone oocytes, Manil-Segalen – forces through MT breaking chromosomes, Mogessie et al 2018 – meiotic spindle (big) review>

### Conservation in sex-specific recombination landscape

Our results extend (the mountain / plethora) or previous data reports for broad scale sex difference in the recombination landscape (Sardell and Kirkpatrick 2020) - data comprised mostly of highly divergence species / large evolutionary distances. In contrast our results demonstrate that this pattern is maintained across much shorter evolutionary distances and even with rapid evolution in the genome-wide recombination rate. We argue that this conservation of the male chromosome end bias // recombination landscape is one of the most conserved features of heterochiasmy and could be connected to fundamental aspects of gametogenesis.

As reviewed in (Sardell and Kirkpatrick 2020), sexual dimorphism in the broad scale recombination landscape is a conserved trait. The two locus modifier and SACE models predict sexual dimorphism in the broad scale recombination landscape, for diminishing the effect of drive systems and maintaining larger chromosome blocks under linkage in males respectively. The COM model, predicts the sex differences in the recombination landscape via interference is due to a combination of the length of the axis and differing strengths of chromosome movements during the pairing process (Hultén 2011).

Under the spindle based model we hypothesize that the sexual dimorphism in the recombination landscapes hinges on sex differences on the requirements for chromosome cohesion in late meiosis I. The irreversible process of the metaphase to anaphase transition is initiated by the protyltic decay of the sister cohesion connecting homologs (Lane and Kauppi 2019), subramanian and Hochwagen , Dumont and Desai (2012)]. The number and placement of crossovers alter the distribution of sister cohesion and the resulting chromosome structure when bivalents are aligned and bi-oriented on the metaphase plate (Veen and Hawley 2003, @altendorfer2020). Differences in timing of cell cycle between oogenesis and spermatogenesis imposes the the different selective pressures on how sister cohesion affects chromosome structure. Faster spermatogenesis may select for synchronization of the separation homologs (cite). While in oogenesis, the slower cell cycle and multiple arrest stages may require chromosome structures with greater stability on the MI spindle, espicially for those with dicyate arrest (Lee 2019).

The higher levels /increased genetic diversity and recombination rates at chromosome ends Haenel et al. (2018) - suggests that this is driven by the male-specific recombination landscape (Sardell and Kirkpatrick 2020). (giving rise to interesting evolutionary predictions).

### Conservation of sex differences in chromatin structure

Our results from musculusMSM and musculusPWD demonstrate that chromatin compaction are uncoupled from the direction of heterochiasmy in house mice. These results slightly depart from predictions which nominate chromatin compaction as the primary driver of recombination rate variation (Petkov et al. 2007). Chromatin compaction could explain variation in heterochiasmy, which is driven by the disinct meiotic contexts across sexes but is a weak predictor for recombination rate variation within the sexes. Our results indicate the sexual dimorphism in chromatin compaction is conserved in house mouse (e.g. females have longer SC than males) and that the rapid male-specific evolution in crossover number per cell proceeded through another aspect of crossover regulation (see below).

Only the COM model predicts sexual dimorphism in chromatin structure and attributes the source to greater cell volume in oocytes. This prediction model might fit broader pattern such as in *Arabidopsis thalania* (Mercier paper? Sera?) where pollen is the larger cell and has longer axis length (Cahoon and Libuda 2019).

As outlined in Haenel et al. (2018), sexual dimorphism in chromatin organization translates to interference strength measured in base pairs. From empirical data in mice (Petkov et al. 2007, @lynn2002) and humans (Gruhn et al. 2013), there seem to be to general configurations for chromatin structure: longer axis and shorter loops in females; shorter axis and longer loops in males. The signal for interference is thought to be mediated though the SC, which is built on top of the chromosome axis (Zickler and Kleckner 2015) regardless of the loop size. Supporting this is the observation that interference strength measured in micrometers of is conserved between sexes (Petkov et al. 2007). As a consequence, since more base pairs are sequestered into the radial loops per unit of the linear central axis, chromatin organization with longer DNA loops (and shorter axis), as seen in males, will have a signal of stronger interference when measured in base pairs compared to ’the typical female chromatin configuration. Stronger interference in males, has been noted across many sex-specific linkage maps (cite) strengthening the hypothesis that sexual dimorphism in the chromatin organization is widespread, however this has only been confirmed by cytological data in mice and humans. (Also large difficulties in observing sperm cells through meiosis).

<The results of sexual dimorphism in chromatin structure is supported by the literature, especially for mammals (Lynn et al. 2002, @gruhn2013), But there’s generally a lack of data for other systems see (Cahoon and Libuda 2019)>

### Evolution of interference strength in males

An expected consequence of our observed elevated genome-wide recombination rate is lower LD across the genome, which may increase the efficiency of selection and impact the dynamics of introgression (cite, Schumer). Given that the higher genome-wide recombination rates are paired with stronger interference these predicted pattern may have heterogeneous signal along chromosomes. **(new, veller paper – in addition to the total gwRR, the location of crossovers (rbar), should be considered in this dynamic)**

Examples of evolution of interference strength are rare and may be complicated by changes in the underlying karyotype structure (Segura et al 2014). The general pattern of empirical measures of interference strength is that it has a negative correlation to the genome wide recombination rate (Otto and Payseur 2019). This fits the logic of the chromosome axis acting as the ‘real estate’ for DSBs and aligns with known molecular mechanisms (cite). Two examples of the opposite direction, a positive correlation of interference strength and genome-wide recombination rate, involve descriptions of observations at the single bivalent level; the between lab-raised and wild mice of *Peromyscus leucopus* from (Peterson, Miller, and Payseur 2019) or large effects on genome wide recombination rates across a short evolutionary differences; the within-sex comparison of two breeds of cattle with different genome wide recombination rates (Ma et al. 2015).

We propose that the spindle based selection model can explain the positive correlation via selection on the amount of sister cohesion connecting homologs at metaphse. The evolution of genome wide recombination rates in our study is driven by a transition of the majority of bivalent having single crossovers to an enrichment of bivalents with two crossovers. All else being equal, interference strength would be expected to be equal or even weaker. Our results show that the two crossovers are spaced further apart when SC length is controlled for and chromosome size effects are minimized, in the strain enriched for two crossover bivalents. Assuming that chromatin compaction between pachtyene and metaphase is uniform along chromosomes, an outcome of this further spacing of two foci results in an increased area of sister cohesion connecting homologs (Figure X).

The COM model predicts that interference and the recombination landscape arises from known oscillatory movements during prophase (Rubin, Macaisne, and Huynh 2020), however it lacks a mechanism for a evolutionary based predictions. While the SACE modifier model does not explicitly model evolution of interference strength we note that a logical outcome of the main prediction of maintaining larger chromosome blocks in males, would be a recombination landscape with stronger interference strength.

We have focused on the model involving direct selection on the recombination pathway, which has an impact on the fitness of an individual, but we acknowledge connections to other models involving indirect selection on recombination rates which involve the fitness outcomes of offspring. A model from Goldstein, Bergman, and Feldman (1993), reviewed in (Otto and Payseur 2019) and Veller, Kleckner, and Nowak (2019), predict that interference strength evolves whenever increased recombination rates evolve. The simulations under this model indicate that the space across multiple loci or between multiple crossovers increases in a positive manner with the genome wide recombination rate. A distinguishing feature of this model from other modifier models is that the number of crossovers per chromosome is kept constant. Empirically, the range of crossovers per chromosome is quite limited, 1-3, for the majority of chromosomes across most taxa (Otto and Payseur 2019, @stapley\_variation\_2017). Constraining the number of crossovers per chromosome in models may fit empirical data better than those where recombination rate across an abstracted genetic space is unconstrained.

### Future steps

There are still many un-known aspects regarding heterochiasmy (Lenormand) , these novel results suggest - we hope ppl we follow up . (fitness - evolutionary dynamics - role in linked selection)

We make three suggestions for future steps in studying recombination variation. First consider the when comparing sex specific meiotic traits consider that evolutionary distinct trajectories due to the fundamental differences in gametogenesis.

Second certain systems can be leveraged to overcome limitations inherent in some approached. For example, identifying chromosomes across cells in cytological data requires chromosome specific probes, (e.g. FISH) but chromosome specific data can be collected from organisms with diverse karyotypes (birds, peromyscus, humans) or backgrounds with Robertsonian trans-locations.

Third we encourage the cross-pollination of physiology based models and more abstract model such as population genetic models with testable hypotheses Dapper and Payseur (2017). A goal of such merging of models could be to connect empirical findings across scales.

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