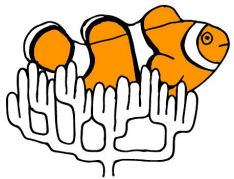
PRDM9, what is it that you do?

Reviews in Quantitative Biology
02/11/2023

Diego A. Hartasánchez



Département de Biologie Computationnelle

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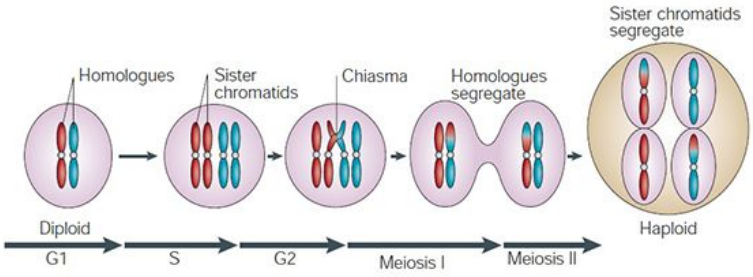
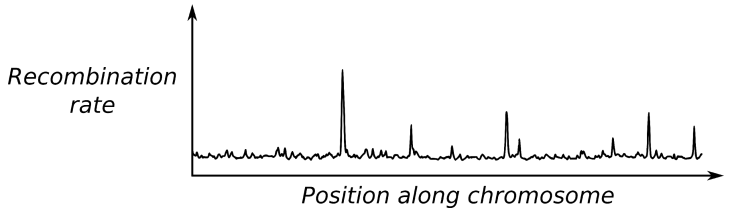
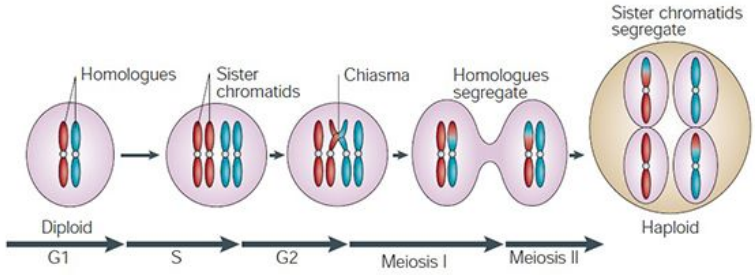
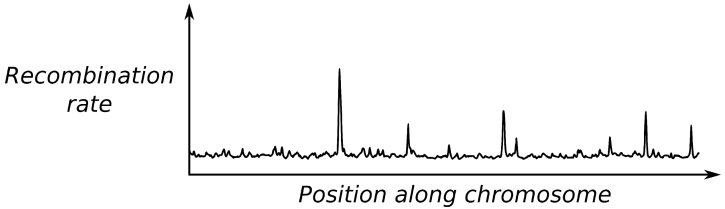
Meiotic recombination





Meiotic recombination in hotspots

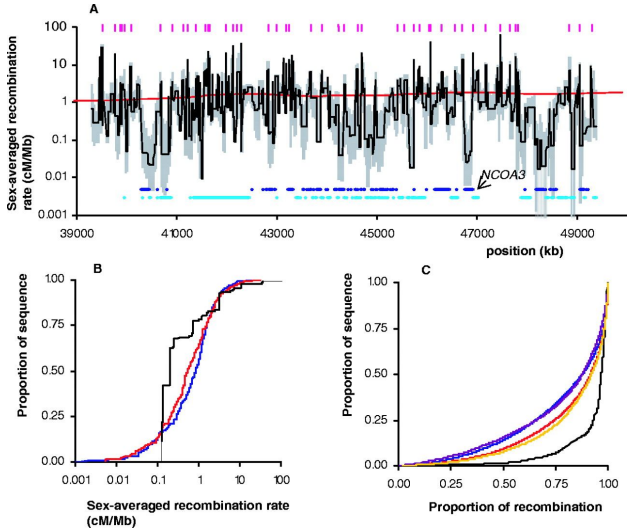




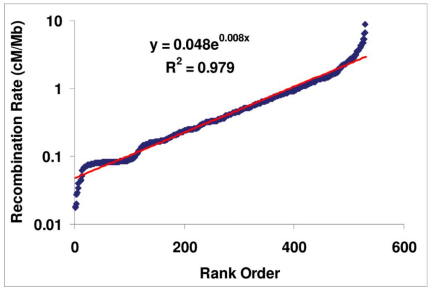
nicolas1994polarity

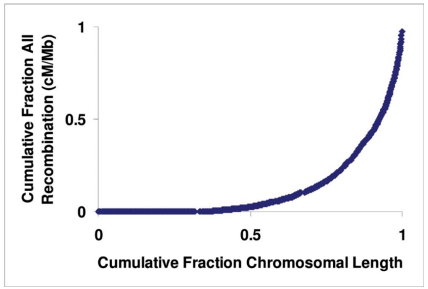
smith1994hotspots

mcvean2004fine



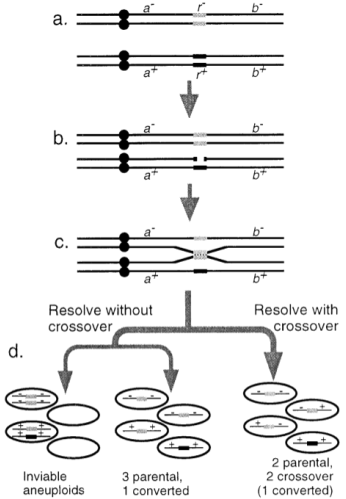
paigen2008recombinational

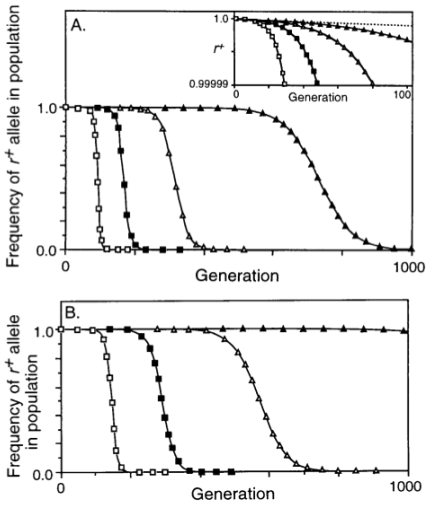


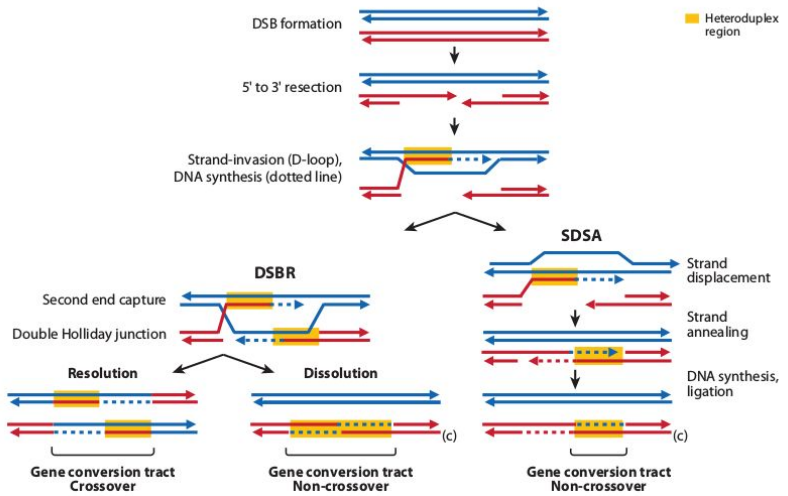


Recombination hotspot paradox

boulton1997hotspot pineda2005persistence coop2007live duret2009biased szostak1983double





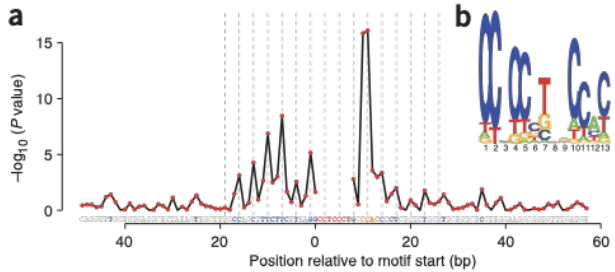


Why do hotspots exist if hotspot binding motifs tend to disappear due to the recombination process they induce themselves?

Motif enrichment & identification of locus determining hotspot activity

myers2005fine

myers2008common



grey2009genome

“We have identified the genetic locus required for Psmb9 activity, named **Dsbc1** for Double-strand break control 1, and mapped this locus within a 6.7-Mb region on Chr 17. Based on cytological analysis of meiotic DNA double-strand breaks (DSB) and crossovers (COs), we show that Dsbc1 influences DSB and CO, not only at Psmb9, but in several other regions of Chr 17.”

parvanov2009trans

“Testing the activity of three activated hotspots in sperm samples from individual male progeny of two genetic crosses, we identified a single trans-acting regulator of hotspot activity, designated **Rcr1**, that is located in a 5.30-Mb interval (11.74–17.04 Mb) on Chr 17. Using an Escherichia coli cloning assay to characterize the molecular products of recombination at two of these hotspots, we found that Rcr1 controls the appearance of both crossover and noncrossover gene conversion events, indicating that it likely controls the sites of the double-strand DNA breaks that initiate the recombination process.”

Hybrid sterility: *Hst-1*, *Meisetz* & *Prdm9*

Genetic studies on male sterility of hybrids between laboratory and wild mice (*Mus musculus* L.)

By J. FOREJT and P. IVÁNYI

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(*Received* 24 *June* 1974)

SUMMARY

The genetic control of the sterility of male hybrids between certain laboratory and wild mice (*Mus musculus* L.) is investigated. The observed sterility is, by definition, hybrid sterility since both parental forms (i.e. wild and laboratory mice) are fully fertile, their male offspring displaying small testes with arrest of spermatogenesis at the stage of spermatogenesis or primary spermatocytes. Results of genetic analysis as well as the failure to detect any chromosomal rearrangements point to a genic rather than a chromosomal type of hybrid sterility.

Fifty-three wild males were classified into three sets, after mating with C57BL/10 inbred females, according to the fertility of their male progeny (set I – only sterile sons; set II – only fertile sons; set III – both fertile and sterile sons). The wild males of set I, which yield only sterile male offspring with C57BL/10 females, sire sterile sons also with females of the following inbred strains: A/Ph, BALB/c, DBA/1, and AKR/J, whereas the same wild males produce fertile offspring with females of C3H/Di, CBA/J, P/J, I/St and F/St inbred strains.

The described hybrid sterility seems to be under the control of several independently segregating genes, one of them (proposed symbol *Hst-1*) being localized on chromosome 17 (linkage group IX), 6 cM distally from dominant *T* (*Brachyury*). A chance to search for the mechanism of hybrid sterility is provided by the finding of two laboratory inbred strains, C57BL/10 and C3H/Di, differing with respect to the *Hybrid sterility* genetic system only at the *Hst-1* gene.

Hst-1 is closely linked but apparently not identical with the sterility factor of recessive *t* alleles of the *T* locus.

1. INTRODUCTION

Hybrid sterility is one of the reproductive isolating mechanisms safeguarding the integrity of species. Infertility of interspecific hybrids belongs to the oldest biological problems to which human attention has been paid. The sterility of the mule had been already discussed by Aristoteles, and infertility of various plant and animal hybrids had been recognized long before Mendel established the first principles of genetics (Mayr, 1963; Dobzhansky, 1951, 1972).

Present knowledge of the genetic control of hybrid sterility comes mainly from studies on Drosophila species (Dobzhansky, 1951; Mayr, 1963). It is generally

forejt1974genetic

A histone H3 methyltransferase controls epigenetic events required for meiotic prophase

Katsuhiko Hayashi[1,2]†, Kayo Yoshida[3] & Yasuhisa Matsui[1,2,4]

Epigenetic modifications of histones regulate gene expression and chromatin structure[1,2]. Here we show that Meisetz (meiosis-induced factor containing a PR/SET domain and zinc-finger motif) is a histone methyltransferase that is important for the progression of early meiotic prophase. *Meisetz* transcripts are detected only in germ cells entering meiotic prophase in female fetal gonads and in postnatal testis. Notably, Meisetz has catalytic activity for trimethylation, but not mono- or dimethylation, of lysine 4 of histone H3, and a transactivation activity that depends on its methylation activity. Mice in which the *Meisetz* gene is disrupted show sterility in both sexes due to severe impairment of the double-stranded break repair pathway, deficient pairing of homologous chromosomes and impaired sex body formation. In *Meisetz*-deficient testis, trimethylation of lysine 4 of histone H3 is attenuated and meiotic gene transcription is altered. These findings indicate that meiosis-specific epigenetic events in mammals are crucial for proper meiotic progression.

In sexual reproduction, meiosis reduces the ploidy of the genome and generates genomic diversity by shuffling information between homologous chromosomes. To accomplish meiosis, the transcription of several meiotic genes must be properly orchestrated over time as meiosis progresses. Transcriptional control of gene expression depends crucially on DNA accessibility, which is epigenetically regulated by histone modification[1,2]. The methylation of lysine 4 of histone H3 (H3K4 methylation) is a well-characterized feature of transcriptionally active genes[3–6], indicating that the action of histone methyltransferase (HMTase) on H3K4 marks genes for transcriptional activation according to specific tissue and temporal patterns. Although HMTases that catalyse H3K4 methylation have been identified in mammals[7–12], it remains unclear how the epigenetic modification is regulated during meiosis.

To elucidate transcriptional factors controlling the initiation and progression of meiosis, we identified genes whose expression was increased during entry into meiosis by subtracting complementary DNAs of mitotic primordial germ cells at embryonic day 11.5 (E11.5) from those of meiotic female primordial germ cells at E13.5. Of the genes identified (Supplementary Fig. S1), one encoded a putative transcription factor that we named Meisetz. The deduced amino acid sequence of Meisetz has a PR/SET domain (the catalytic domain of HMTases) in its amino-terminal portion and a C2H2-type zinc-finger

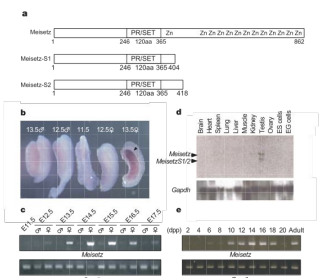

Figure 1 | Molecular structure and expression of the *Meisetz* gene. a, Domains in the deduced sequences of Meisetz protein and its short isoforms. Numbers indicate the amino acid sequence positions of each domain. **b**, *In situ* hybridization analysis of *Meisetz* expression in fetal gonads. *Meisetz* transcripts were detected in only E13.5 female gonad (arrowhead). **c**, RT–PCR analysis of *Meisetz* expression in fetal gonads. cDNAs obtained from fetal gonads at the indicated developmental stages were amplified with primers for *Meisetz* and *Gapdh*. **d**, Northern blot analysis of *Meisetz* expression in adult tissues. *Gapdh* is shown as a control. **e**, RT–PCR analysis of *Meisetz* expression in the first round of spermatogenesis. cDNAs obtained from testis at the indicated days after birth were amplified with primers for *Meisetz* and *Gapdh*.

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hayashi2005histone

A Mouse Speciation Gene Encodes a Meiotic Histone H3 Methyltransferase

Ondrej Mihola,[1]* Zdenek Trachtulec,[1]* Cestmir Vlcek,[1] John C. Schimenti,[2] Jiri Forejt[1]†

Speciation genes restrict gene flow between the incipient species and related taxa. Three decades ago, we mapped a mammalian speciation gene, hybrid sterility 1 (*Hst1*), in the intersubspecific hybrids of house mouse. Here, we identify this gene as *Prdm9*, encoding a histone H3 lysine 4 trimethyltransferase. We rescued infertility in male hybrids with bacterial artificial chromosome carrying *Prdm9* from a strain with the "fertility" *Hst1*^{f} allele. Sterile hybrids display down-regulated microrchidia 2B (*Morc2b*) and fail to compartmentalize γH2AX into the pachynema sex (XY) body. These defects, seen also in *Prdm9*-null mutants, are rescued by the *Prdm9* transgene. Identification of a vertebrate hybrid sterility gene reveals a role for epigenetics in speciation and opens a window to a hybrid sterility gene network.

Hybrid sterility is one of the postzygotic reproduction isolating mechanisms that play an important role in speciation. Hybrid sterility is defined as a situation where parental forms, each fertile inter se, produce infertile offspring (*1*, *2*). Hybrid sterility follows Haldane's rule by affecting predominantly the heterogametic sex (XY or ZW) in crosses where one sex of the progeny is sterile or missing (*3*). Identification of speciation genes has not been particularly successful. Despite decades of effort, only two hybrid sterility genes have been isolated, both from *Drosophila* species (*4*, *5*).

Here, we report identification of a hybrid sterility gene in a vertebrate species. Hybrid sterility 1 (*Hst1*) is one of several genes responsible for spermatogenic failure in *Mus m. musculus*–*Mus m. domesticus* (*Mmm*-*Mmd*) hybrids (*6*, *7*). It was genetically mapped to mouse chromosome 17 (Chr17) in hybrids between the *Mmm*-derived PWD/Ph inbred strain (*8*) and several classical laboratory strains, mostly of *Mmd* origin (*9*). Whereas most laboratory inbred strains, including C57BL/6J (B6), carry the *Hst1*^{s} (sterility) allele, a few strains, such as C3H/DiSnPh (C3H) or P/J, carry the *Hst1*^{f} (fertility) allele (table S1) (*10*). In sterile male hybrids, the *Hst1* interacts, among other genes, with *Hst2*^{mm} locus on Chr17 of *Mmm* subspecies. However, it remains to be determined whether *Hst1* and *Hst2*^{mm} are identical genes.

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*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: forejt@img.cas.cz

A series of high-resolution genetic mapping experiments (*11*–*13*) and haplotype analyses (*14*, *15*) localized *Hst1* to a 255-kb single-copy candidate region on Chr17, harboring six protein-coding genes (*Dll1*, *Pgcc1*, *Pomb1*, *Tbp*, *Pdcd2*, and *Prdm9*) and six pseudogenes (Fig. 1A). To narrow the *Hst1* critical region, we attempted rescue of the hybrid sterility phenotype by transgenesis with bacterial artificial chromosomes (BACs) derived from the C3H/HeJ strain carrying the "fertile" *Hst1*^{f} allele. Four overlapping BAC clones (CHORI-34-45F17; hereafter BAC5, CHORI-34-255E14 -BAC19, CHORI-34-289M8 -BAC21, and CHORI-34-331G23-BAC24) (*16*, *17*) were transfected into embryonic stem (ES) cells of (129 × B6)F$_1$, predominantly of *Mmd* origin. The mice with BAC19 did not transmit the BAC to progeny and were not studied further. The other three BACs were transmitted, and as expected, none of them interfered with fertility after outcrossing to the B6

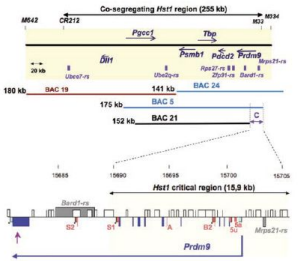
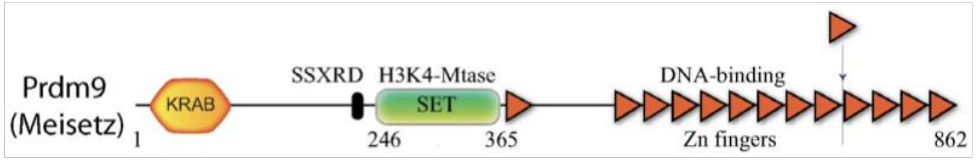


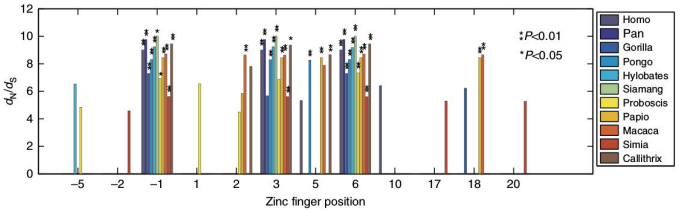
Fig. 1. The *Prdm9* gene encodes *Hst1*. **(A)** The cosegregating *Hst1* region is defined by the markers *CR212* and *M33* (table S2). The arrows point in the direction of gene transcription; the boxes denote pseudogenes. The C3H BAC clones used for transgenesis are shown as horizontal lines with their sizes on the left. The BAC19 chimeras did not transmit the transgene (red line). The blue lines show the BACs rescuing hybrid sterility, whereas BAC21 did not rescue sterility; the C region is necessary for the rescue. **(B)** The *Hst1* critical region. Dark blue boxes: coding exons; light blue box: untranslated region; red boxes: alternative exons (marked 5a, 5u, B2, A, S1, and S2); gray boxes: putative pseudogenes; empty boxes or vertical black lines: repetitive sequences; and asterisks: polyadenylation sites. The vertical arrow points to the site of insertion of a zinc-finger in the last exon of *Prdm9* in the C3H mouse strain. The numbers at the top indicate the positions on Chr17 (in kb, NCBI m37 assembly).

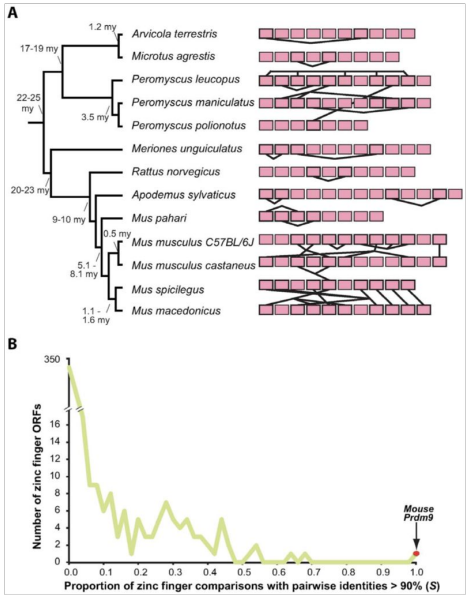
mihola2009mouse

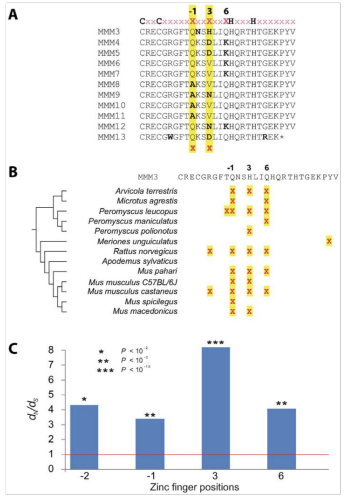
Accelerated evolution of *Prdm9*

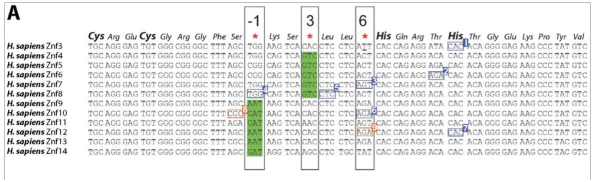


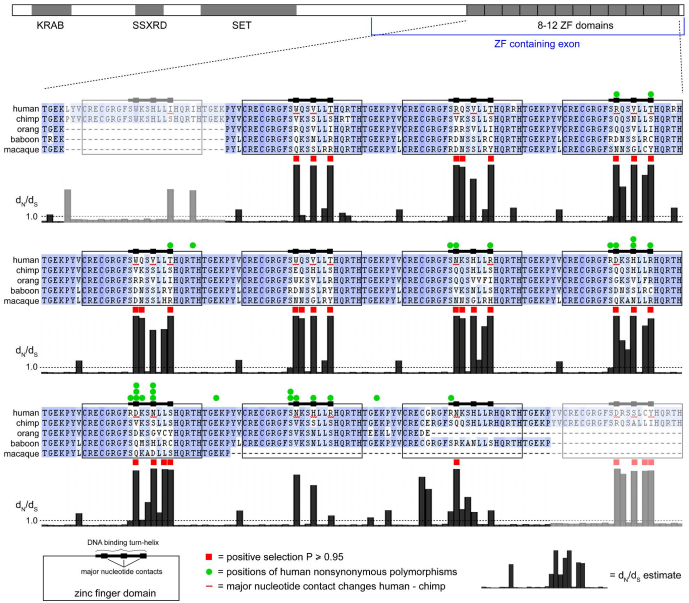
schwartz2014primate











oliver2009accelerated

thomas2009extraordinary

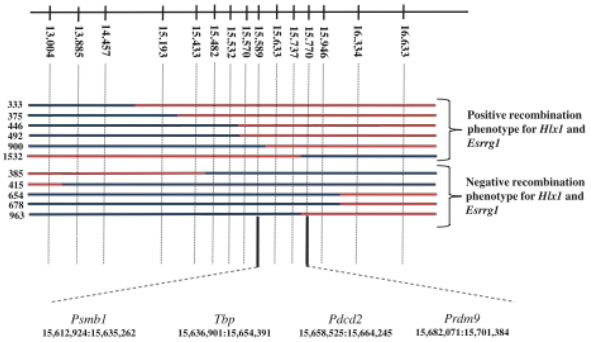
PRDM9 determines recombination hotspots!!

Homing in on Hotspots
The clustering of recombination in the genome, around locations known as hotspots, is associated with specific DNA motifs. Now, using a variety of techniques, three studies implicate a chromatin-modifying protein, the histone-methyltransferase PRDM9, as a major factor involved in human hotspots (see the Perspective by **Cheung *et al.***). **Parvanov *et al.*** (p. 835, published online 31 December) mapped the locus in mice, and analyzed allelic variation in mice and humans, whereas **Myers *et al.*** (p. 876, published online 31 December) used a comparative analysis between human and chimpanzees to show that the recombination process leads to a self-destructive drive in which the very motifs that recruit hotspots are eliminated from our genome. **Baudat *et al.*** (p. 836, published online 31 December) took this analysis a step further to identify human allelic variants within Prdm9 that differed in the frequency at which they used hotspots. Furthermore, differential binding of this protein to different human alleles suggests that this protein interacts with specific DNA sequences. Thus, PDRM9 functions in the determination of recombination loci within the genome and may be a significant factor in the genomic differences between closely related species.

parvanov2010prdm9

Prdm9 Controls Activation of Mammalian Recombination Hotspots

Emil D. Parvanov, Petko M. Petkov,* Kenneth Paigen*

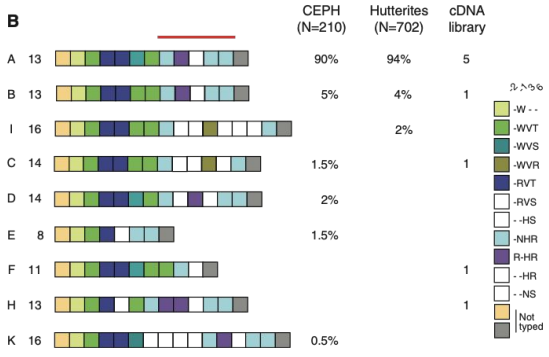


baudat2010prdm9

PRDM9 Is a Major Determinant of Meiotic Recombination Hotspots in Humans and Mice

F. Baudat,[1*] J. Buard,[1*] C. Grey,[1*] A. Fledel-Alon,[2] C. Ober,[2] M. Przeworski,[2,3] G. Coop,[4] B. de Massy[1]†

Meiotic recombination events cluster into narrow segments of the genome, defined as hotspots. Here, we demonstrate that a major player for hotspot specification is the *Prdm9* gene. First, two mouse strains that differ in hotspot usage are polymorphic for the zinc finger DNA binding array of PRDM9. Second, the human consensus PRDM9 allele is predicted to recognize the 13-mer motif enriched at human hotspots; this DNA binding specificity is verified by in vitro studies. Third, allelic variants of PRDM9 zinc fingers are significantly associated with variability in genome-wide hotspot usage among humans. Our results provide a molecular basis for the distribution of meiotic recombination in mammals, in which the binding of PRDM9 to specific DNA sequences targets the initiation of recombination at specific locations in the genome.

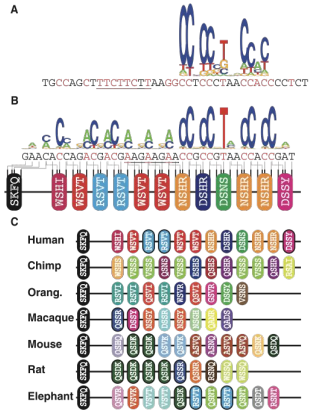


myers2010drive

Drive Against Hotspot Motifs in Primates Implicates the *PRDM9* Gene in Meiotic Recombination

Simon Myers,[1,2*†] Rory Bowden,[1,2*] Afidalina Tumian,[1] Ronald E. Bontrop,[3] Colin Freeman,[2] Tammie S. MacFie,[4‡] Gil McVean,[1,2§] Peter Donnelly[1,2§]

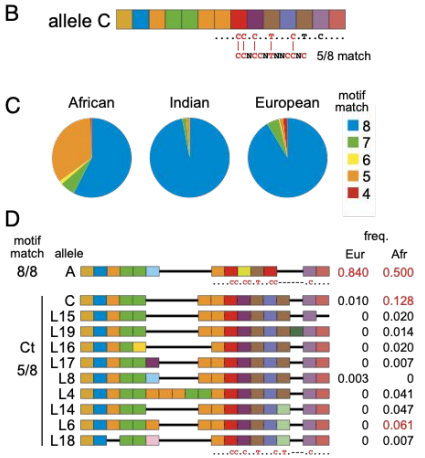
Although present in both humans and chimpanzees, recombination hotspots, at which meiotic crossover events cluster, differ markedly in their genomic location between the species. We report that a 13–base pair sequence motif previously associated with the activity of 40% of human hotspots does not function in chimpanzees and is being removed by self-destructive drive in the human lineage. Multiple lines of evidence suggest that the rapidly evolving zinc-finger protein PRDM9 binds to this motif and that sequence changes in the protein may be responsible for hotspot differences between species. The involvement of PRDM9, which causes histone H3 lysine 4 trimethylation, implies that there is a common mechanism for recombination hotspots in eukaryotes but raises questions about what forces have driven such rapid change.

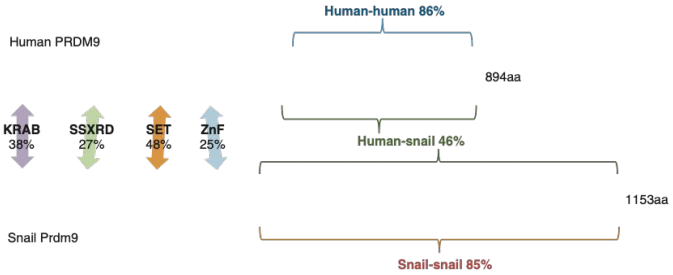


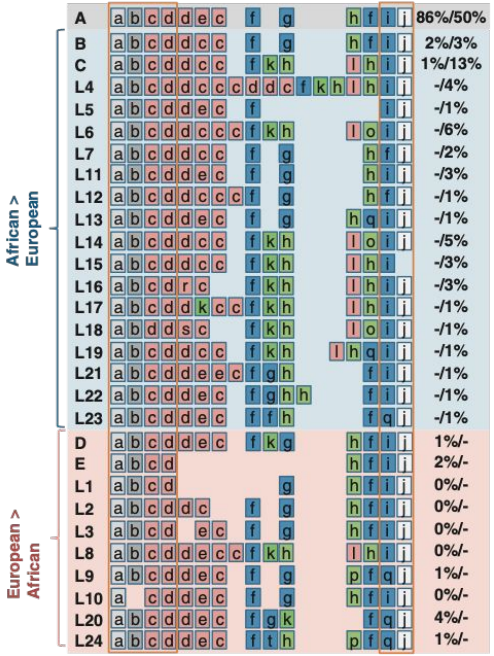
PRDM9 diversity

berg2010prdm9 berg2011variants fledel2011variation ponting2011genomic

mcvean2010prdm9







Many open questions

segurel2011case

Unsolved Mystery

The Case of the Fickle Fingers: How the PRDM9 Zinc Finger Protein Specifies Meiotic Recombination Hotspots in Humans

Towards a Solution

Some of the incongruous observations might be explained if PRDM9 is responsible for the specification of all or almost all hotspots; if PRDM9 variants interact with one another and are dosage sensitive, and if the first half of the zinc fingers also affects binding. What is now required is a diverse set of experiments contributed from many fields, ranging from structural and molecular biology to speciation and evolutionary biology. Further knowledge about the structure of PRDM9, its binding properties and its possible cofactors, as well as its characterization in other species, will then allow us to address questions raised by recent findings, notably: Given the hundreds of thousands of motif instances in the genome to which PRDM9 could bind, how are recombination hotspots specified? How does the zinc finger evolve to find new motifs without deleterious effects on alignment and segregation, and what are the constraints on the state space of possible motifs? Is its rapid change due specifically to its role in recombination or is the change in hotspot activity a pleiotropic consequence of some other function [37]? Is variation in the PRDM9 zinc fingers repeatedly involved in hybrid sterility among species [26]? The story of PRDM9 nicely illustrates the benefits of integrating approaches from many disciplines. Conversely, cracking the curious case of PRDM9 promises to provide important insights into large swaths of biology, from human genetics to speciation.

Absence of PRDM9

grey2011mouse

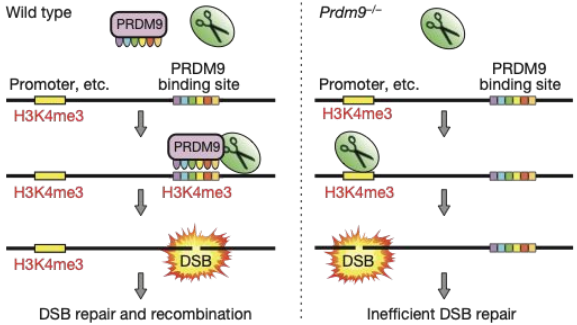
"Taken together, these results provide the direct demonstration that Prdm9 is a master regulator of hotspot localization through the DNA binding specificity of its zinc finger array and that binding of PRDM9 at hotspots promotes local H3K4me3 enrichment."

axelsson2012death

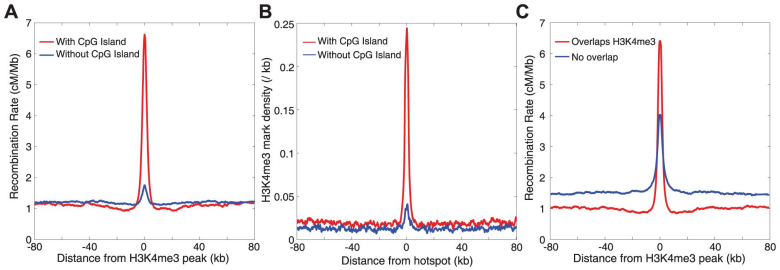
"...The *PRDM9* coding sequence is disrupted in the dog genome assembly. …In contrast to human hotspots, 40% of canine hotspots are characterized by a distinct peak in GC content. A comparative genomic analysis indicates that these peaks are present also as weaker peaks in the panda, suggesting that the hotspots have been continually reinforced by accelerated and strongly GC biased nucleotide substitutions, consistent with the long-term action of biased gene conversion on the dog lineage. These results are consistent with the loss of *PRDM9* in canids, resulting in a greater evolutionary stability of recombination hotspots. "

brick2012genetic

"...In the absence of PRDM9, most recombination is initiated at promoters and at other sites of PRDM9-independent H3K4 trimethylation. Such sites are rarely targeted in wild-type mice, indicating an unexpected role of the PRDM9 protein in sequestering the recombination machinery away from gene-promoter regions and other functional genomic elements."



auton2013genetic

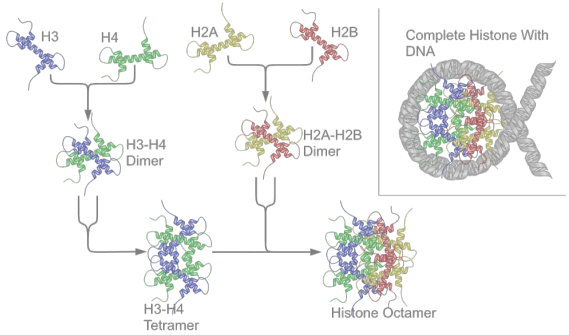


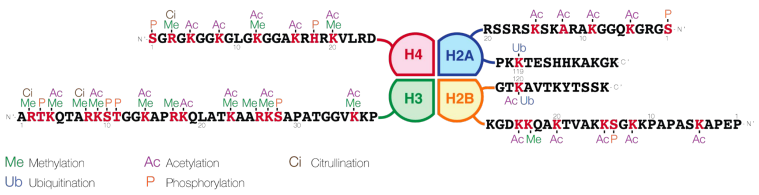
Mechanism behind PRDM9's role in DSB

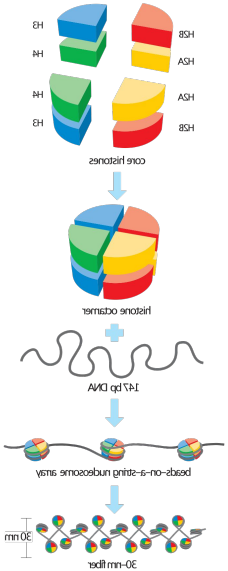
de2013initiation

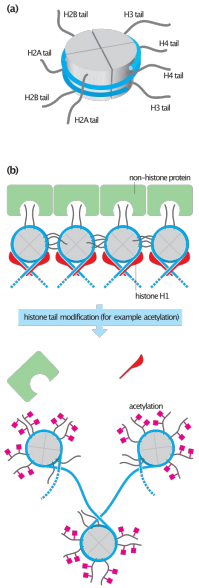
eram2014trimethylation

Trimethylation of histone H3 lysine 36 by human methyltransferase PRDM9 protein









More mechanism!

baker2014prdm9

PRDM9 binding organizes hotspot nucleosomes and limits Holliday junction migration

Christopher L. Baker,[1] Michael Walker,[1] Shimpei Kajita,[1,2] Petko M. Petkov,[1] and Kenneth Paigen[1,3]

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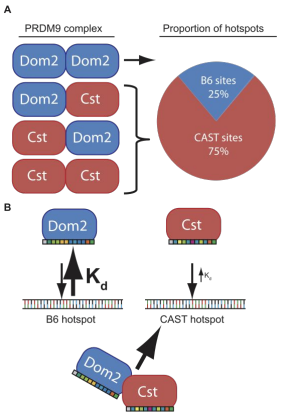
In mammals, genetic recombination during meiosis is limited to a set of 1- to 2-kb regions termed hotspots. Their locations are predominantly determined by the zinc finger protein PRDM9, which binds to DNA in hotspots and subsequently uses its SET domain to locally trimethylate histone H3 at lysine 4 (H3K4me3). This sets the stage for double-strand break (DSB) formation and reciprocal exchange of DNA between chromatids, forming Holliday junctions. Here we report genome-wide analyses of PRDM9-dependent histone modifications using two inbred mouse strains differing only in their PRDM9 zinc finger domain. We show that PRDM9 binding actively reorganizes nucleosomes into a symmetrical pattern, creating an extended nucleosome-depleted region. These regions are centered by a consensus PRDM9 binding motif, whose location and identity was confirmed in vitro. We also show that DSBs are centered over the PRDM9 binding motif within the nucleosome-depleted region. Combining these results with data from genetic crosses, we find that crossing-over is restricted to the region marked by H3K4me3. We suggest that PRDM9-modified nucleosomes create a permissible environment that first directs the location of DSBs and then defines the boundaries of Holliday junction branch migration.



baker2015prdm9

RESEARCH ARTICLE

Multimer Formation Explains Allelic Suppression of PRDM9 Recombination Hotspots

Christopher L. Baker[1], Pavlina Petkova[1], Michael Walker[1], Petr Flachs[2], Ondrej Mihola[2], Zdenek Trachtulec[2], Petko M. Petkov[1], Kenneth Paigen[1]*

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Abstract

Genetic recombination during meiosis functions to increase genetic diversity, promotes elimination of deleterious alleles, and helps assure proper segregation of chromatids. Mammalian recombination events are concentrated at specialized sites, termed hotspots, whose locations are determined by PRDM9, a zinc finger DNA-binding histone methyltransferase. *Prdm9* is highly polymorphic with most alleles activating their own set of hotspots. In populations exhibiting high frequencies of heterozygosity, questions remain about the influences different alleles have in heterozygous individuals where the two variant forms of PRDM9 typically do not activate equivalent populations of hotspots. We now find that, in addition to activating its own hotspots, the presence of one *Prdm9* allele can modify the activity of hotspots activated by the other allele. PRDM9 function is also dosage sensitive; $Prdm9^{+/-}$ heterozygous null mice have reduced numbers and less active hotspots and increased numbers of aberrant germ cells. In mice carrying two *Prdm9* alleles, there is allelic competition; the stronger *Prdm9* allele can partially or entirely suppress chromatin modification and recombination at hotspots of the weaker allele. In cell cultures, PRDM9 protein variants form functional heteromeric complexes which can bind hotspots sequences. When a heteromeric complex binds at a hotspot of one PRDM9 variant, the other PRDM9 variant, which would otherwise not bind, can still methylate hotspot nucleosomes. We propose that in heterozygous individuals the underlying molecular mechanism of allelic suppression results from formation of PRDM9 heteromers, where the DNA binding activity of one protein variant dominantly directs recombination initiation towards its own hotspots, effectively titrating down recombination by the other protein variant. In natural populations with many heterozygous individuals, allelic competition will influence the recombination landscape.

baker2015multimer

PRDM9 Drives Evolutionary Erosion of Hotspots in *Mus musculus* through Haplotype-Specific Initiation of Meiotic Recombination

Christopher L. Baker[1], Shimpei Kajita[1,2], Michael Walker[1], Ruth L. Saxl[1], Narayanan Raghupathy[1], Kwangbom Choi[1], Petko M. Petkov[1], Kenneth Paigen[1]*

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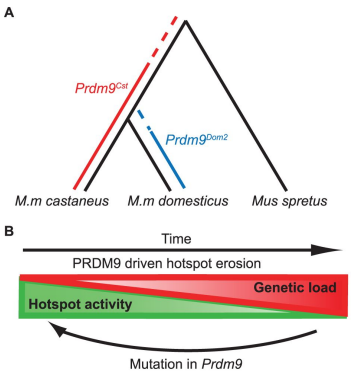
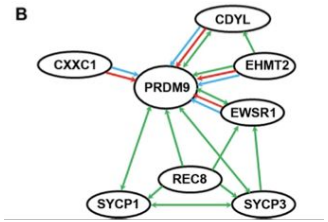
Abstract

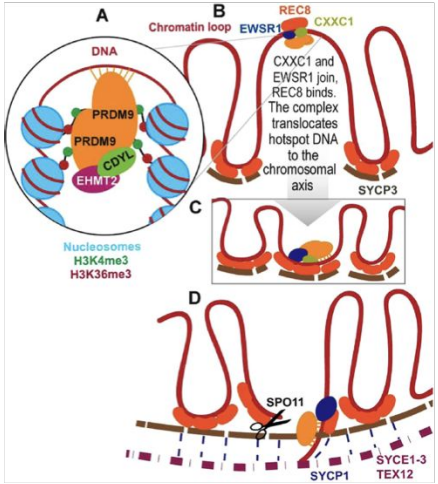
Meiotic recombination generates new genetic variation and assures the proper segregation of chromosomes in gametes. PRDM9, a zinc finger protein with histone methyltransferase activity, initiates meiotic recombination by binding DNA at recombination hotspots and directing the position of DNA double-strand breaks (DSB). The DSB repair mechanism suggests that hotspots should eventually self-destruct, yet genome-wide recombination levels remain constant, a conundrum known as the hotspot paradox. To test if PRDM9 drives this evolutionary erosion, we measured activity of the $Prdm9^{Cst}$ allele in two *Mus musculus* subspecies, *M.m. castaneus*, in which $Prdm9^{Cst}$ arose, and *M.m. domesticus*, into which $Prdm9^{Cst}$ was introduced experimentally. Comparing these two strains, we find that haplotype differences at hotspots lead to qualitative and quantitative changes in PRDM9 binding and activity. Using *Mus spretus* as an outlier, we found most variants affecting $PRDM9^{Cst}$ binding arose and were fixed in *M.m. castaneus*, suppressing hotspot activity. Furthermore, *M.m. castaneus*×*M.m. domesticus* F1 hybrids exhibit novel hotspots, with large haplotype biases in both PRDM9 binding and chromatin modification. These novel hotspots represent sites of historic evolutionary erosion that become activated in hybrids due to crosstalk between one parent's *Prdm9* allele and the opposite parent's chromosome. Together these data support a model where haplotype-specific PRDM9 binding directs biased gene conversion at hotspots, ultimately leading to hotspot erosion.



KRAB and PR/SET domains are active

parvanov2017prdm9



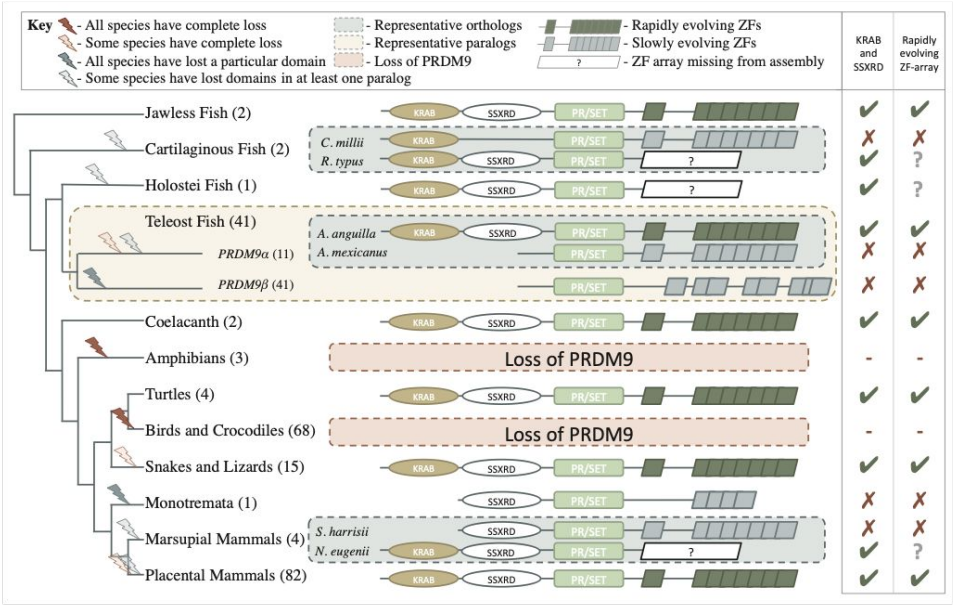


baker2017repeated

It remains unclear when PRDM9 first evolved its role in recombination, or why different methods of directing recombination have developed. To begin answering these questions, Baker, Schumer et al. investigated whether 225 species of vertebrates (backboned animals) have a gene that encodes PRDM9. This analysis revealed that even distantly related animals have genes that produce equivalents of the complete PRDM9 protein. However, several species have independently lost the ability to produce PRDM9. In certain other species, particular regions of the gene have been removed or shortened. Notably, only species that carry genes that contain regions called the KRAB and SSXRD domains show relatively rapid evolution of where PRDM9 binds in the DNA.

To investigate this phenomenon further, Baker, Schumer et al. constructed a map of recombination events in swordtail fish, which carry a version of the gene that lacks the KRAB and SSXRD domains. The PRDM9 protein produced by this gene does not direct where recombination events occur.

Overall, it appears that the KRAB and SSXRD domains are necessary for PRDM9 to direct meiotic recombination. Furthermore, Baker, Schumer et al. predict that those species that have complete versions of PRDM9 use this protein to localize recombination events. Knowing which species use PRDM9 in this way is the first step towards understanding why recombination mechanisms change in evolution, and with what consequences.



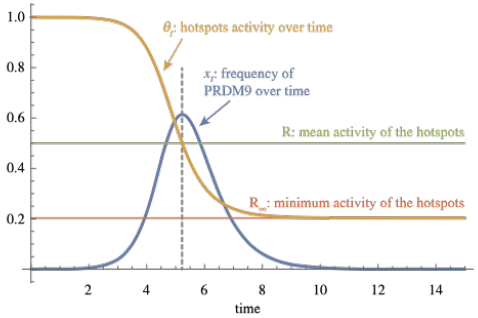
Red-Queen dynamics

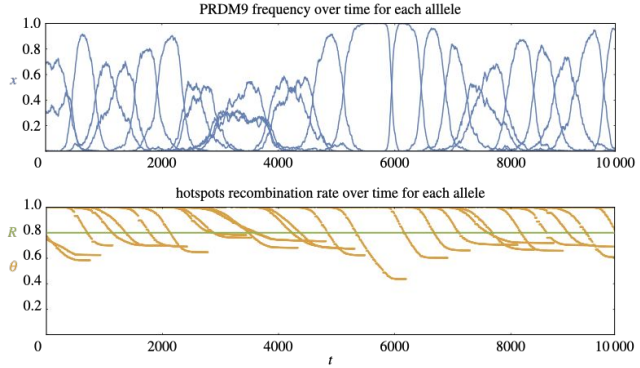
latrille2017red

ubeda2011red ubeda2022co

“Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!”

Through the Looking-Glass and What Alice Found There





lesecque2014red

The Red Queen Model of Recombination Hotspots Evolution in the Light of Archaic and Modern Human Genomes

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Abstract

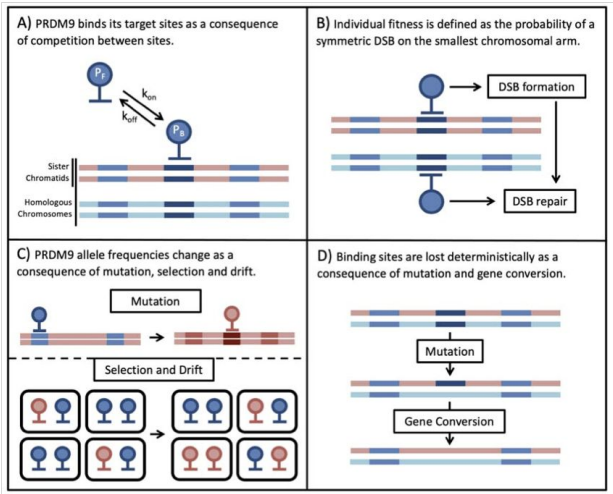
Recombination is an essential process in eukaryotes, which increases diversity by disrupting genetic linkage between loci and ensures the proper segregation of chromosomes during meiosis. In the human genome, recombination events are clustered in hotspots, whose location is determined by the PRDM9 protein. There is evidence that the location of hotspots evolves rapidly, as a consequence of changes in PRDM9 DNA-binding domain. However, the reasons for these changes and the rate at which they occur are not known. In this study, we investigated the evolution of human hotspot loci and of PRDM9 target motifs, both in modern and archaic human lineages (Denisovan) to quantify the dynamic of hotspot turnover during the recent period of human evolution. We show that present-day human hotspots are young: they have been active only during the last 10% of the time since the divergence from chimpanzee, starting to be operating shortly before the split between Denisovans and modern humans. Surprisingly, however, our analyses indicate that Denisovan recombination hotspots did not overlap with modern human ones, despite sharing similar PRDM9 target motifs. We further show that high-affinity PRDM9 target motifs are subject to a strong self-destructive drive, known as biased gene conversion (BGC), which should lead to the loss of the majority of them in the next 3 MYR. This depletion of PRDM9 genomic targets is expected to decrease fitness, and thereby to favor new PRDM9 alleles binding different motifs. Our refined estimates of the age and life expectancy of human hotspots provide empirical evidence in support of the Red Queen hypothesis of recombination hotspots evolution.

Link to hybrid sterility??

genestier2023bridging

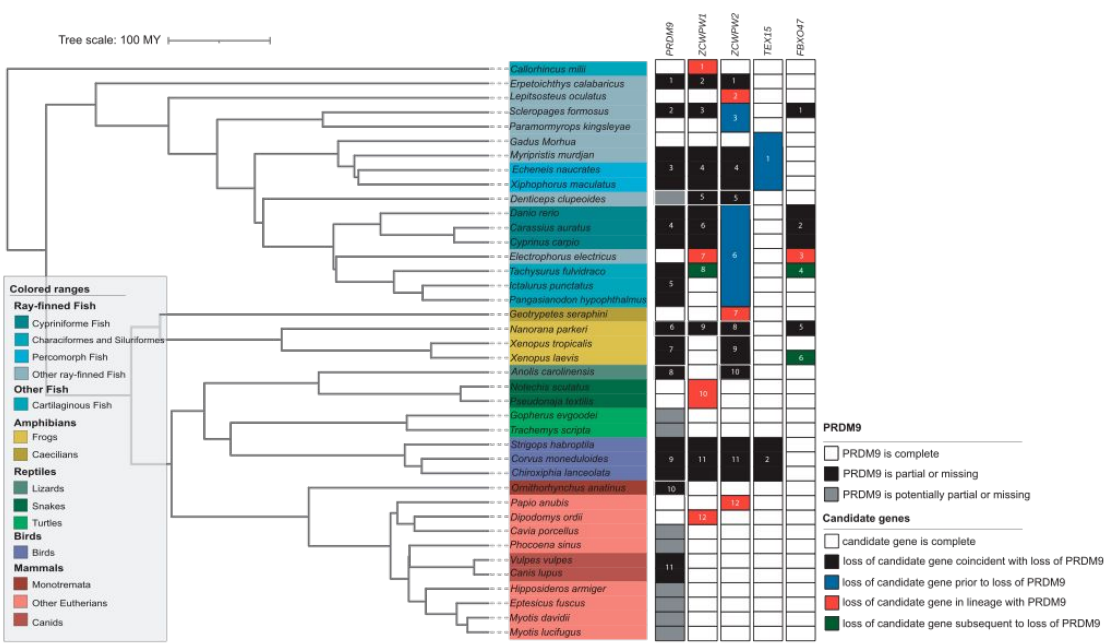
“Although this model predicts many empirical observations, the exact causes of the positive selection acting on new *PRDM9* alleles is still not well understood. In this direction, experiment on mouse hybrids have suggested that, in addition to targeting double strand breaks, PRDM9 has another role during meiosis. Specifically, **PRDM9 symmetric binding (simultaneous binding at the same site on both homologues) would facilitate homology search and, as a result, the pairing of the homologues.** Although discovered in hybrids, this second function of *PRDM9* could also be involved in the evolutionary dynamics observed within populations. To address this point, here, we present a theoretical model of the evolutionary dynamics of meiotic recombination integrating current knowledge about the molecular function of PRDM9. Our modeling work gives important insights into the selective forces driving the turnover of recombination hotspots. Specifically, the reduced symmetrical binding of PRDM9 caused by the loss of high affinity binding sites induces a net positive selection eliciting new *PRDM9* alleles recognizing new targets.”

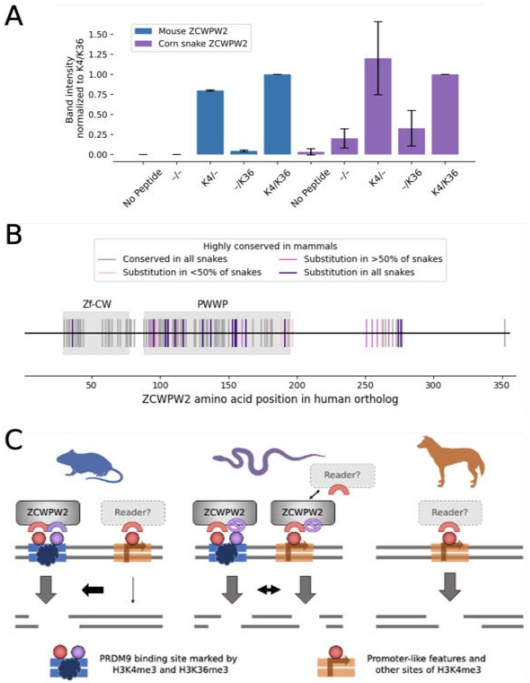
baker2023down



ZCWPW1 & ZCWPW2

huang2020histone mahgoub2020dual wells2020zcwpw1 cavassim2022prdm9 hoge2023patterns





Mechanistic origin of diversity

alleva2021cataloging