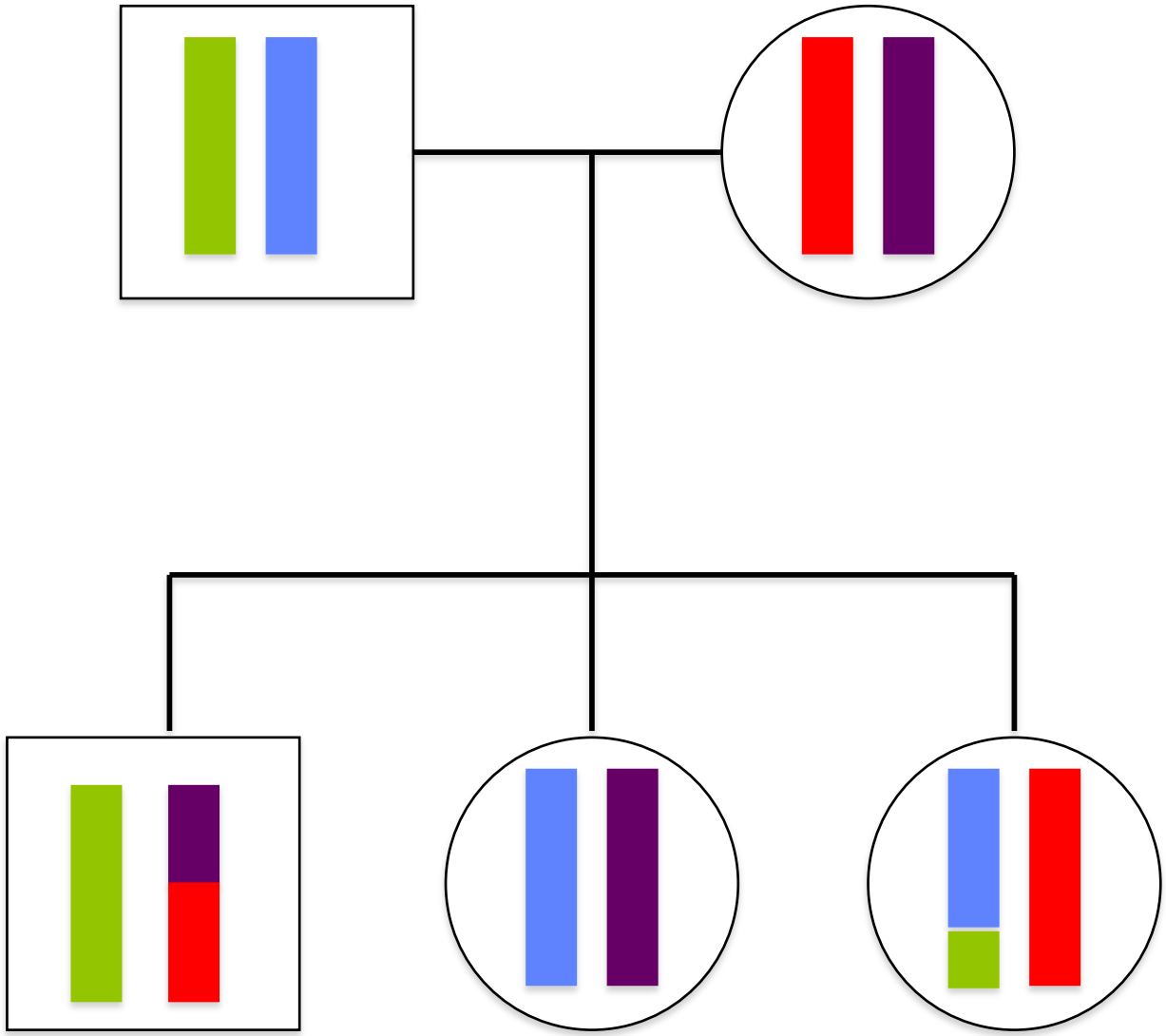
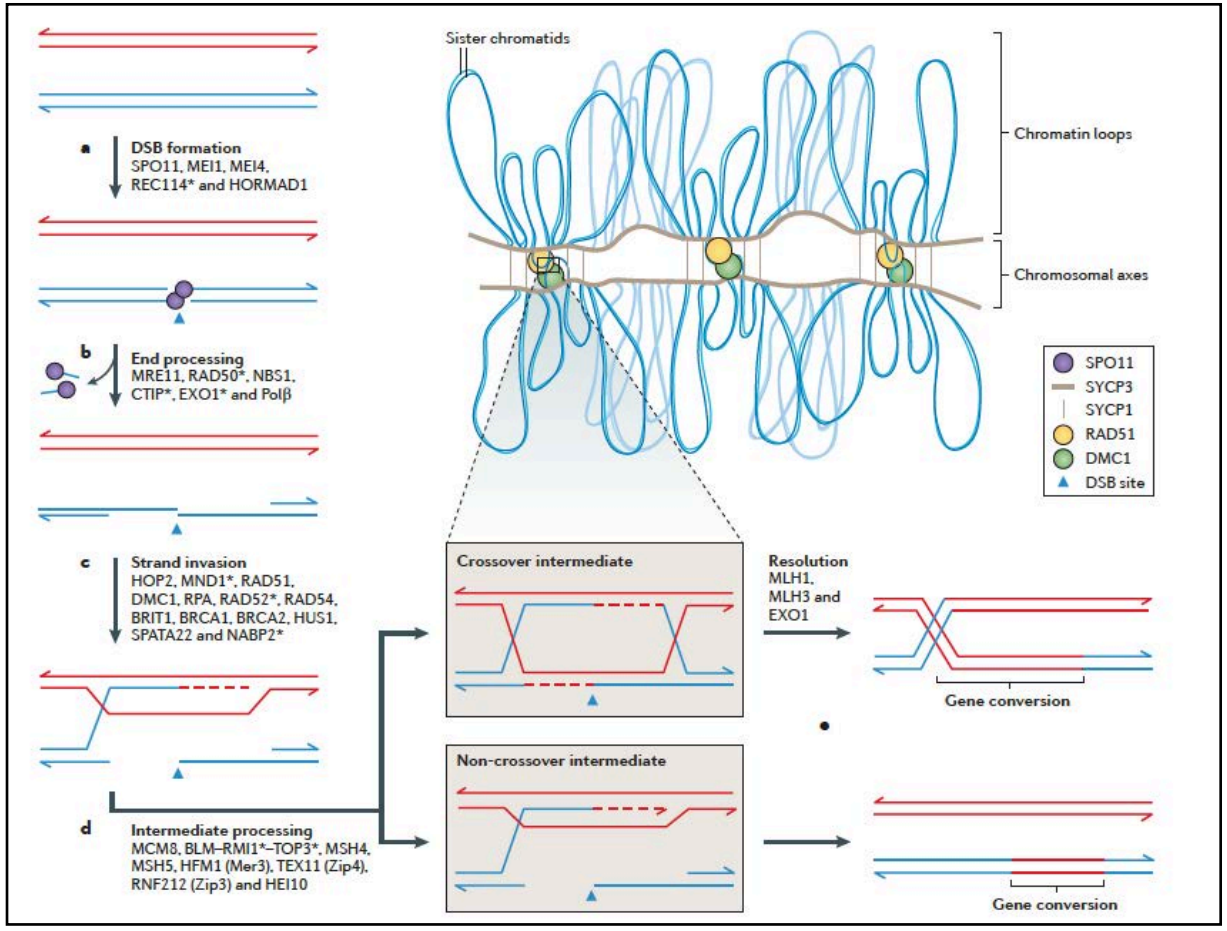
Causes de la variation du taux de recombinaison chez les vertébrés

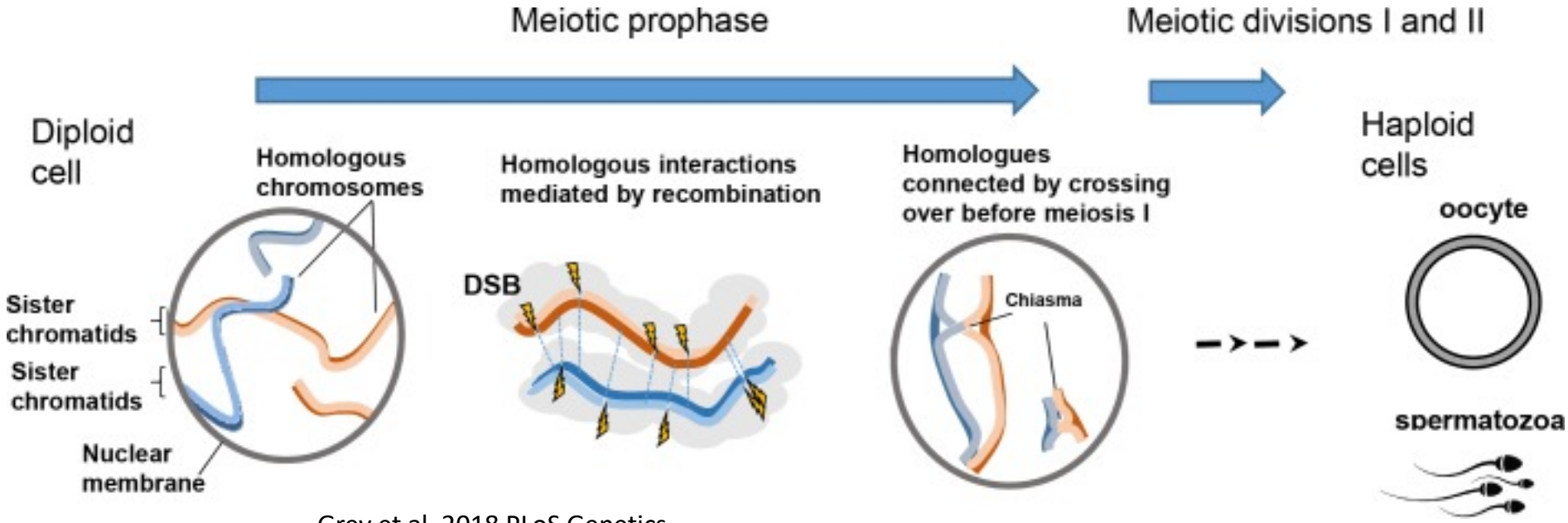
Molly Przeworski

Cours #4





Baudat et al. 2013 Nat Rev Gen



Grey et al. 2018 PLoS Genetics

"Crossover assurance"

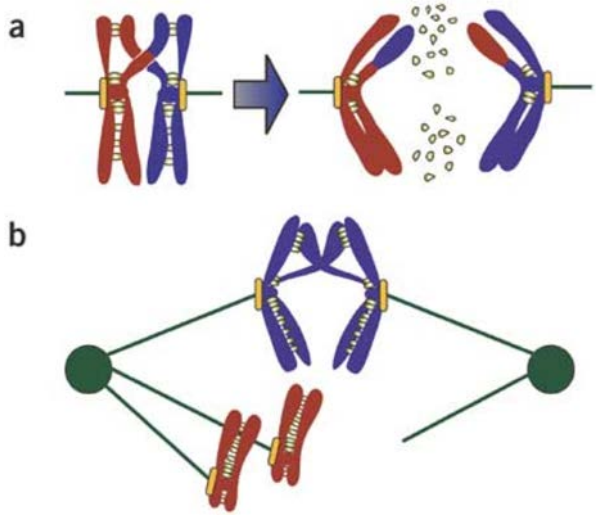
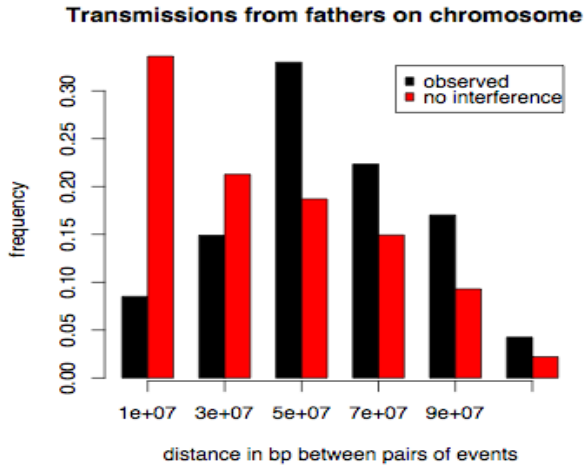
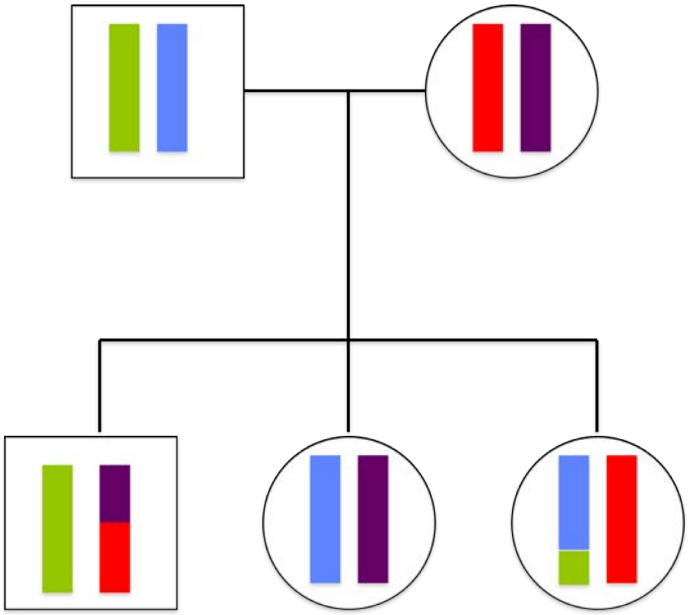


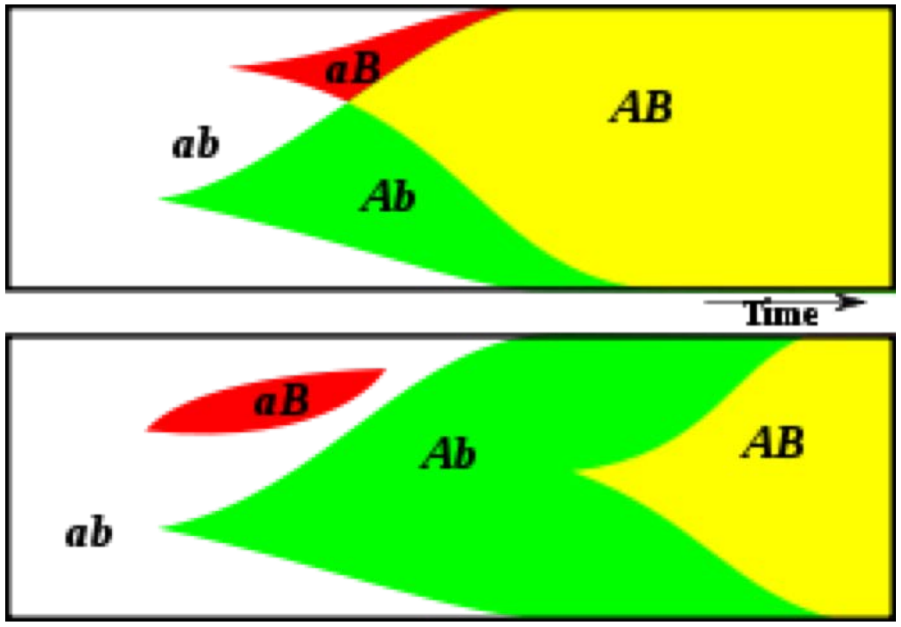
Figure from Cheslock et al. 2005

"Crossover interference"



Fledel-Alon et al. 2009 PLoS Gen





With recombination

Without recombination

https://upload.wikimedia.org/wikipedia/commons/thumb/5/5f/Evolsex-dia2a.svg/250px-Evolsex-dia2a.svg.png

A 2x difference in mean recombination rate

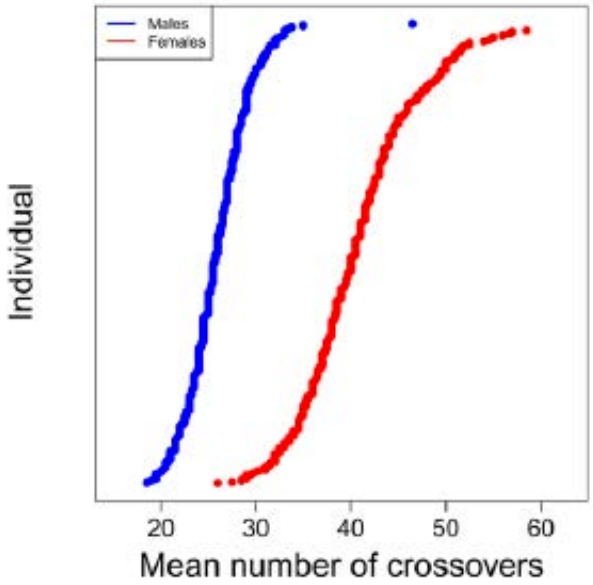
Only females recombine

Inter-individual variability in crossover numbers in humans

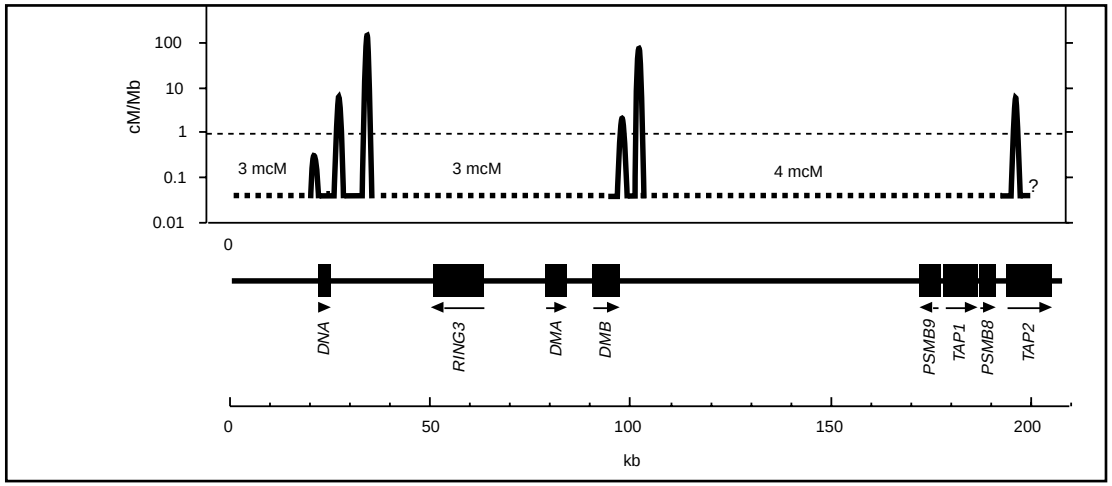
Observed Recombination Events on the 22 Autosomes, for Male and Female Meioses, within Each Family

Family	Mean ± SD No. of Recombination Events in	
	Mother	Father
1416	44 ± 6	22 ± 4
1413	44 ± 7	24 ± 3
1362	37 ± 4	24 ± 4
1347	47 ± 7	24 ± 3
1332	33 ± 4	22 ± 3
1331	38 ± 7	21 ± 4
884	40 ± 7	22 ± 4
102	39 ± 8	23 ± 4
Overall	40 ± 8	23 ± 4

From Broman et al. 1998



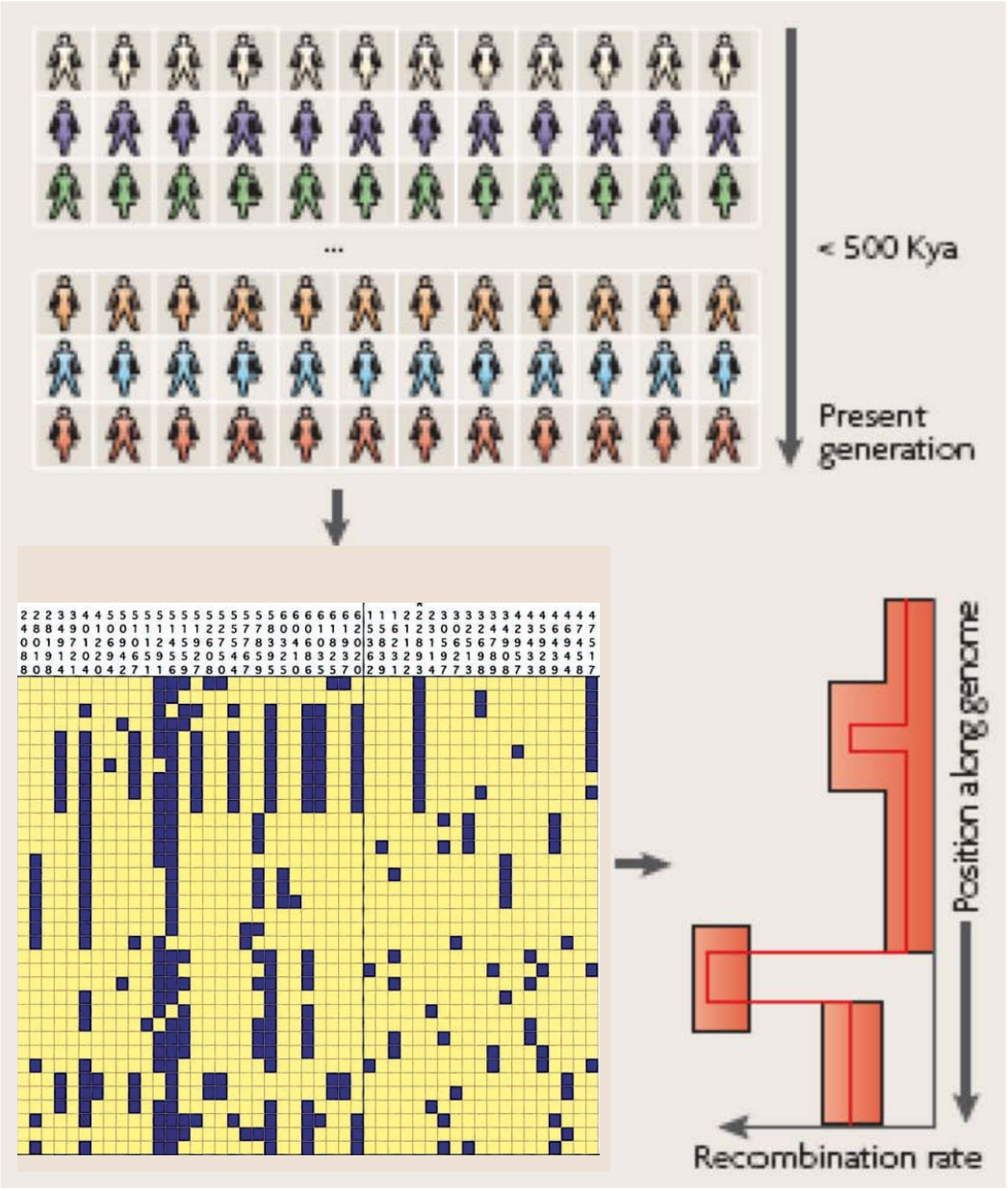
Fledel-Alon et al. 2011 PLoS One



From Jeffreys et al. 2001

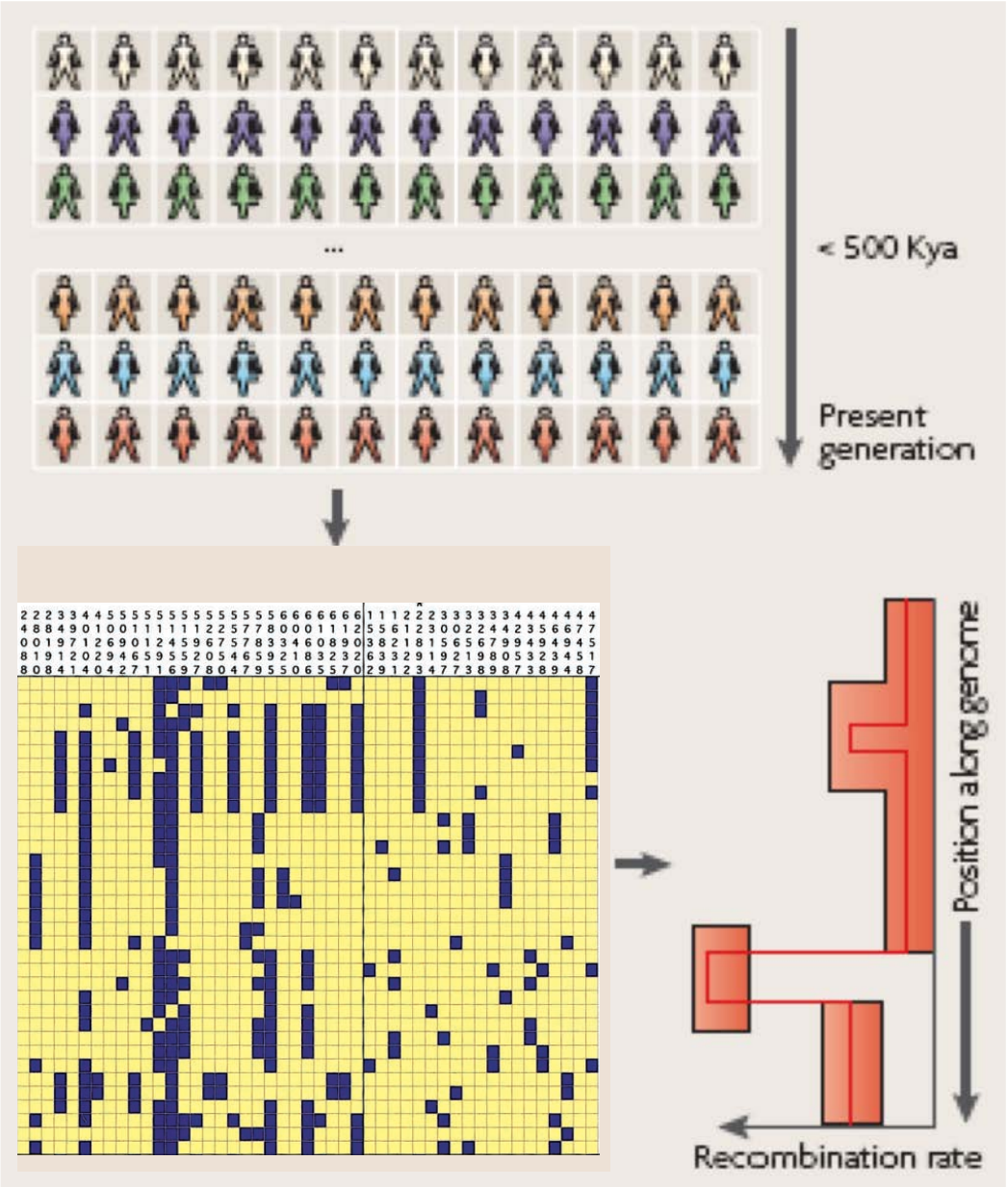
Recombination in the ancestors of the extant sample.

Allelic associations (linkage disequilibrium) among polymorphic sites (SNPs).



modified from Coop and Przeworski 2007

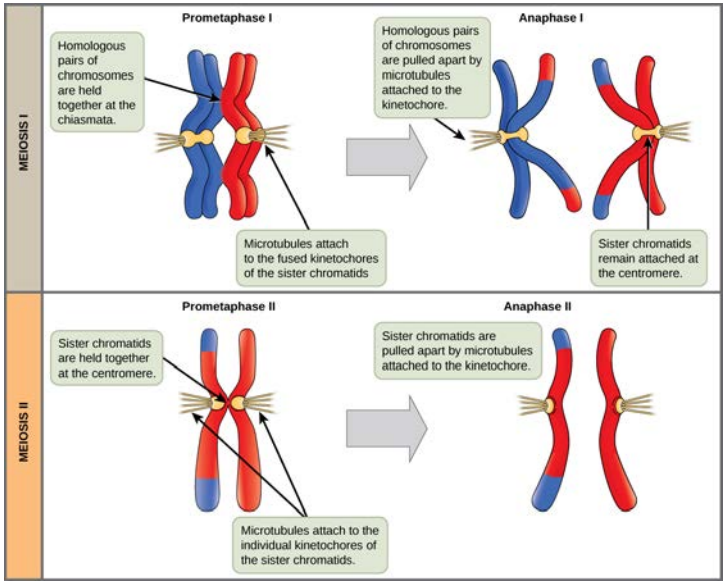
Chakravarti et al. 1984; Kaplan and Hudson 1985; Hudson 2001; McVean et al. 2004



modified from Coop and Przeworski 2007 NRG

Inferred rates are time-averaged and sex-averaged, "population recombination rates"

Chakravarti et al. 1984; Kaplan and Hudson 1985; Hudson 2001; McVean et al. 2004



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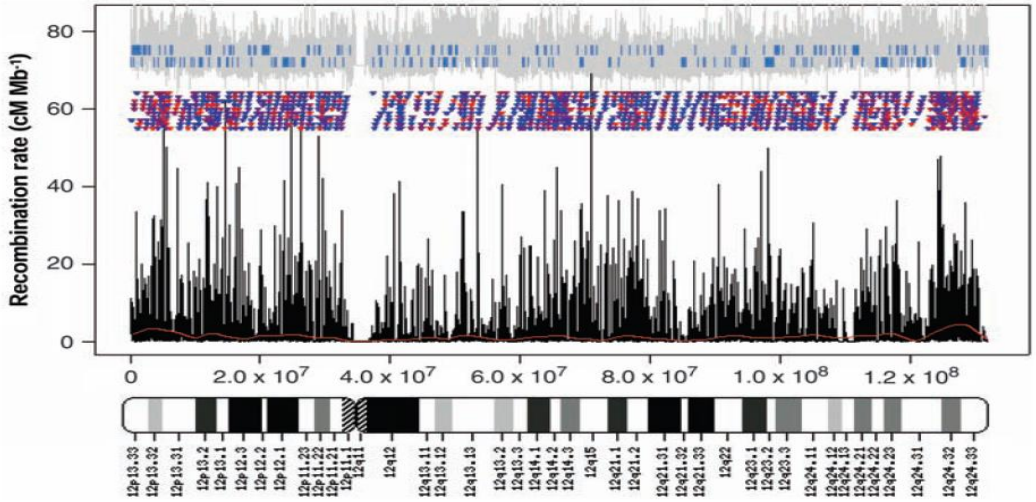
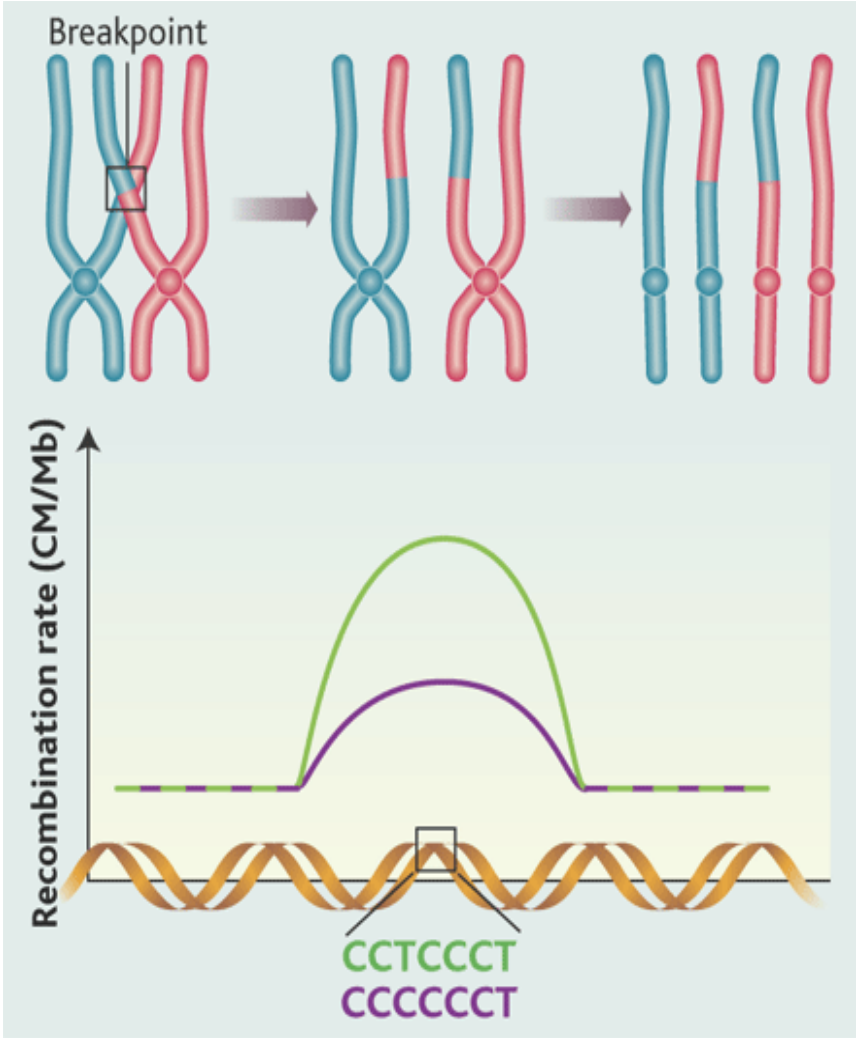


Recombination rates and hotspots across human chromosome 12

Borrowed from Myers et al. 2005

Motif influencing hotspot activity

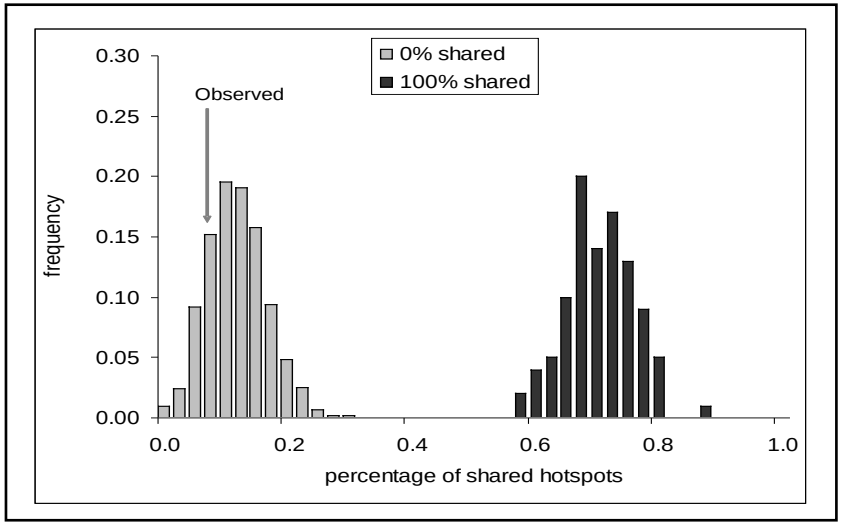
Length	Ranking	Element	# of hotspots[1]	# of coldspots[2]	Difference[3]
9	**1**	**CCCCACCCC**	**987**	**656**	**331**
	2	CCCACCCCC	730	432	298
	3	CCCCCACCC	810	518	292
	4	GAAAAAAAA	3257	2974	283
	5	AAAAAAAAA	4042	3765	277
8	**1**	**CCTCCCTG**	**1868**	**1269**	**599**
	2	CCCCACCC	1844	1280	564
	3	CCCACCCC	1750	1222	528
	4	CCTCCTCT	1950	1431	519
	5	TCCTCCCT	1943	1429	514
7	**1**	**CCTCCCT**	**4366**	**3380**	**986**
	2	CCTTCCC	4272	3351	921
	3	CTCCTCC	4130	3216	914
	4	TCCCCAG	4008	3118	890
	5	CCCCACC	3475	2587	888



From Myers et al. 2005

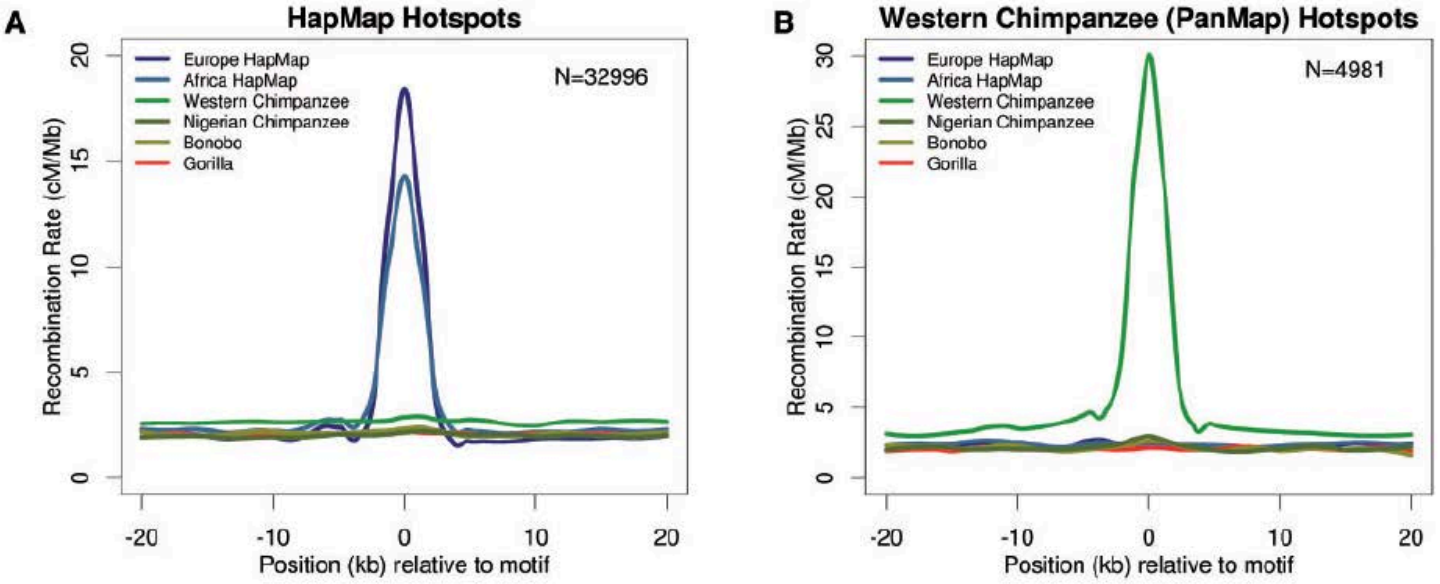
Split time 7-8 Mya

95-99% sequence identity

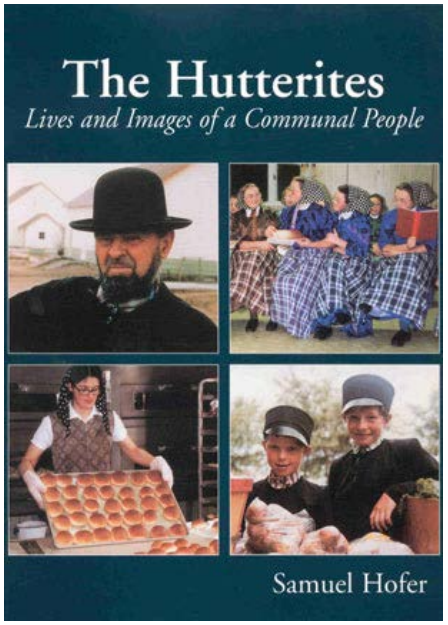


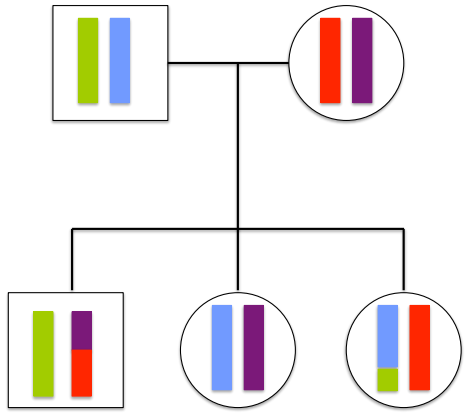
Ptak et al. 2004 PLoS Biol, 2005 NG

See also Winckler et al. 2005 Science

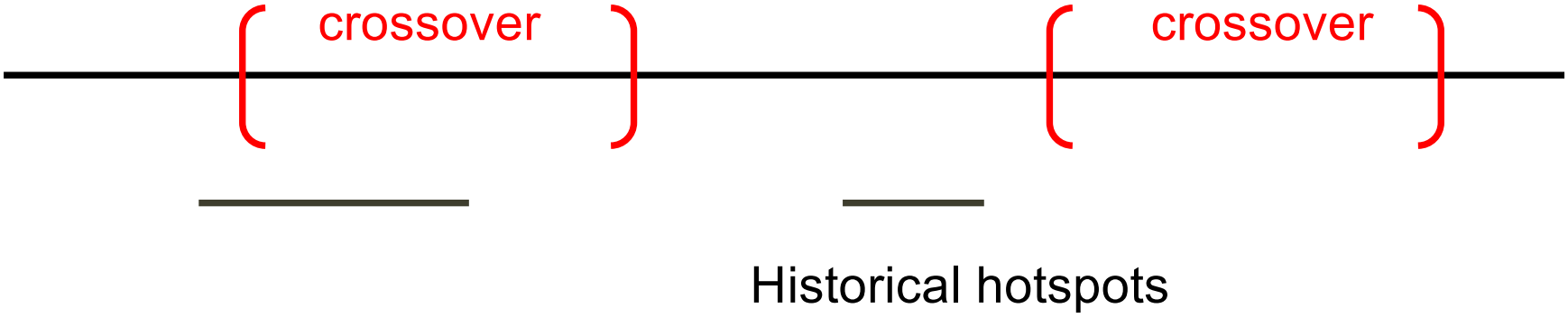


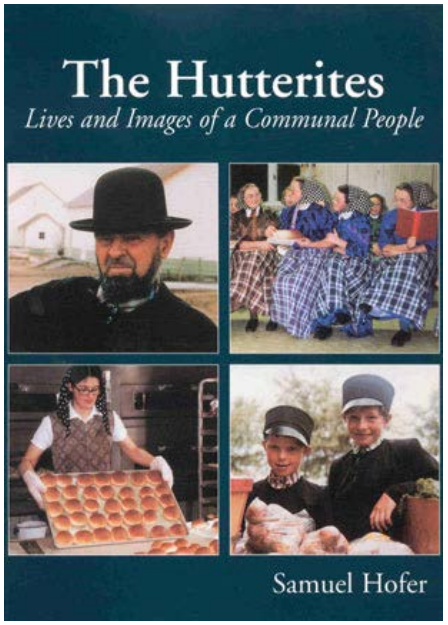
From Stevison et al. 2015 MBE

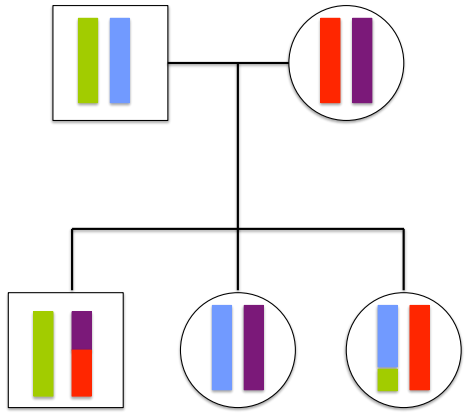




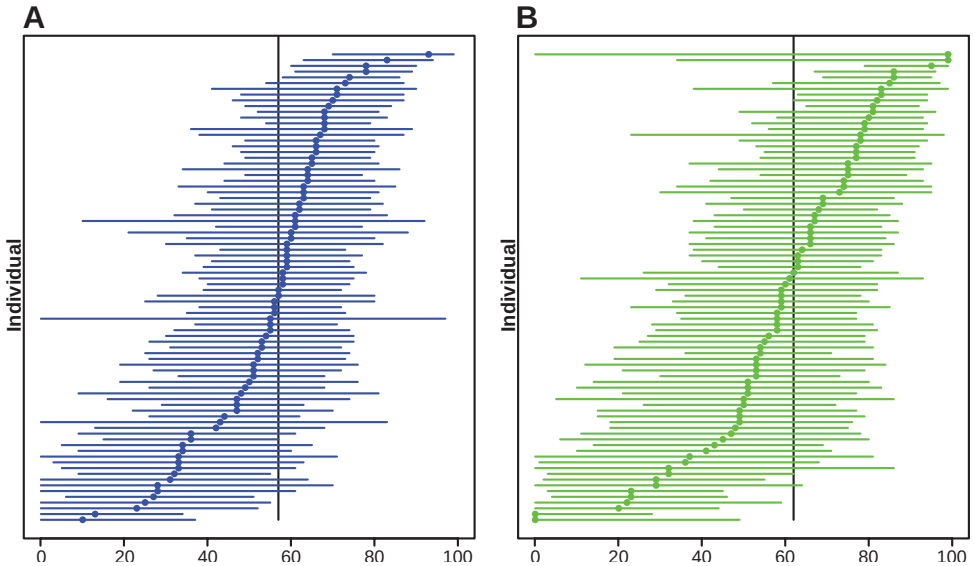
How much of the crossing-over takes place in historical recombination hotspots?







$h^2 > 0$
⇔ the trait is heritable



Pr. of recombination events that occur in a set of historical hotspots

Coop et al. 2008 Science

- Grey et al. (2009) and Parvanov et al. (2009) independently mapped a trans acting region, which influences recombination activity (>2000 fold) at various hotspots.
- Appears to control the position of recombination hotspots, but has little effect on the total number of crossovers.
- Interval further refined to PRDM9 in Baudat et al. (2010), Parvanov et al. (2010)

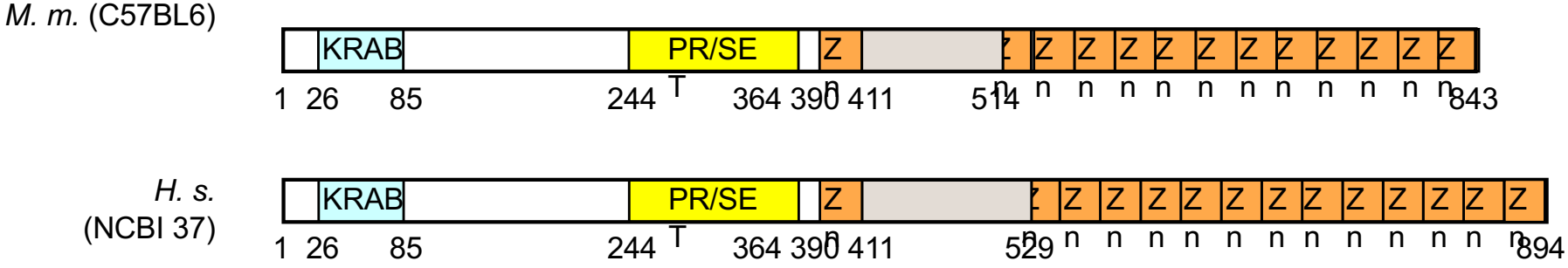
PRDM9 is a zinc finger H3K4 methyltransferase

– histone H3K4 trimethylation associated with hotspots in mouse and in *S. cerevisiae* (Borde et al. 2009)

– expressed in meiotic prophase

– knockouts have defective DSB repair (Hayashi et al. 05)

– is the only known hybrid sterility gene between *Mus m. musculus and Mus m. domesticus* (Mihola et al. 2009)

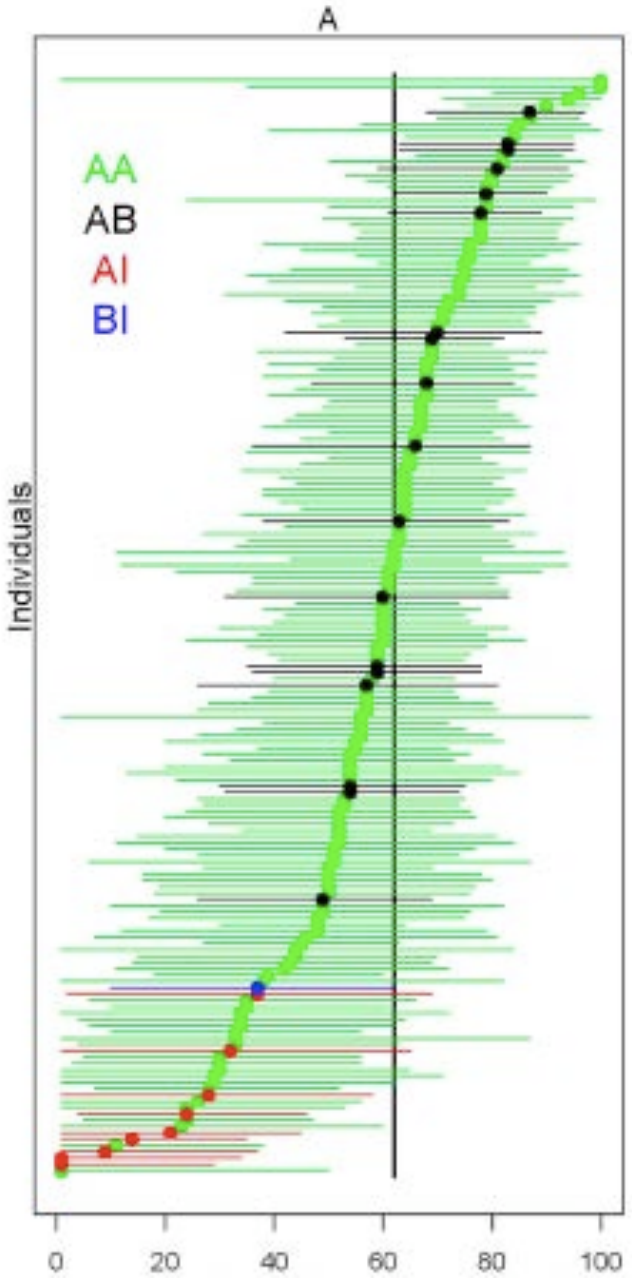


PRDM9 contributes to variation in genome-wide usage of historical hotspots

In combined sex sample:

p_{AB}= 0.033, p_{AI} = 9.3 x 10^{-12}

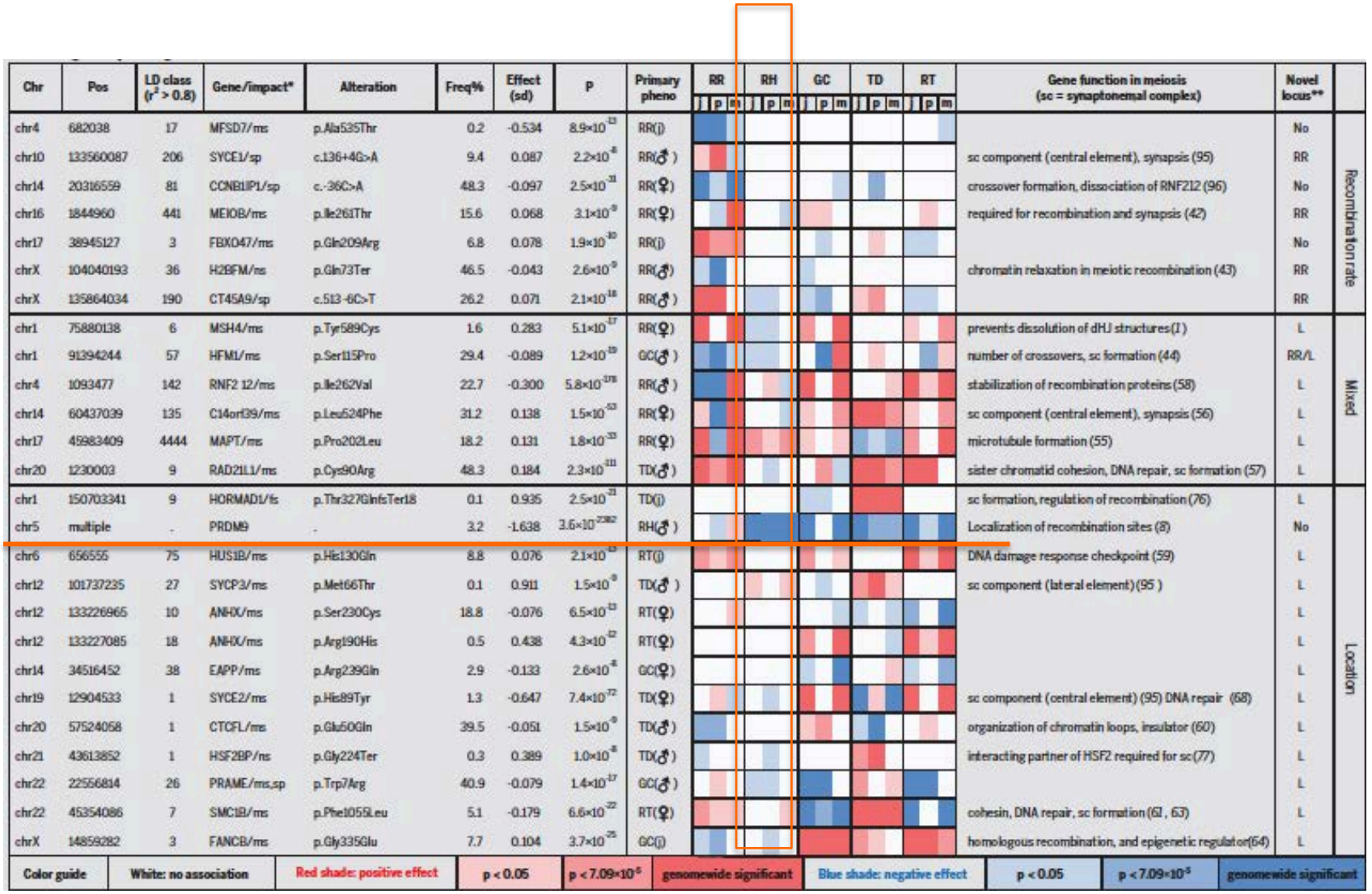
AA: N= 142; AB: N = 18; AI: N=9



Baudat et al. 2010

Percentage of crossover events in historical hotspots

Hotspot usage



Chr	Pos	LD class (r^2 > 0.8)	Gene/impact*	Alteration	Freq%	Effect (sd)	P	Primary pheno	RR	RH	GC	TD	RT	Gene function in meiosis (sc = synaptonemal complex)	Novel locus**	
									j p m	j p m	j p m	j p m	j p m			
chr4	682038	17	MFSD7/ms	p.Ala535Thr	0.2	-0.534	8.9×10^{-13}	RR(j)							No	Recombination rate
chr10	133560087	206	SYCE1/sp	c.136+4G>A	9.4	0.087	2.2×10^{-8}	RR(♂)						sc component (central element), synapsis (95)	RR	
chr14	20316559	81	CCNB1IP1/sp	c.-36C>A	48.3	-0.097	2.5×10^{-31}	RR(♀)						crossover formation, dissociation of RNF212 (96)	No	
chr16	1844960	441	MEIOB/ms	p.Ile261Thr	15.6	0.068	3.1×10^{-9}	RR(♀)						required for recombination and synapsis (42)	RR	
chr17	38945127	3	FBXO47/ms	p.Gln209Arg	6.8	0.078	1.9×10^{-10}	RR(j)							No	
chrX	104040193	36	H2BFM/ns	p.Gln73Ter	46.5	-0.043	2.6×10^{-9}	RR(♂)						chromatin relaxation in meiotic recombination (43)	RR	
chrX	135864034	190	CT45A9/sp	c.513-6C>T	26.2	0.071	2.1×10^{-18}	RR(♂)							RR	
chr1	75880138	6	MSH4/ms	p.Tyr589Cys	1.6	0.283	5.1×10^{-17}	RR(♀)						prevents dissolution of dHJ structures(1)	L	Mixed
chr1	91394244	57	HFM1/ms	p.Ser115Pro	29.4	-0.089	1.2×10^{-19}	GC(♂)						number of crossovers, sc formation (44)	RR/L	
chr4	1093477	142	RNF212/ms	p.Ile262Val	22.7	-0.300	5.8×10^{-178}	RR(♂)						stabilization of recombination proteins (58)	L	
chr14	60437039	135	C14orf39/ms	p.Leu524Phe	31.2	0.138	1.5×10^{-53}	RR(♀)						sc component (central element), synapsis (56)	L	
chr17	45983409	4444	MAPT/ms	p.Pro202Leu	18.2	0.131	1.8×10^{-33}	RR(♀)						microtubule formation (55)	L	
chr20	1230003	9	RAD21L1/ms	p.Cys90Arg	48.3	0.184	2.3×10^{-111}	TD(♂)						sister chromatid cohesion, DNA repair, sc formation (57)	L	
chr1	150703341	9	HORMAD1/fs	p.Thr327GlnfsTer18	0.1	0.935	2.5×10^{-21}	TD(j)						sc formation, regulation of recombination (76)	L	Location
chr5	multiple	.	PRDM9	.	3.2	-1.638	3.6×10^{-2382}	RH(♂)						Localization of recombination sites (8)	No	
chr6	656555	75	HUS1B/ms	p.His130Gln	8.8	0.076	2.1×10^{-13}	RT(j)						DNA damage response checkpoint (59)	L	
chr12	101737235	27	SYCP3/ms	p.Met66Thr	0.1	0.911	1.5×10^{-9}	TD(♂)						sc component (lateral element) (95)	L	
chr12	133226965	10	ANHX/ms	p.Ser230Cys	18.8	-0.076	6.5×10^{-13}	RT(♀)							L	
chr12	133227085	18	ANHX/ms	p.Arg190His	0.5	0.438	4.3×10^{-12}	RT(♀)							L	
chr14	34516452	38	EAPP/ms	p.Arg239Gln	2.9	-0.133	2.6×10^{-8}	GC(♀)							L	
chr19	12904533	1	SYCE2/ms	p.His89Tyr	1.3	-0.647	7.4×10^{-72}	TD(♀)						sc component (central element) (95) DNA repair (68)	L	
chr20	57524058	1	CTCFL/ms	p.Glu560Gln	39.5	-0.051	1.5×10^{-9}	TD(♂)						organization of chromatin loops, insulator (60)	L	
chr21	43613852	1	HSF2BP/ns	p.Gly224Ter	0.3	0.389	1.0×10^{-8}	TD(♂)						interacting partner of HSF2 required for sc (77)	L	
chr22	22556814	26	PRAME/ms,sp	p.Trp7Arg	40.9	-0.079	1.4×10^{-17}	GC(♂)							L	
chr22	45354086	7	SMCB/ms	p.Phe1055Leu	5.1	-0.179	6.6×10^{-22}	RT(♀)						cohesin, DNA repair, sc formation (61, 63)	L	
chrX	14859282	3	FANCB/ms	p.Gly335Glu	7.7	0.104	3.7×10^{-25}	GC(j)						homologous recombination, and epigenetic regulator(64)	L	

Color guide	White: no association	Red shade: positive effect	$p < 0.05$	$p < 7.09\times10^{-5}$	genomewide significant	Blue shade: negative effect	$p < 0.05$	$p < 7.09\times10^{-5}$	genomewide significant

Halldorsson et al. 2019 Science

PRDM9

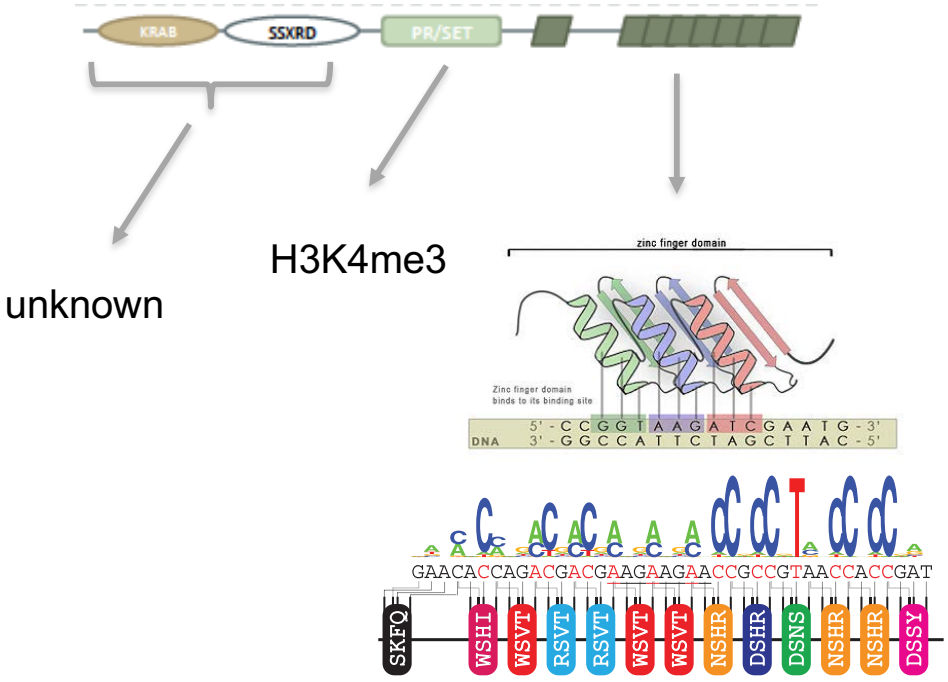


Figure from Myers et al. 2010

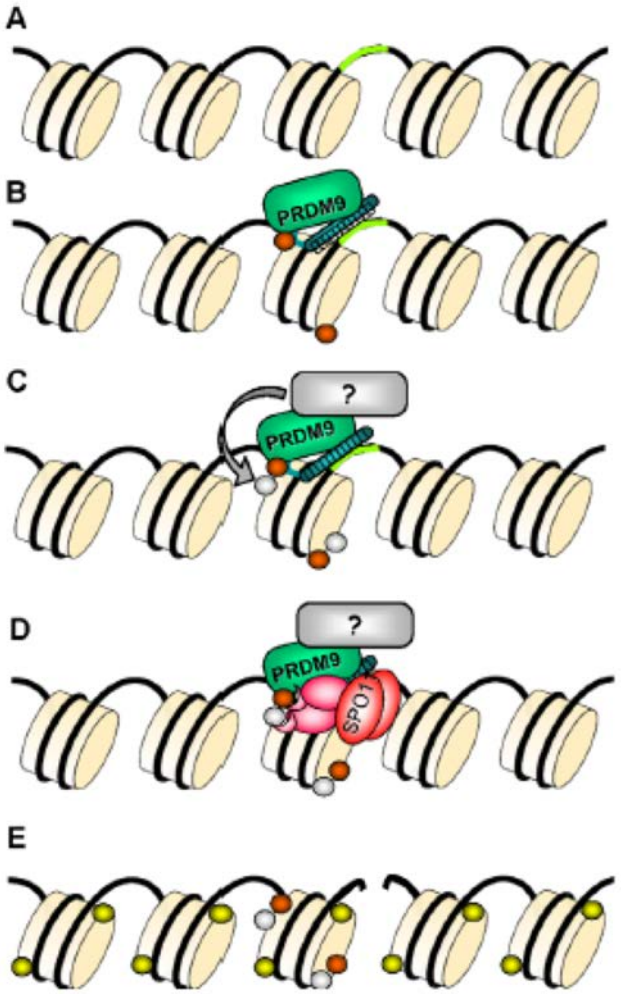
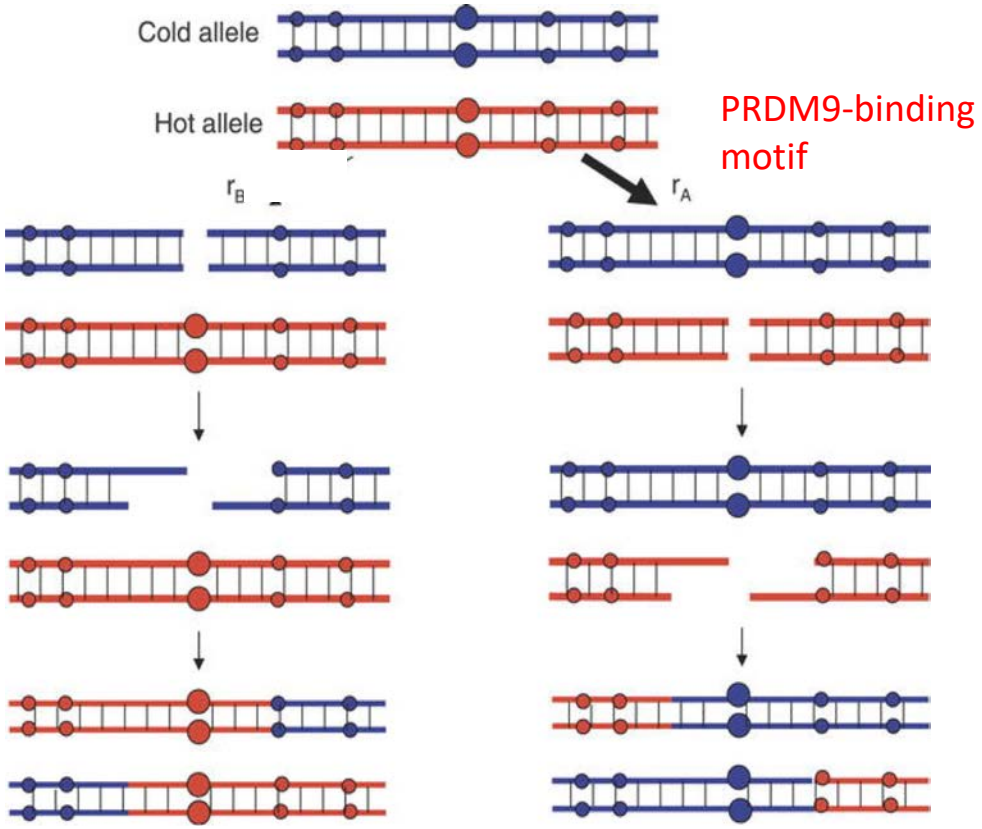


Figure from Grey et al. 2011

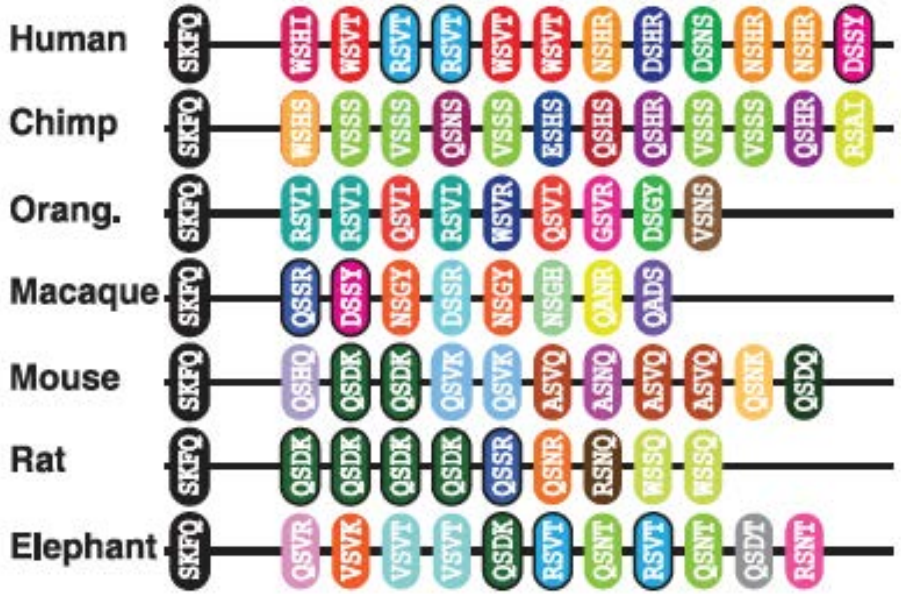
Baudat et al. 2010 Science; Myers et al. 2010; Parvanov et al. 2010

PRDM9 motifs are rapidly lost

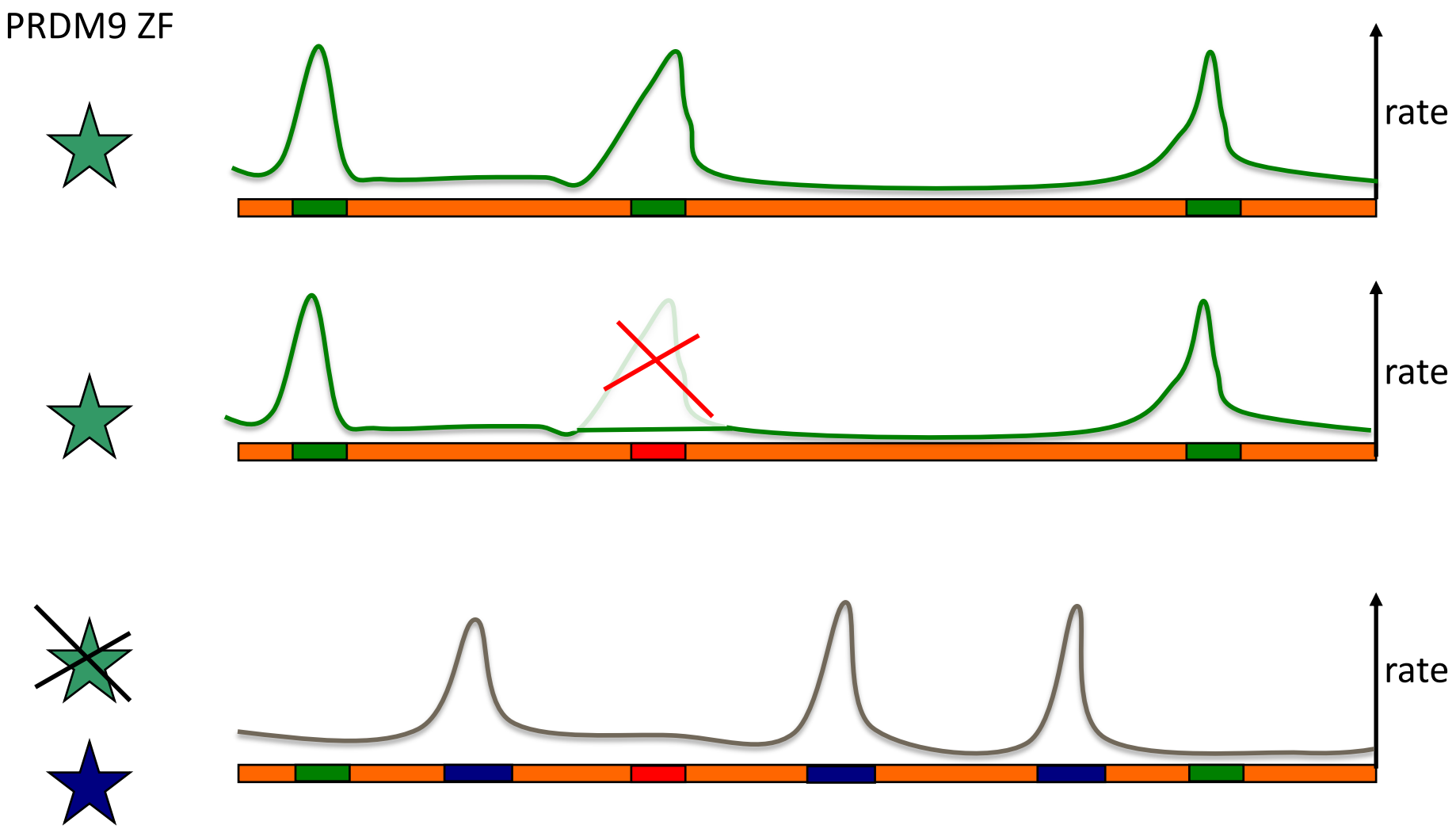


Borrowed from Coop and Myers 2007

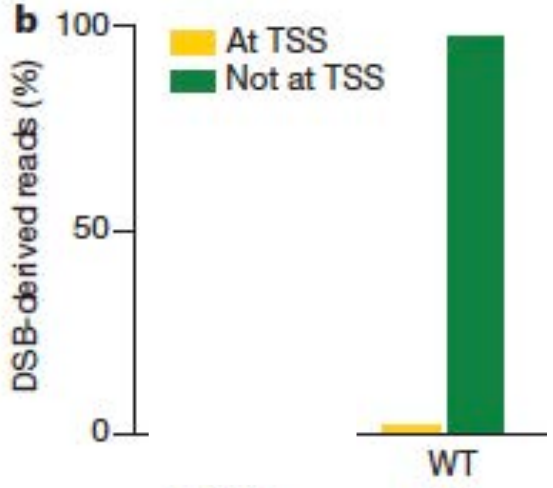
The PRDM9 zinc finger evolves rapidly



Borrowed from Myers et al. 2010


PRDM9 ZF
rate
rate
rate

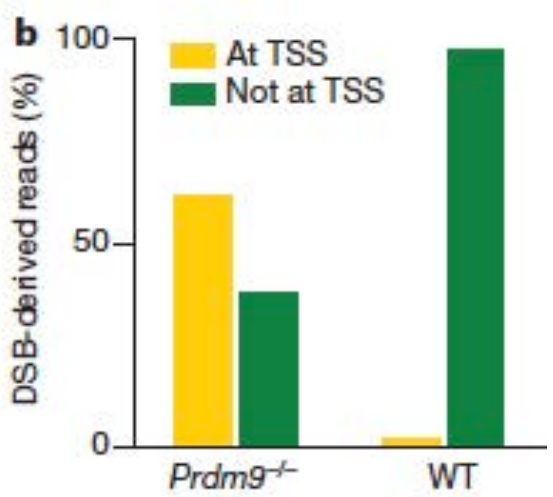
In mice



Borrowed from Brick et al. 2012

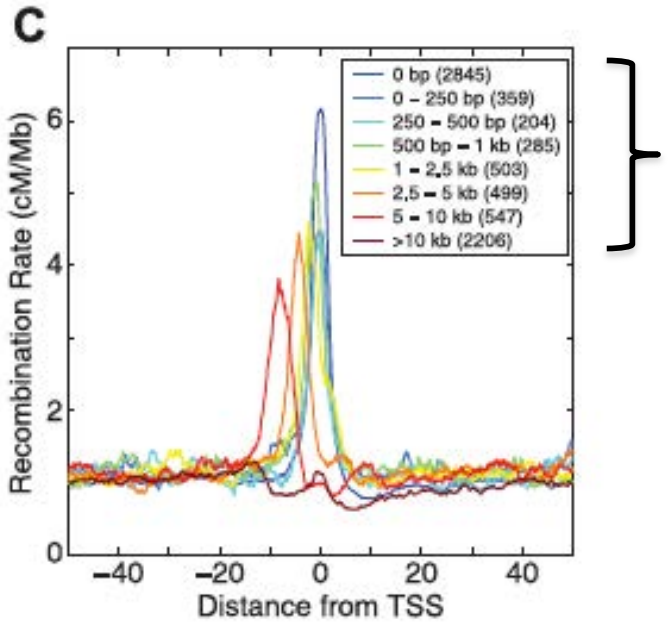
In the absence of PRDM9

In PRDM9 knockout mice



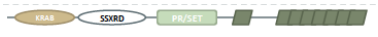
Borrowed from Brick et al. 2012

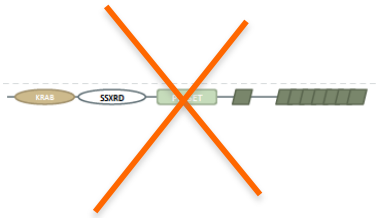
In dogs, where PRDM9 pseudogene

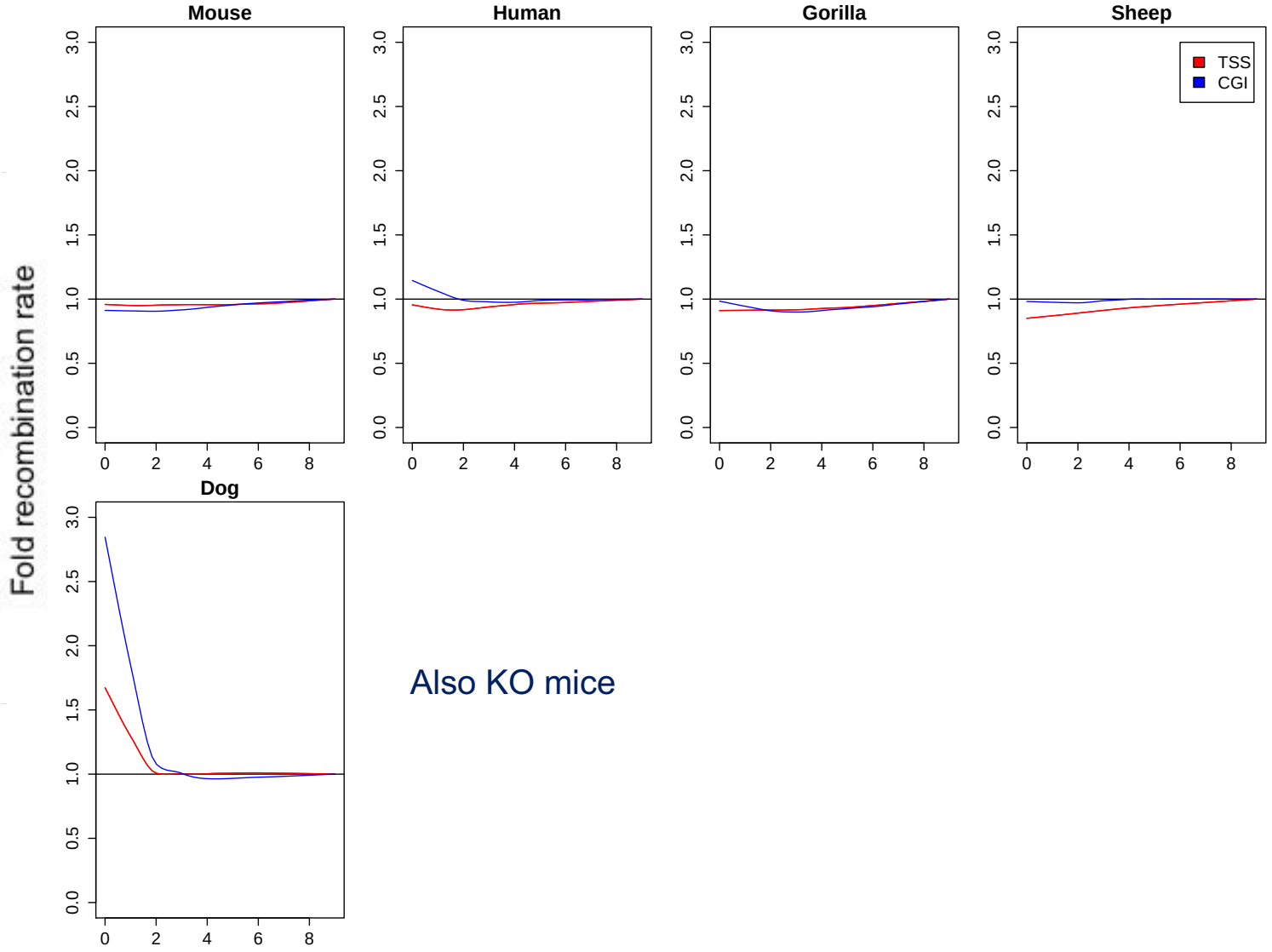


Distance to CpG island

Borrowed from Auton et al. 2013







Also KO mice

Baker et al. 2017 eLife

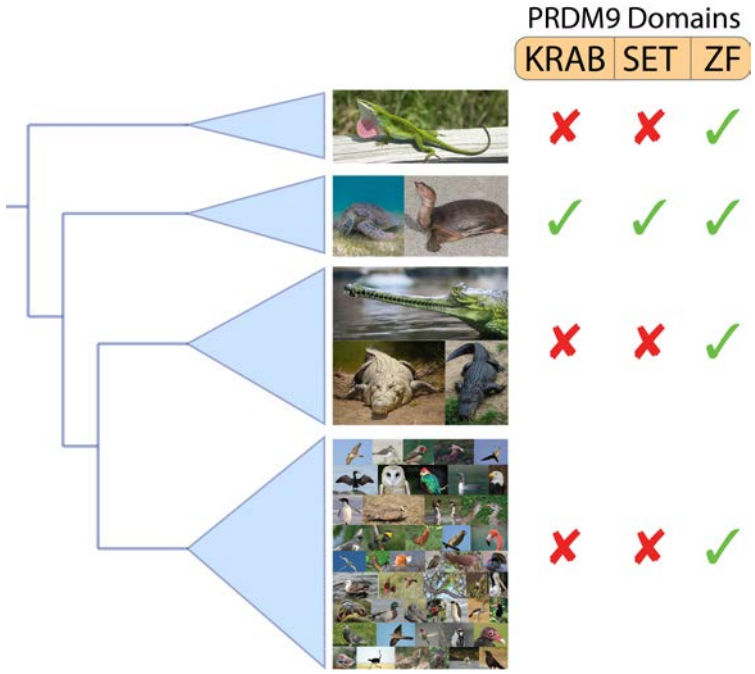
Summary

- In humans, like most sexually reproducing organisms, recombination events ensure the proper alignment and segregation of homologous chromosomes
- Yet at the scale of kilobases, recombination rates are extremely variable, both across species and even within humans.
- This rapid evolution between species, and the inter-individual variability in hotspot usage is driven by PRDM9
- PRDM9 appears to lead to less recombination in promoter like regions than what would happen otherwise

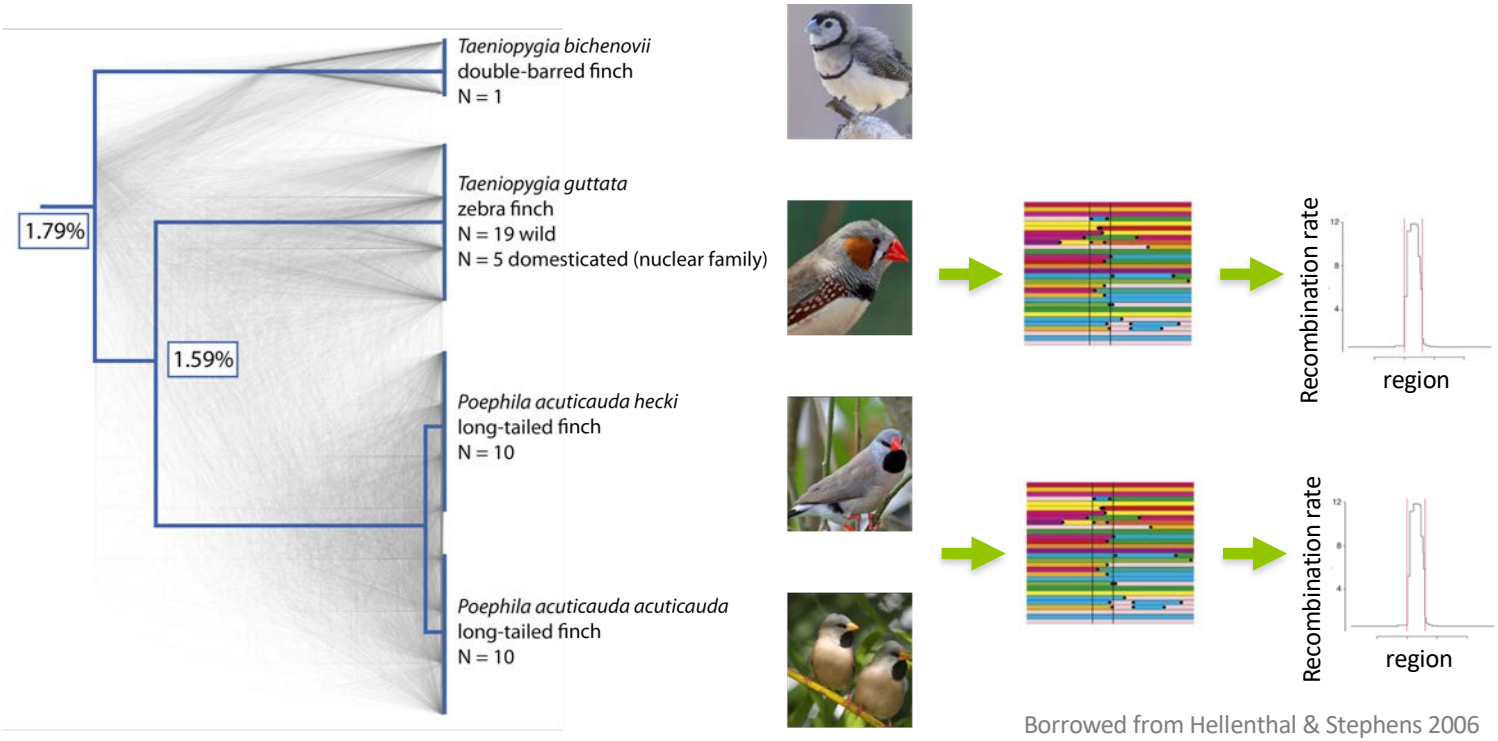
What happens when PRDM9 is absent?

Ellen Leffler
(soon faculty, U. Utah)

Sonal Singhal
(now faculty, Cal. State)



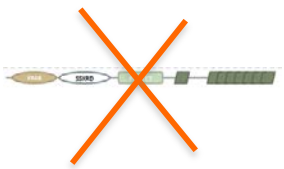
Singhal, Leffler et al. 2015 Science

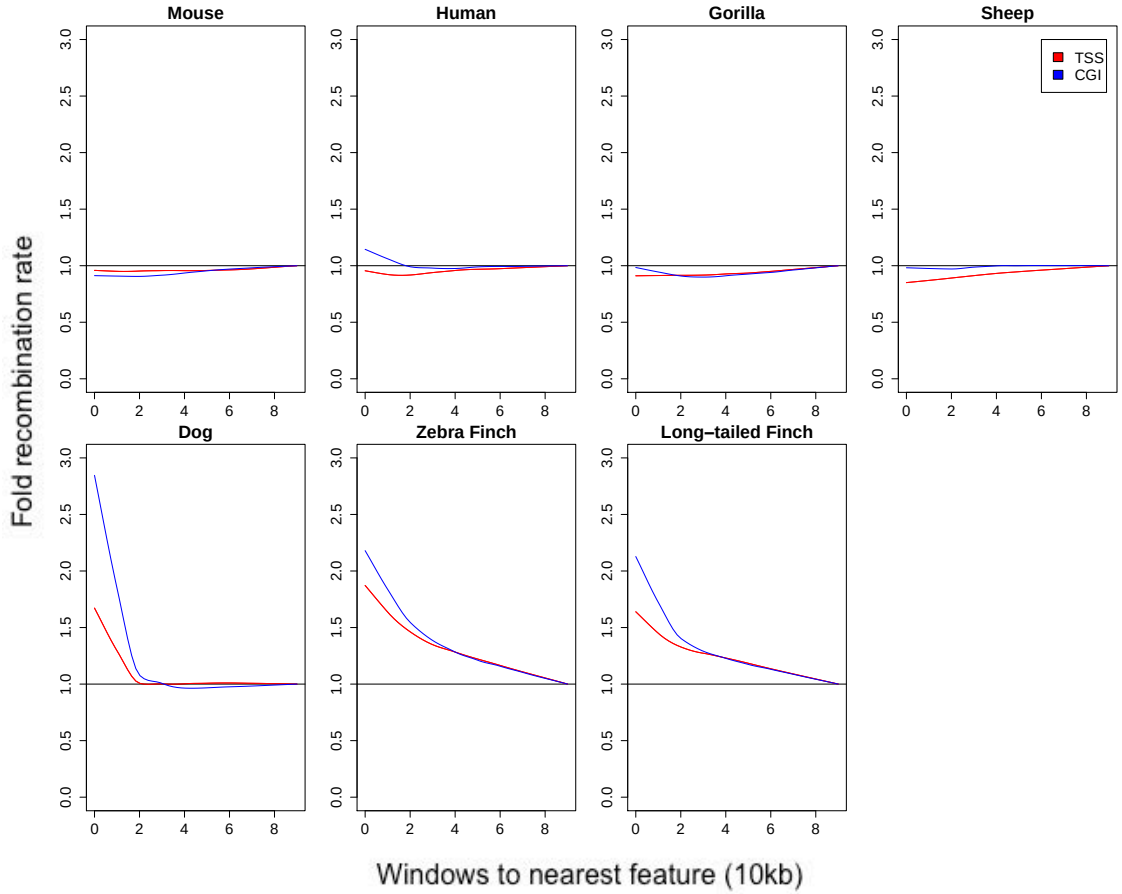


Borrowed from Hellenthal & Stephens 2006

Singhal, Leffler et al. 2015 Science

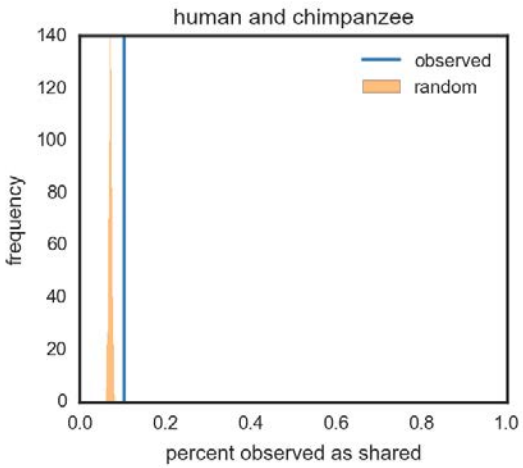
Where does recombination occur?

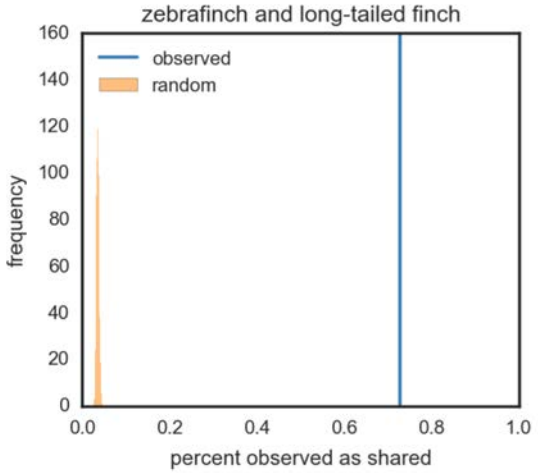




Baker et al. 2017 eLife

- Do hotspots evolve rapidly?





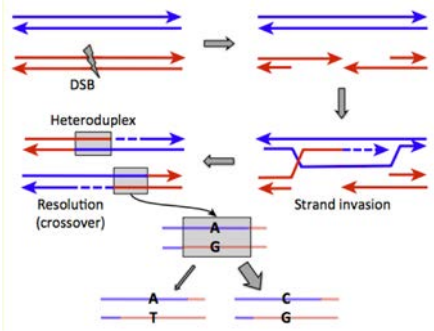
No

Hotspots are largely shared between species (>70%)

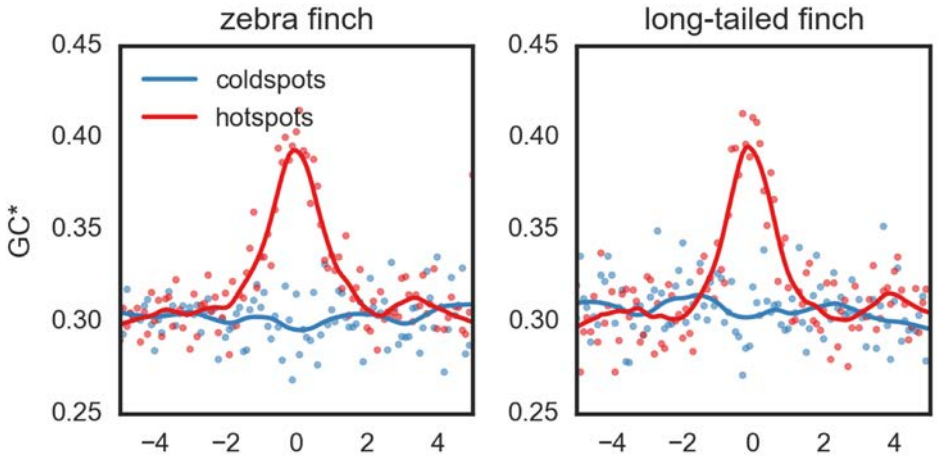
Singhal, Leffler et al. 2015 Science

Independent evidence for hotspots: peak in GC substitutions

GC-biased gene conversion



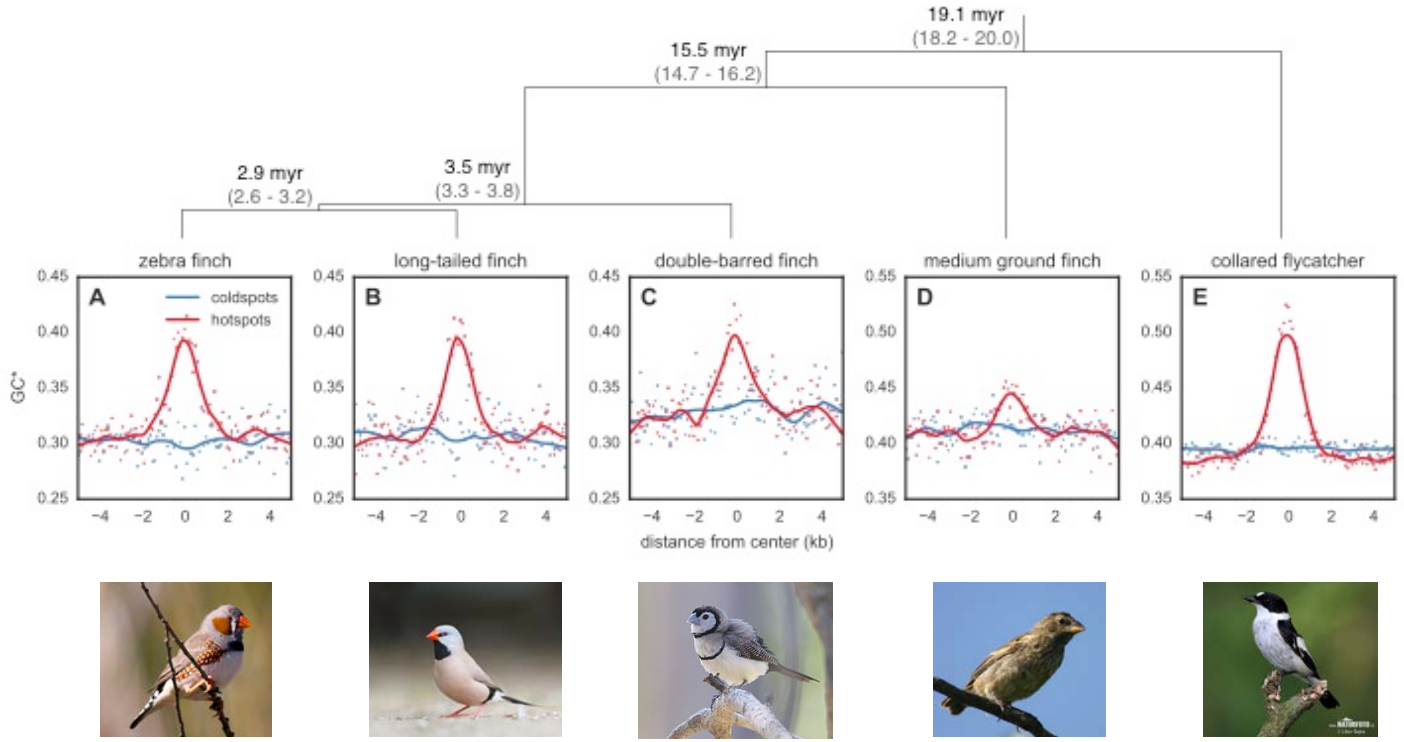
Borrowed from Glemin et al. 2014



Distance from center of hotspot (kb)

Singhal, Leffler et al. 2015 Science

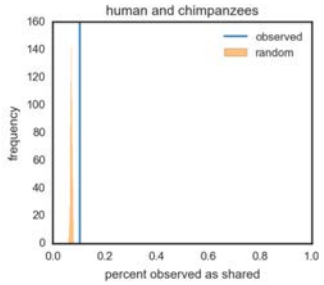
Conservation over large evolutionary distances



Singhal, Leffler et al. 2015 Science

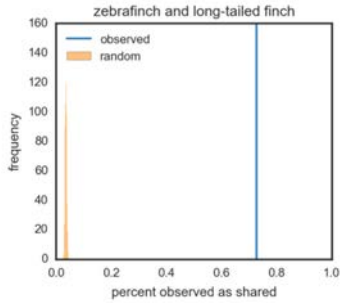
In apes

with PRDM9

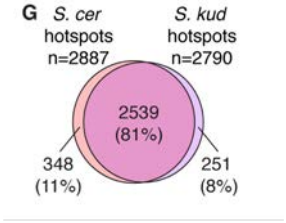


In finches

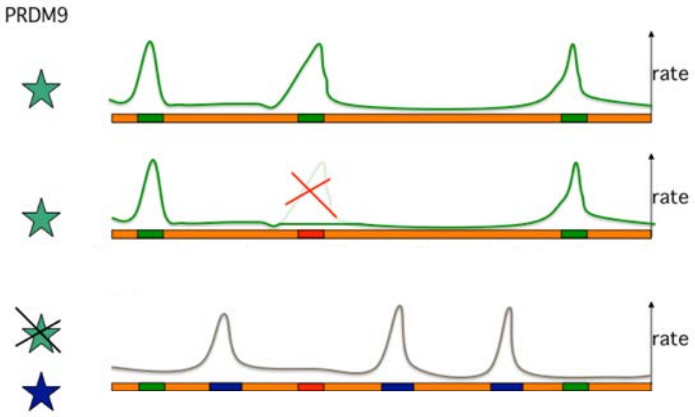
without PRDM9



* Also in yeasts (Lam & Keeney 2015)

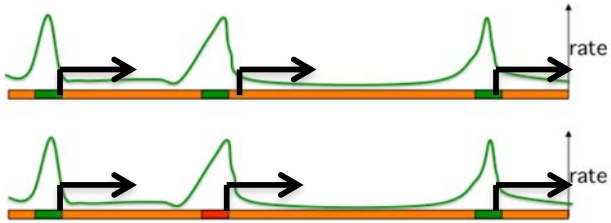


Directed by PRDM9



Apes, mice, others…?

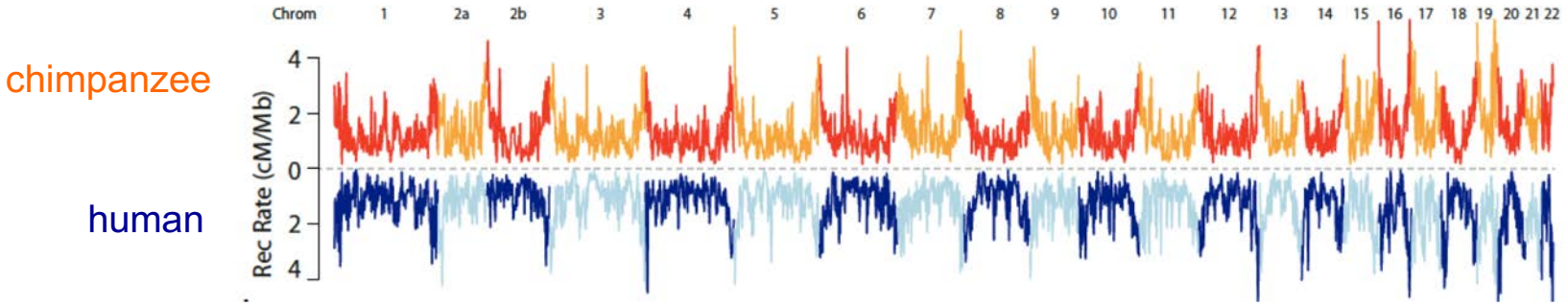
When targeting functional elements



Birds, yeasts,…?

Summary

- In species with PRDM9, recombination is not elevated near promoters. The binding specificity of PRDM9 and hotspot locations evolve very rapidly. Despite this rapid evolution, broad scale rates are conserved.



- In species without PRDM9, recombination is elevated near promoter like features and in particular CpG islands. Hotspots seem to be conserved over long periods of time.