**Molecular Evolution of the Meiotic Recombination Pathway in Mammals**

*Investigations*

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## Abstract

Meiotic recombination, the exchange of genetic material between homologous chromosomes during meiosis, is required for successful gametogenesis in most sexually reproducing species. Recombination is also a fundamental evolutionary force, influencing the fate of new mutations and determining the genomic scale over which selection shapes genetic variation. Despite the central importance of recombination, basic questions about its evolution have yet to be addressed. Although many genes that play roles in recombination have been identified, the molecular evolution of most of these genes remains uncharacterized. Using a phylogenetic comparative approach, we measure rates of evolution in 32 recombination pathway genes across 16 mammalian species, spanning primates, murids, and laurasithians. By analyzing a carefully-selected panel of genes involved in key components of recombination – spanning double strand break formation, strand invasion, the crossover/non-crossover decision, and resolution – we generate a comprehensive picture of the evolution of the recombination pathway in mammals. Recombination genes exhibit marked heterogeneity in the rate of protein evolution, both across and within genes. We report signatures of rapid evolution and positive selection that could underlie species differences in recombination rate. [**WORK HERE**]

Abstract Word Count : (< 250)

## Introduction

The reciprocal exchange of DNA between homologous chromosomes during meiosis – recombination – is required for successful gametogenesis in most species that reproduce sexually (Hassold and Hunt 2001). The rate of recombination is a major determinant of patterns of genetic diversity in populations, influencing the fate of new mutations (Hill and Robertson 1966), the efficacy of selection (Felsenstein 1974; Charlesworth *et al.* 1993; Comeron *et al.* 1999; Gonen *et al.* 2017), and important features of the genomic landscape (Begun and Aquadro 1992; Charlesworth *et al.* 1994; Duret and Arndt 2008).

Although recombination rate is often treated as a constant, this fundamental parameter evolves over time. Genomic regions ranging in size from short sequences to entire chromosomes vary in recombination rate – both within and between species (Burt and Bell 1987; Broman *et al.* 1998; Jeffreys *et al.* 2005; Coop and Przeworski 2007; Kong *et al.* 2010; Dumont *et al.* 2011; Smukowski and Noor 2011; Comeron *et al.* 2012; Segura *et al.* 2013; Dapper and Payseur 2017; Stapley *et al.* 2017).

Genome-wide association studies are beginning to reveal the genetic basis of differences in recombination rate within species. Individual recombination rates have been associated with variation in specific genes in populations of *Drosophila melanogaster* (Hunter *et al.* 2016), humans (Kong *et al.* 2008, 2014; Chowdhury *et al.* 2009; Fledel-Alon *et al.* 2011), domesticated cattle (Sandor *et al.* 2012; Ma *et al.* 2015; Kadri *et al.* 2016; Shen *et al.* 2018), domesticated sheep (Petit *et al.* 2017), Soay sheep (Johnston *et al.* 2016), and red deer (Johnston *et al.* 2018). Variants in several of these genes correlate with recombination rate in multiple species, including: *Rnf212* (Kong *et al.* 2008; Chowdhury *et al.* 2009; Fledel-Alon *et al.* 2011; Sandor *et al.* 2012; Johnston *et al.* 2016; Kadri *et al.* 2016; Petit *et al.* 2017), *Rnf212B* (Johnston *et al.* 2016, 2018; Kadri *et al.* 2016), *Rec8* (Sandor *et al.* 2012; Johnston *et al.* 2016, 2018), *Hei10/Ccnb1ip1* (Kong *et al.* 2014; Petit *et al.* 2017), *Msh4* (Kong *et al.* 2014; Ma *et al.* 2015; Kadri *et al.* 2016; Shen *et al.* 2018), *Cplx1* (Kong *et al.* 2014; Ma *et al.* 2015; Johnston *et al.* 2016; Shen *et al.* 2018) and *Prdm9* (Fledel-Alon *et al.* 2011; Sandor *et al.* 2012; Kong *et al.* 2014; Ma *et al.* 2015; Shen *et al.* 2018).

In contrast, the genetics of recombination rate variation among species remains poorly understood. Divergence at the di-cistronic gene *mei-217/mei-218* explains much of the disparity in genetic map length between *D. melanogaster* and *D. mauritiana* (Brand *et al.* 2018). *mei-217/mei-218* is the only gene known to confer a recombination rate difference between species, though quantitative trait loci that contribute to shifts in rate among subspecies of house mice have been identified (Dumont and Payseur 2010; Murdoch *et al.* 2010; Balcova *et al.* 2016).

One strategy for understanding how species diverge in recombination rate is to inspect patterns of molecular evolution at genes involved in the recombination pathway. This approach incorporates knowledge of the molecular and cellular determinants of recombination and is motivated by successful examples. *mei-217/mei-218* was targeted for functional analysis based on its profile of rapid evolution between *D. melanogaster* and *D. mauritiana* (Brand *et al.* 2018). *Prdm9*, a protein that positions recombination hotspots in house mice and humans through histone methylation (Myers *et al.* 2010; Parvanov *et al.* 2010; Grey *et al.* 2011, Paigen2018; 2018), shows accelerated divergence across mammals (Oliver *et al.* 2009). The rapid evolution of *Prdm9* – which localizes to its zinc-finger DNA binding domain (Oliver *et al.* 2009) – appears to be driven by selective pressure to recognize new hotpot motifs as old ones are destroyed via biased gene conversion (Myers *et al.* 2010; Ubeda and Wilkins 2011; Lesecque *et al.* 2014; Latrille *et al.* 2017). Although these examples demonstrate the promise of signatures of molecular evolution for illuminating recombination rate differences between species, patterns of divergence have yet to be reported for most genes involved in meiotic recombination.

Mammals provide a useful system for dissecting the molecular evolution of the recombination pathway for several reasons. First, the evolution of recombination rate has been measured along the mammalian phylogeny (Dumont and Payseur 2008; Segura *et al.* 2013). Second, recombination rate variation has been associated with specific genes in mammalian populations (Kong *et al.* 2008, 2014; Chowdhury *et al.* 2009; Sandor *et al.* 2012; Ma *et al.* 2015; Johnston *et al.* 2016, 2018; Kadri *et al.* 2016; Petit *et al.* 2017; Shen *et al.* 2018). Third, laboratory mice have proven to be instrumental in the identification and functional characterization of recombination genes (Vries *et al.* 1999; Baudat *et al.* 2000; Romanienko and Camerini-Otero 2000; Yang *et al.* 2006; Ward *et al.* 2007; Schramm *et al.* 2011; Bisig *et al.* 2012; Bolcun-Filas and Schimenti 2012; La Salle *et al.* 2012; Kumar *et al.* 2015; Finsterbusch *et al.* 2016; Stanzione *et al.* 2016) .

Work in mice indicates that the mammalian recombination pathway is roughly divided into five major steps, each of which is regulated by a handful of genes. The first step is the formation of hundreds of double strand breaks (DSBs) throughout the genome (Bergerat *et al.* 1997; Keeney *et al.* 1997; Baudat *et al.* 2000; Romanienko and Camerini-Otero 2000; Baudat and Massy 2007; Finsterbusch *et al.* 2016; Lange *et al.* 2016). After formation, DSBs are identified, processed, and paired with their corresponding location on the homologous chromosome through the processes of homology search and strand invasion (Keeney 2007; Cloud *et al.* 2012; Brown and Bishop 2014; Finsterbusch *et al.* 2016; Kobayashi *et al.* 2016; Oh *et al.* 2016; Xu *et al.* 2017). The pairing of homologous chromosomes is then stabilized by a proteinaceous structure referred to as the synaptonemal complex (SC) (Meuwissen *et al.* 1992; Schmekel and Daneholt 1995; Costa *et al.* 2005; Vries *et al.* 2005; Hamer *et al.* 2006; Yang *et al.* 2006; Schramm *et al.* 2011; Fraune *et al.* 2014; Hernández-Hernández *et al.* 2016). The SC also forms a substrate on which the eventual crossover events will take place [**citations**]. It is at this point that a small subset of DSBs is designated to mature into crossovers, leaving the majority of DSBs to be resolved as non-crossovers (Snowden *et al.* 2004; Yang *et al.* 2008; Reynolds *et al.* 2013; Finsterbusch *et al.* 2016; Rao *et al.* 2017). Finally, this designation is followed, and each DSB is repaired as a crossover or a non-crossover (Baker *et al.* 1996; Edelmann *et al.* 1996; Lipkin *et al.* 2002; Rogacheva *et al.* 2014; Xu *et al.* 2017).

In this article, we examine the molecular evolution of 32 key recombination genes, evenly distributed across each major step in the recombination pathway, in 16 mammalian species spanning Primates, Rodents and Laurasiatherians. In addition to revealing patterns of divergence across diverse mammalian species, we leverage human polymorphism data to make robust evolutionary inferences. Our results provide a comprehensive picture of evolution in the recombination pathway in mammals and identify steps of the pathway most likely to contribute to differences in recombination rate between species.

## Materials and Methods

### Data Acquisition & Processing

We selected a focal panel of 32 recombination genes (See Table1). The genes included in this panel were selected to: (1) cover each major step in the recombination pathway as evenly as possible, (2) choose genes that we know are have integral functions in each step, and (3) include genes that have been associated with variation in recombination rate within mammalian populations. Reference sequences were downloaded for each gene from both NCBI and Ensembl (Release-89) [citations].

Alternative splicing is widespread and presents a challenge for molecular evolution studies [citations]. We used available testes expression datasets to select the isoform expressed in tissues of interest and to validate the computationally imputated annotations for each gene in each species. We downloaded the raw testes expression data for each mammalian species from NCBI GEO (Table S1) [citations]. We converted the SRA files into FASTQ files using SRAtoolkit [citation]. The reads were mapped to an indexed reference genome (Table S2,3) [Bowtie2, citation] using tophat [citation]. The resulting bam files were sorted using Samtools and visualized using IGV 2.4.10 [citations]. This allowed us to: (1) identify the transcript that is expressed in the testes tissue, (2) check the reference transcript for errors, (3) revise the reference transcript based upon the transcript data.

We compared expression data to annotations from both the Ensembl & NCBI [citations]. When both transcripts were identical, we selected he NCBI transcript was the default. Ensembl transcript was used instead when: (1) the NCBI reference sequences was not available for a given gene in a given species, (2) when none of the NCBI matched the expression data, or (3) when there were sequence differences between the two transcripts and the Ensembl transcript was more parsimonious. The use of testes expression data sets was a key data processing step and the inclusion of species in this study was primarily determined by the availability of testes expression data.

### Phylogenetic Comparative Approach in Mammals

For each gene, we conducted a phylogenetic analysis by maximum liklihood (PAML 4.8) to measure the rate of evolution across the mammalian phylogeny and to detect molecular signatures indicative of positive selection [citations]. This approach requires a sequences alignment for each gene and a phylogenetic tree. For each gene, sequences were aligned using Translator X, a codon-based alignment tool powered by MUSCLE v3.8.31 (citations). Each alignment was examined by hand and, as necessary, edited. We selected a species tree for our analyses, based upon our current understanding of the phylogenetic relationship of the mammals included in our study (Figure1) [citations].

Due to the ambiguity in the relationship between Laurasithians and the placement of Tree Shrews, we also inferred the gene trees using MrBayes [citations]. This also allowed us to control for effects of incomplete lineage sorting (ILS) [citations]. The results using the gene trees did not differ in any significant manner and can be found in the supplemental info (Table S4).

For the majority of genes, transcripts from all 16 species were used (19 genes). However, for a number of genes, the chimpanzee and bonobo sequences were identical, in which case only the chimpanzee sequence was included in the analyses (11 genes). In one case, the chimpanzee, bonobo and human sequences were all identical, in which case only the human sequence was included in the analyses. In only a small number of instances, a suitable reference sequences could not be identified for a given species.

We estimated rates of synonymous and nonsynonymous substitutions per site using the CODEML program in PAML4.8 (citations). This program considers multiple substitutions per site, different rates of transitions and transversions, and effects of codon usage (citations). Rates of subsitutions were computed for 6 different models: 0,1,2,7,8,8a (Table 2). The fit of each model was compared using a liklihood ratio test and the rates of substitutions are reported for the model of best fit for each gene.

[TURN INTO TABLE] (1) Comparison 1: Model 0 - one dN/dS ratio for all sites (<1); Model 1 - two dN/dS ratios (<1, =1); Model 2 - three dN/dS ratios (<1, =1, >1). (2) Comparison 2: Model 7 - beta distribution of 10 dN/dS values, all between 0 & 1; Model 8 - beta distribution of 10 dN/dS values, all between 0 & 1, plus 11th category > 1. (3) Comparison 3: Model 8 - beta distribution of 10 dN/dS values, all between 0 & 1, plus 11th category > 1; Model 8a - beta distribution of 5 dN/dS values, all between 0 & 1, plus 6th category =1.

### Identifying Signatures of Selection

Model comparison

### Multi-nucleotide Mutations

Multi-Nucleotide Mutations (MNMs) occur when two mutations happen simultaneously in close proximity (non-independent) [citations]. MNMs violate the assumption of PAMLs maximum likelihood model, which assumes that the probability of two simultaneous mutations in the same codon is zero [citations]. Recent work has shown that MNMs can frequently result in false positive signatures of positive selection in branch-site models in HyPhy [citations]. While we are not using branch-site models, the possibility remains that MNMs could be contributing to the signature of positive selection we are observing in some recombination genes. It is not possible to identify MNMs in our dataset, but we can identify codons with multiple differences (CMDs) that are likely to have arisen on a single branch in the phylogeny. We removed all CMDs that putatively arose on a single branch and then re-analyzed the subset of genes that exhibited a significant signature of positive selection in our original analyses.

To identify CMDs, we used PAML to reconstruct the ancestral sequence at each node in the phylogeny. For the reconstruction, Model 8 was chosen because we were specifically analyzing genes with a significant signature of positives selection when comparing Model 7 & Model 8. From the ancestrally reconstructed sequences, we identified any codons in which PAML inferred more than one substitution on a single branch. All identified CMDs were removed from the sequences in which they occurred. For example, if a CMD was identified in an external branch, that codon would be replaced with ‘---’ only in the sequence of that species. If a CMD was inferred on an internal branch, the codon would be replaced with ‘---’ in all species connected to that internal branch. We re-ran our analyses in PAML with the sequences in which all CMDs were removed.

### Polymorphism & Divergence in the Primate Lineage

Human polymorphism data was downloaded from ExAC database.

Not available for 3 genes. Issues with ExAC data for: RNF212, MEI4 (and REC8)?

Pairwise divergence between humans and macaques was calculated using YN00 package in PAML.

Compared polymorphism within humans to divergence between human and macaques using the McDonald-Kreitman test.

**Table 1** : Recombination Genes

|  |  |  |
| --- | --- | --- |
| Gene | Function | Meiosis-Specific? |
| A) | **DSB Formation** |  |  |
| *HORMAD1* | chromosome axis, promotes DSB formation | Yes |  |
| *HORMAD2* | chromosome axis | Yes |  |
| *MEI4* | promotes DSB formation (*MCD recombinosome*) | Yes |  |
| *REC114* | promotes DSB formation (*MCD recombinosome*) | Yes |  |
| *IHO1* | promotes DSB formation (*MCD recombinosome*) | Yes |  |
| *SPO11* | transesterase, catalyzes the formation of DSBs | Yes |  |
| B) | **DSB Processing/Strand Invasion** |  |  |
| *MRE11* | Nuclease, required for DSB formation & processing  (*MRN Complex*) | No |
| *NBS1* | Phosphopeptide binding, required for DSB formation | No |  |
|  | & processing (*MRN Complex*) |  |  |
| *RAD50* | ATPase/DNA binding protein, required for DSB formation & processing (*MRN Complex*) | No |  |
| *BRCC3* | deubiquitinase, DSB processing | No |  |
| *DMC1* | recombinase, strand invasion & homologous pairing | Yes |  |
| *RAD51* | recombinase, strand invasion & homologous pairing | No |  |
| *SPATA22* | strand invasion & homologous pairing | Yes |  |
| *MEIOB* | oligonucleotide binding, strand invasion & homologous pairing | Yes |  |
| *MCMDC2* | Helicase, stabilizes homologous pairing | Yes |  |
| C) | **Homologous Pairing** |  |  |
| *REC8* | cohesion core | Yes |
| *RAD21L* | cohesion core | Yes |  |
| *SYCP1* | synaptonemal complex - transverse filament |  |  |
| *SYCP2* | synaptonemal complex - axial element |  |  |
| *TEX12* | synaptonemal complex - central element |  |  |
| D1) | **Crossover vs. Non-Crossover - MutS Recruitment** |  |  |
| *TEX11* |  |  |
| *SHOC1* |  |  |  |
| *CNTD1* |  |  |  |
| *RNF212* |  |  |  |
| *RNF212B* |  |  |  |
| *MSH4* | recombination crossover control |  |  |
| *MSH5* | recombination crossover control |  |  |
| D2) | **Crossover vs. Non-Crossover - MutL Recruitment** |  |  |
| *MER3* |  |  |
| *HEI10* |  |  |  |
| *MLH1* | promotion of meiotic crossing over |  |  |
| *MLH3* | promotion of meiotic crossing over |  |  |
| *MUS81* |  |  |  |

## 

**Figure 1**: Species Tree

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**Table S1**: Testes Expression Datasets

|  |  |  |
| --- | --- | --- |
| ***Species*** | **GEO Accession** | **Reference** |
| *Bos taurus* | GSM1020728 & GSM1020746 | Merkin *et al.* (2012) |
| *Callithrix jacchus* | GSM1227961, GSM1227962 & GSM1227963 | Cortez *et al.* (2014) |
| *Canis lupus familiaris* | GSM747469 & GSM1359286 | Derti *et al.* (2012), Vandewege *et al.* (2016) |
| *Eptesicus fuscus* | GSM1359287 | Vandewege *et al.* (2016) |
| *Equus caballus* | GSM1139276 & GSM1359288 | Coleman *et al.* (2013), Vandewege *et al.* (2016) |
| *Gorilla gorilla* | GSM752663 | Brawand *et al.* (2011) |
| *Homo sapiens* | GSM752707 & GSM752708 | Brawand *et al.* (2011) |
| *Macaca mulatta* | GSM752642 & GSM752643 | Brawand *et al.* (2011) |
| *Mus musculus* | GSM752629 & GSM752630 | Brawand *et al.* (2011) |
| *Ovis aries* | GSM1666944 & GSM1666936 | Guan *et al.* (2017) |
| *Pan paniscus* | GSM752690 | Brawand *et al.* (2011) |
| *Pan troglodytes* | GSM752678 | Brawand *et al.* (2011) |
| *Pongo pygmaeus* | GSM1858310 & GSM1858311 | Carelli *et al.* (2016) |
| *Rattus norvegicus* | GSM1278058 | Cortez *et al.* (2014) |
| *Sus scrofa* | GSM1902350, GSM2033157 & GSM2033163 | Li *et al.* (2016), Yang *et al.* (2017) |
| *Tupaia chinensis* | GSM957062 | Fan *et al.* (2013) |

**Table S2**: NCBI Reference Genomes (O’Leary *et al.* 2015)

|  |  |  |  |
| --- | --- | --- | --- |
| ***Species*** | **Assembly** | **RefSeq Accession** | **WGS Project Reference** |
| *Bos taurus* | Bos\_taurus\_UMD\_3.1.1 | GCF\_000003055.6 | Zimin *et al.* (2009) |
| *Callithrix jacchus* | Callithrix\_jacchus-3.2 | GCF\_000004665.1 | - |
| *Canis lupus familiaris* | CanFam3.1 | GCF\_000002285.3 | Lindblad-Toh *et al.* (2005) |
| *Eptesicus fuscus* | EptFus1.0 | GCF\_000308155.1 | - |
| *Equus caballus* | EquCab2.0 | GCF\_000002305.2 | Wade *et al.* (2009) |
| *Gorilla gorilla* | gorGor4 | GCF\_000151905.2 | Scally *et al.* (2012) |
| *Homo sapiens* | GRCh38.p10 | GCF\_000001405.36 | - |
| *Macaca mulatta* | Mmul\_8.0.1 | GCF\_000772875.2 | Zimin *et al.* (2014) |
| *Mus musculus* | GRCm38.p5 | GCF\_000001635.25 | - |
| *Ovis aries* | Oar\_v4.0 | GCF\_000298735.2 | Consortium *et al.* (2010) |
| *Pan paniscus* | panpan1.1 | GCF\_000258655.2 | Prüfer *et al.* (2012) |
| *Pan troglodytes* | Pan\_tro\_3.0 | GCF\_000001515.7 | Consortium *et al.* (2005) |
| *Pongo abelii* | P\_pygmaeus\_2.0.2 | GCF\_000001545.4 | Locke *et al.* (2011) |
| *Rattus norvegicus* | Rnor\_6.0 | GCF\_000001895.5 | Consortium and others (2004) |
| *Sus scrofa* | Sscrofa11.1 | GCF\_000003025.6 | - |
| *Tupaia chinensis* | TupChi\_1.0 | GCF\_000334495.1 | Fan *et al.* (2013) |

**Table S3**: Ensembl Reference Genomes

|  |  |  |  |
| --- | --- | --- | --- |
| ***Species*** | **Assembly** | **RefSeq Accession** | **WGS Project Reference** |
| *Bos taurus* | Bos\_taurus\_UMD\_3.1 | GCF\_000003055.3 | Zimin *et al.* (2009) |
| *Callithrix jacchus* | Callithrix\_jacchus-3.2 | GCF\_000004665.1 | - |
| *Canis lupus familiaris* | CanFam3.1 | GCF\_000002285.3 | Lindblad-Toh *et al.* (2005) |
| *Eptesicus fuscus* | - | - | - |
| *Equus caballus* | EquCab2.0 | GCF\_000002305.2 | Wade *et al.* (2009) |
| *Gorilla gorilla* | gorGor3.1 | GCF\_000151905.1 | - |
| *Homo sapiens* | GRCh38.p10 | GCF\_000001405.36 | - |
| *Macaca mulatta* | Mmul\_8.0.1 | GCF\_000772875.2 | Zimin *et al.* (2014) |
| *Mus musculus* | GRCm38.p5 | GCF\_000001635.25 | - |
| *Ovis aries* | Oar\_v3.1 | GCF\_000298735.1 | Consortium *et al.* (2010) |
| *Pan paniscus* | panpan1.1 | GCF\_000258655.2 | Prüfer *et al.* (2012) |
| *Pan troglodytes* | CHIMP2.1.4 | GCF\_000001515.6 | Consortium *et al.* (2005) |
| *Pongo abelii* | PPYG2 | GCF\_000001545.4 | Locke *et al.* (2011) |
| *Rattus norvegicus* | Rnor\_6.0 | GCF\_000001895.5 | Consortium and others (2004) |
| *Sus scrofa* | Sscrofa11.1 | GCF\_000003025.6 | - |
| *Tupaia chinensis* | - | - | - |

## 

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