Molecular Evolution of the Meiotic Recombination Pathway in Mammals

Investigations

Amy L. Dapper[1,2*] and Bret A. Payseur[1]

[1] Laboratory of Genetics, University of Wisconsin, Madison, WI 53706, USA

[2] Current Address: Department of Biological Sciences, Mississippi State University, Mississippi State, MS 39762, USA

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* Corresponding Author : Amy L. Dapper

Address: 295 E. Lee Blvd., P.O. Box GY, Mississippi State, MS 39762

Phone: (662) 325-7575

Email: dapper@biology.msstate.edu

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 transcript 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 genes 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 takes into account 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.

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.

Identifying Signatures

Model comparison

Multinucleotide 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.

Results

Heterogeneous rates of evolution of recombination genes across the mammalian phylogeny

Do we observe elevated rates of evolution in certain steps in the recombination pathway? No - No significant difference in mean omega values among genes that function ($p = 0.09767$, Kruskal-Wallis rank sum test).

Do we observe more genes with signatures of positive selection in certain steps in the recombination pathway? Values too small to compare all 5 groups. Compared earlier steps (N = 15) to later steps (N=17). Signifcantly more genes with signatures of positve selection in the second half of the recombination pathway ($p = 0.0457$, Pearson's Chi-squared test)

Evidence of positive selection - PAML

Of the 9 genes with significant signatures of positive selection (7vs8), only one (TEX11) retained the significant signature of selection after removing all CMDs. Two additional genes (REC8, RAD21L), also showed that model 8 was a significantly better fit than model 7. However, this is because models that allow a class of sites with a dN/dS of 1 are preferred over models that require all sites to have dN/dS values < 1. There is limited to no support for a class of sites with dN/dS > 1.

Polymorphism & Divergence Data

Discussion

The rate of meiotic recombination shapes major features of the genomic landscape and influences the efficacy of selection (**???**).

Recombination rate varies between species (**???**), between populations (**???**), within populations (**???**), and between the sexes (**???**).

Ample evidence indicates that phenotypic variation in recombination rate has a genetic component.

Recombination rate shows resemblance among relatives in human pedigrees [77,106,107], differs among lines raised in a common environment [74,83,85,96,108,109], and responds to artificial selection in Drosophila melanogaster and other insects.

Broad-sense or narrow-sense heritability estimates from humans, mice, insects, and maize range from 0.08 to 0.69 [73,106,107,110–115].

A host of experiments using insects attempted to increase and/or decrease the recombination rate [71,73,110,111,115,145–157], demonstrating the potential for recombination rate to respond to directional selection in nature.

Phylogenetic comparative methods suggest that the genome-wide recombination rate has increased during mammalian evolution [97].

PRDM9, a protein that helps determine the position of crossovers in mice and humans, possesses one of the most rapidly evolving (zinc-finger) domains in mammals [163,164].

Fecundity and recombination rate may be positively correlated in human mothers [77,165,166].

Finally, cellular needs to avoid nondisjunction (by generating at least one crossover per chromosome or chromosome arm) and to minimize costs of double-strand break repair should impose selective bounds on the genome-wide crossover rate in nature [1–4].

There is limited empirical evidence for a role of selection in the evolution of recombination rate.

1. Recombination rate evolves.
2. There is a genetic basis.
3. The same few genes pop up over and over again, suggesting there may be a relatively simple genetic basis to variation in recombination rate.
4. There has recently been an accelleration in our understanding of the genes involved in the recombination pathway.
5. Divergence in a subset of these genes is very likely to underlie trait differences.
6. This should be true whether or not those trait differences are generated by selection or drift.

7. Motivates a phylogenetic comparative study of genes in the recombination pathway among mammals.
8. Analyzing these genes from a pathway perspective may provide insight into which genes, or steps of the pathway, are most likely to be contributing to variation in recombination rate in mammals.
9. Also provides the opportunity to look for molecular signatures of adaptive evolution.

Meiotic recombination begins with the generation of 100's of double strand breaks (DSB) across the genome. **SPO11** directly produces the DSBs, but is recruited and activated by a handful of other proteins. The location of DSB are non-randomly distributed across the genome. **PRDM9** lays down methylation patterns via sequence-specific DNA binding.

Results

Discussion

Recombination rate shows resemblance among relatives in human pedigrees [citations], differs among lines raised in a common environment [citations], and responds to artificial selection [citations]. Artifical selection experiments to increase and/or decrease the recombination rate [citations], demonstrate the potential for recombination rate to respond to directional selection in nature. Beyond the lab, comparisons between species and between populations have uncovered pervasive, and in some cases, rapid evolution of recombination rate [citations]. There is limited direct, empirical evidence for a role of selection in the evolution of recombination rate. Indirect evidence includes the observation via phylogenetic comparative methods that the genome-wide recombination rate appears to have increased during mammalian evolution [citation] and the observation that fecundity and recombination rate may be positively correlated in human mothers [citations]. However, due to the importance of recombination rate in shaping the genome and response to evolution, the value of understanding its evolution is not strictly tied to the role of selection in shaping the trait.

While Prdm9 clearly plays a major role in the positioning of recombination events within the genome, it is less clear that Prdm9 significantly impacts the total number of recombination events in the genome [citations]. Prdm9 plays an very early role in the patterning of recombination events.

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	No

Gene	Function	Meiosis-Specific?
—	& processing (*MRN Complex*)	
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		

Results

Table 2: PAML analysis of 32 recombination genes in mammals (Yang 2007).

Gene	***bp***	***N***	ω	***M***	***M1-M2***	***p-value***	***M7-M8***	***p-value***	***M8a-M8***	***p-value***
A)										
HORMAD1	1212	16	0.3036	7	0	*1.000*	1.795	*0.4076*	—	—
HORMAD2	981	15	0.3153	7	0	*1.000*	3.650	*0.1612*	—	—
MEI4	1170	16	0.4332	7	0	*1.000*	0.005	*0.9976*	—	—
REC114	870	15	0.4003	7	0	*1.000*	5.384	*0.0677*	—	—
IHO1	1824	16	0.7095	**8**	13.061	***0.0015***	17.571	***0.0002***	14.527	***0.0001***
SPO11	1188	15	0.1654	7	0	*1.000*	4.648	*0.0980*	—	—
B)										
MRE11	2136	16	0.1688	**8**	0.363	*0.8342*	11.931	***0.0026***	4.706	***0.0301***
NBS1	2289	15	0.4183	**8**	0	*1.000*	12.763	***0.0017***	4.087	***0.0432***
RAD50	3936	16	0.1006	7	0	*1.000*	0.301	*0.8605*	—	—-
BRCC3	954	15	0.0602	7	0	*1.000*	0.250	*0.8826*	—	—
DMC1	1020	15	0.0351	1	0.488	*0.7835*	5.000	*0.0821*	—	—
RAD51	1017	16	0.0268	7	0	*1.000*	0	*1.000*	—	—
SPATA22	1101	16	0.4893	7	0	*1.000*	0.429	*0.8070*	—	—
MEIOB	1425	16	0.2341	7	0	*1.000*	0.665	*0.7172*	—	—
MCMDC2	2052	16	0.2239	7	0	*1.000*	0.628	*0.7307*	—	—
C)										
REC8	1833	16	0.3698	**8**	0	*1.000*	14.690	***0.0006***	5.927	***0.0149***
RAD21L	1686	15	0.503	**8**	12.124	***0.0023***	32.050	***>0.0001***	12.049	***0.0005***
SYCP1	3015	16	0.4337	**8**	8.711	***0.0128***	26.860	***>0.0001***	9.243	***0.0024***
SYCP2	4650	16	0.5572	**8**	11.584	***0.0031***	37.200	***>0.0001***	15.838	***0.0001***
TEX12	369	14	0.2297	7	0.0565	*0.9721*	1.549	*0.4610*	—	—
D1)										
TEX11	2844	15	0.8483	**8**	60.872	***>0.0001***	82.665	***>0.0001***	61.141	***>0.0001***
SHOC1	4644	16	0.6113	**8**	12.447	***0.0020***	30.561	***>0.0001***	15.645	***0.0001***
CNTD1	1026	15	0.2496	7	0	*1.000*	0.936	*0.6263*	—	—
RNF212	948	16	0.5014	**8**	0	*1.000*	16.366	***0.0003***	5.202	***0.0226***
RNF212B	906	14	0.4066	7	0	*1.000*	0.500	*0.7788*	—	—
MSH4	2814	16	0.2132	**8**	16.608	***0.0002***	39.447	***>0.0001***	23.238	***>0.0001***

Gene	***bp***	***N***	ω	***M***	***M1-M2***	***p-value***	***M7-M8***	***p-value***	***M8a-M8***	***p-value***
MSH5	2565	15	0.1642	7	0	*1.000*	4.214	*0.1216*	—	—
D2)										
MER3	4458	16	0.3633	8a	0	*1.000*	12.838	***0.0016***	3.109	*0.0779*
HEI10	831	15	0.1226	7	0	*1.000*	0.250	*0.8826*	—	—
MLH1	2313	15	0.1652	8a	0	*1.000*	12.221	***0.0022***	0.280	*0.5970*
MLH3	4419	16	0.4444	7	0	*1.000*	3.757	*0.1528*	—	—
MUS81	1665	16	0.2124	7	0	*1.000*	0.628	*0.7304*	—	—

Table 3: PAML - MNM Analysis

Gene	***bp***	***N***	ω	***M***	***M1-M2***	***p-value***	***M7-M8***	***p-value***	***M8a-M8***	***p-value***
IHO1	1824	16	0.6104	7	0	*1.000*	0.258	*0.8789*	—	—
MRE11	2136	16	0.1330	7	0.226	*0.8930*	3.056	*0.2169*	—	—
NBS1	2289	15	0.3413	7	0	*1.000*	1.956	*0.3761*	—	—
REC8	1833	16	0.2905	7	0	*1.000*	5.321	*0.0699*	—	—
RAD21L	1686	15	0.4271	8a	2.329	*0.3121*	9.497	***0.0087***	1.620	*0.2031*
SYCP1	3015	16	0.3731	8a	3.328	*0.1893*	13.440	***0.0012***	2.122	*0.1452*
SYCP2	4650	16	0.4752	7	0	*1.000*	1.758	*0.4151*	—	—
TEX11	2844	15	0.7287	**8**	9.989	***0.0068***	18.776	***0.0001***	10.656	***0.0011***
SHOC1	4644	16	0.5519	8a	0	*1.000*	7.439	***0.0242***	0.292	*0.5887*
RNF212	948	16	0.3685	7	0	*1.000*	0	*1.000*	—	—
MSH4	2814	16	0.1509	7	0	*1.000*	2.079	*0.3536*	—	—

Table 4: Polymorphism & Divergence Data

Gene	***bp***	***Pn***	***Ps***	***Pn/Ps***	***Dn***	***Ds***	***Dn/Ds***	***MK Test***	α	***NI***	
A)											
HORMAD1	XXX	84	35	2.4000	5	12	0.4167	***0.0018***	-4.7600	5.7600	Neg.
HORMAD2	XXX	80	31	2.5806	7	9	0.7778	***0.0404***	-2.3180	3.3180	Neg.
MEI4	XXX	15	7	2.1429	24	9	2.6667	*0.7679*	0.1964	0.8036	—
REC114	XXX	76	37	2.0541	11	14	0.7857	***0.0392***	-1.6143	2.6143	Neg.
IHO1	XXX	130	64	2.0313	36	19	1.8947	*0.8718*	-0.0720	1.0720	—
SPO11	XXX	118	52	2.2692	11	22	0.5000	***0.0001***	-3.5385	4.5385	Neg.
B)											
MRE11	XXX	211	86	2.4535	5	35	0.1429	***>0.0001***	-16.1744	17.1744	Neg.
NBS1	XXX	221	93	2.3763	34	25	1.3600	*0.0666*	-0.7473	1.7473	—
RAD50	XXX	303	118	2.5678	8	43	0.1860	***>0.0001***	-12.8019	13.8019	Neg.
BRCC3	XXX	13	21	0.6190	2	6	0.3333	0.6888	-0.8571	1.8571	—
DMC1	XXX	72	42	1.7143	0	11	0.0000	***>0.0001***	—	—	Neg.
RAD51	XXX	50	48	1.0417	0	13	0.0000	***>0.0001***	—	—	Neg.
SPATA22	XXX	114	45	2.5333	21	10	2.1000	*0.6700*	-0.2063	1.2063	—
MEIOB	XXX	91	40	2.2750	20	22	0.9091	***0.0200***	-1.5025	2.5025	Neg.
MCMDC2	XXX	165	54	3.0556	16	26	0.6154	***>0.0001***	-3.9653	4.9653	Neg.
C)											
REC8	XXX	147	76	1.9342	38	31	1.2258	*0.1164*	-0.5779	1.5779	—
RAD21L	XXX	51	17	3.000	27	13	2.0769	*0.5051*	-0.4444	1.4444	—
SYCP1	XXX	213	100	2.1300	33	37	1.2222	*0.0546*	-0.7427	1.7427	—
SYCP2	XXX	429	154	2.8506	74	53	1.3962	***0.0005***	-1.0417	2.0417	Neg.
TEX12	XXX	31	16	1.9375	2	4	0.5000	0.1836	-2.875	3.875	—
D1)											
TEX11	XXX	126	81	1.5556	55	25	2.200	*0.2234*	0.2929	0.7071	—
SHOC1	XXX	368	124	2.9677	85	37	2.2973	*0.2521*	-0.2918	1.2918	—
CNTD1	XXX	81	47	1.7234	13	8	1.6250	*1.0000*	-0.0606	1.0606	—
RNF212	XXX	—	—	—	17	18	0.9444	—	—	—	—
RNF212B	XXX	368	124	2.9677	8	12	0.6667	***0.0013***	-3.4516	4.4516	Neg.
MSH4	XXX	260	94	2.7660	24	29	0.8276	***>0.0001***	-2.3422	3.3422	Neg.

Gene	***bp***	***Pn***	***Ps***	***Pn/Ps***	***Dn***	***Ds***	***Dn/Ds***	***MK Test***	α	***NI***	
MSH5	XXX	197	104	1.8942	19	33	0.5758	***0.0002***	-2.2900	3.2900	Neg.
D2)											
MER3	XXX	402	143	2.8112	54	44	1.2273	***0.0004***	-1.2906	2.2906	Neg.
HEI10	XXX	73	33	2.2121	4	5	0.8000	*0.1541*	-1.7652	2.7652	—
MLH1	XXX	255	90	2.8333	9	29	0.3103	***>0.0001***	-8.1296	9.1296	Neg.
MLH3	XXX	437	167	2.6168	77	57	1.3509	***0.0012***	-0.9370869	1.937087	Neg.
MUS81	XXX	208	81	2.5679	17	40	0.4250	***>0.0001***	-5.0421	6.0421	Neg.

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Table R1: 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 R2: 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)

Species	**Assembly**	**RefSeq Accession**	**WGS Project Reference**
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 R3: Ensembl Annotations

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	-	-	-

Table S1: Sequence divergence between Human (*Homo sapiens*) and Rhesus Macaque (*Macaca mulatta*) (Yang and Nielsen 2000,Yang (2007)). Steps: A - double strand break (DSB) formation, B - DSB processing & Strand Invasion, C - Homologous Pairing, D1 - crossover (CO) vs. non-crossover (NCO) step1 - MutS, D2 - CO vs. NCO step 2 - MutL.

Gene	***bp***	ω	***S***	***N***	***t***	κ	***dN***	***dS***
A)								
HORMAD1	XXX	**0.0901**	273.9	908.1	0.0443	3.8819	0.0044 +- 0.0022	0.0490 +- 0.0137
HORMAD2	XXX	**0.295**	256.7	664.3	0.0531	4.2164	0.0106 +- 0.0040	0.0360 +- 0.0121
MEI4	XXX	**0.7252**	331	824	0.0822	4.6295	0.0247 +/- 0.0056	0.0341 +/- 0.0104
REC114	XXX	**0.3239**	237.2	557.8	0.0974	2.9455	0.0200 +/- 0.0061	0.0618 +/- 0.0168
IHO1	XXX	**0.6608**	509	1273	0.0951	3.6035	0.0276 +- 0.0047	0.0418 +- 0.0094
SPO11	XXX	**0.1434**	291.2	896.8	0.0872	2.5317	0.0118 +/- 0.0036	0.0823 +/- 0.0178
B)								
MRE11	XXX	**0.0392**	479.4	1644.6	0.0597	2.6154	0.0030 +- 0.0014	0.0778 +- 0.0135
NBS1	XXX	**0.4155**	553.7	1705.3	0.0804	5.0955	0.0199 +- 0.0035	0.0480 +- 0.0097
RAD50	XXX	**0.0714**	1118.7	2817.3	0.0401	5.0903	0.0028 +- 0.0010	0.0399 +- 0.0062
BRCC3	XXX	**0.0979**	264	609	0.028	4.6	0.0025 +- 0.0020	0.0252 +- 0.0100
DMC1	XXX	**0.0000**	273.7	746.3	0.0335	5.1279	0.0000 +- 0.0000	0.0416 +- 0.0127
RAD51	XXX	**0.0000**	306.5	710.5	0.0398	6.7467	0.0000 +- 0.0000	0.0441 +- 0.0124
SPATA22	XXX	**0.4523**	247.8	841.2	0.0879	3.6505	0.0230 +- 0.0053	0.0508 +- 0.0150
MEIOB	XXX	**0.2462**	348.9	1064.1	0.0927	4.3887	0.0176 +- 0.0041	0.0715 +- 0.0151
MCMDC2	XXX	**0.2108**	534	1509	0.0635	7.8547	0.0107 +- 0.0027	0.0507 +- 0.0101
C)								
REC8	XXX	**0.477**	497	1138	0.1293	2.8869	0.0323 +- 0.0054	0.0678 +- 0.0122
RAD21L	XXX	**0.6334**	427.5	1237.5	0.0735	5.6876	0.0213 +- 0.0042	0.0337 +- 0.0091
SYCP1	XXX	**0.3676**	761.6	2166.4	0.0628	4.8307	0.0145 +- 0.0026	0.0393 +- 0.0074
SYCP2	XXX	**0.3873**	1070.7	3519.3	0.0854	5.994	0.0208 +- 0.0025	0.0537 +- 0.0074
TEX12	XXX	**0.1349**	80.2	288.8	0.05	1.9678	0.0070 +- 0.0049	0.0516 +- 0.0260
D1)								
TEX11	XXX	**0.9068**	805.9	1933.1	0.0897	7.8022	0.0290 +- 0.0040	0.0320 +- 0.0064
SHOC1	XXX	**0.7225**	1203	3129	0.0865	9.5737	0.0261 +- 0.0029	0.0361 +- 0.0057
CNTD1	XXX	**0.6803**	335.3	651.7	0.065	8.0721	0.0187 +- 0.0054	0.0274 +- 0.0092
RNF212	XXX	**0.387**	243.2	572.8	0.1342	4.996	0.0304 +- 0.0074	0.0785 +- 0.0189
RNF212B	XXX	**0.2566**	255.6	644.4	0.0685	3.4122	0.0125 +- 0.0044	0.0488 +- 0.0143
MSH4	XXX	**0.2635**	731.3	2073.7	0.058	7.5194	0.0112 +- 0.0023	0.0425 +- 0.0079
MSH5	XXX	**0.2106**	728.7	1770.3	0.0643	3.9993	0.0102 +- 0.0024	0.0486 +- 0.0085

Gene	***bp***	ω	***S***	***N***	***t***	κ	***dN***	***dS***
D2)								
MER3	XXX	**0.3247**	987.6	3317.4	0.0703	7.0099	0.0159 +- 0.0022	0.0488 +- 0.0074
HEI10	XXX	**0.3235**	241.5	589.5	0.0329	5.9591	0.0068 +- 0.0034	0.0211 +- 0.0095
MLH1	XXX	**0.0924**	602.3	1665.7	0.0522	2.4752	0.0048 +- 0.0017	0.0521 +- 0.0097
MLH3	XXX	**0.4919**	1209.8	3149.2	0.0949	6.4296	0.0246 +- 0.0028	0.0500 +- 0.0067
MUS81	XXX	**0.1299**	465.8	1187.2	0.1106	5.7915	0.0128 +- 0.0033	0.0983 +- 0.0158

Table S2: PAML - Gene Trees

Gene	***bp***	***N***	ω	***M***	***M1-M2***	***p-value***	***M7-M8***	***p-value***	***M8a-M8***	***p-value***
A)										
HORMAD1	1212	16	0.3037	7	0	*1.000*	3.135	*0.2086*	—	—
HORMAD2	981	15	0.3290	1	0	*1.000*	3.881	*0.1436*	—	—
MEI4	1170	16	0.4310	7	0	*1.000*	0.058	*0.9715*	—	—
REC114	870	15	0.4237	7	0	*1.000*	4.1874	*XXXX*	—	—
IHO1	1824	16	0.7099	**8**	13.384	***0.0012***	17.714	***0.0001***	14.707	***0.0001***
SPO11	1188	15	0.1701	7	0	*1.000*	4.697	*0.0955*	—	—
B)										
MRE11	2136	16	0.1686	**8**	0.636	*0.7277*	12.014	***XXXX***	4.822	***XXXX***
NBS1	2289	15	0.4185	**8**	0	*1.000*	12.899	***XXXX***	4.298	***XXXX***
RAD50	3936	16	XXXX	XXXX	XXXX	*XXXX*	XXXX	*XXXX*	—	—-
BRCC3	954	15	0.0601	7	0	*1.000*	0.573	*XXXX*	—	—
DMC1	1020	15	0.0365	7	0	*1.000*	4.288	*0.1172*	—	—
RAD51	1017	16	0.0322	1	0	*1.000*	0.562	*XXXX*	—	—
SPATA22	1101	16	0.4932	7	0	*1.000*	0.200	*XXXX*	—	—
MEIOB	1425	16	0.2340	7	0	*1.000*	0.221	*XXXX*	—	—
MCMDC2	2052	16	0.2242	7	0	*1.000*	0.610	*0.7370*	—	—
C)										
REC8	1833	16	0.3698	**8**	0	*1.000*	14.690	***0.0006***	5.927	***0.0149***
RAD21L	1686	15	0.503	**8**	12.124	***0.0023***	32.050	***>0.0001***	12.049	***0.0005***
SYCP1	3015	16	0.4337	**8**	8.711	***0.0128***	26.860	***>0.0001***	9.243	***0.0024***
SYCP2	4650	16	0.5572	**8**	11.584	***0.0031***	37.200	***>0.0001***	15.838	***0.0001***
TEX12	369	14	0.2297	7	0.0565	*0.9721*	1.549	*0.4610*	—	— **D1)**
TEX11	2844	15	0.8483	**8**	60.872	***>0.0001***	82.665	***>0.0001***	61.141	***>0.0001***
SHOC1	4644	16	0.6113	**8**	12.447	***0.0020***	30.561	***>0.0001***	15.645	***0.0001***
CNTD1	1026	15	0.2496	7	0	*1.000*	0.936	*0.6263*	—	—
RNF212	948	16	0.5014	**8**	0	*1.000*	16.366	***0.0003***	5.202	***0.0226***
RNF212B	906	14	0.4066	7	0	*1.000*	0.500	*0.7788*	—	—
MSH4	2814	16	0.2132	**8**	16.608	***0.0002***	39.447	***>0.0001***	23.238	***>0.0001***
MSH5	2565	15	0.1642	7	0	*1.000*	4.214	*0.1216*	—	— **D2)**

MER3 | 4458 | 16 | 0.3633 | 8a | 0 | *1.000* | 12.838 | ***0.0016*** | 3.109 | *0.0779* |
HEI10 | 831 | 15 | 0.1226 | 7 | 0 | *1.000* | 0.250 | *0.8826* | — | — *MLH1* | 2313 | 15 | 0.1652 | 8a | 0 | *1.000* |
12.221 | ***0.0022*** | 0.280 | *0.5970* | *MLH3* | 4419 | 16 | 0.4444 | 7 | 0 | *1.000* | 3.757 | *0.1528* | — | — *MUS81*
| 1665 | 16 | 0.2124 | 7 | 0 | *1.000* | 0.628 | *0.7304* | — | —

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