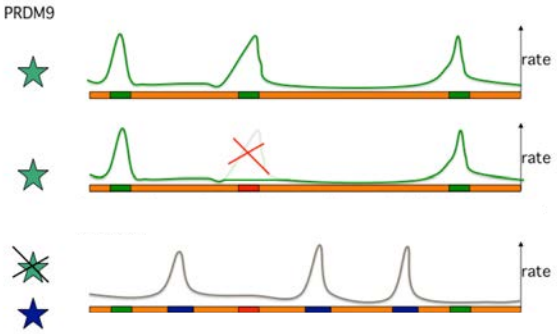
Conséquences de la variation du taux de recombinaison chez les vertébrés

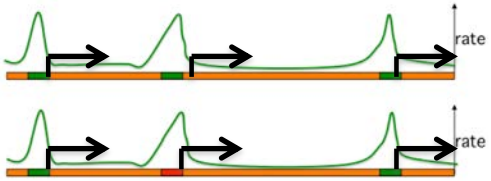
Molly Przeworski

Cours #5

Directed by PRDM9

When targeting functional elements



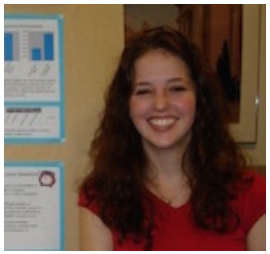


Apes, mice, others…?

Birds, yeasts,…?

How general is this?

Zachary Baker
(PhD Student, Columbia)

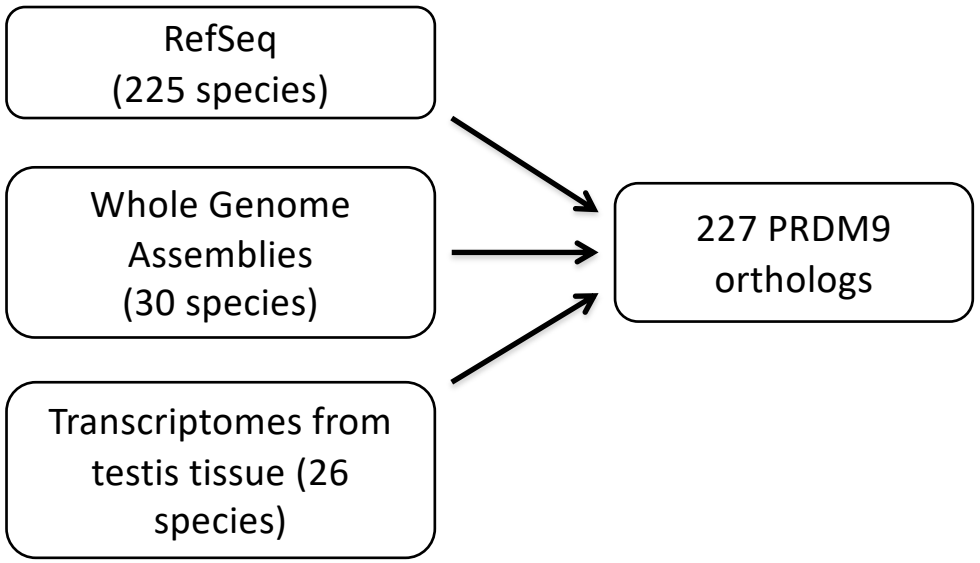


Molly Schumer
(soon, faculty at Stanford)

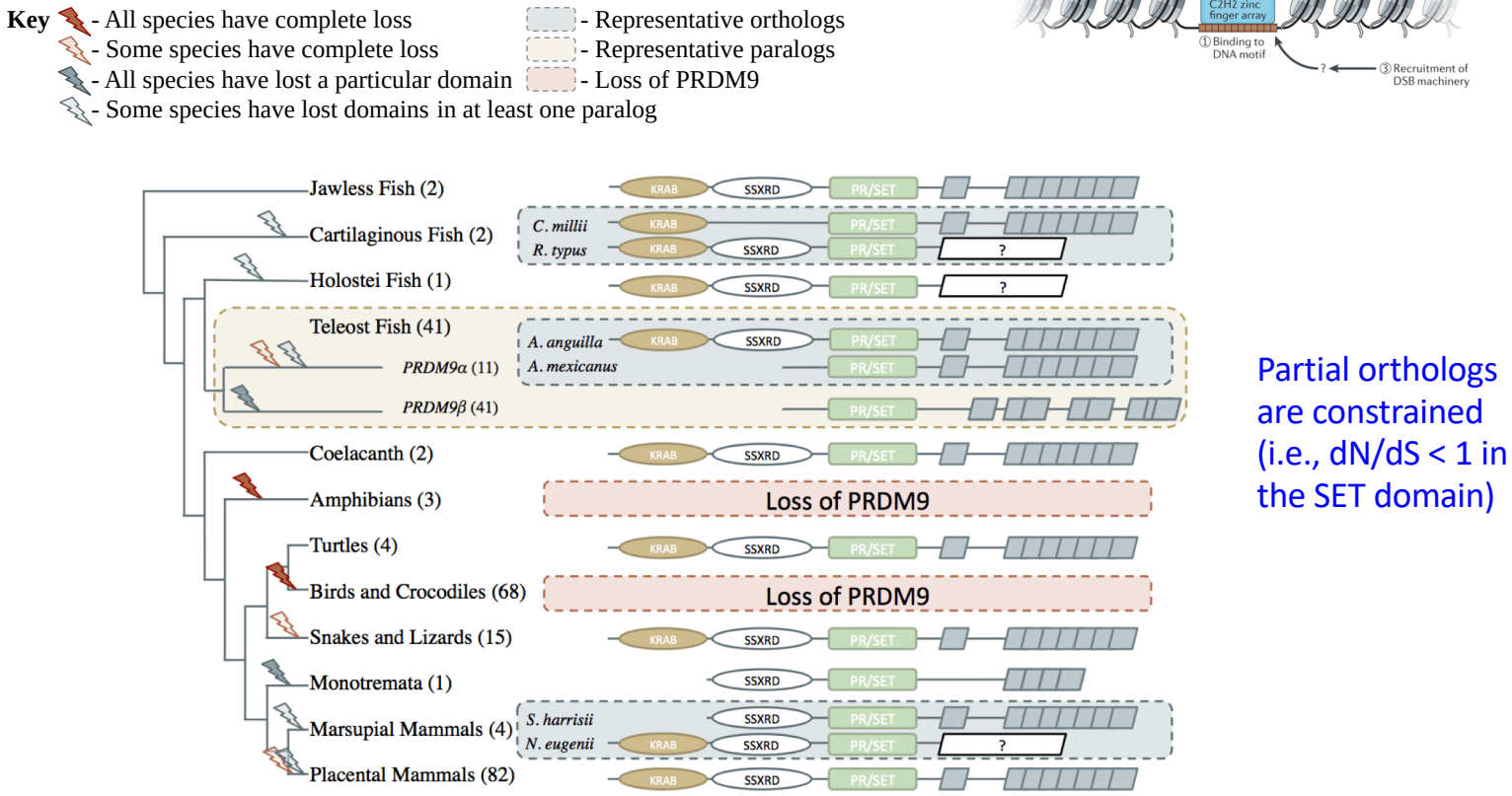
Yuki Haba
(MA student, now Princeton grad)

Baker, Schumer et al. 2017 eLife

How general is this?

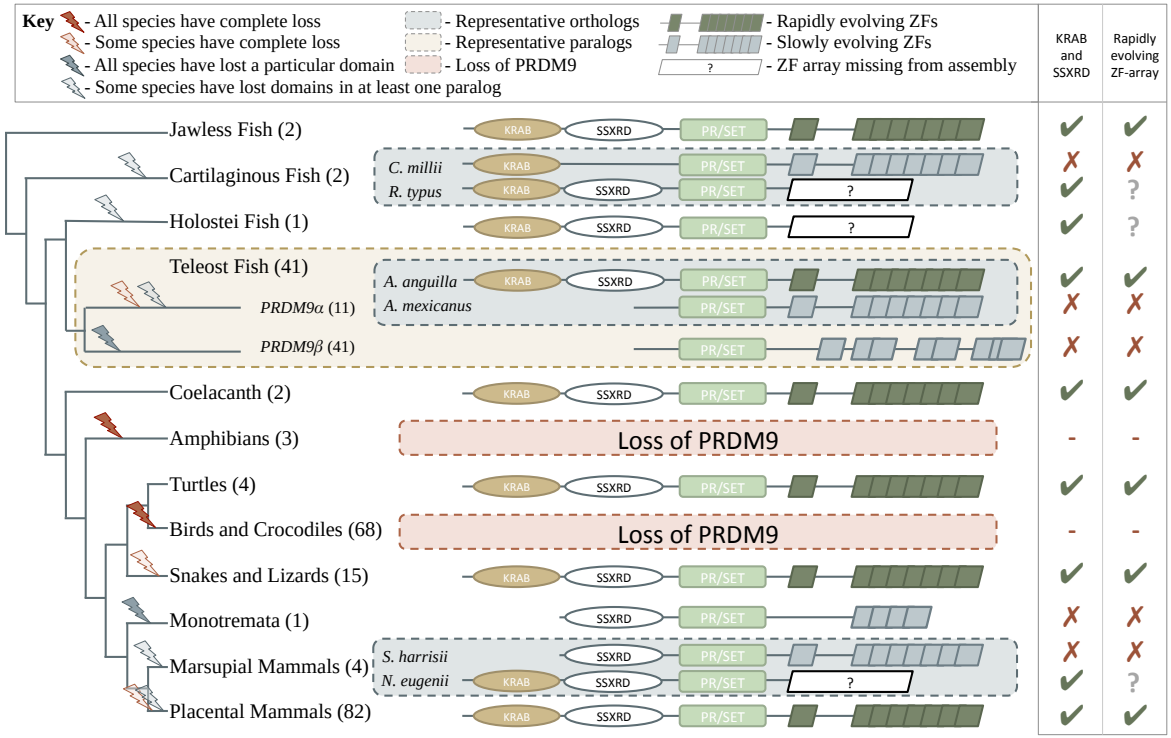


PRDM9 in (225) vertebrates



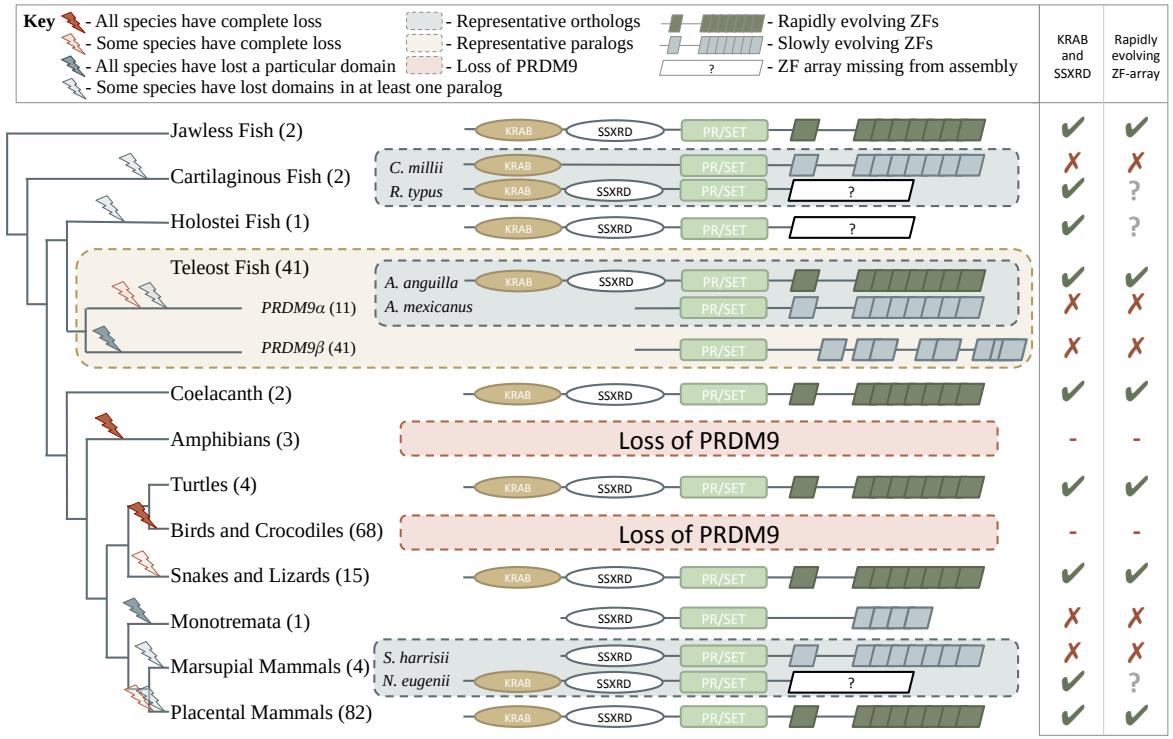
Partial orthologs are constrained (i.e., dN/dS < 1 in the SET domain)

The ZF evolves rapidly if & only if the gene is intact



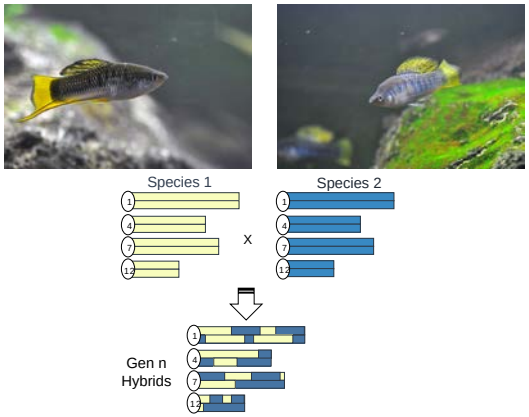
$p < 10^{-6}$, controlling for the phylogeny

Role in recombination of partial ortholog?

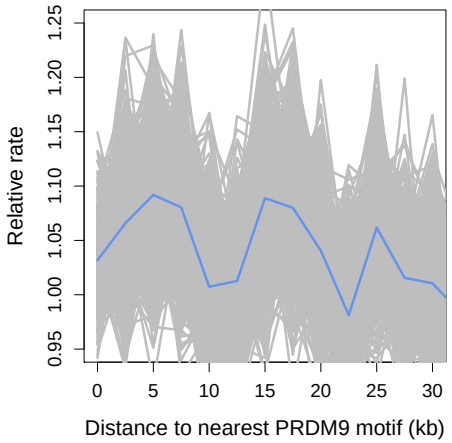


Swordtail fish carry only one, partial ortholog

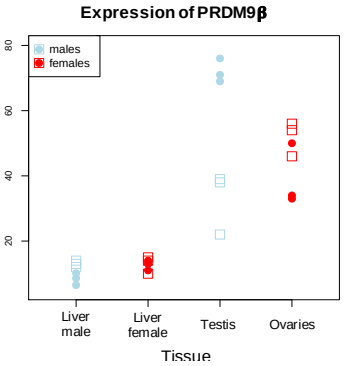
An admixture-based genetic map

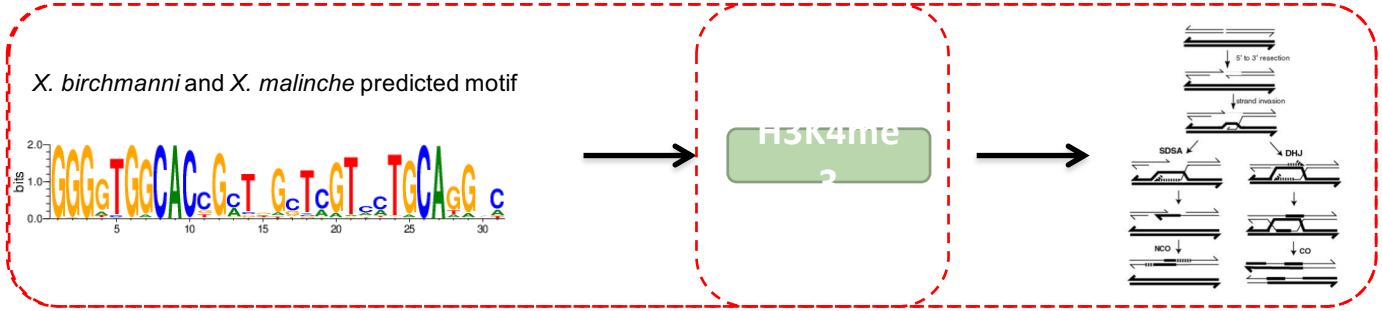


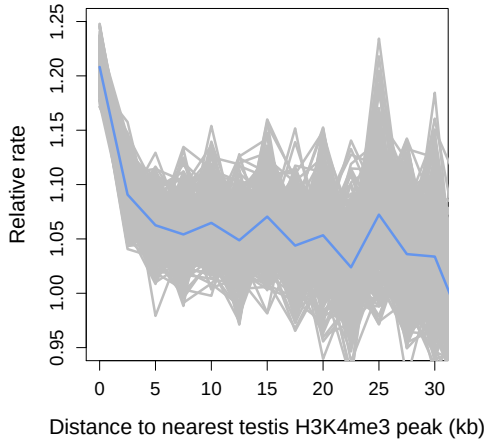
Sequenced 286 hybrids at ~1X coverage

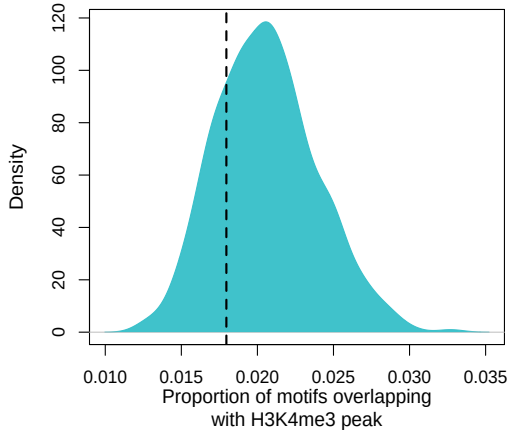


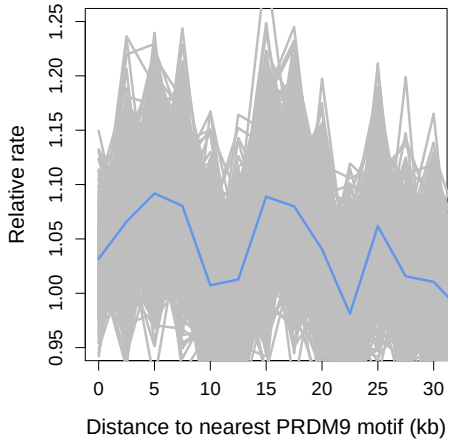
Role in recombination of partial ortholog?







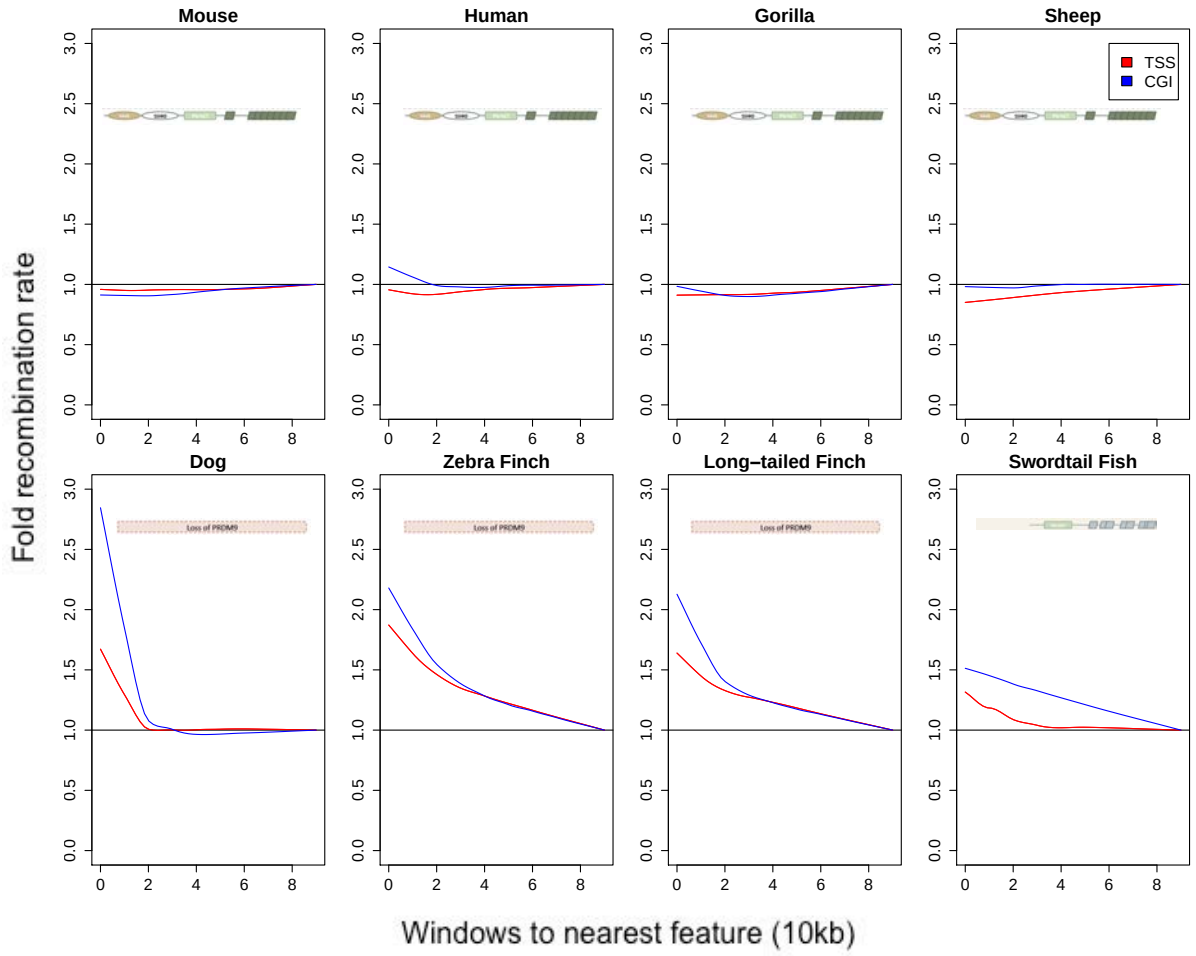




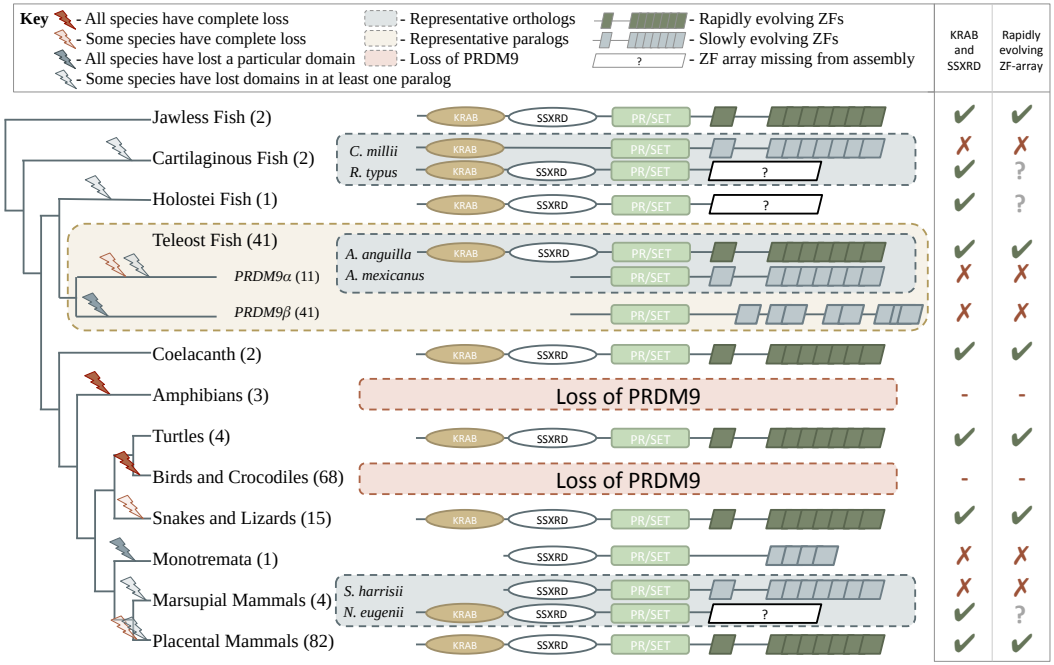
H3K4me3 is associated with the recombination rate

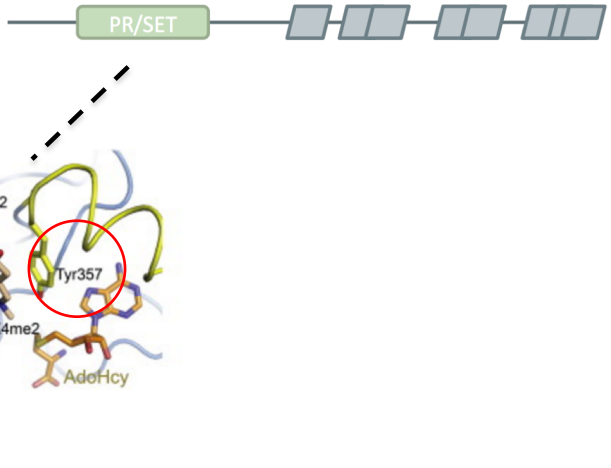
PRDM9 binding motif not associated with H3K4me3

PRDM9 binding motif not associated with increased recombination

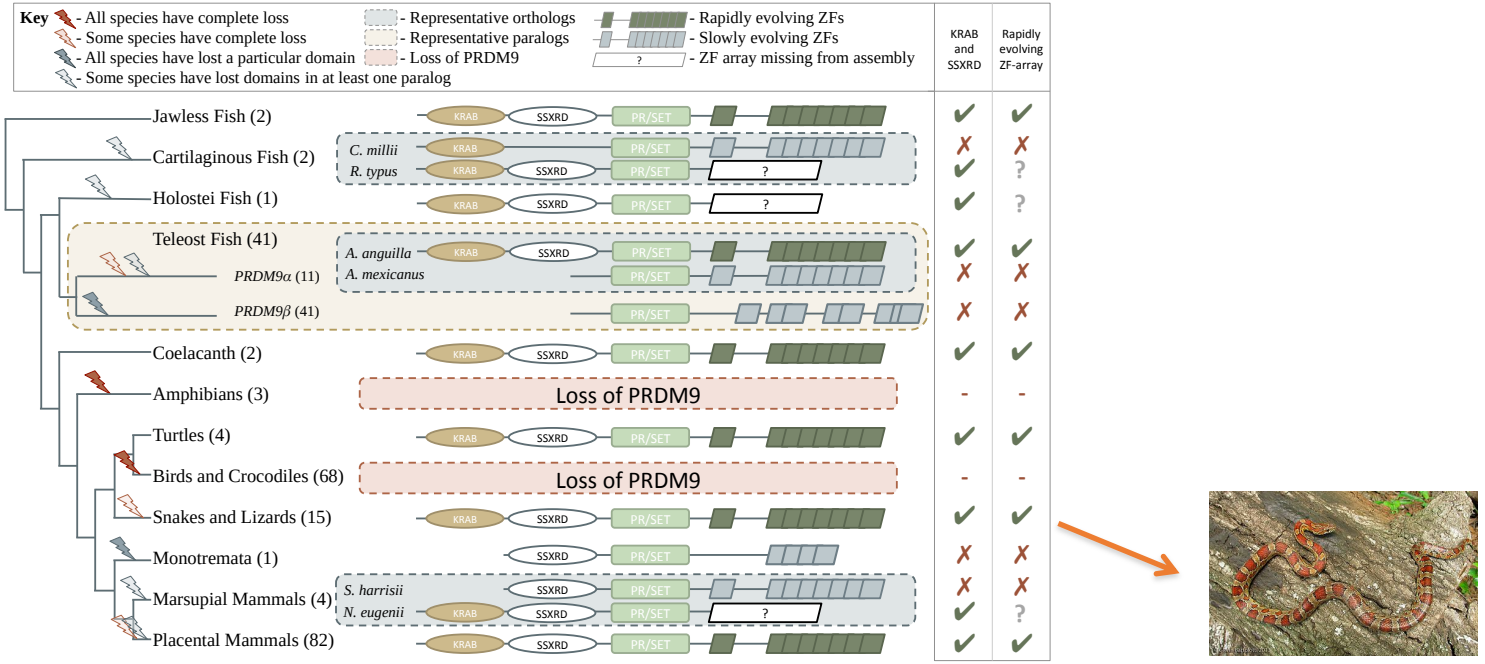

Mouse
Human
Gorilla
Sheep
Dog
Zebra Finch
Long−tailed Finch
Swordtail Fish
TSS
CGI
Fold recombination rate
Windows to nearest feature (10kb)

The partial ortholog of PRDM9 does not direct recombination



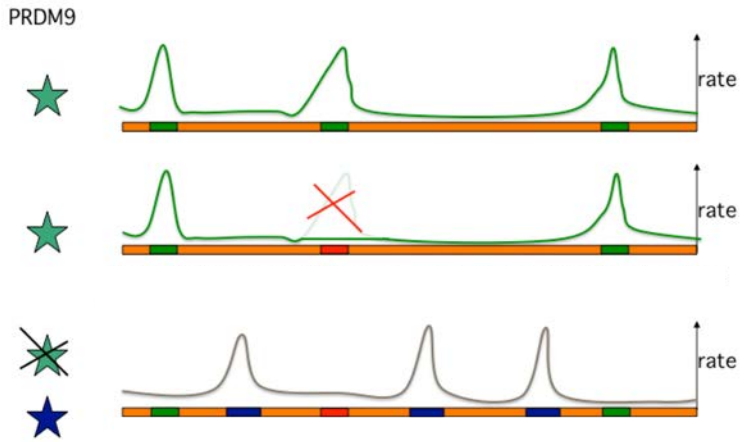


Does the complete ortholog of PRDM9 direct recombination outside of mammals?



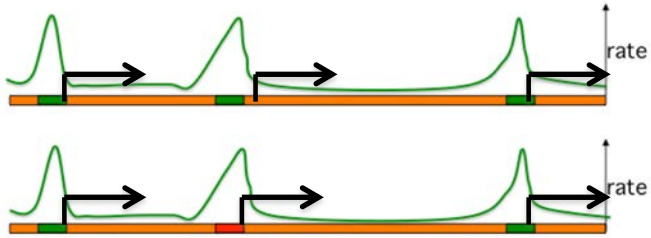
Two mechanisms for directing recombination in vertebrates

Directed by the complete PRDM9

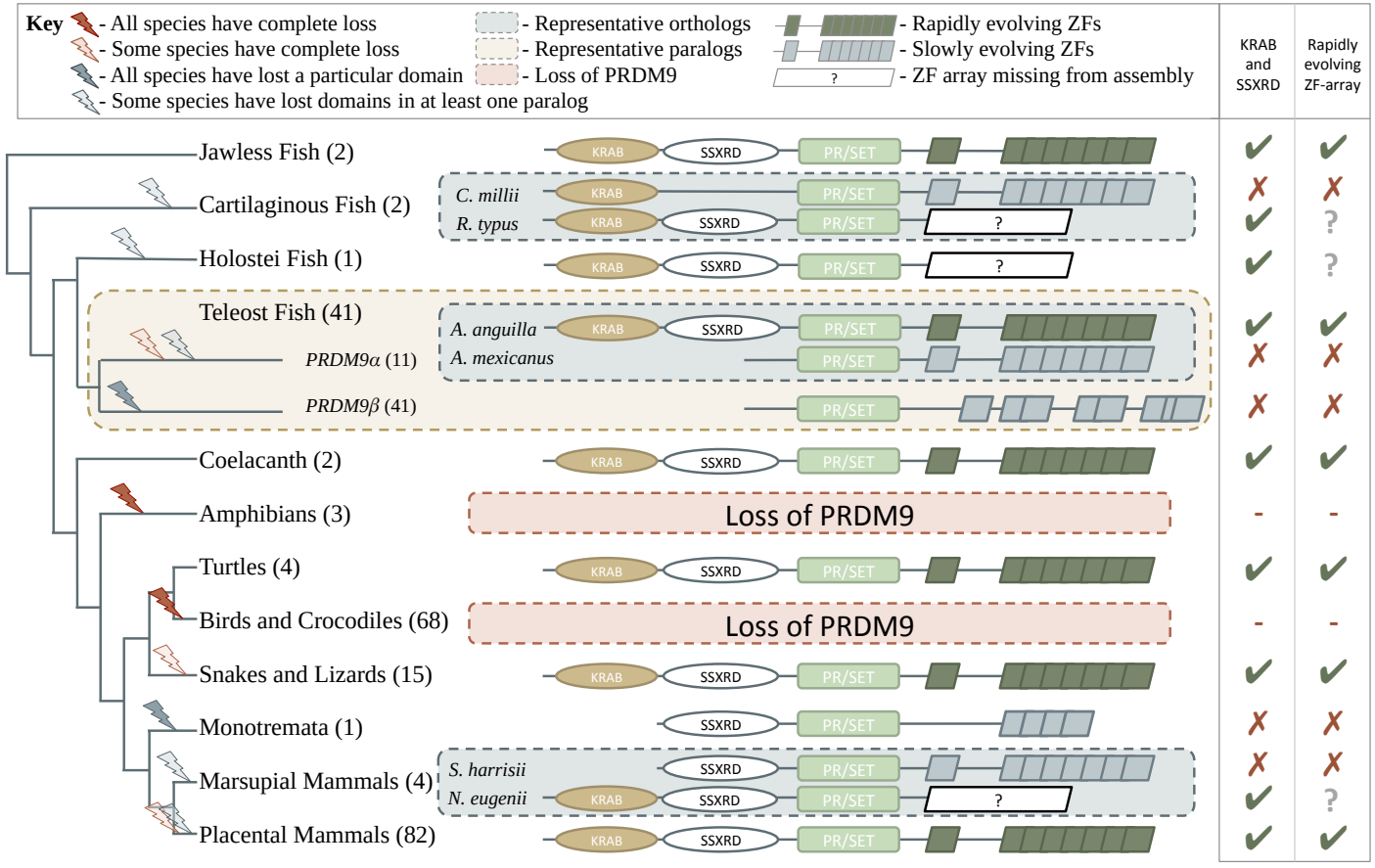


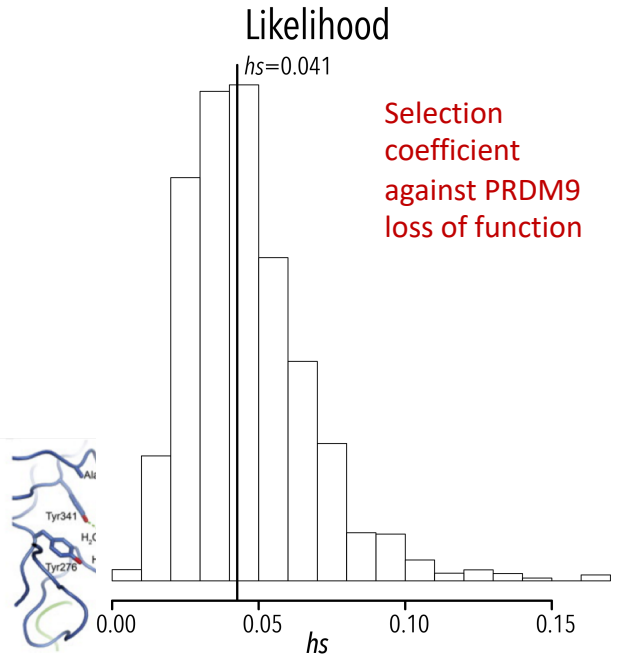
primates, rodents, snakes (?)
Also turtles, some fish?

Without a complete PRDM9



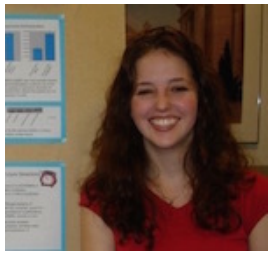
birds, some fish
amphibians, monotremes?





Zachary Fuller

Implications for patterns of between species introgression



Molly Schumer
(soon faculty, Stanford)

Schumer et al. 2018 Science

Many species have hybridized or are hybridizing

Staubach et al 2012

Rosenthal et al 2003

Green et al 2010

Brelsford et al 2011

Arnold et al 1993

Dasmahapatra et al. 2012

Carney et al 2000

Many species have hybridized or are hybridizing

Staubach et al 2012

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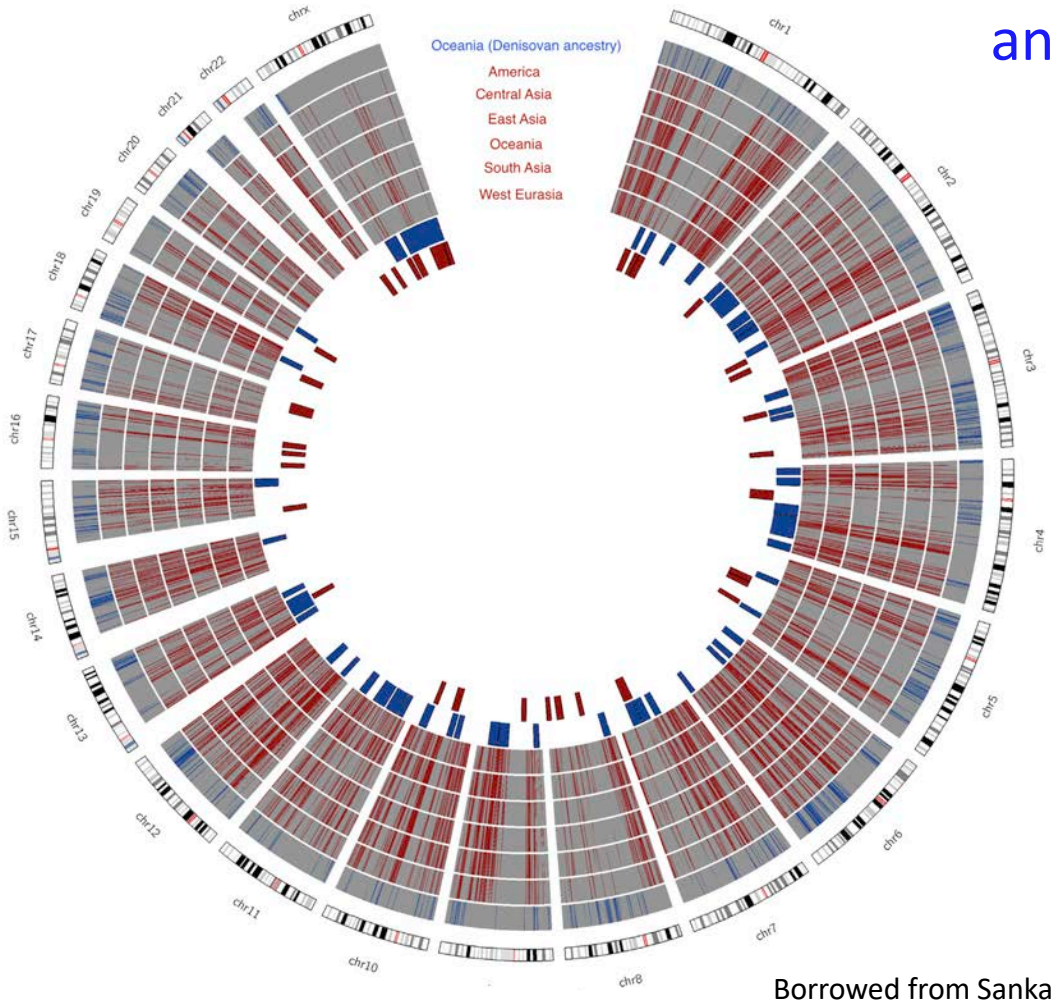
Arnold et al 1993

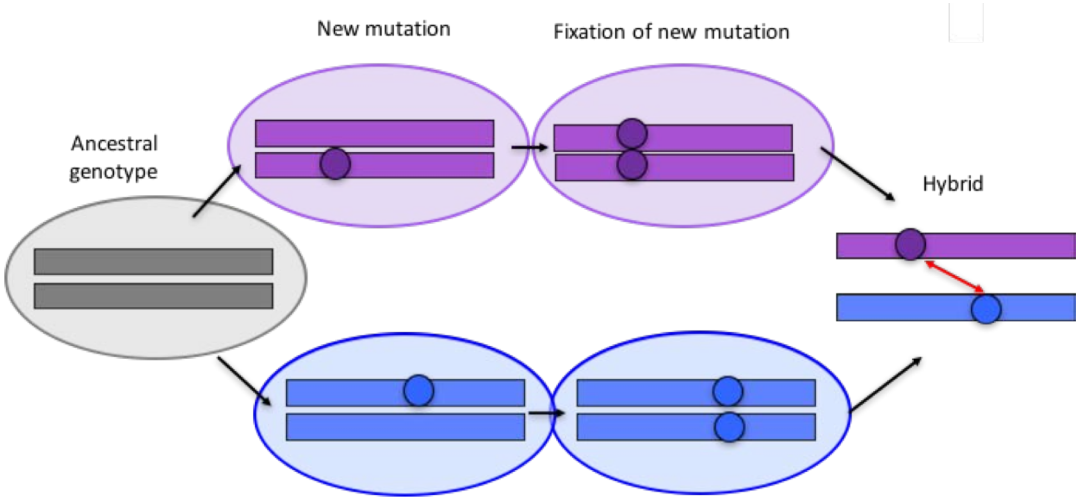
Carney et al 2000

Da: mahapatra et al. 2012

Europeans have ~2% Neanderthal ancestry

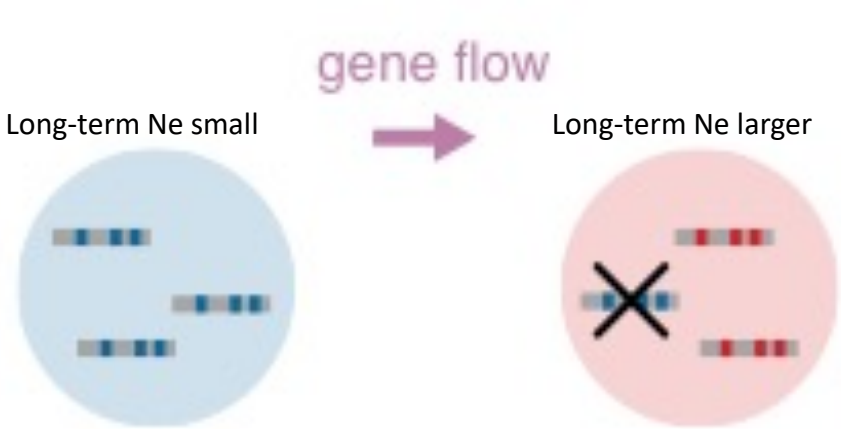


Borrowed from Sankararaman et al. 2016



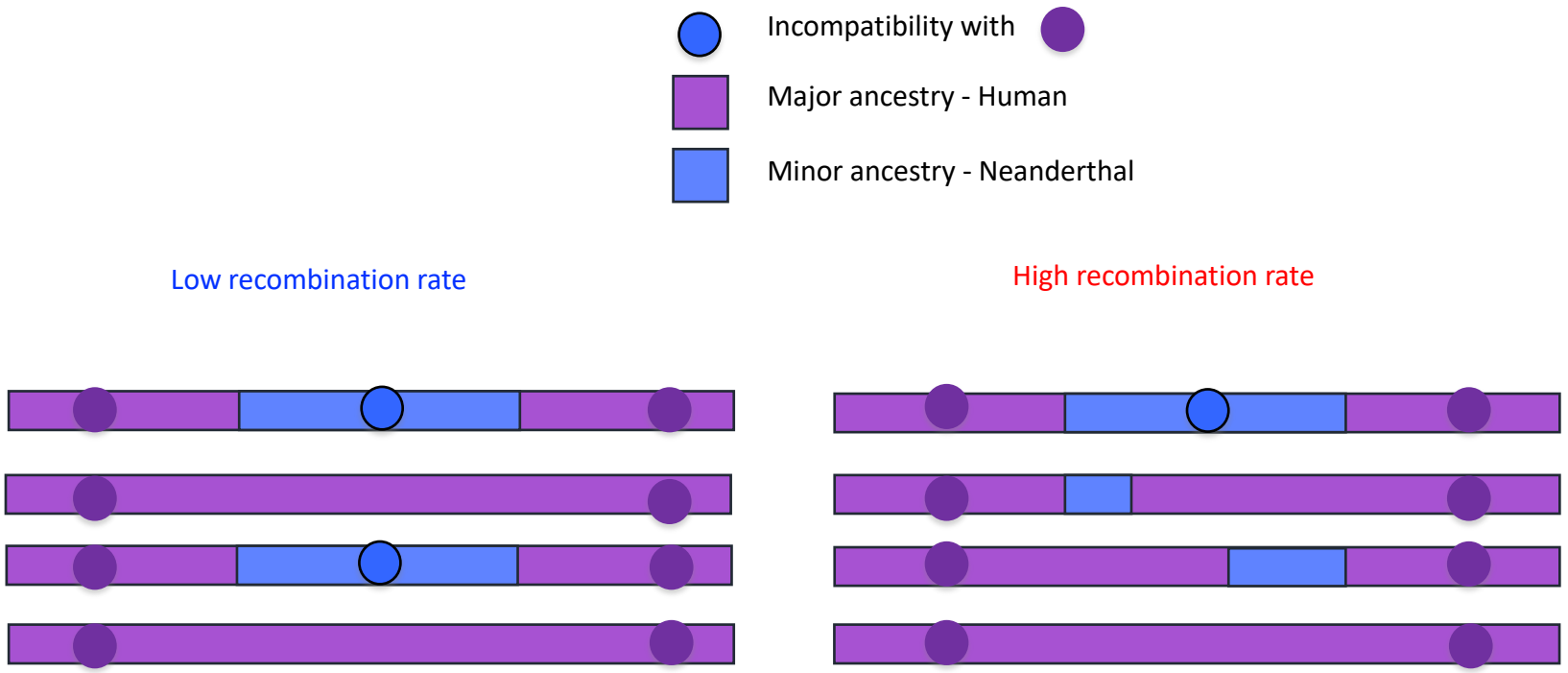
Dobzhansky-Muller incompatibilities

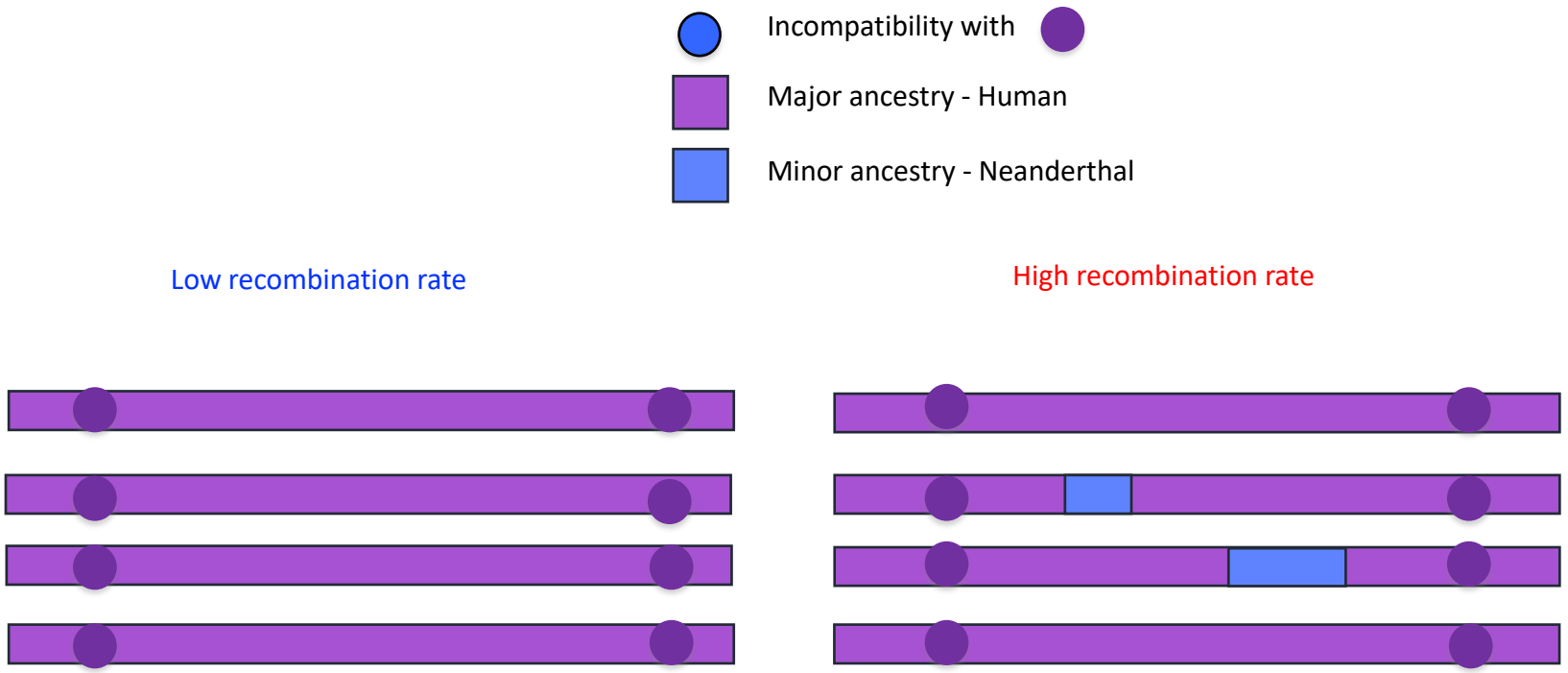
PRDM9 is an example of a DMI in some mice crosses



Harris & Nielsen 2016; Juric et al. 2016

Figure from Simon Aeschbacher


Incompatibility with
Major ancestry - Human
Minor ancestry - Neanderthal
Low recombination rate
High recombination rate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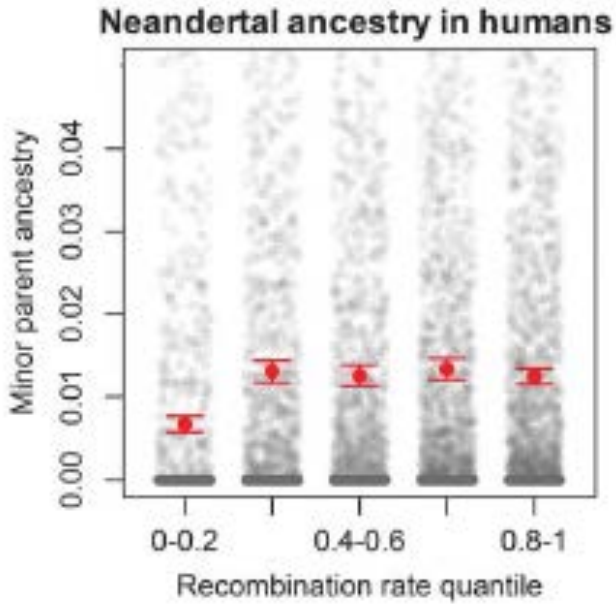
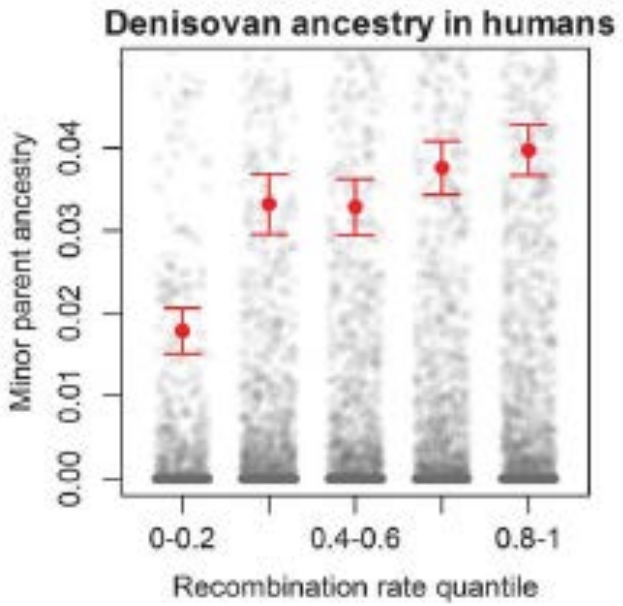
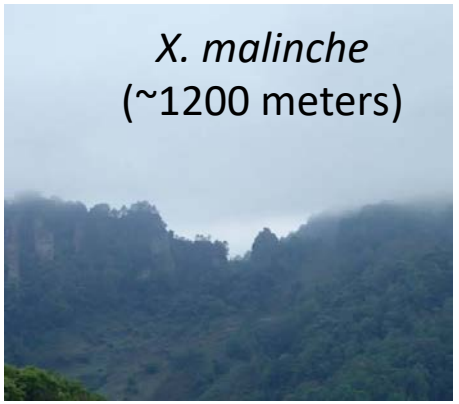




Population	Spearman's correlation between minor ancestry and rate		
	50 kb	250 kb	500 kb
Neandertal ancestry in humans (diCal-admix)	$\rho = 0.09$ $p = 10^{-17}$	$\rho = 0.17$ $p = 10^{-33}$	$\rho = 0.19$ $p = 10^{-42}$
Denisovan ancestry in humans	$\rho = 0.08$ $p = 10^{-14}$	$\rho = 0.14$ $p = 10^{-24}$	$\rho = 0.15$ $p = 10^{-29}$

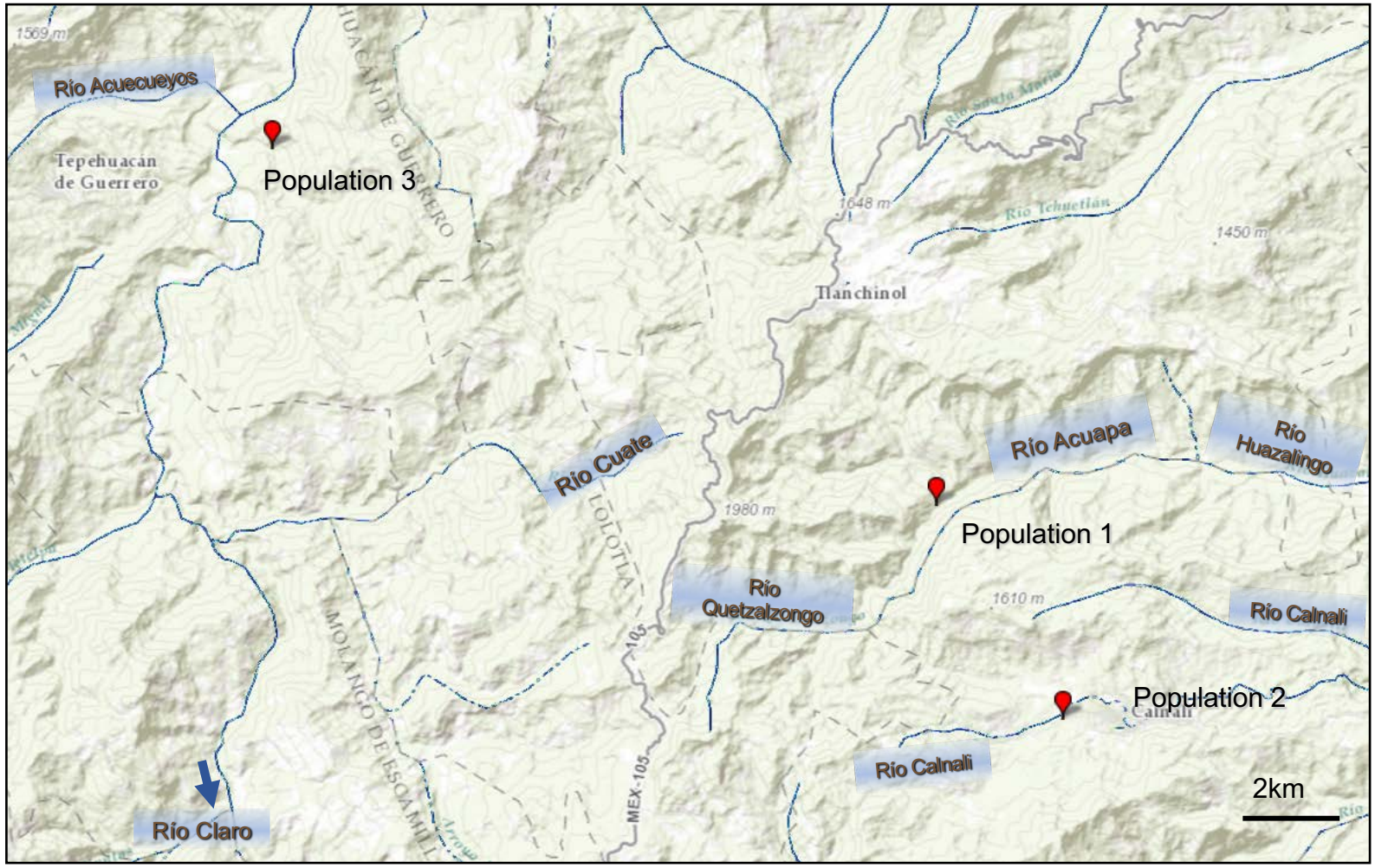
Hybridization between swordtail species

0.5% sequence divergence



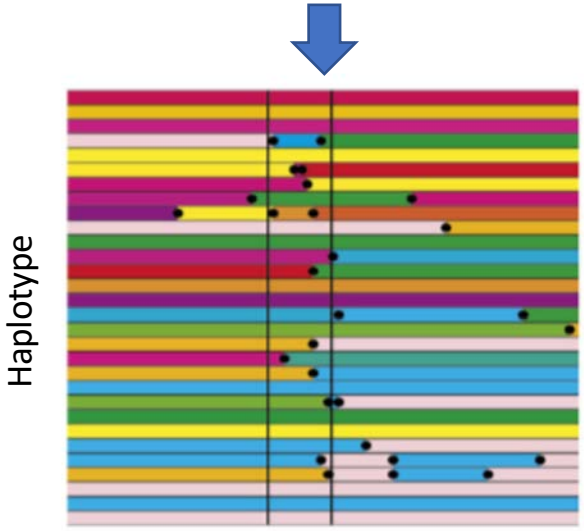
X. birchmanni
(~400 meters)

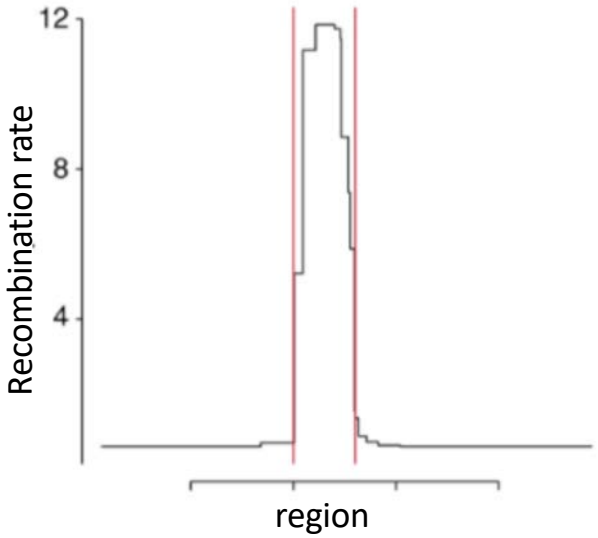
Three independent hybrid populations in Mexico



A fine-scale genetic map for *X. birchmanni*

>30X genomes
20 unrelated *X. birchmanni*
& five offspring of two individuals

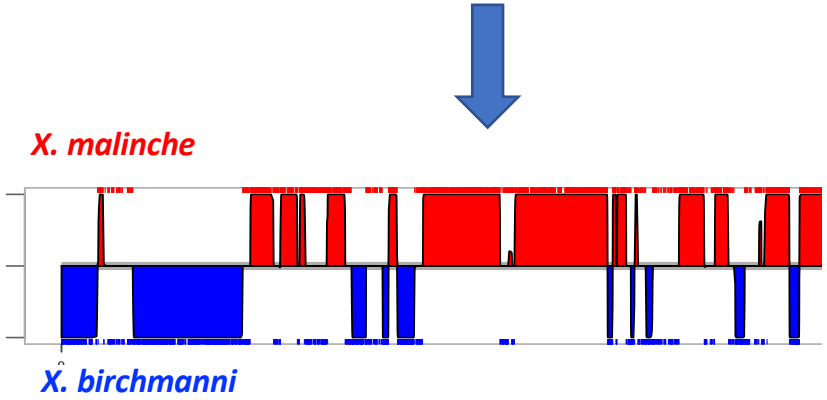


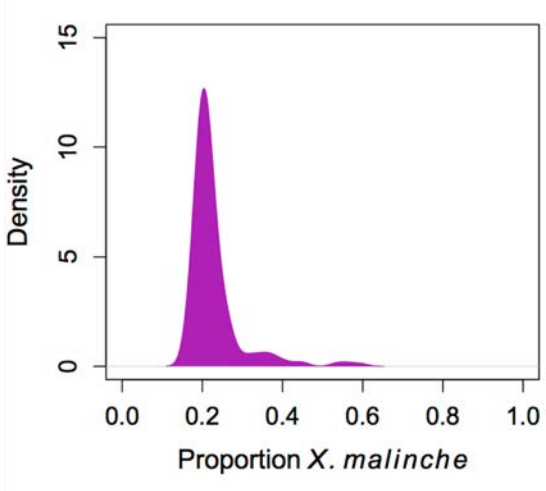


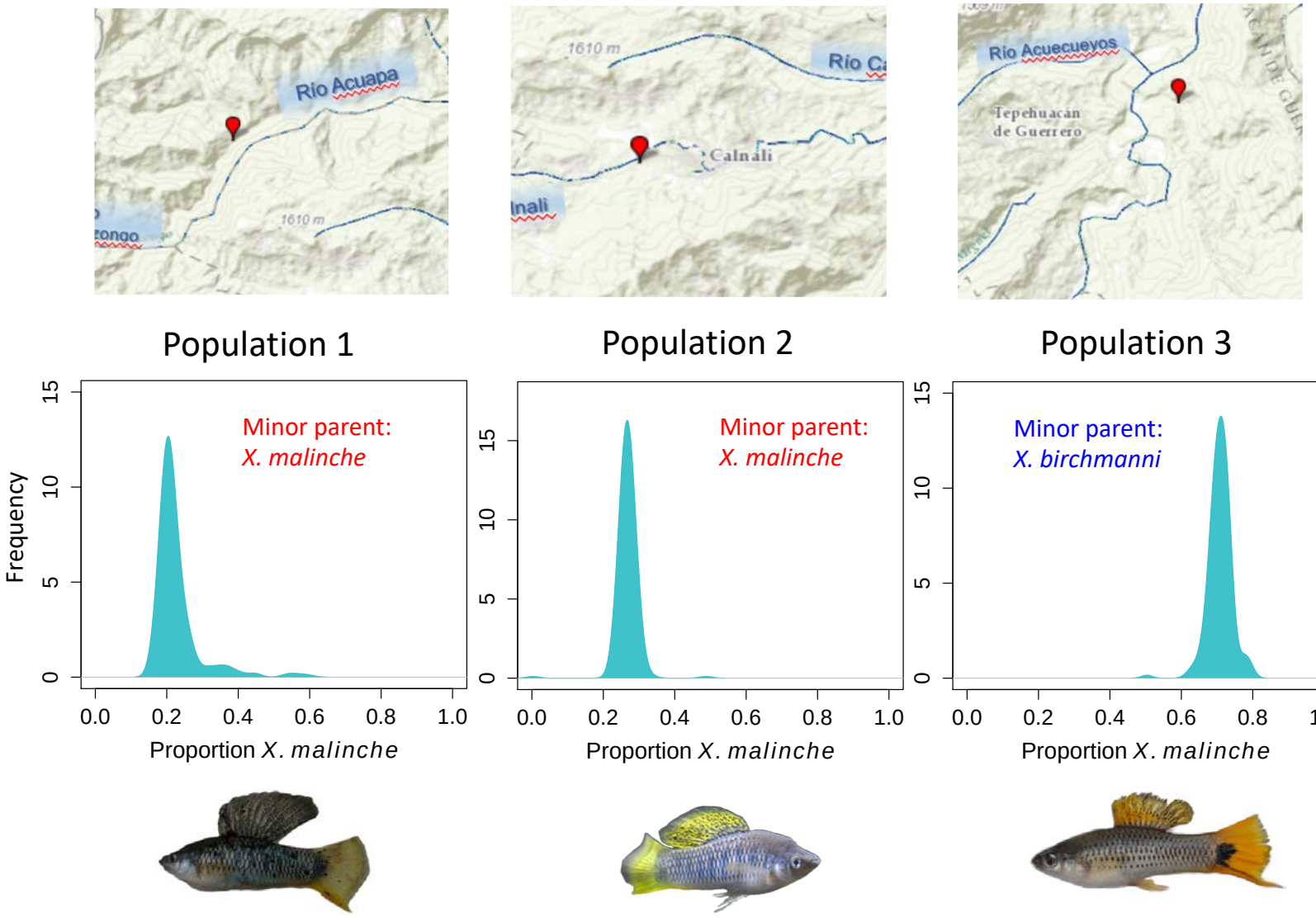
Borrowed from Hellenthal & Stephens 2006

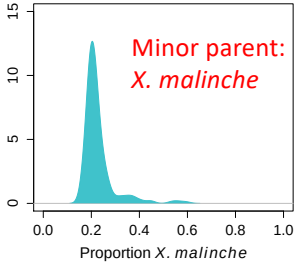
Ancestries of the three hybrid populations

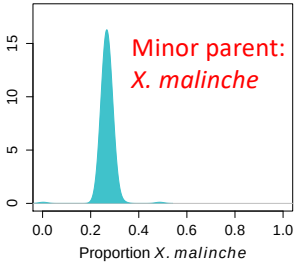
~1X genome coverage for 690 hybrids
from the three hybrid populations

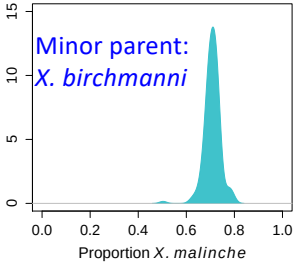




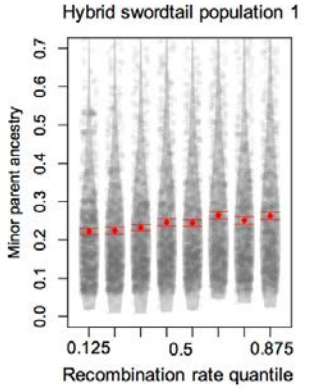

Río Acuapa
1610 m
Río Ca
1610 m
Calnali
Río Acuecueyos
Tepehuacan
de Guerrero
Population 1
Population 2
Population 3
Frequency
Minor parent:
X. malinche
Minor parent:
X. malinche
Minor parent:
X. birchmanni
0
5
10
15
0.0
0.2
0.4
0.6
0.8
1.0
Proportion X. malinche

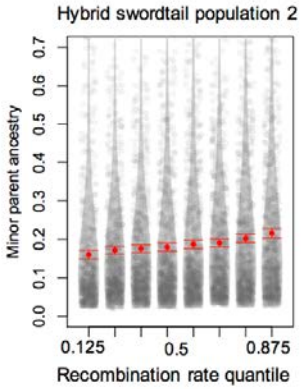


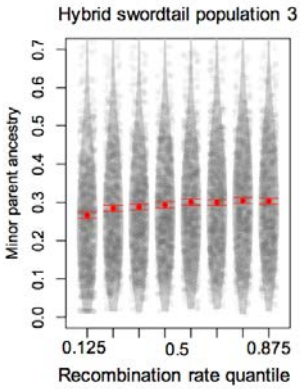


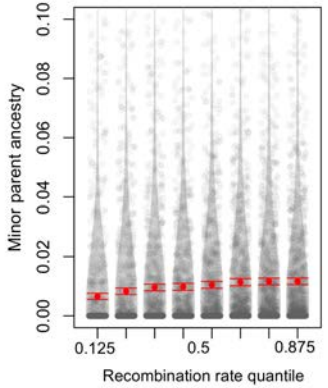


Minor parent:
Neanderthal

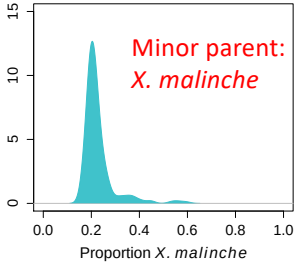


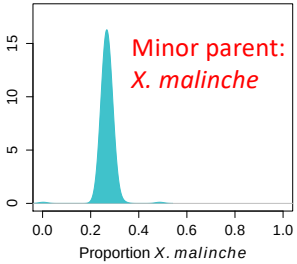


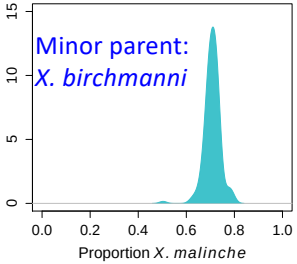




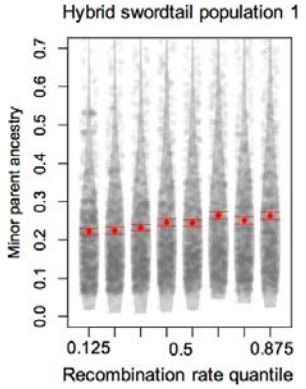
at a 50 kb scale, ρ=0.15, p=10^{-7} in pop. 1; ρ =0.10, p=8x10^{-4} in pop. 2; ρ = 0.10, p=10^{-4} in pop. 3; ρ = 0.08, p=10^{-8} in humans

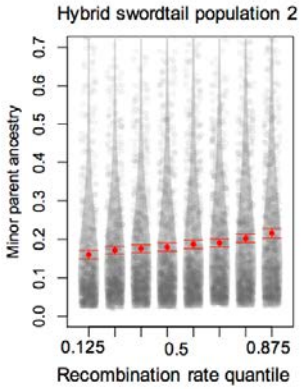


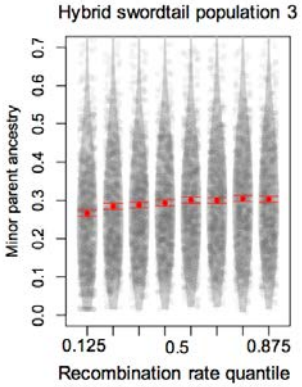


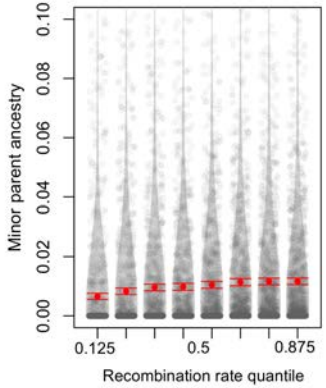


Minor parent:
Neanderthal

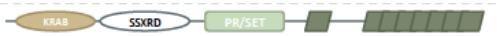


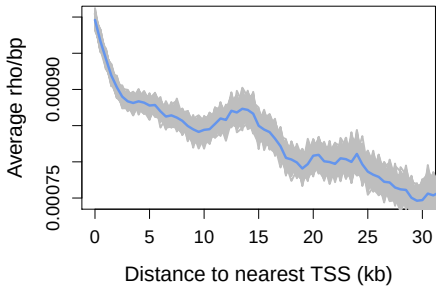


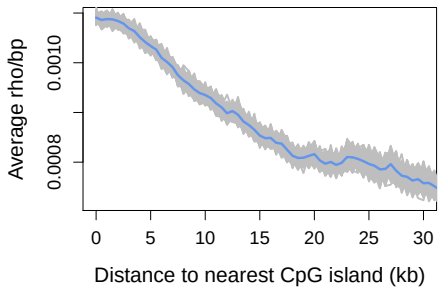


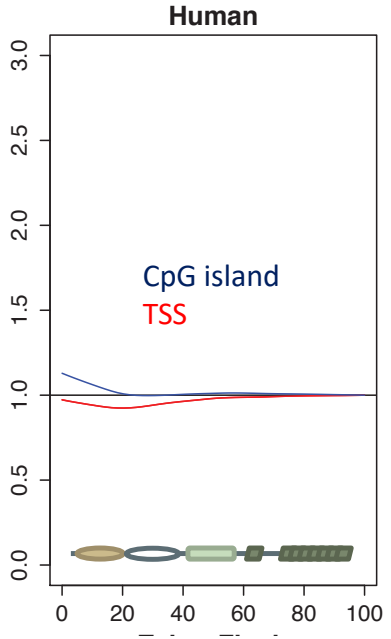


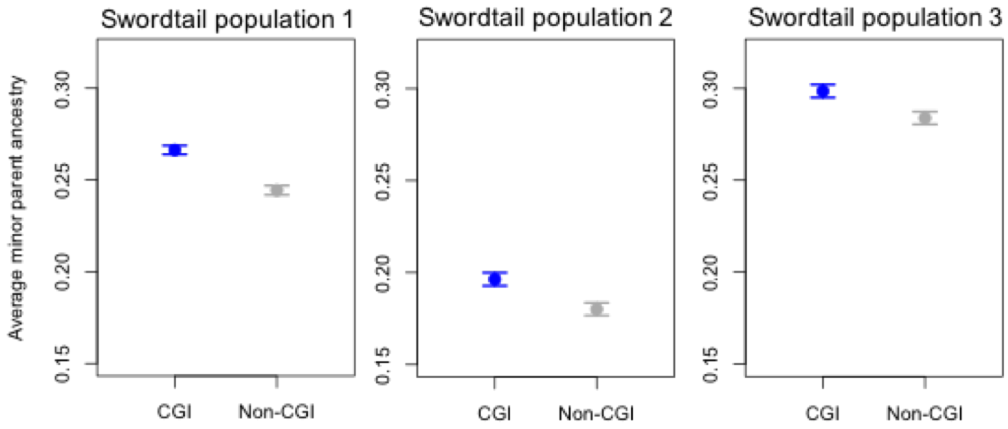

PR/SET

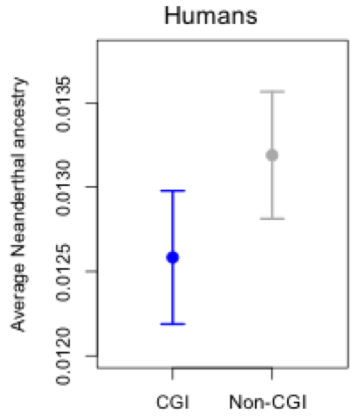

KRAB
SSXRD
PR/SET


Average rho/bp
0.00090
0.00075
0
5
10
15
20
25
30
Distance to nearest TSS (kb)

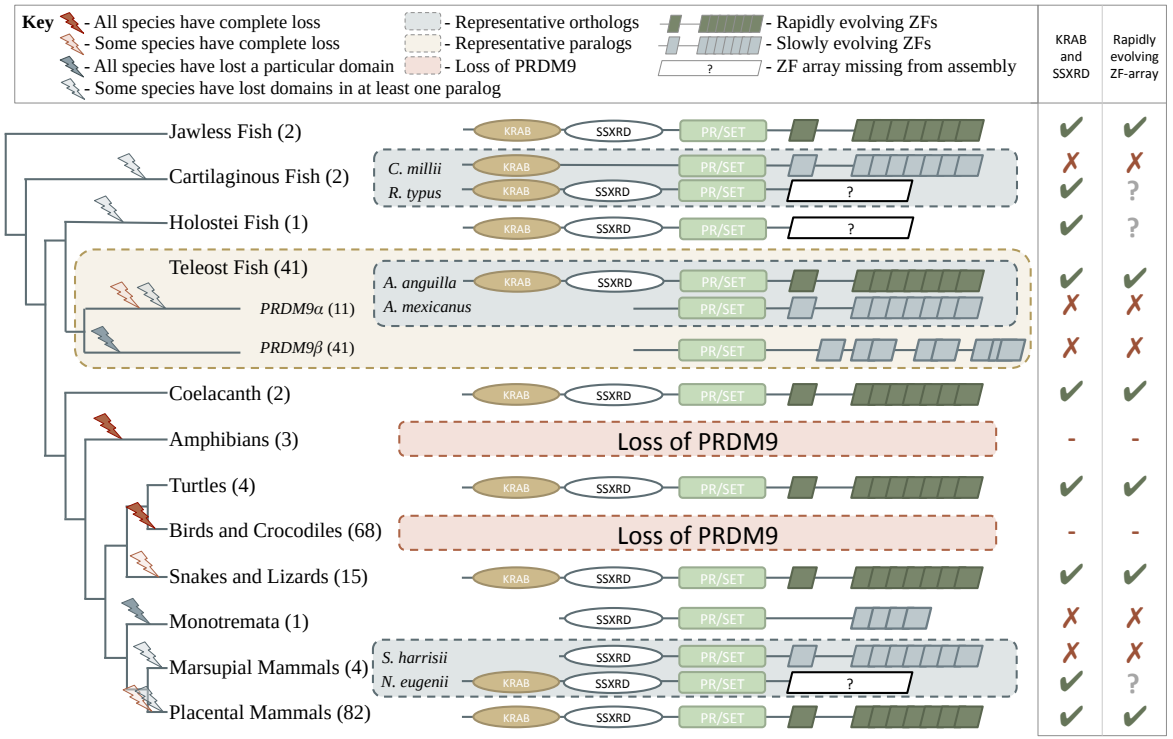

Average rho/bp
0.0010
0.0008
0
5
10
15
20
25
30
Distance to nearest CpG island (kb)


Human
CpG island
TSS
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
100





One-tailed $p < 0.005$ in all three populations


Key
- All species have complete loss
- Some species have complete loss
- All species have lost a particular domain
- Some species have lost domains in at least one paralog
- Representative orthologs
- Representative paralogs
- Loss of PRDM9
- Rapidly evolving ZFs
- Slowly evolving ZFs
- ZF array missing from assembly
KRAB and SSXRD
Rapidly evolving ZF-array
Jawless Fish (2)
Cartilaginous Fish (2)
C. millii
R. typus
Holostei Fish (1)
Teleost Fish (41)
PRDM9α (11)
PRDM9β (41)
A. anguilla
A. mexicanus
Coelacanth (2)
Amphibians (3)
Loss of PRDM9
Turtles (4)
Birds and Crocodiles (68)
Loss of PRDM9
Snakes and Lizards (15)
Monotremata (1)
Marsupial Mammals (4)
S. harrisii
N. eugenii
Placental Mammals (82)
KRAB
SSXRD
PR/SET
?

Summary

- Vertebrates seem to employ at least two strategires to direct recombination to the genome: through PRDM9 binding or by using promoter-like features

- The use of PRDM9 to direct recombination is associated with rapid evolution of the zinc finger and of recombination hotspots. In contrast, using promoter like features is associated with the conservation of hotspots.

- Recombination is an important predictor of where introgression occurs between hybridizing species. Therefore introgression patterns may differ between species that do and do not use PRDM9.