**ABSTRACT 150 words**

Although meiotic recombination is required for successful gametogenesis in most species that reproduce sexually, the rate of crossing over varies among individuals. Differences in recombination rate between females and males are perhaps the most striking form of this variation. Existing data fail to directly address the extent to which recombination experiences similar evolutionary pressures. To fill this gap, we measured meiotic recombination in both sexes for a panel of house mouse cross three subspecies. Using inbred strains and single cell immunohistochemistry allowed us to place sex-specific observations within the same genetic background and meiotic context. Our results indicate highly discordant evolutionary patterns in the two sexes. Whereas male recombination rates show evidence of rapid evolution over short evolutionary timescales, female recombination rates measured in the same strains are mostly static. These results strongly indicate that house mouse has two genome wide recombination rates which display distinct evolutionary trajectories.

The rapid evolution in male gwRR is significantly predicted/correlated by the number of double strand breaks and spacing of double crossovers.

However the relative spacing of double crossovers in the high recombining group is greater compared to the low recombining group – (that is the relative recombination landscape – is less dense – but has more recombination).

<understanding the pathway>

**INTRO**

**1. Importance of recombination**

**gwRR scale**

Meiosis can be reduced to the expression (2n -> 4n -> 2n -> 1n) which highlights/reflects the process diploid genome producing haploid cell products. (In most species) The meiotic program relies on crossovers and the process of recombination to ensure the correct separation of chromosomes. The total number of COs per cell (at the 4n stage) is equal to the genome wide recombination rate (gwRR).

(gwRR framed within genetic diversity and population)

In the indirect manner, the recombination rate regulates populations’ response to selection, and determine the fate of novel mutations by transferring beneficial mutations onto novel genetic backgrounds or by breaking linkage of negative mutations from beneficial genetic backgrounds (cite). This process shapes the genomic patterns of genetic variation, with high recombination areas of genome having more nucleotide variation while areas of low recombination have decreased genetic variation (Begun Aquadro, Nachman, Payseur).

\*\*(because of how it facilitates chromosomes disjunction / segregation, )the cell based metric of genome wide recombination rates are tightly connected to organisms fitness and fertility.\*\*

When the genome wide recombination rate is framed within the cell context ….the single cell context it is closely connected to the constraints which are imposed at the single cell level.

The process of chromosome segregation is integral to the process of producing haploid gametes and can be considered a constraint in regards to the evolution.

Reflecting the importance of it's role in chromosome segregation is that the number of haploid pairs of chromosomes is strong predictor for genome wide RR across large species(taxa) / divergence scales [@ottoPaysuer2019; @stapley\_variation\_2017]. (the number of crossovers per chromosome are highly conserved)

\*\*connection of single cell based gwRR to thresholds imposed at the single cell level\*\* (why is gwRR the better scale for evolutionary patterns?)

**2.variation in recombination rate**

1. **Thresholds –sex most notable forms of variation across individuals**

Ensuring at least one crossover per chrm while minimizing the rates of DNA damage and ectopic recombination (cite) are considered to be the lower and upper bounds/thresholds for gwrr respectively [@nagaoka2012]. Yet, within these bounds/thresholds the genome wide recombination rate still varies across species and individuals.

Notably, sex is one of the most notable axes of this form of variation.

(examples,

Humans 1.7 female to male

alligators female to male ratio is X, temperature dependent sex determination)

1. **Gap is due to Lack of comparable measures**

(given the lack of empirical data from both sexes/given difficulties-complications)

An understanding of how sex shapes the evolution of recombination cannot be achieved with available data. Comprehensive comparisons of female and male recombination rates usually come from outbred populations humans [@Kong2004;, @Kong2008; @Kong2014; @halldorsson2019], dog, cattle [@ma2015\_cattle; @Shen2018\_cattle], (other sheep) sheep [@johnston2016\_soay], and mouse (CC cite) in which the role of sex is confounded with the contributions of genetic variation.

1. **Open Q, no first principle**

Under anisogamy where gametogenesis is modified to produce distinct gametes (cite Gorelick?), the meiotic program is the same and there are no first principles which would predict the evolution of sexually dimorphic recombination rates. Yet heterochiasmy is commonly observed in dioecious species, suggesting that other meiotic traits which distinguish the gametes and their meiotic programs, for example symmetrical vs asymmetrical cell division, may impose selection for sexually dimorphic recombination rates. Although it is clear that the relationship between female and male recombination rates can differ among species, comparisons between and within closely related species are missing. Direct contrasts between females and males across a common, diverse set of genomic backgrounds would reveal whether the recombination rate evolves differently in the sexes.

1. Additional metrics (more nuanced)

Initial focus/evidence on heterochiasmy was primarily focused on which sex had more recombination – the field has advanced since it’s first documentation (cite morgan 1914). Recently two specific features have been highlighted as conserved patterns of heterochiasmy: @CahoonLibuda2019 show that in species with meiotic chromatin (SC axis length) quantified for both sexes, longer chromosome axis generally has higher recombination rates.

In @sardell\_sex\_2020, a survey of 51 species shows there are conserved broad scale recombination landscape differences. Generally males have telomere-bias crossover placement and females have more uniform placement.

These observations raise the question of how conservation in sexually dimorphic patterns are maintained with the gwRR and it’s decomposed traits.

**3.  The House Mouse is a great model for uncovering evolutionary patterns at a short timescale.**

-short divergence time (tool for rapid evolution)

-same genome for males and females (inbred lines)

- condusive for cytology approaches

The House mouse species complex arose from a recent radiation providing an opportunity to interrogate natural variation at short evolutionary scales, potentially narrowing the mutational space for identifying variants which would cause gwRR variation. Add divergence ranges. divergence spanning 0.5 mya to 5 mya (cite / Geraldes et al 2008 and Geraldes et al 2010).

Classical lab strains of mice have generated extensive knowledge central to meiosis and outcomes on recombination through extensive studies on the genes involved in the meiotic recombination pathway (cite) and previous crosses for understanding the genetic architecture of recombination rate variation @dumont2011house; @murdoch2010; @Wang2017island].

Additionally due to their global distribution allows us to compare samples of natural diversity from a broad geographic range. (wild derived inbred strains – will capture genetic diversity not represented in classical lab strains.)

\*\*Wild derived **inbred** strains generate the best comparison of females and males, besides the sex chromosomes, the mouse for each genome are almost identical\*\*. Inbred strains enable one of the most direct comparison of both female and male gametogenesis and enable us to conclude that sex is a primary factor.

While there are strains with Robertsonian translocations, in house mouse and related murid species it is possible to assemble sets of strains with identical karyotypes, 20 pairs of acrocentric chromosomes.

House mouse is well suited for single cell cytology approaches (due to large cell sizes). The single cell level allows integration of data at a closer connection to the molecular pathway and meiotic program. In addition to the quantification of gwRR. This study quantifies precursors to crossovers, double strand breaks (DSBs), and meiotic chromosome morphology across stages of meiosis which would not be accessible to with genetic linkage data and crosses.

**3. What we did in this study**

**Main messages: these results are centered/focused on a unique evo comparison**

**Advantages / importance of using multiple strains from and multiple subspecies**

**-importance / advantage of sampling for multiple geographic locations.**

**Chromosome morphology / general recombination landscape**

**-results for general landscape – conserved sex differences and**

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OUR results for genome wide recombination rate (variation) we observed highly distinct evolutionary trajectories between males and females. This is due to rapid male specific evolution in the gwRR from two strains in musculus and 1 strain in molossinus. (this pattern of rapid evolution was not observed in females). **We observed up to a 30% difference (translating into approximately ~7 more crossovers per cell), a surprising amount considering the short evolutionary time scale.**

The metric of the genome wide recombination rate reflects a non-random process of crossover formation on individual chromosomes // the recombination landscape at the single chromosome level. The recombination landscape for single chromosome scale can be general summarized by i) spacing of crossovers and ii) the linear area of synapsed homologous chromosomes where crossovers can form.

We quantified the general recombination landscape because patterns in the recombination landscape are important to document because they can shed light on constraints and regulation of the processes ( could end up leading to variation in the genome wide recombination rates. Our results confirm (well established) previously reported patterns for sex differences in the general recombination landscape – and add by demonstrating that these patterns hold even in the case of genome more crossovers, but general landscape patterns still maintain sex-specific patterns.

Conserved patterns of the recombination landscape of the single chromosome level – reflect constraints At the single chromosome level – (crossover number is conserved – suggesting processes regulating the rec landscape at this scale might face similar constraints

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JUNK

For the first time in many of these strains, We report a rare, direct, evolutionary comparison of recombination rate in females and males for this short evolutionary scale. We choose *Mus musculus* because of the available strains across subspecies. Our design of using multiple inbred strains within subspecies and multiple subspecies across the species -- (can provide information anaglogous to polymorphism within and divergence within subspecies of the house mouse. Our results indicate rapid male specific evolution of gwRR occurred in a subset of house mouse lines.

**We observed up to a 30% difference (translating into approximately ~7 more crossovers per cell), a surprising amount considering the short evolutionary time scale. (found**

**Brief mouse background and (touch on polymorphism**

-musculus subspecies – have mostly been samples from central Europe – we extend with samples from more eastern extent of the subspecies range in Russia and Kazakhstan.

-molossinus is endemic to the japan – a hybrid that arose with humans brining musculus and castaneus to the islands. (AGAIN the divergence between mus musculus subspecies is ~500K – and males and females share the same phylogeny)

* While there are strains with Robertsonian translocations, in house mouse and related murid species it is possible to assemble sets of strains with identical karyotypes, 20 pairs of acrocentric chromosomes.