CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2017-2018 :
"Le chromosome X -
paradigme de la génétique et l'épigénetique"

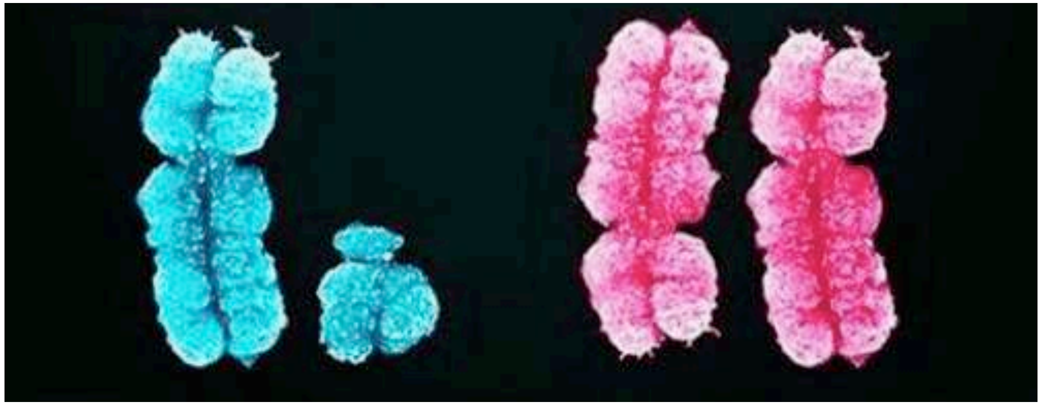
29 janvier, 2018

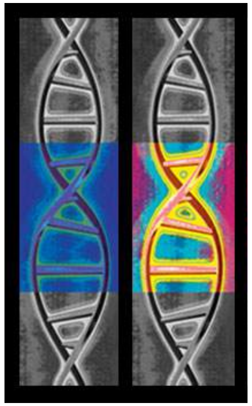
Cours I
Chromosomes sexuels et compensation de dose
Sex chromosomes and Dosage Compensation

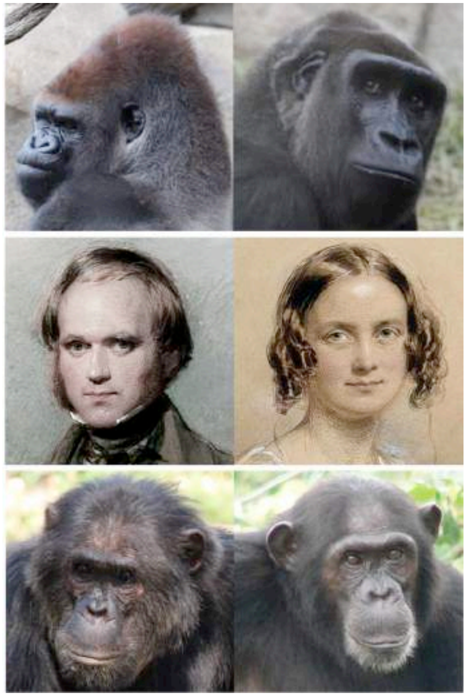
E. Heard, January 29th, 2018

COLLÈGE
DE FRANCE
1530

Sex Chromosomes
At the interface between Genetics and Epigenetics



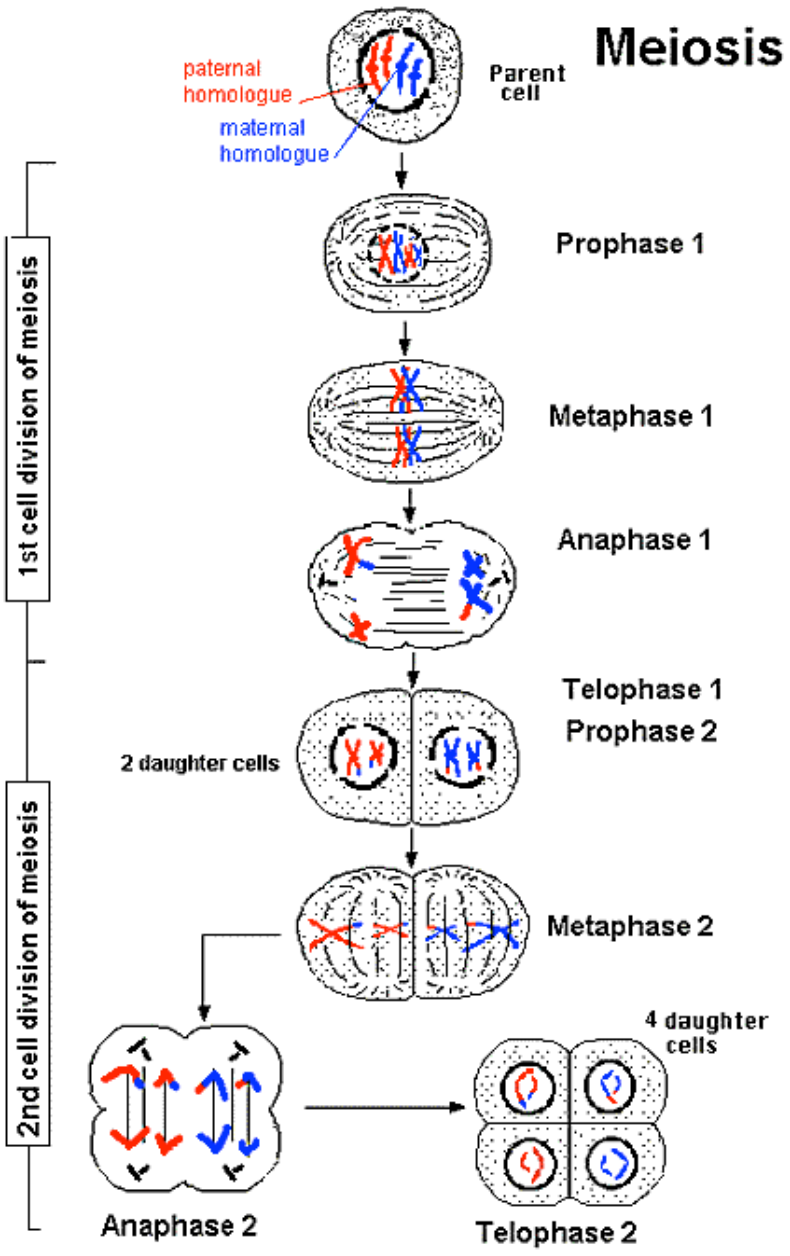




Discovery of Sex Chromosomes

Hermann Paul August Otto Henking
(cytologist 1858-1942)

- Discovered the X chromosome in ~1891.
- Light microscopy: testicles of the firebug (Pyrrhocoris) Henking noted that one chromosome did not take part in meiosis.
- Named the **X element** because its strange behavior made him unsure whether it was genuinely a chromosome.
- Later known as the **X chromosome**
- Speculated it might play a role in sex determintation



Henking H. 1891 Uber spermatogenese und deren beziehung zur entwicklung bei Pyrrhocoris apterus L. Z. Wiss. Zool. 51, 685–736.

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Prior to Henking, McClung, and Sutton's reports, sex determination was attributed to factors other than gametes, such as the environment in which egg cells existed.

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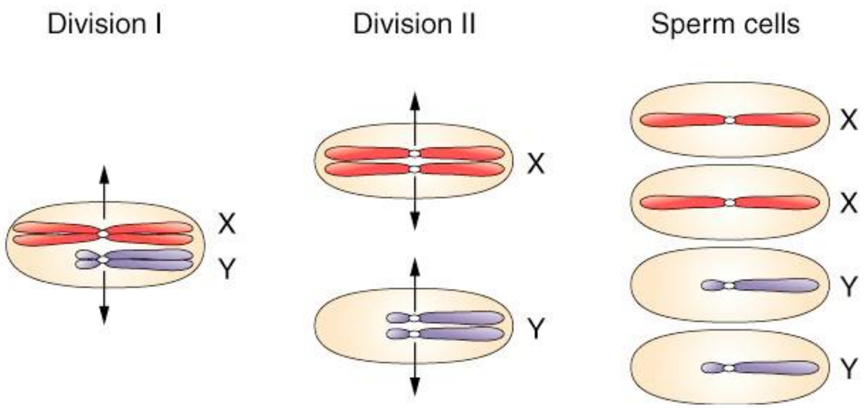
CE McClung (US geneticist)

- Renamed the X element the "accessory chromosome," because it appeared to have a separate purpose compared to the other chromosomes.
- Noted two types of sperm cells (50/50) with or without the Accessory chromosome
- 1901/1902- proposed that this could influence sex determination of the zygote



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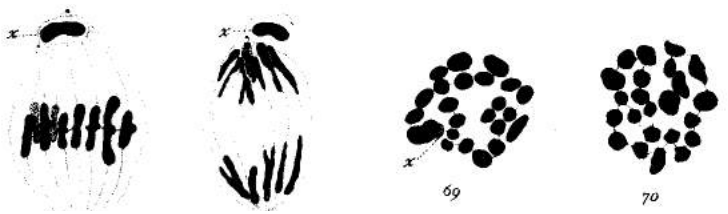


- Nettie Stevens analyzed beetle karyotypes and found that females' diploid cells contain 20 large chromosomes; but males' diploid cells have 19 large and 1 small (Y) chromosomes.
  - Y chromosomes pair with the large X chromosome during meiosis I.

- X and Y chromosomes are now called **sex chromosomes**—they determine the sex of the offspring.
  - In beetles, females have two X chromosomes while males have an X and Y.
    - Other species have other systems.

EB Wilson
(1856-1939,
US geneticist)

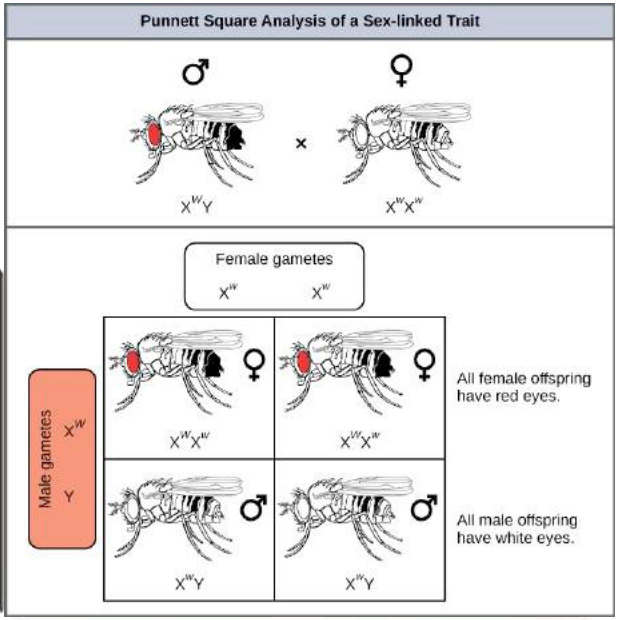
1905: Co-discovery of sex chromosomes
and their proposed role in sex determination
Nettie Stevens and EB Wilson

Discovery of Sex Chromosomes

Morgan definitively linked “trait” inheritance to a specific chromosome

Using the fruitfly Drosophila melanogaster - he demonstrated that traits could in fact be passed on in the same manner predicted by the inheritance of sex chromosomes.

Thomas Hunt Morgan
(1866-1945)
(US evolutionary biologist, geneticist)



Nobel Prize in 1933
for “discoveries elucidating the role that the chromosome plays in heredity”

E. Heard, January 29th, 2018

Discovery of Sex Chromosomes

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His student – Muller - later discovered dosage compensation based on the the same trait (eye color).

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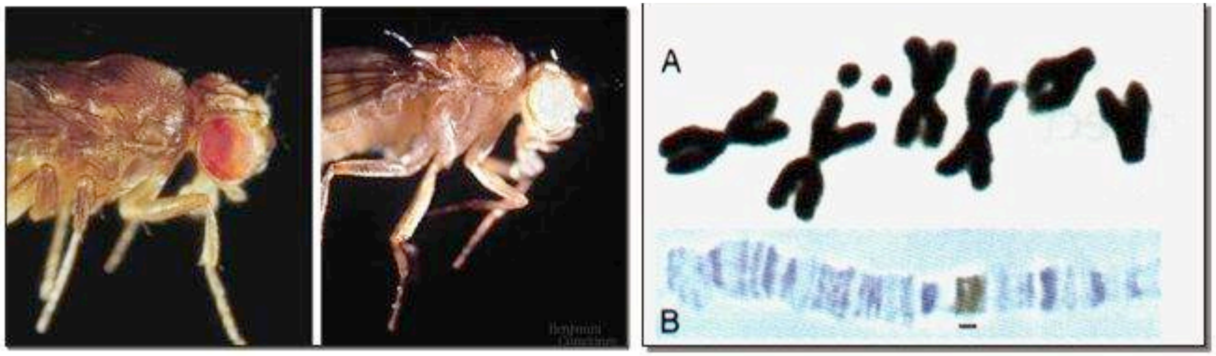

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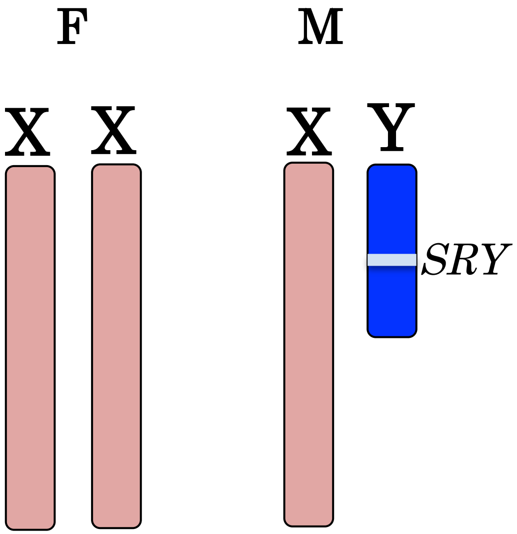
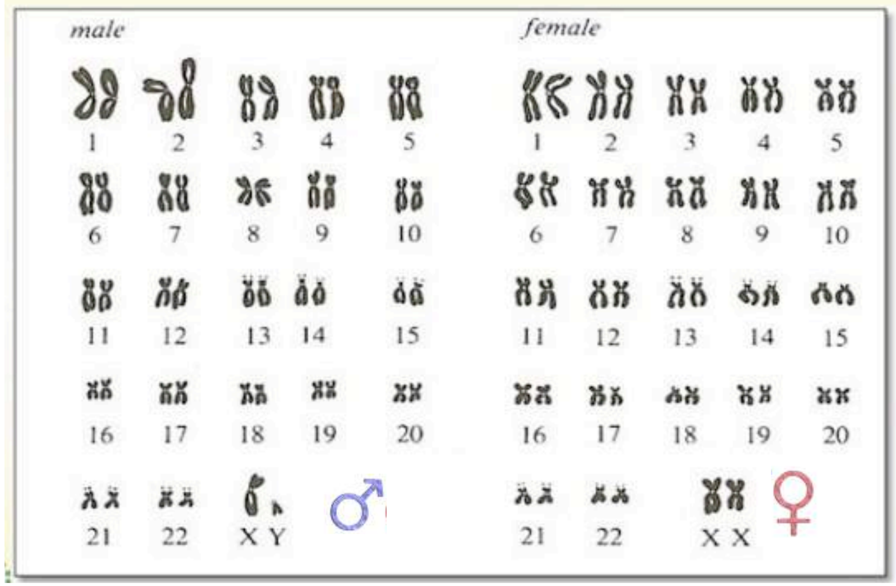
Sex chromosome systems

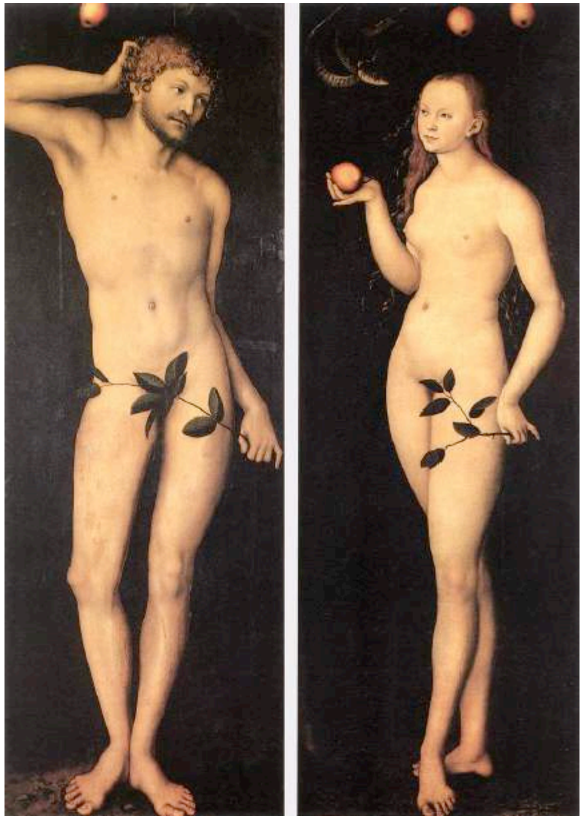
Male heterogamety



Male dominant gene on Y
e.g. SRY, human

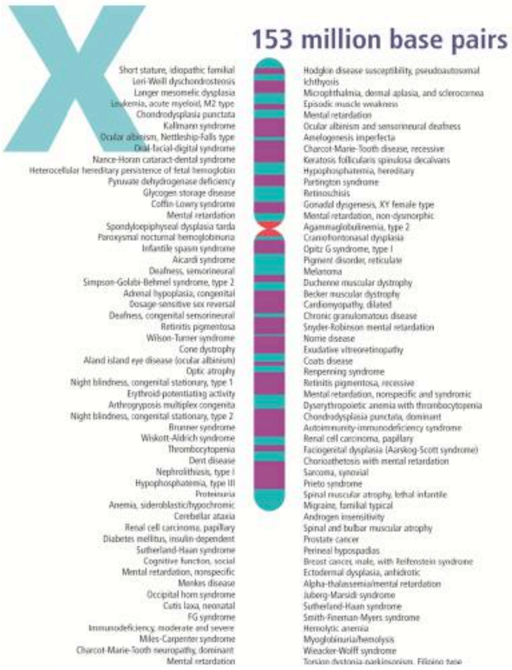
Human Sex Chromosomes

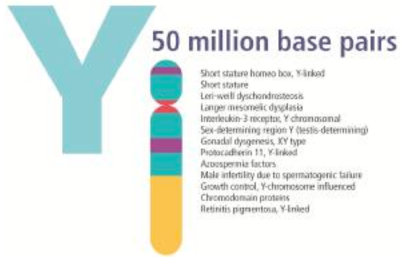




- Humans normally have 46 chromosomes:
- 23 pairs, one set from each parent
- 1 pair of chromosomes = the sex chromosomes, X and Y
- The other chromosomes are numbered 1-22
- A person with 2 X chromosomes (46, XX) is female
- A person with an X and a Y (46, XY) is male
- The sex chromosomes lead to dramatic differences in gene content and expression => How is this tolerated? How did it evolve?

Human Sex Chromosomes





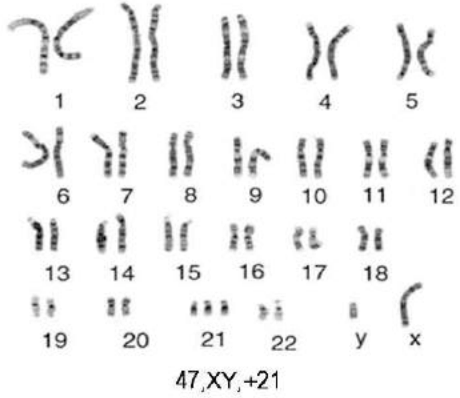
X: 1300 genes

Y: ~50 genes

Sry (testis determinant factor)

Eif2s3y (spermatogenesis)

Down's syndrome:
Trisomy 21



Why have Sex Chromosomes?

- Pairing problems during meiosis
- Frequent sex-linked diseases (hemizygosity in one sex)
- Gene dosage problems

1) One X vs two Autosomes in males

2) Two Xs in females vs one X in males

Sex chromosomes evolve as a consequence of Sexual Reproduction

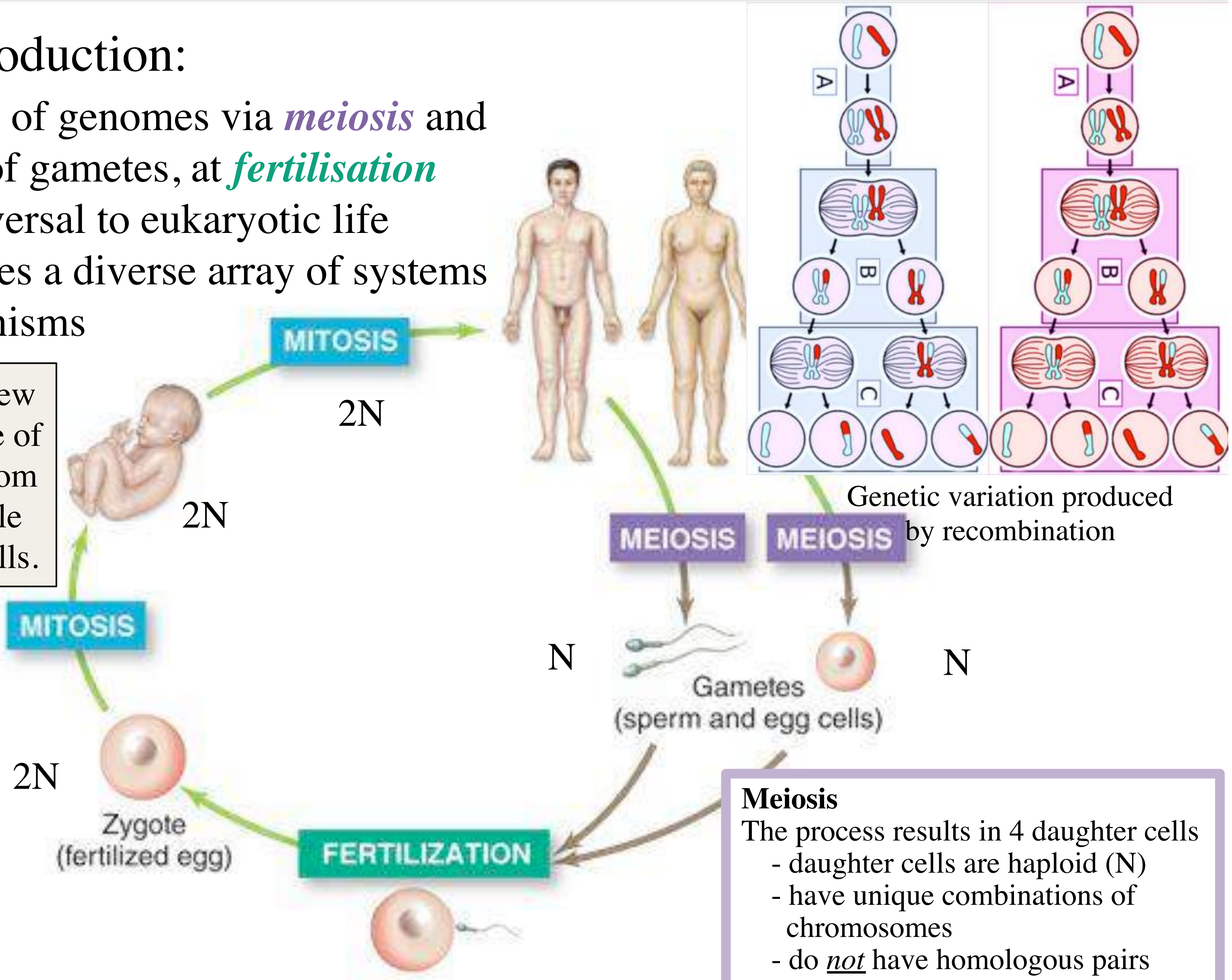
E. Hear

What is Sex?

Sexual Reproduction:

- The mixing of genomes via ***meiosis*** and the fusion of gametes, at ***fertilisation***
- Nearly universal to eukaryotic life
- Encompasses a diverse array of systems and mechanisms

Offspring with a new and unique mixture of genetic material from two different (male and female) sex cells.



Genetic variation produced by recombination

Meiosis
The process results in 4 daughter cells
- daughter cells are haploid (N)
- have unique combinations of chromosomes
- do ***not*** have homologous pairs

Meiosis => gametes (sperm and eggs)

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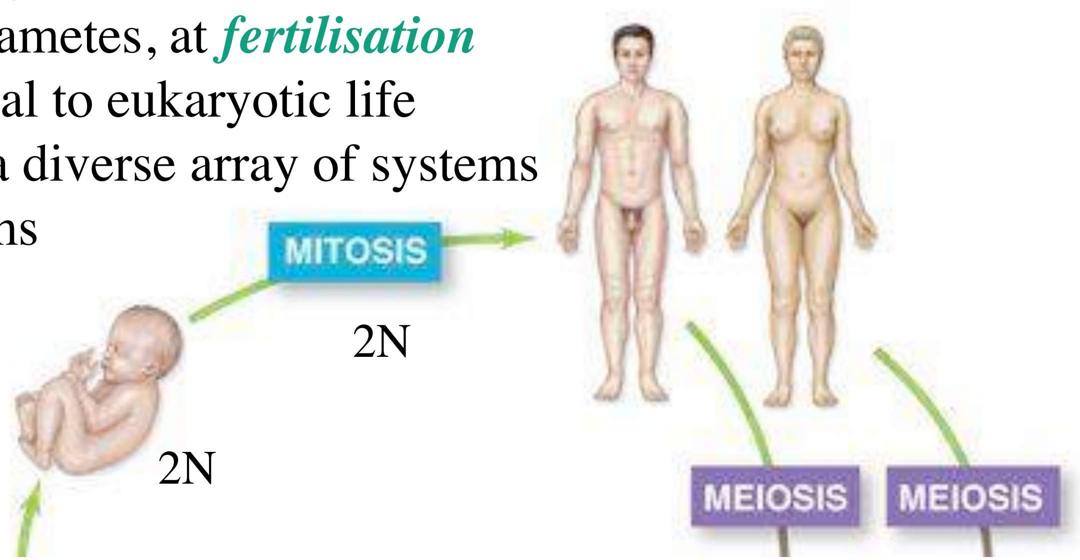

One of the greatest puzzles in evolutionary biology is the high frequency of sexual reproduction and recombination.

Given that individuals surviving to reproductive age have genomes that function in their current environment, why should they risk shuffling their genes with those of another individual?

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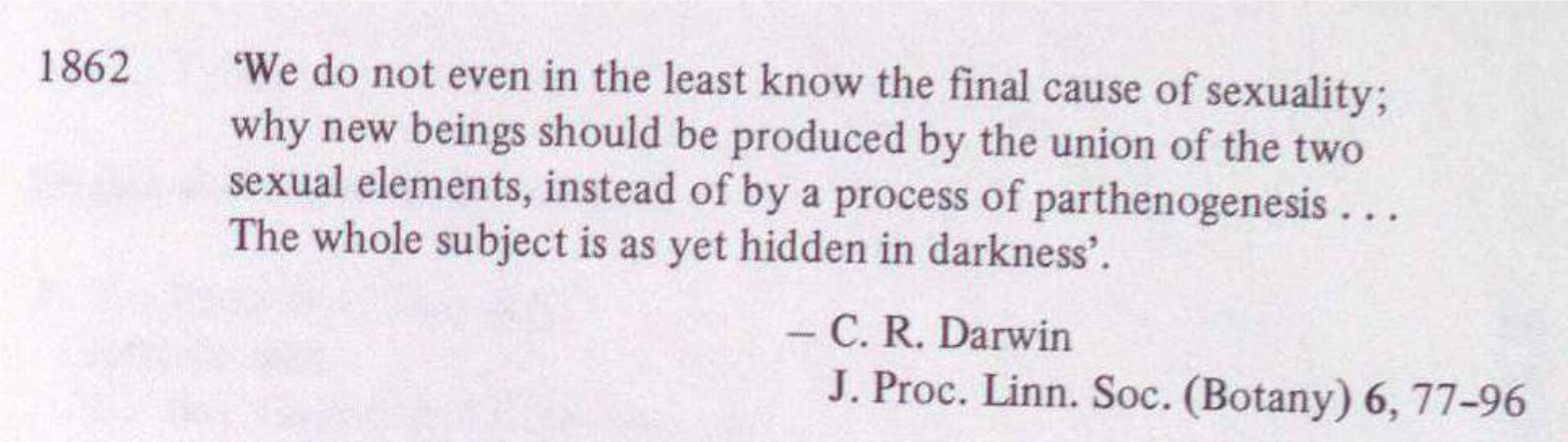
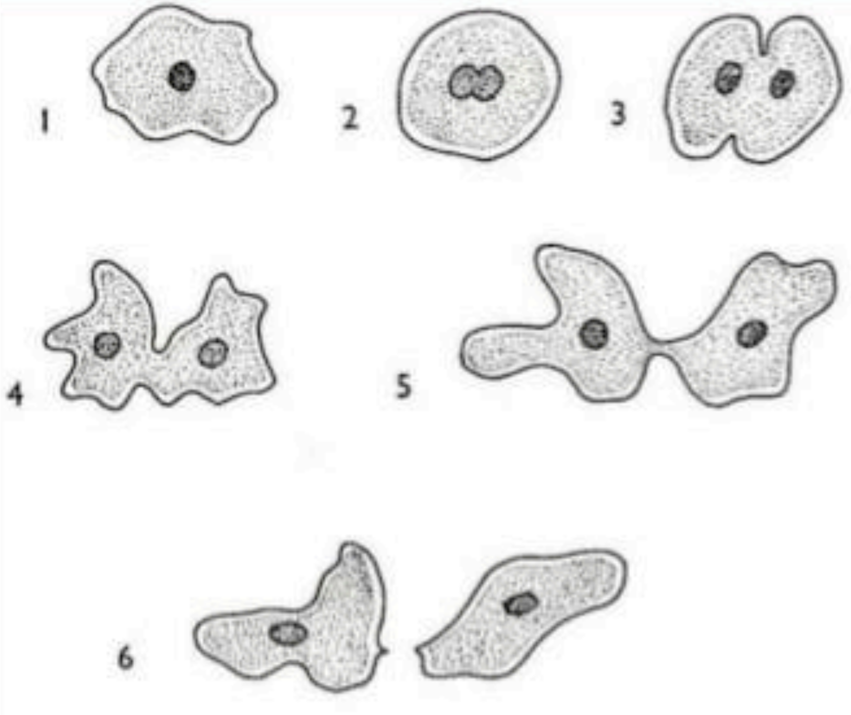


1862 ‘We do not even in the least know the final cause of sexuality; why new beings should be produced by the union of the two sexual elements, instead of by a process of parthenogenesis . . . The whole subject is as yet hidden in darkness’.

– C. R. Darwin
J. Proc. Linn. Soc. (Botany) **6**, 77–96

Asexual Reproduction



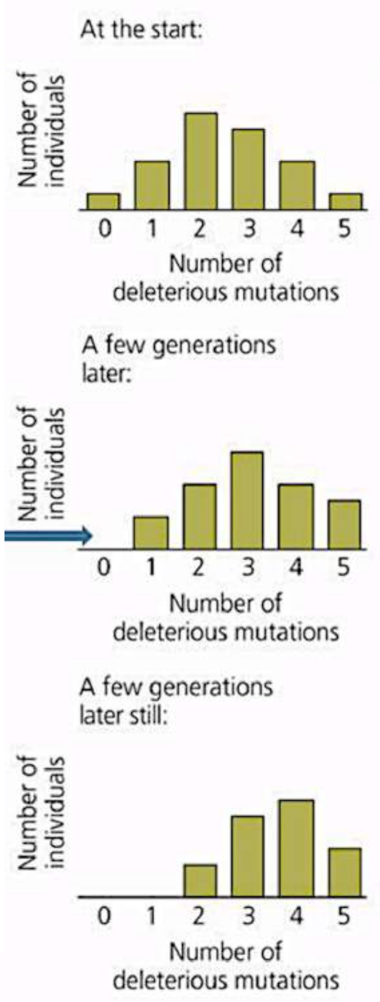
ASEXUAL Reproduction

- Primitive and prevalent
- Oldest eukaryotes reproduce asexually
- Involves one parent
- Each member of an asexual population can produce young: intrinsic capacity to grow more rapidly with each generation
  No cost to "find" partner
- Genetically identical offspring
- Exact same DNA
- => if one gets sick, all progeny are sick…mutations accumulate and accumulate…to extinction

MULLER'S RATCHET…

Muller’s Ratchet (*Cliquet de Muller)*

Muller's ratchet (named after Hermann Joseph Muller, by analogy with a ratchet effect): process by which the genomes of an asexual population accumulate deleterious mutations in an irreversible manner.



The negative effect of accumulating irreversible deleterious mutations may not be prevalent in organisms which, while they reproduce asexually, also undergo other forms of recombination.

Asexual reproduction results in reduced fitness

Vegetative (asexual) reproduction ("apomixis" in plants) - results in clonal populations of genetically identical individuals

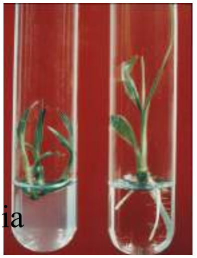
Some aphids and many trees, shrubs, vines - parts of a plant may become detached by fragmentation and grow on to become separate clonal individuals….

Some European cultivars of grapes represent clones that have been propagated for over two millennia

Natural clones


An 80,000 year old clone - Pando "The Trembling Giant" is a single clonal colony of Quaking Aspen trees in Utah.

Artificially generated clones



Cloning oil palm trees in Malaysia
(Courtesy R. Martienssen)

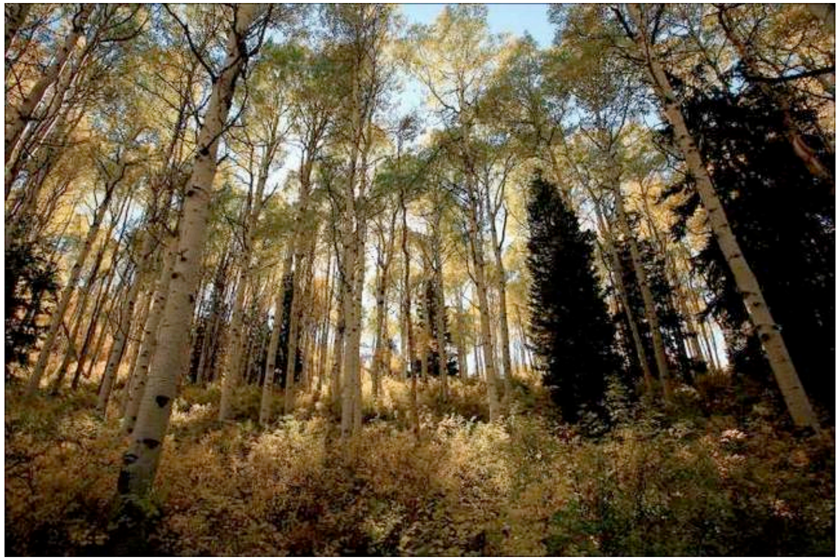
Asexual reproduction results in reduced fitness

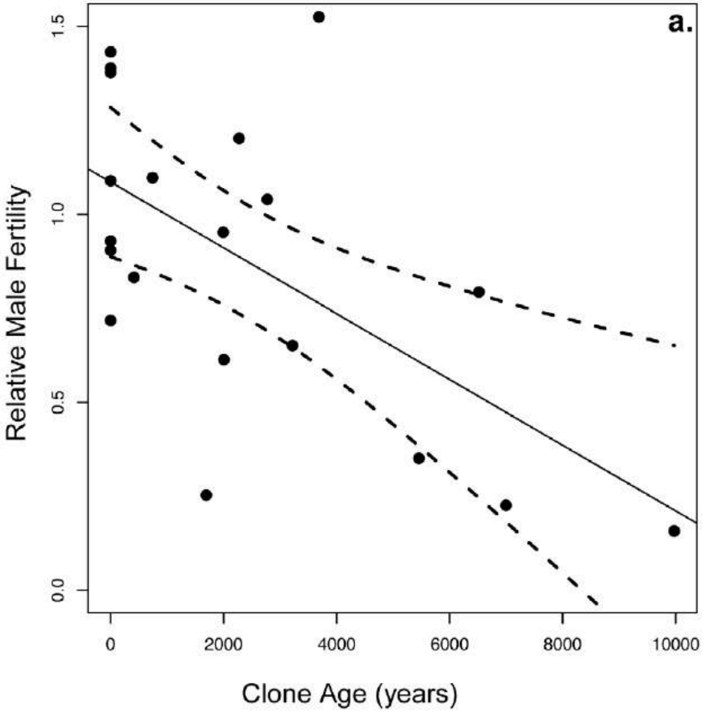
OPEN ACCESS Freely available online PLoS BIOLOGY

Aging in a Long-Lived Clonal Tree

Dilara Ally[1,2]*, Kermit Ritland[3], Sarah P. Otto[2]

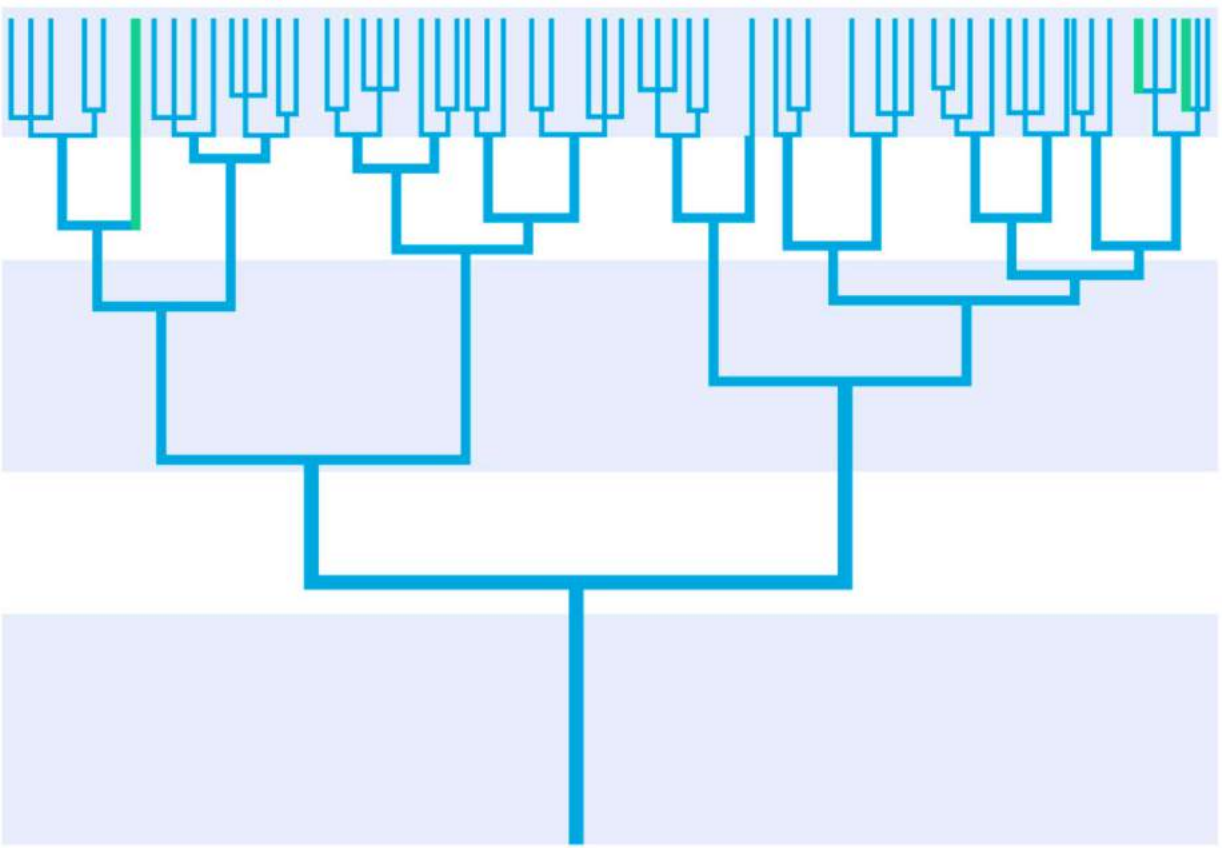
[1] Department of Biological Sciences, University of Idaho, Moscow, Idaho, United States of America, [2] Department of Zoology, University of British Columbia, Vancouver, British Columbia, Canada, [3] Department of Forest Sciences, University of British Columbia, Vancouver, British Columbia, Canada





Disadvantages: mutations, genetic errors, that gradually and steadily build up in the genetic material of the plants' cells. The longer an aspen depends on cloning to survive, the worse it is at sexual reproduction

Asexual reproduction results in reduced fitness

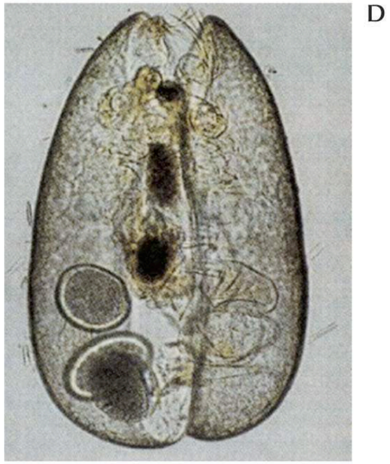


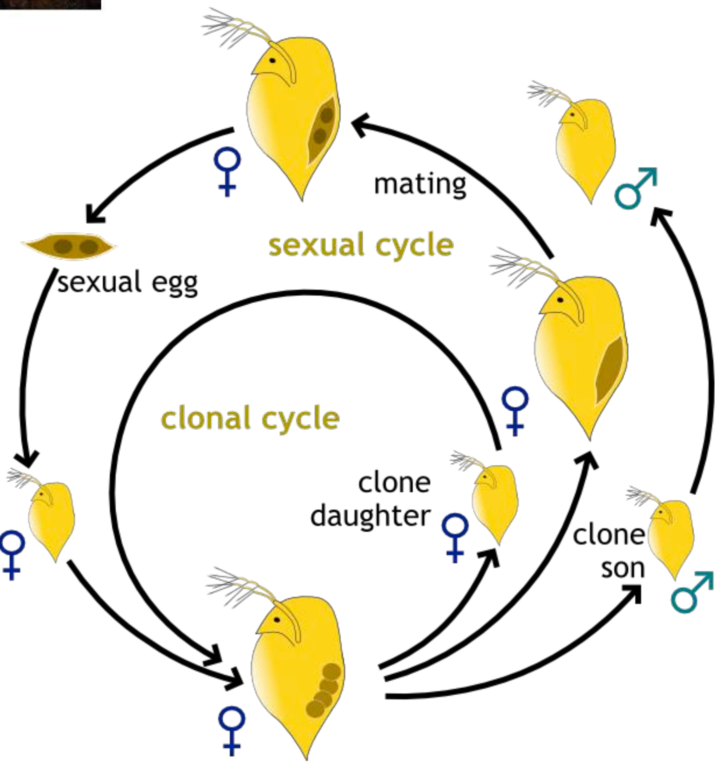
Asexual taxa are almost always confined to the tips of phylogenetic trees, indicating that they are short lived on an evolutionary timescale

Evolution © 2007 Cold Spring Harbor Laboratory Press

Asexual and Sexual Reproduction in the same organism

Organisms including aphids and daphnia reproduce asexually when resources are abundant and switch to sex only at the end of the season, when the potential for asexual reproduction is limited and when potential mates are more available. Similarly, many single-celled organisms have sex only when starved, which minimizes the time cost of switching to meiosis because mitotic growth has already ceased



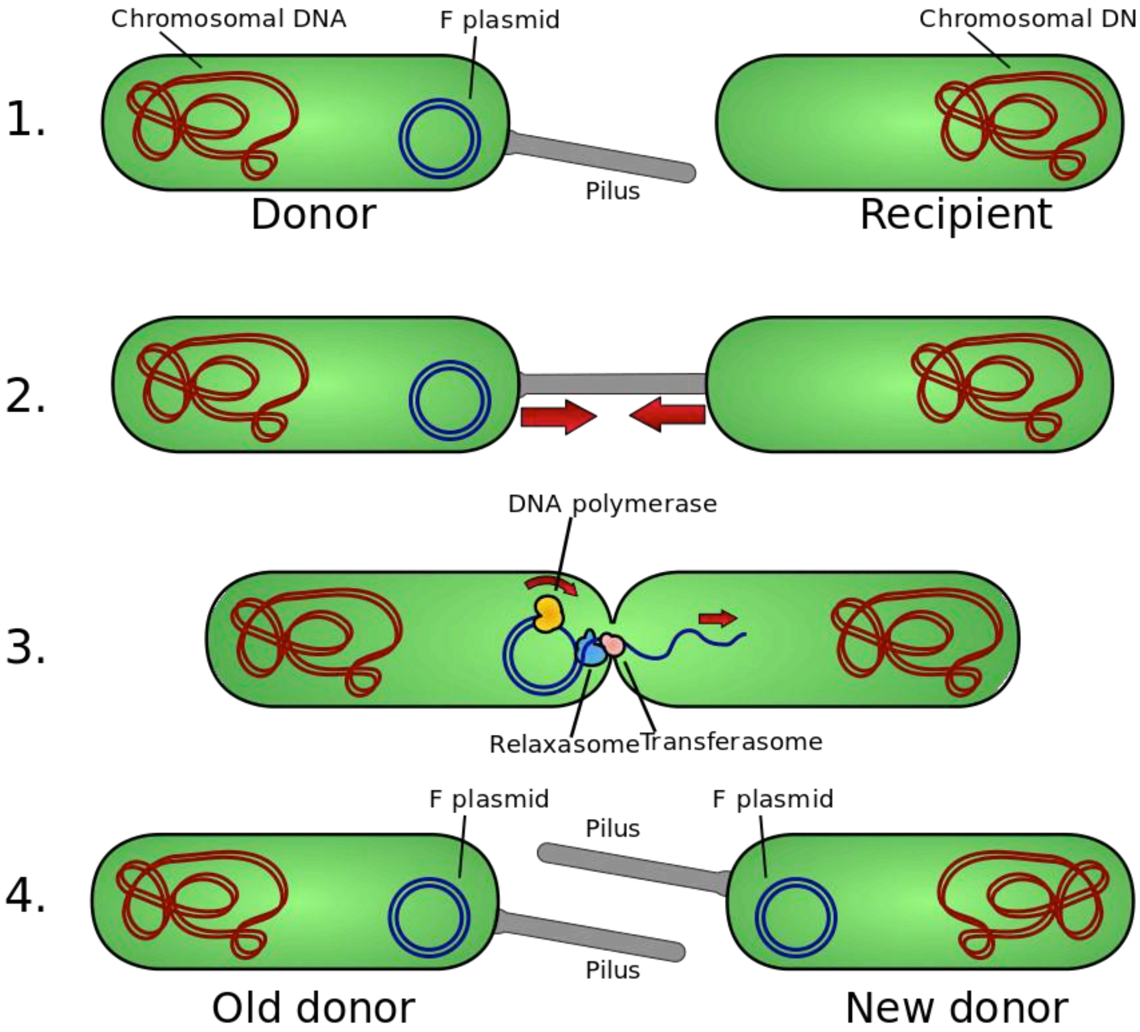


PF (Parthenogenetic female)

SF (Sexual female)

Even Bacteria have Sex

NB Sex and Reproduction are distinct



Advantages and Disadvantages of Sex

WHY SEX?

Nearly every eukaryote on the planet has the capacity to reproduce sexually, and scientists still don't know why. Sex is extremely costly, and many of the proposed benefits do not seem to outweigh those costs.

COSTS:

- Investment of time and energy to find and woo a mate
- Sacrifice of half of the genetic contribution to the next generation, as compared with asexual cloning
- Reshuffling of genetic material can break apart favorable gene combinations

POSSIBLE BENEFITS:

- In a changing environment, the genetic diversity that sex bestows upon a lineage can be critical for adaptation (**Weismann's hypothesis**).
- Sexual recombination purges the genome of deleterious mutations, which can accumulate with devastating costs in asexual populations (**Muller's ratchet hypothesis**).
- Sex can also generate beneficial mutations and bring together new gene combinations (**the Fisher-Muller hypothesis**).
- The genetic diversity introduced by sexual reproduction can help species escape parasitic infection (**the Red Queen hypothesis**).

Advantages of Sexual Reproduction

1. Sexual reproduction produces offspring that have a new combination of DNA. This results in genetic variation among individuals.

2. Genetic variation gives individuals within a population slight differences that can be an advantageous if the environment changes, or if the species needs to escape parasitic infection.

3. Sexual recombination removes deleterious mutations (which accumulate in asexual populations).

Darwin concluded that the adaptive advantage of sex is hybrid vigor :

"*The offspring of two individuals, especially if their progenitors have been subjected to very different conditions, have a great advantage in height, weight, constitutional vigor and fertility over the self fertilised offspring from either one of the same parents.*"

Sexual Reproduction

Sex produces offspring that have a new combination of DNA and thus results in genetic variation among individuals:

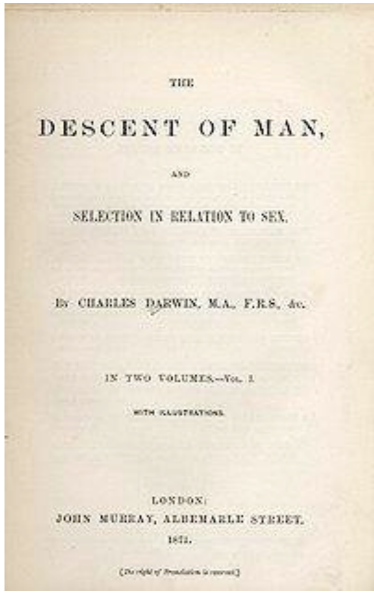
- Sex reduces likelihood of accumulating deleterious mutations
- Masks deleterious mutations
- Increasing rate of adaptation to changing environments
- Deals with competition
- Red Queen race against evolving rapidly parasites

"Well in our country," said Alice, still panting a little. "you'd generally get to somewhere else-if you ran very fast for a longtime as we've been doing."

"A slow sort of county!" said the Queen. "Now, here, you see, it takes all the running you can do to keep in the same place."

- Enables sexual selection: a mode of natural selection whereby some individuals out-reproduce others of a population because they are better at securing mates for sexual reproduction.

Sexual dimorphism and sexual selection



THE

DESCENT OF MAN,

AND

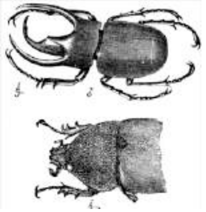
SELECTION IN RELATION TO SEX.

By CHARLES DARWIN, M.A., F.R.S., &c.

IN TWO VOLUMES.—Vol. I.

WITH ILLUSTRATIONS.

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1871.



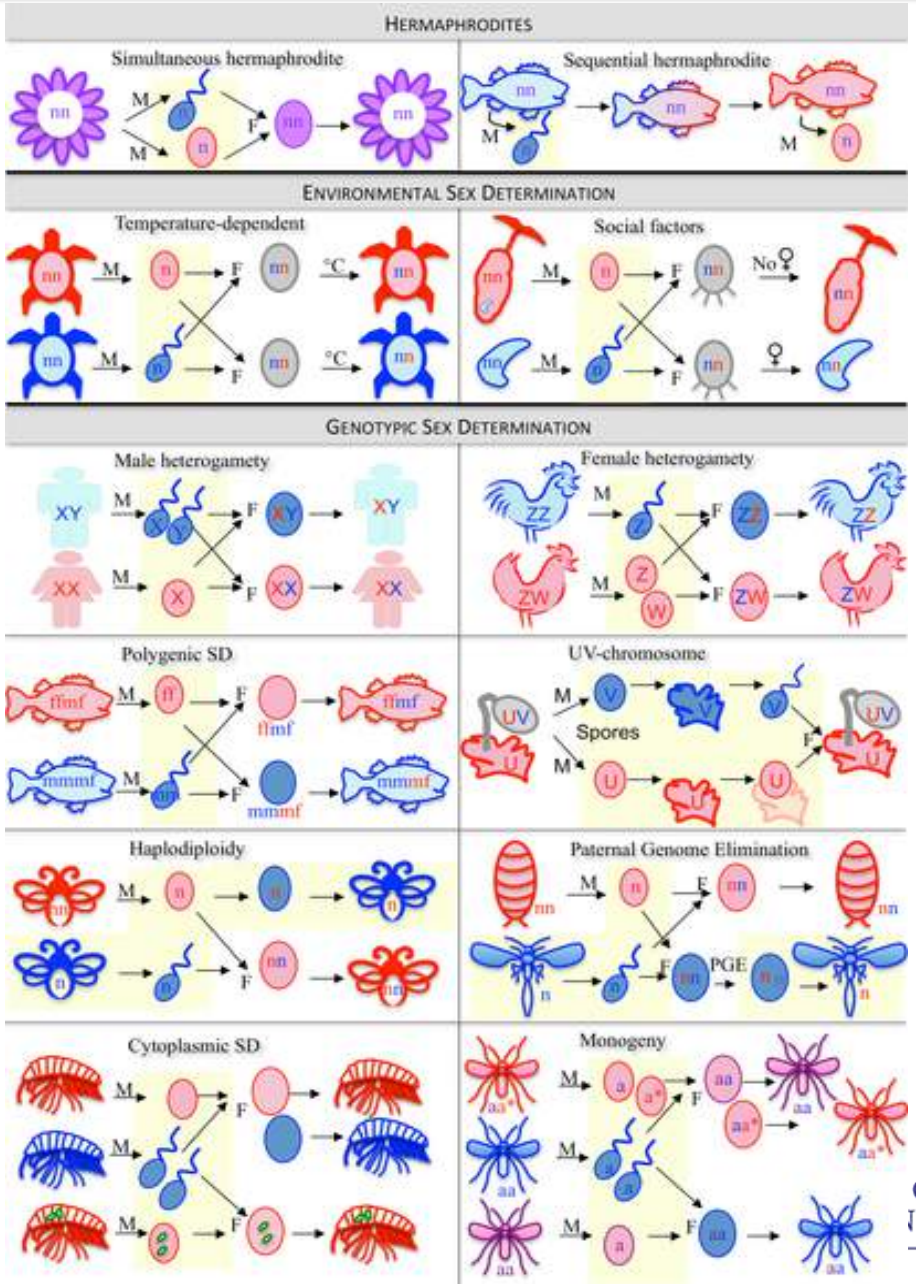
- In “The Descent of Man, and Selection in Relation to Sex” (1871) Darwin described in detail the mechanism of sexual selection, initially proposed in “The Origin of Species” (1859)
- The ultimate aim in Descent of Man was to demonstrate that evolutionary principles applied to humans and that humans descended from some ape-like common ancestor.
- Darwin believed that sexual selection played a major role in the evolution of humans and the divergence among distinct human populations

Darwin’s definition of sexual selection still holds:

This depends on the advantage which certain individuals have over other individuals of the same sex and species, in exclusive relation to reproduction.”

How has sex determination evolved?

- Sexual reproduction is an ancient feature of life on earth
- => sex determination mechanisms could be imagined to be old and conserved?
- Not so - males and females are determined by diverse mechanisms that evolve rapidly in many taxa.
- However - diversity in primary sex-determining signals is coupled with conserved molecular pathways that trigger male or female development.

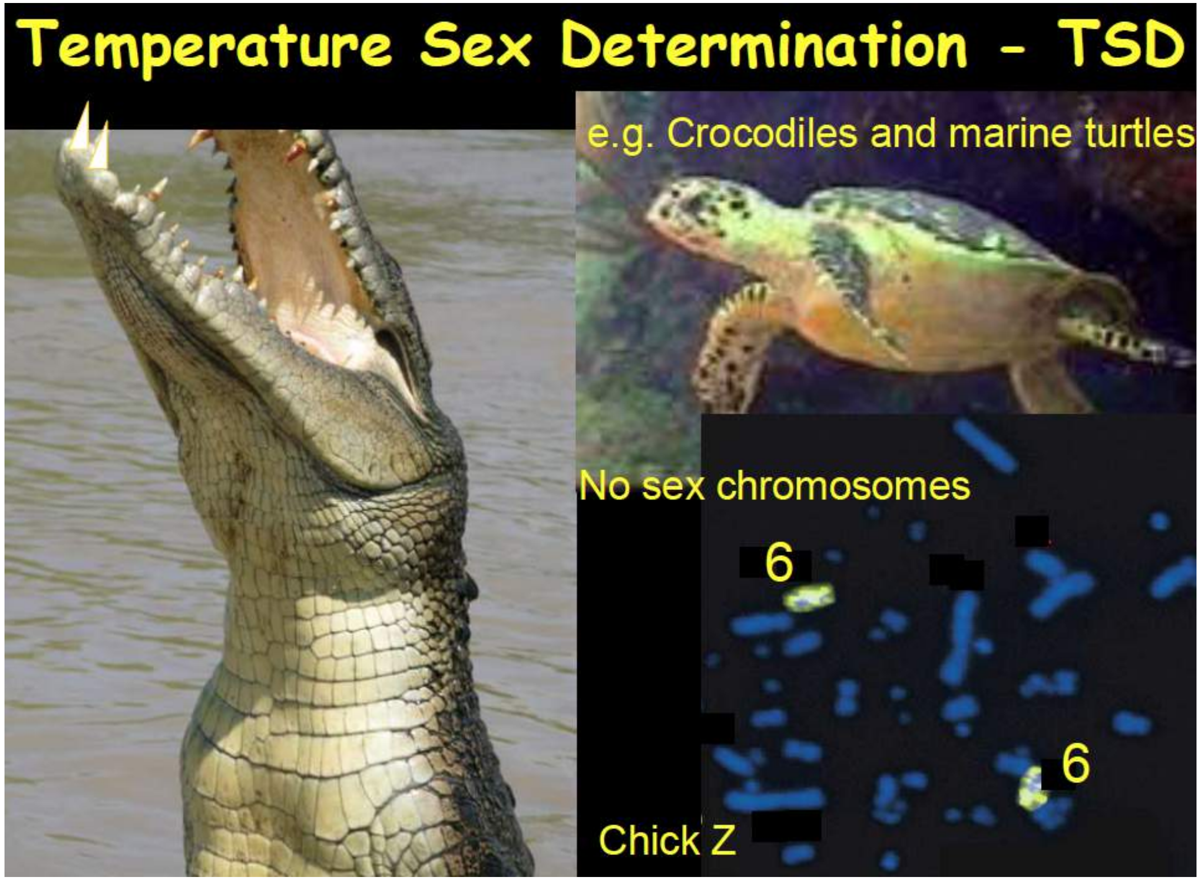


Bachtrog lab, Plos Genet 2014

Sex Determination

Multiple Strategies: genetic and non-genetic

Non-genetic (ie no DNA sequence difference between the sexes) can be environmental, temperature-dependent, epigenetic…



Courtesy of J. Graves

Sex Determination

Multiple Strategies: genetic and non-genetic

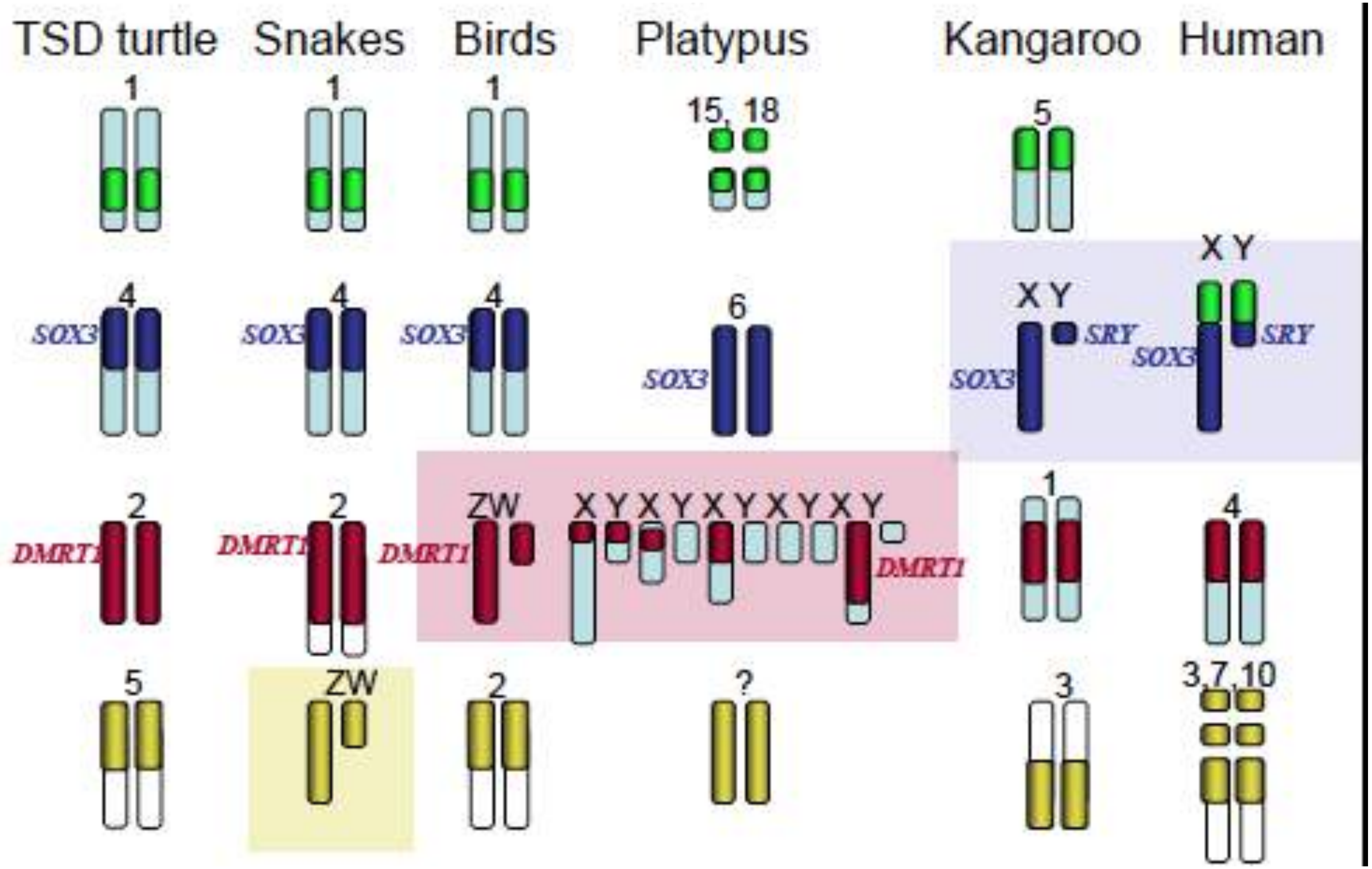
Non-genetic (ie no DNA sequence difference between the sexes)
can be environmental, temperature-dependent, epigenetic…

Genetic
Sex determining locus or loci – can lead to evolution of sex chromosomes

Mixed: genetic and non-genetic
Sex chromosomes and environmental sex determination
Eg many Fish, plants…

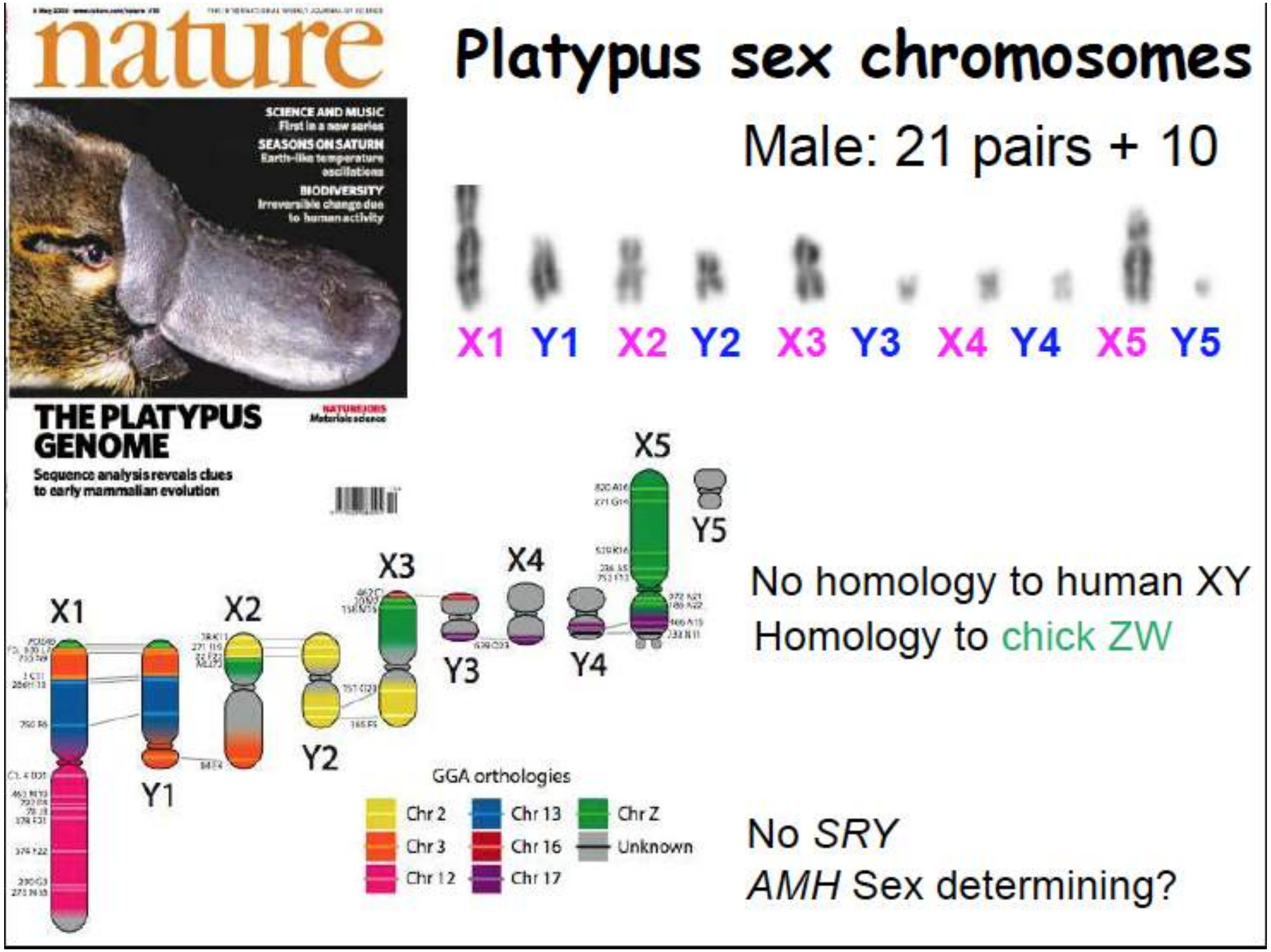
Many animals and some plants have sex chromosomes. In these species, sexual development is decided from a major sex-determining region, which triggers a cascade of sex-specific genes that control development into a male or female

Different genome regions became sex chromosomes in different vertebrates



Graves JA, Nature Reviews Genetics, 2016

Monotreme sex chromosomes



Platypus sex chromosomes

Male: 21 pairs + 10

X1 Y1 X2 Y2 X3 Y3 X4 Y4 X5 Y5

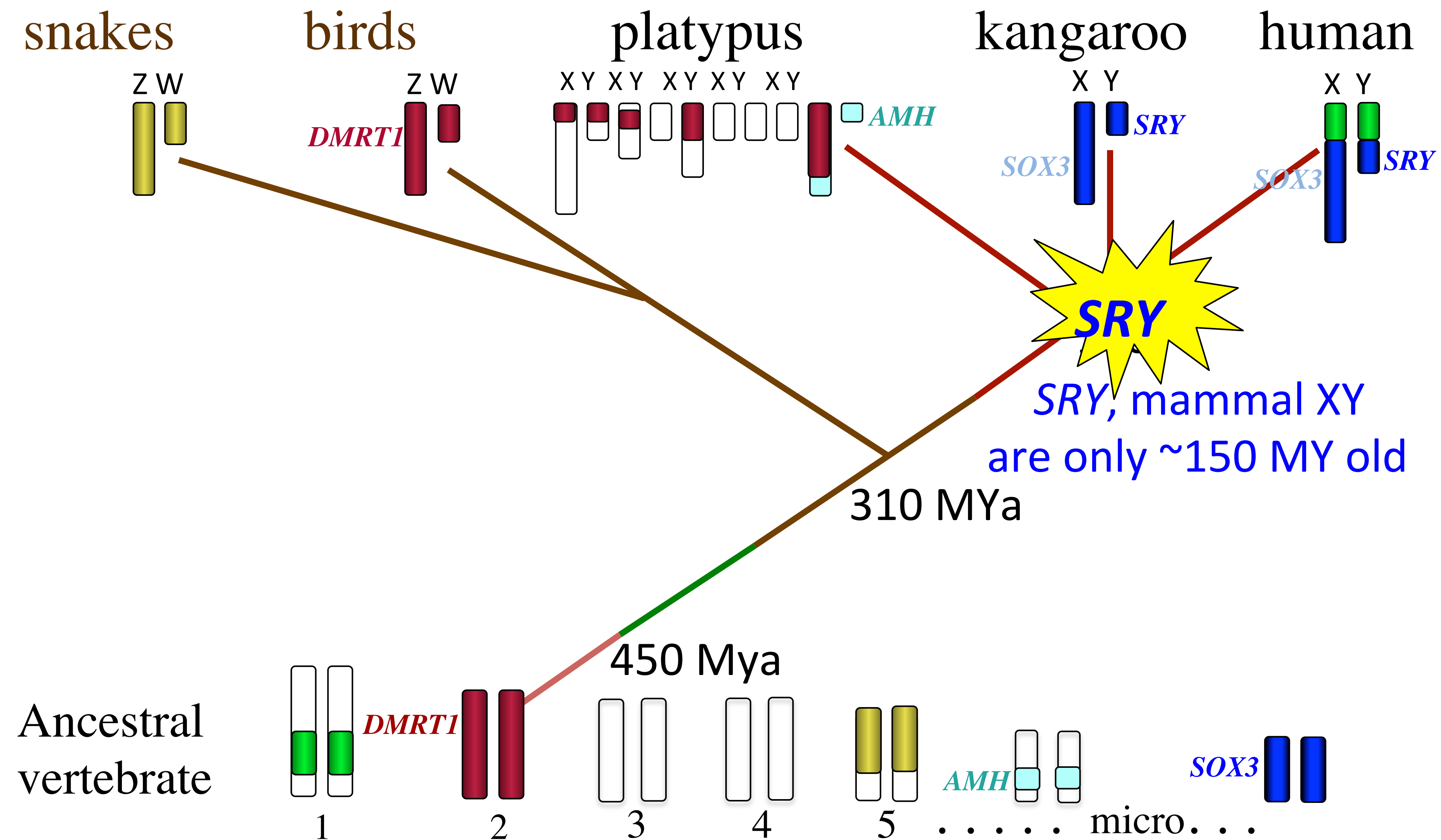
No homology to human XY
Homology to chick ZW

No *SRY*
AMH Sex determining?

Courtesy of Jenny Graves

How and why did sex determination evolve?

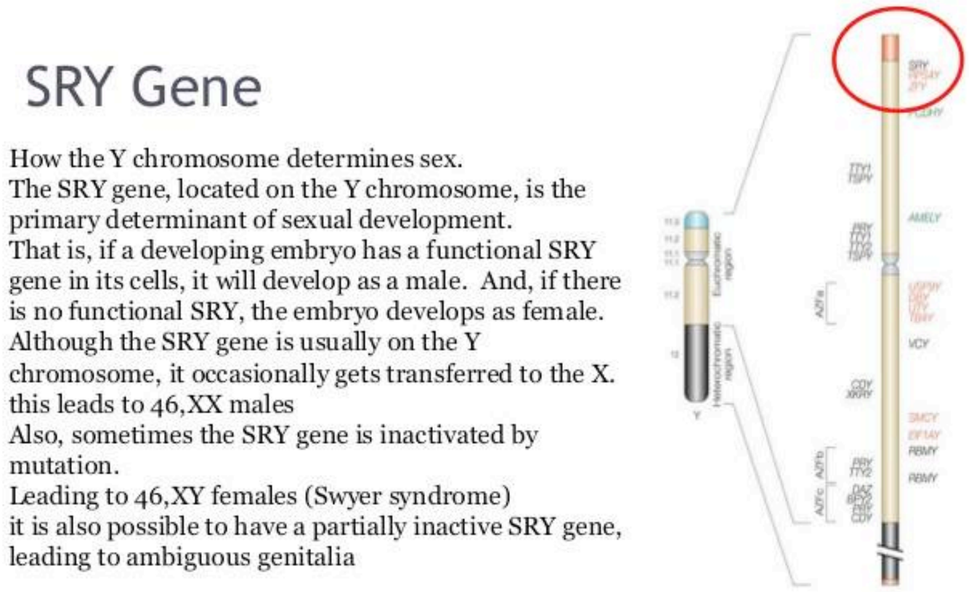
different regions determine sex



Courtesy of Jenny Graves

Sry: a master switch in mammalian sex determination

- In placental mammals, sex determination (male/female) at the biological level is determined by the presence or absence of the Y chromosome.
- Initially, this factor was unknown and it was designated the "testis determining factor" (TDF).
- In 1990, TDF found to be protein product encoded by the SRY gene on the Y chromosome.
- Without SRY the potential sex is female.
- For some time, female was considered "default" sex in the absence of SRY,; now know several genes specifically required for ovary formation.
- In females, sex determination involves at least one X gene: DAX1 encoding a nuclear hormone receptor.



SRY Gene

How the Y chromosome determines sex.
The SRY gene, located on the Y chromosome, is the primary determinant of sexual development.
That is, if a developing embryo has a functional SRY gene in its cells, it will develop as a male. And, if there is no functional SRY, the embryo develops as female.
Although the SRY gene is usually on the Y chromosome, it occasionally gets transferred to the X. this leads to 46,XX males
Also, sometimes the SRY gene is inactivated by mutation.
Leading to 46,XY females (Swyer syndrome)
it is also possible to have a partially inactive SRY gene, leading to ambiguous genitalia

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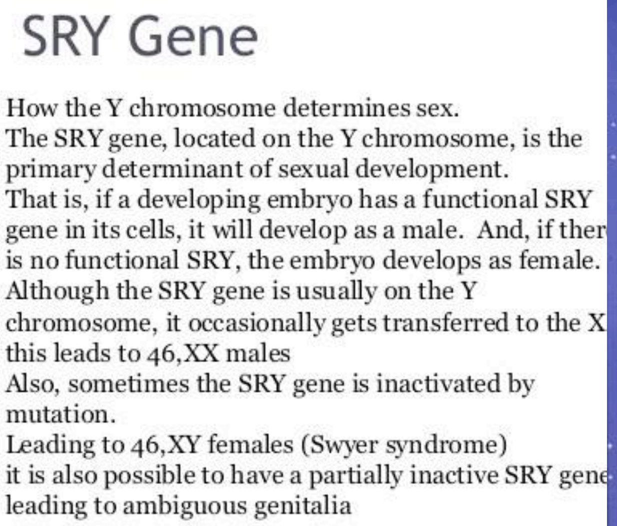

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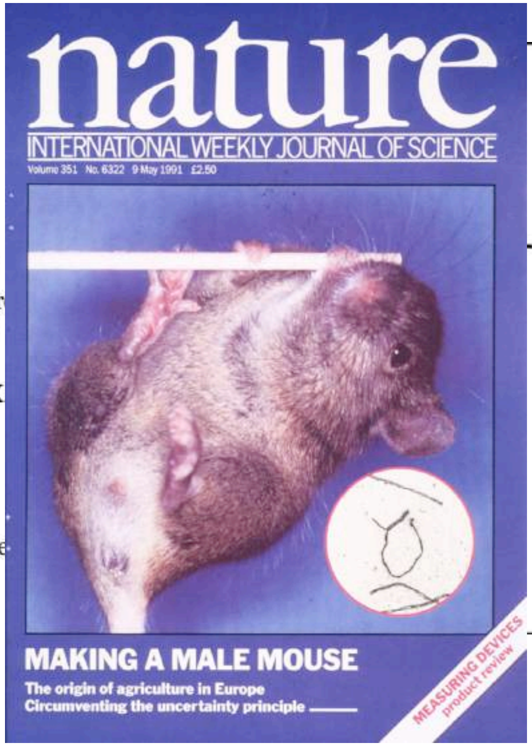
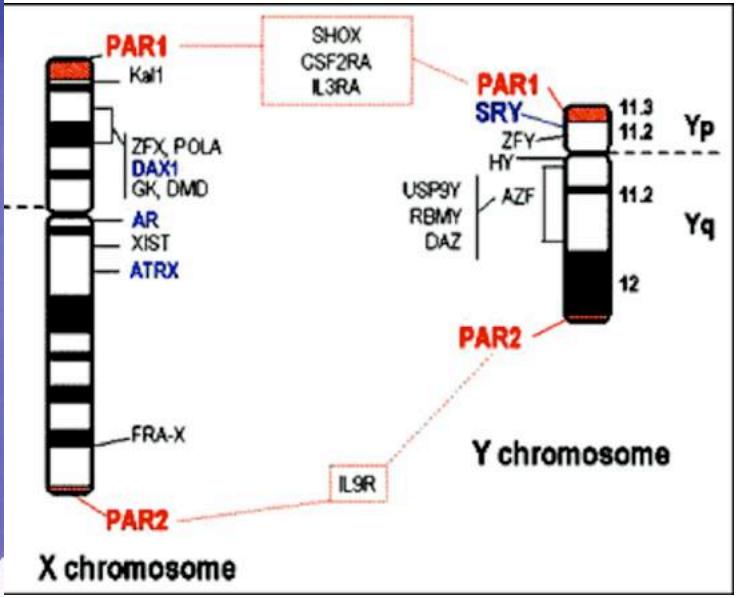
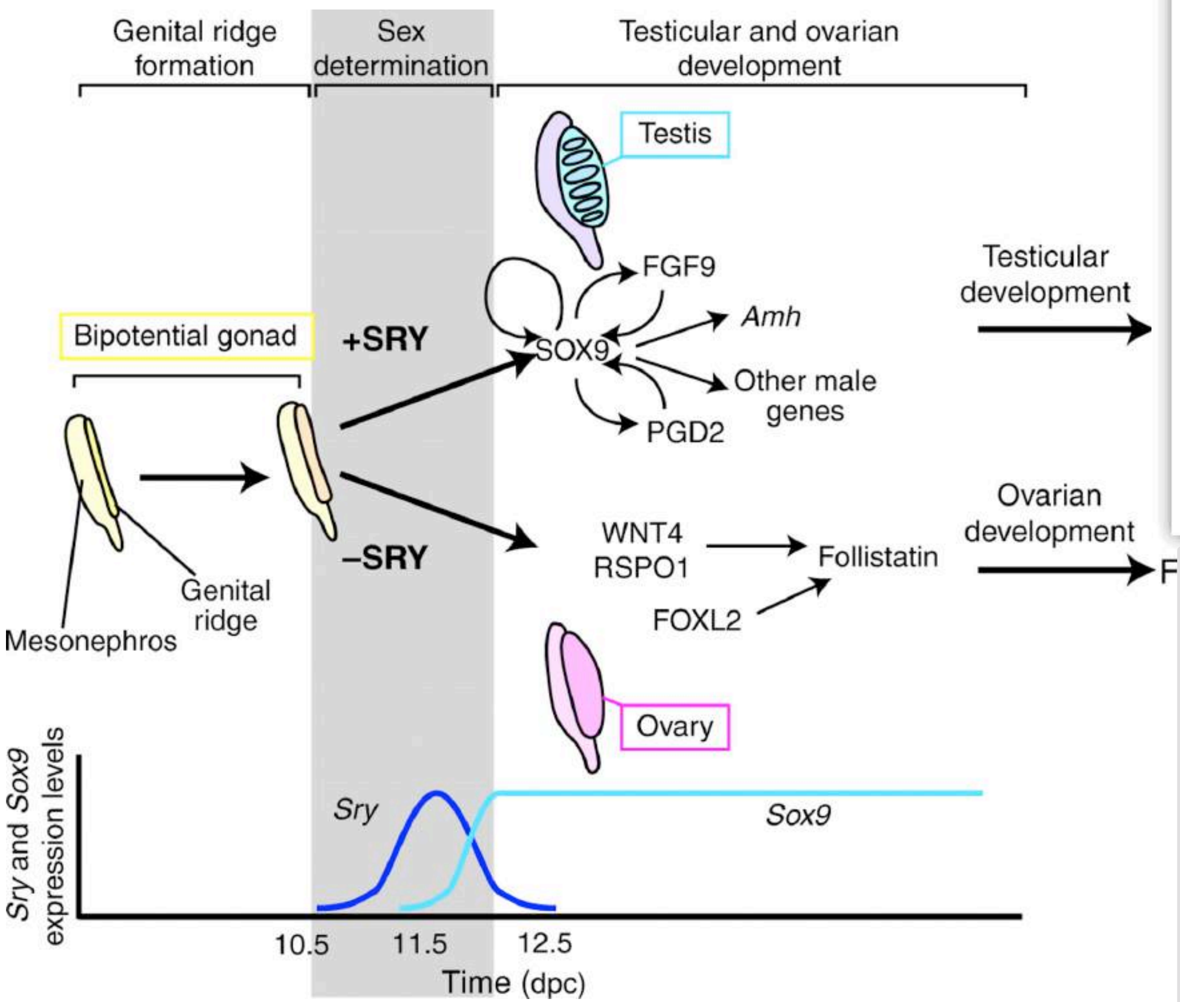
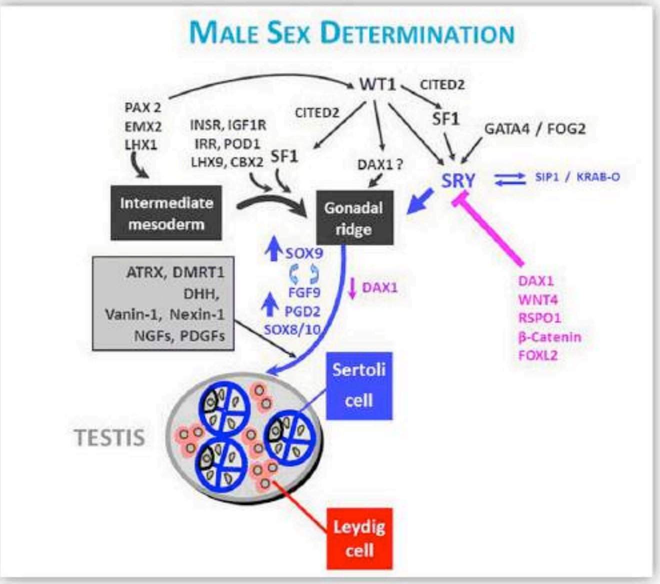


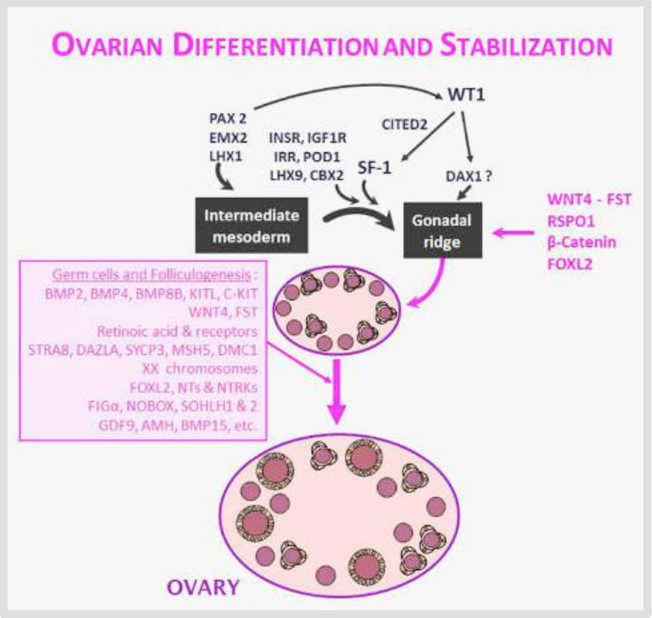


Kenichi Kashimada, Peter Koopman
Development 2010 137: 3921-3930; doi: 10.1242/dev.048983

Sry: a master switch in mammalian sex determination





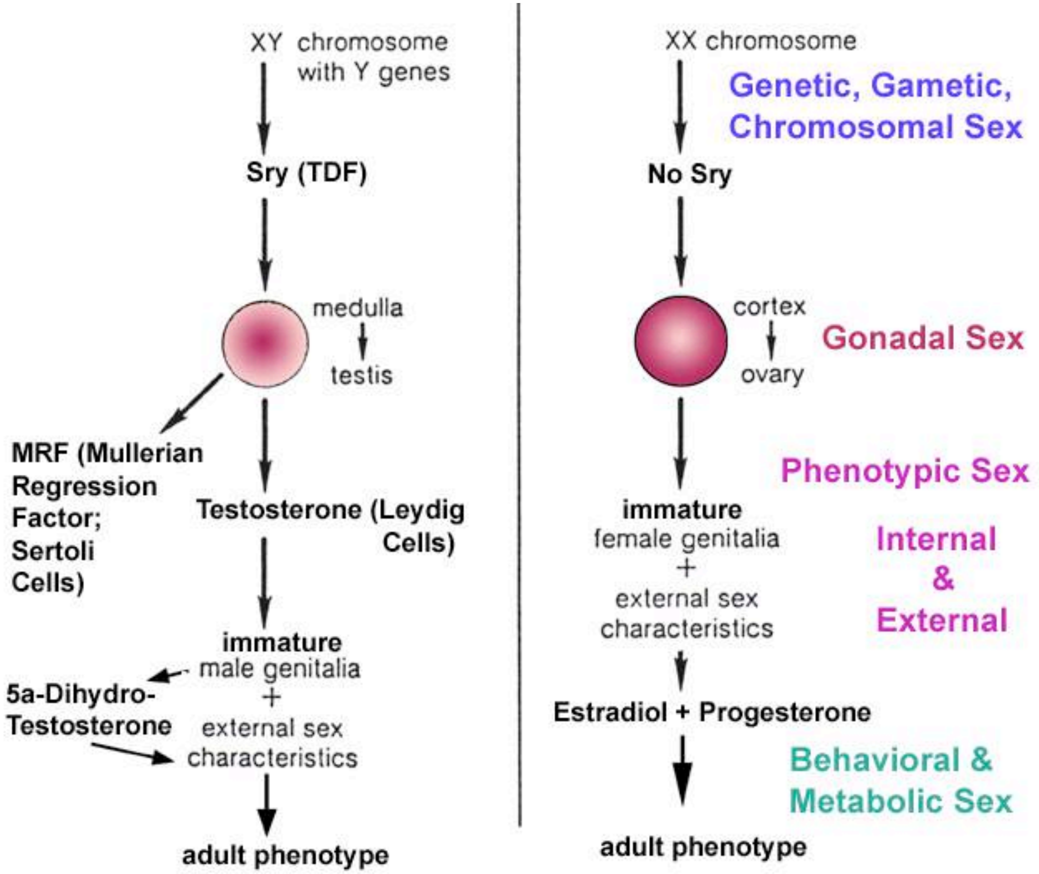


NB It is not the primordial germ cells which respond to SRY presence or absence, but the **supporting cells** within the developing gonad.

pman
0.1242/dev.048983

Dmrt1 and FoxL2: in adult sex determination?

- Recent studies in mice have provided evidence that it is possible for the gonadal sex phenotype to be switched even in adulthood.
- Two key genes, doublesex and mad-3 related transcription factor 1 (Dmrt1) and forkhead box L2 (Foxl2), function in a Yin and Yang relationship to maintain the fates of testes or ovaries in adult mammals
- mutations in either gene have a dramatic effect on gonadal phenotype (female to male sex reversal in adult Dmrt1 Tg mouse; in humans, deletion of Ch9p with Dmrt1->XY male-to-female sex reversal.
- Thus, adult gonad maintenance in addition to fetal sex determination may both be important for fertility.



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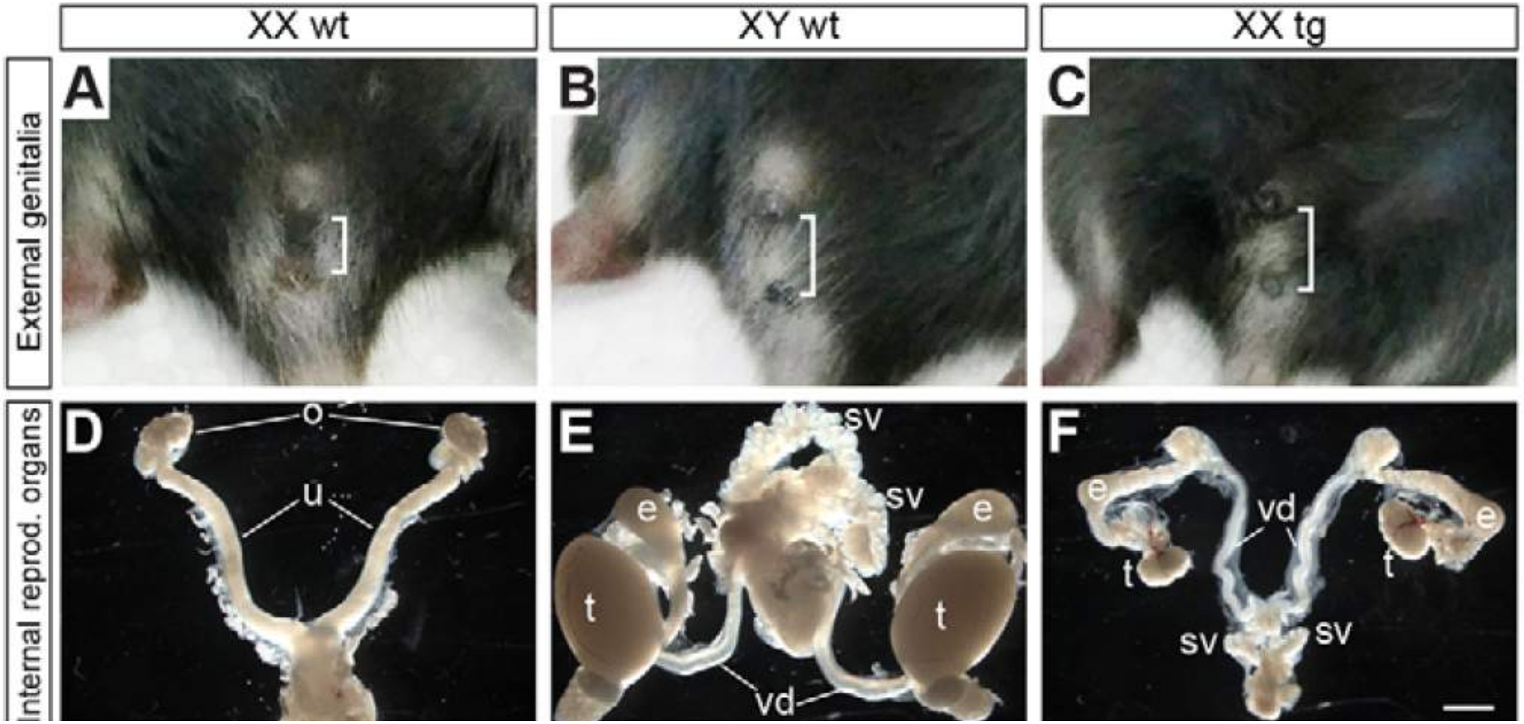
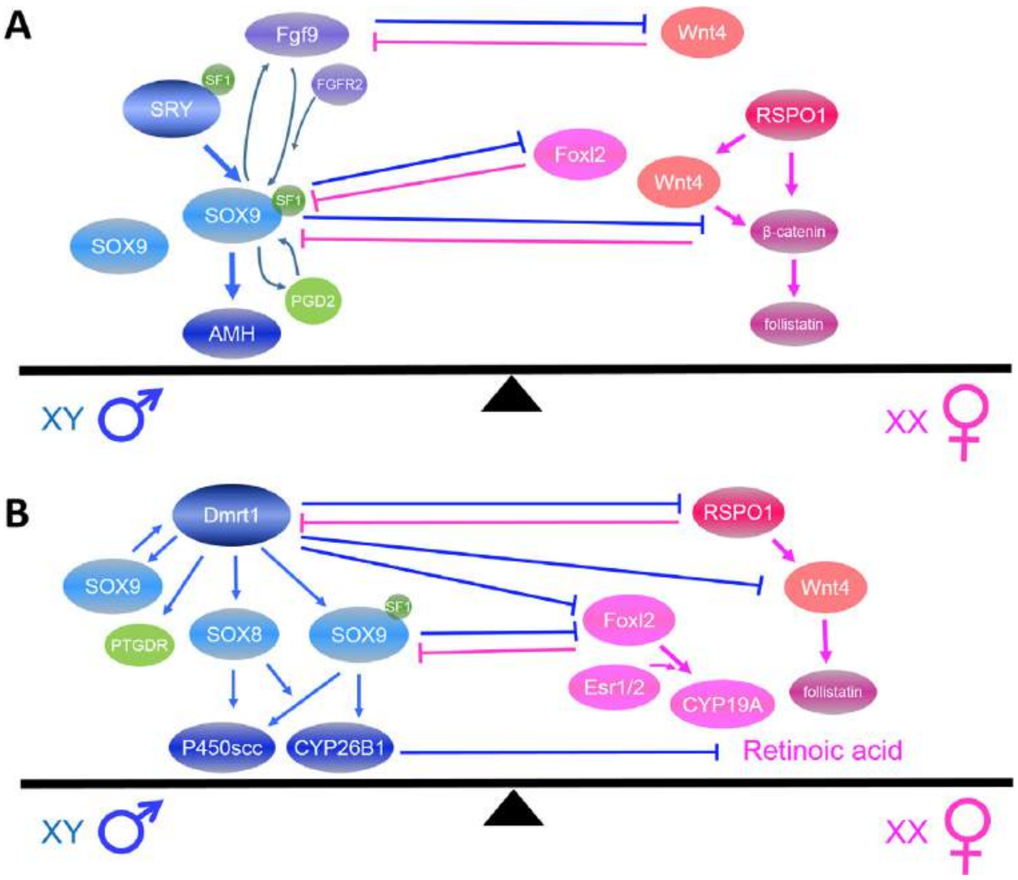


Matson et al, Nature (2011) DMRT1 prevents female reprogramming in the postnatal mammalian testis
Zhao et al, Development (2015) Female-to-male sex reversal in mice caused by transgenic overexpression of Dmrt1.
Uehlenhaut et al, Cell (2009) Somatic sex reprogramming of adult ovaries to testes by FOXL2 ablation
Shengsong Huang et al , Asian J. Androl. (2017) Sex determination and maintenance: the role of DMRT1 and FOXL2.

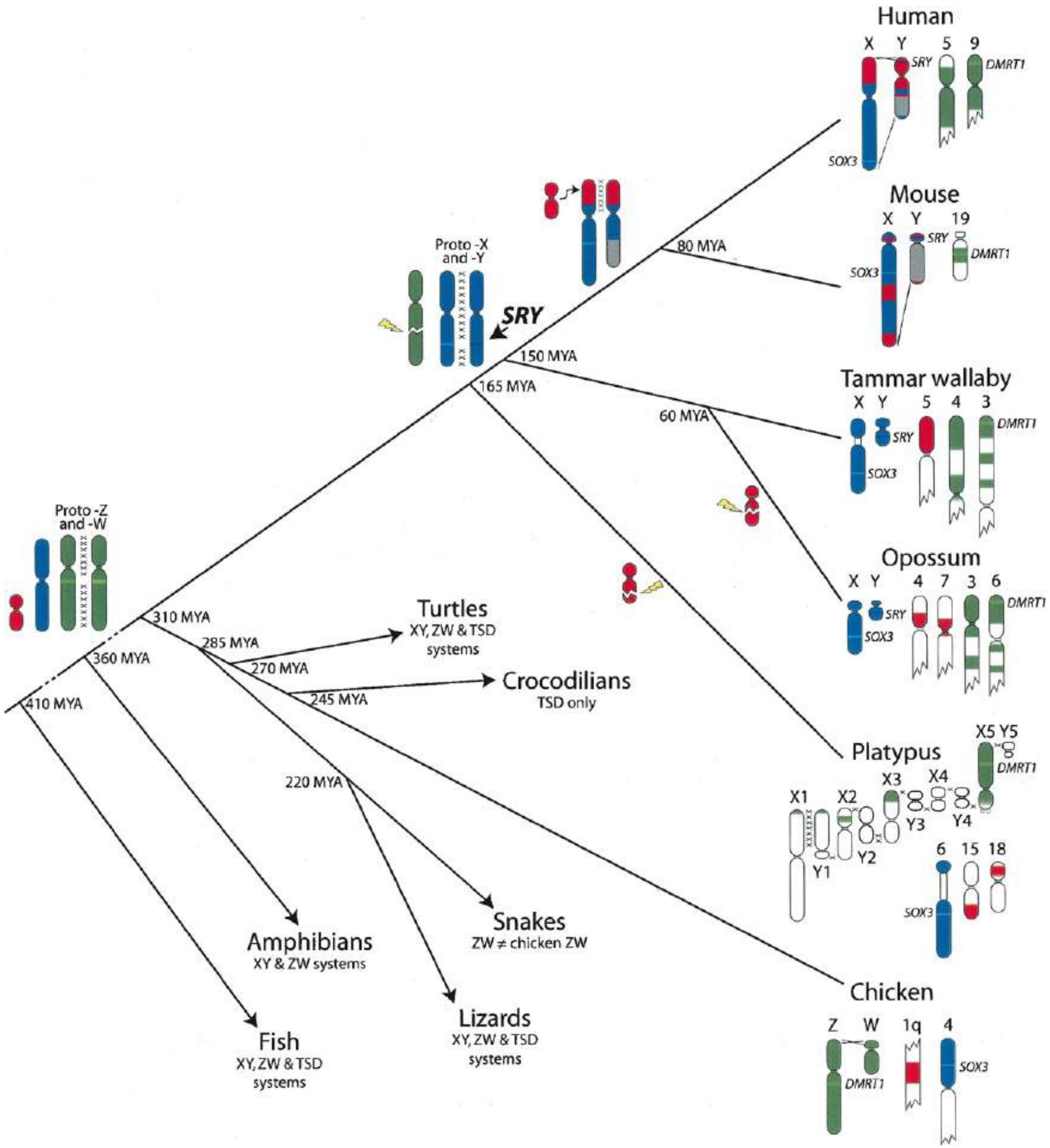
Sex Determination in Humans



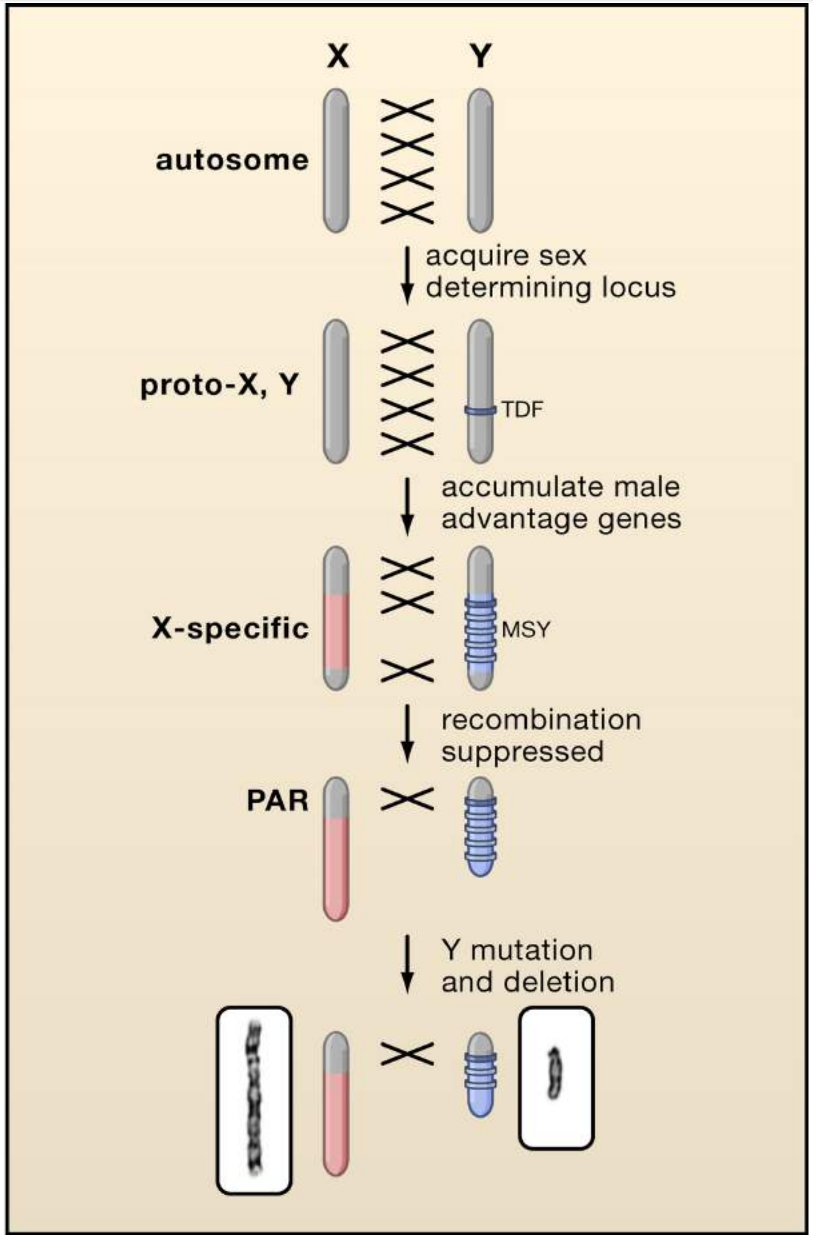
Delicate balance between male and female signaling pathways during sex development both in embryogenesis and adult

Lifelong antagonistic signaling pathways occurring throughout the adult life of both sexes have not yet been fully characterized

How did vertebrate sex chromosomes evolve?



Differentiation of an X and Y Chromosome from an Ancient Autosome

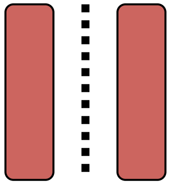


Cell 2006 124, 901-914DOI: (10.1016/j.cell.2006.02.024)

E. Heard, January 29th, 2018

COLLÈGE DE FRANCE
1530

XY evolution



Once the X and Y were an ordinary pair

The Y is a degraded X

Why does the Y degrade?

High variation

- many genetic accidents in testis

Selection doesn't work well

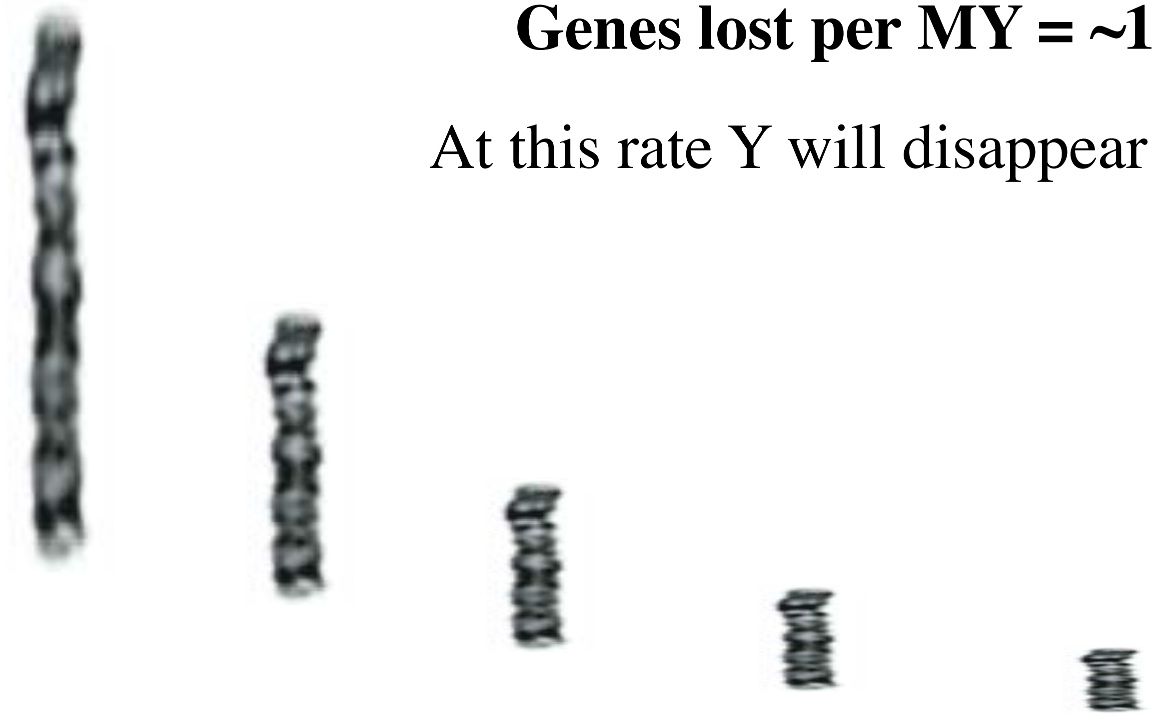
- no recombination, no repair

166 MYA – the Y had 1669 genes

Today – the Y has 45

Genes lost per MY = ~1624/166 = ~9.8

At this rate Y will disappear in 4.6 MY



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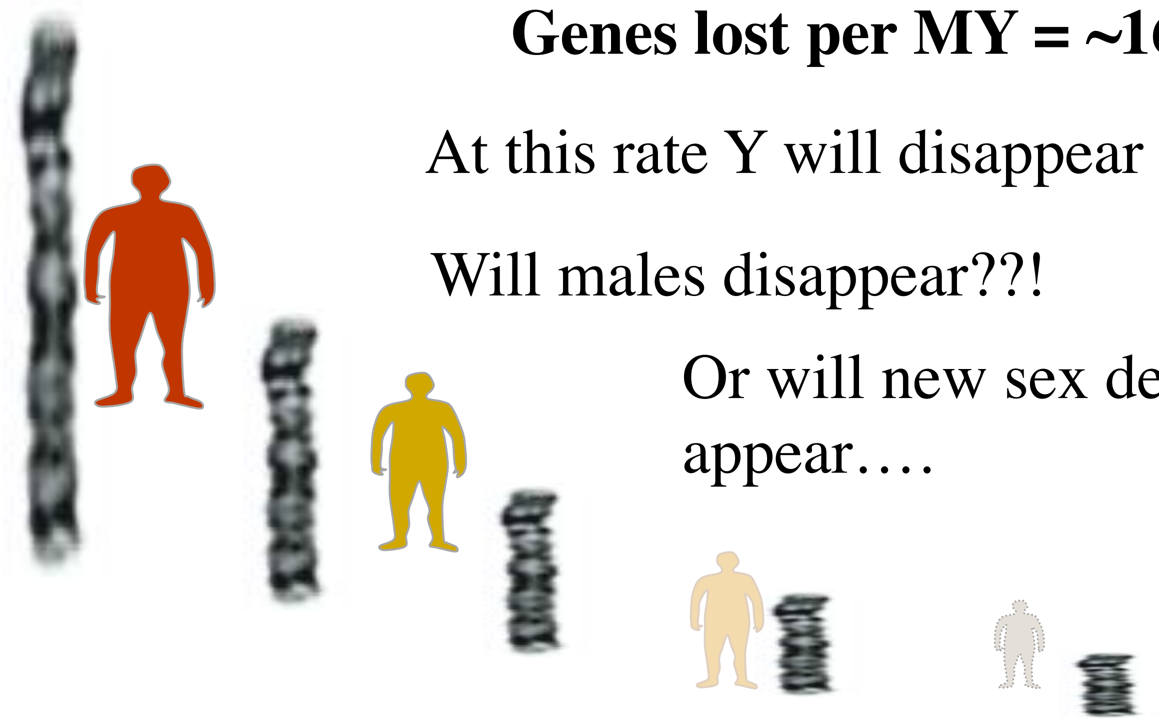
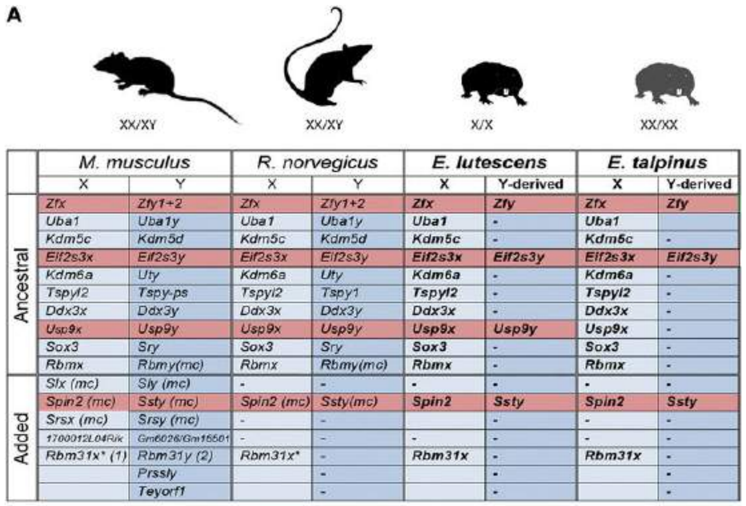
Will males disappear??!

Or will new sex determining genes appear….



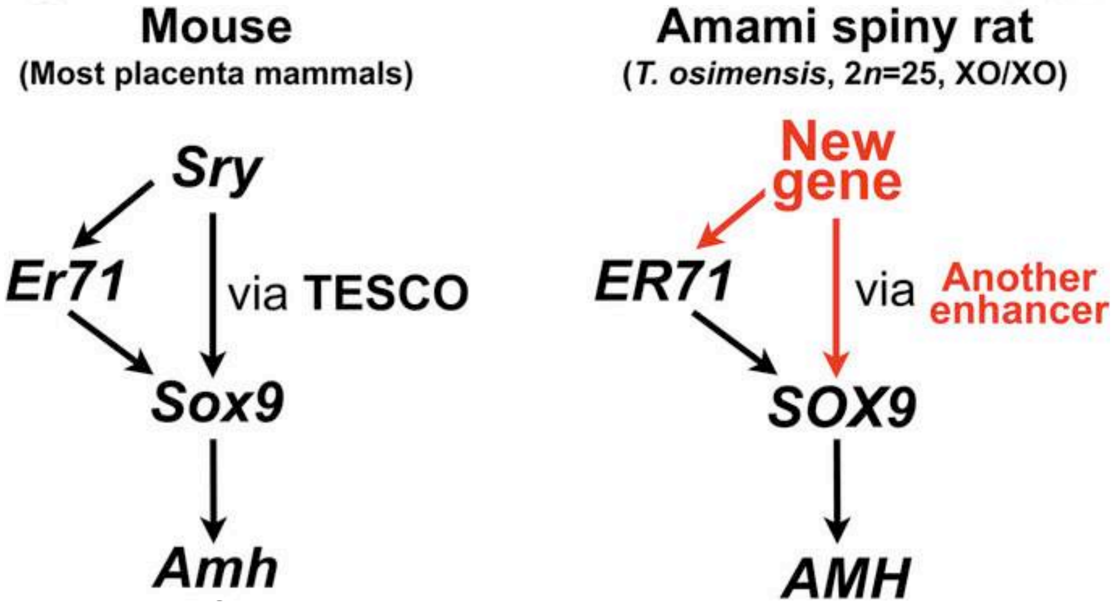
At least two mammals have **lost** their Y chromosome entirely: *Ellobius* and the *Okinawa Spiny Rat*



	M. musculus		*R. norvegicus*		*E. lutescens*		*E. talpinus*	
	X	Y	X	Y	X	Y-derived	X	Y-derived
Ancestral	*Zfx*	*Zfy1+2*	*Zfx*	*Zfy1+2*	*Zfx*	*Zfy*	*Zfx*	*Zfy*
	Uba1	*Uba1y*	*Uba1*	*Uba1y*	*Uba1*	-	*Uba1*	
	Kdm5c	*Kdm5d*	*Kdm5c*	*Kdm5d*	*Kdm5c*	-	*Kdm5c*	-
	Eif2s3x	*Eif2s3y*	*Eif2s3x*	*Eif2s3y*	*Eif2s3x*	*Eif2s3y*	*Eif2s3x*	*Eif2s3y*
	Kdm6a	*Uty*	*Kdm6a*	*Uty*	*Kdm6a*	-	*Kdm6a*	-
	Tspyl2	*Tspy-ps*	*Tspyl2*	*Tspy1*	*Tspyl2*	-	*Tspyl2*	-
	Ddx3x	*Ddx3y*	*Ddx3x*	*Ddx3y*	*Ddx3x*	-	*Ddx3x*	-
	Usp9x	*Usp9y*	*Usp9x*	*Usp9y*	*Usp9x*	*Usp9y*	*Usp9x*	-
	Sox3	*Sry*	*Sox3*	*Sry*	*Sox3*	-	*Sox3*	-
	Rbmx	*Rbmy(mc)*	*Rbmx*	*Rbmy(mc)*	*Rbmx*	-	*Rbmx*	-
Added	*Slx (mc)*	*Sly (mc)*	-	-	-	-	-	-
	Spin2 (mc)	*Ssty (mc)*	*Spin2 (mc)*	*Ssty(mc)*	*Spin2*	*Ssty*	*Spin2*	*Ssty*
	Srsx (mc)	*Srsy (mc)*	-	-		-	-	-
	1700012L04Rik	*Gm6026/Gm16501*	-	-	-	-	-	-
	Rbm31x (1)*	*Rbm31y (2)*	*Rbm31x**	-	*Rbm31x*	-	*Rbm31x*	-
		Prssly		-		-		-
		Teyorf1		-		-		-

**Rbm31x* is poorly annotated in the mouse as *Gm4916*, and in the rat the X-linked homolog has been named *Rbm31y*. We have adapted the names here for clarity purposes

- Transcaucasian mole vole Ellobius lutescens,:
- The Y Chromosome including Sry has been lost
- Both females +males have 17,X diploid karyotype.
- Related Ellobius talpinus, also no Y - has a 54,XX karyotype in both females and males.
- Four functional homologs of mouse Y-Chromosomal genes detected in both female and male E. lutescens, of which three were also detected in the E. talpinus genome. These included Eif2s3y, known as the only Y-derived gene that is *crucial for successful male meiosis*.



Mouse
(Most placenta mammals)

Sry
Er71
via **TESCO**
Sox9
Amh

Amami spiny rat
(*T. osimensis*, 2*n*=25, XO/XO)

New gene
ER71
via **Another enhancer**
SOX9
AMH

(a) Evolutionary events inferred from the present study (red) and previous studies (black) are shown in the phylogeny, together with the geographical distribution of Tokudaia species. (b) Adult female and (c) male Okinawa spiny rat

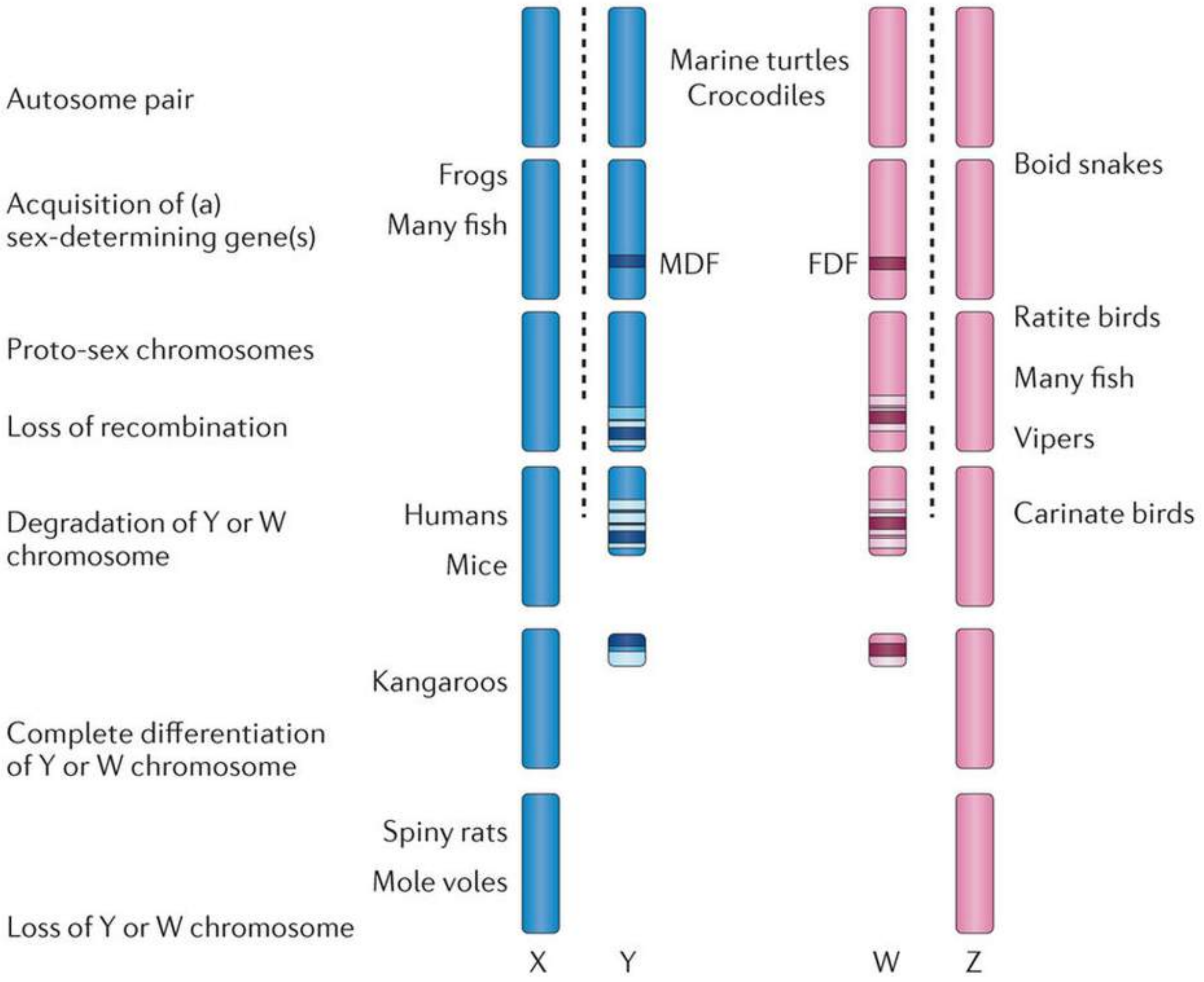
iPS cells made from Amami rat and then chimeras with mice: iPS cells appeared both in the ovary as immature egg cells, and others in the testis as

cells in

Mulugeta et al, Genome Res

Hunt for new Male Determining Factors
(Genetic, Environmental, Epigenetic)

Y-or W-Chromosome degeneration are highly variable

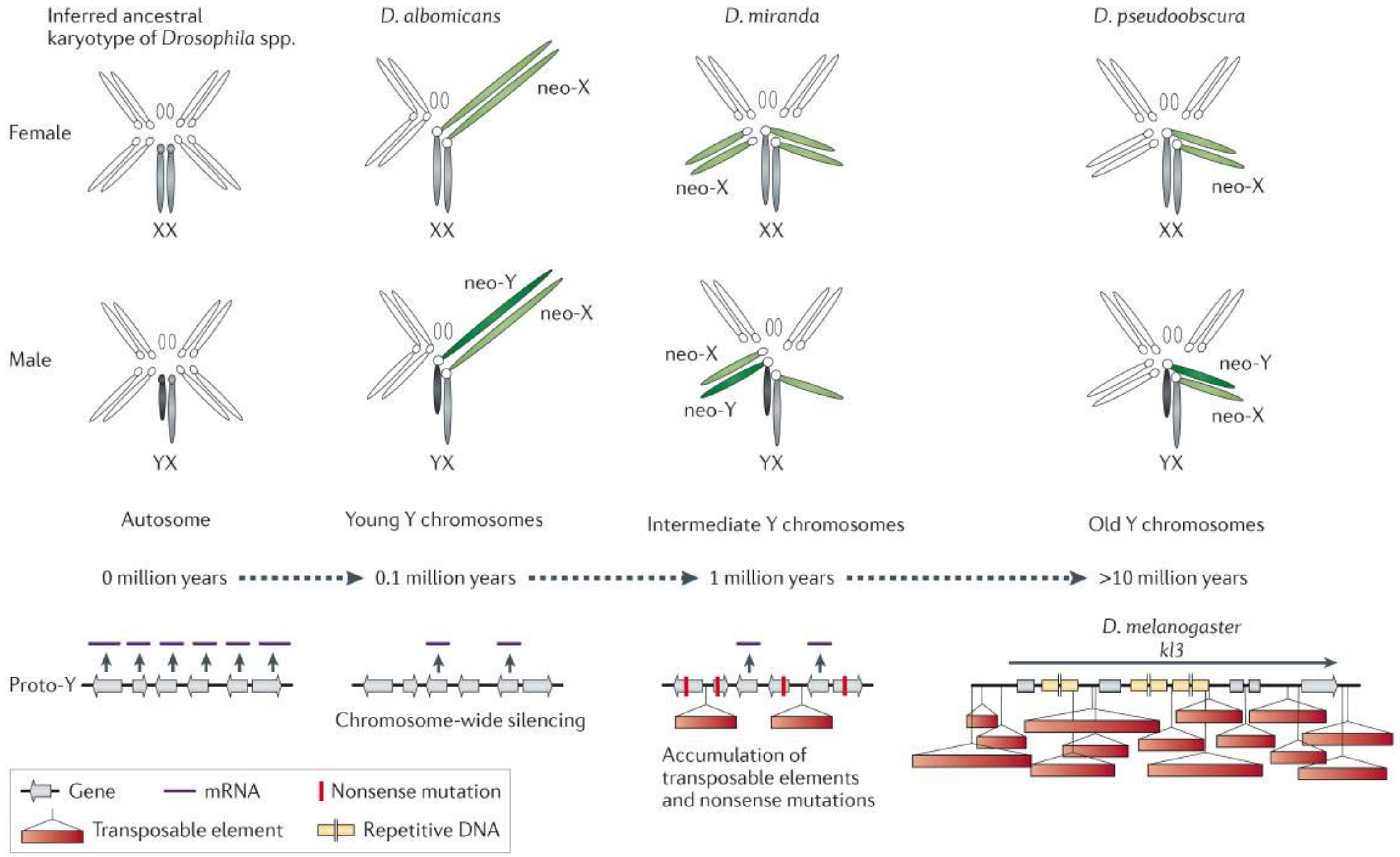


Nature Reviews | Genetics

E. Heard, January 29th, 2018

Graves JA, Nature Reviews Genetics, 2016

Neo-Y Chromosome Evolution in Drosophila

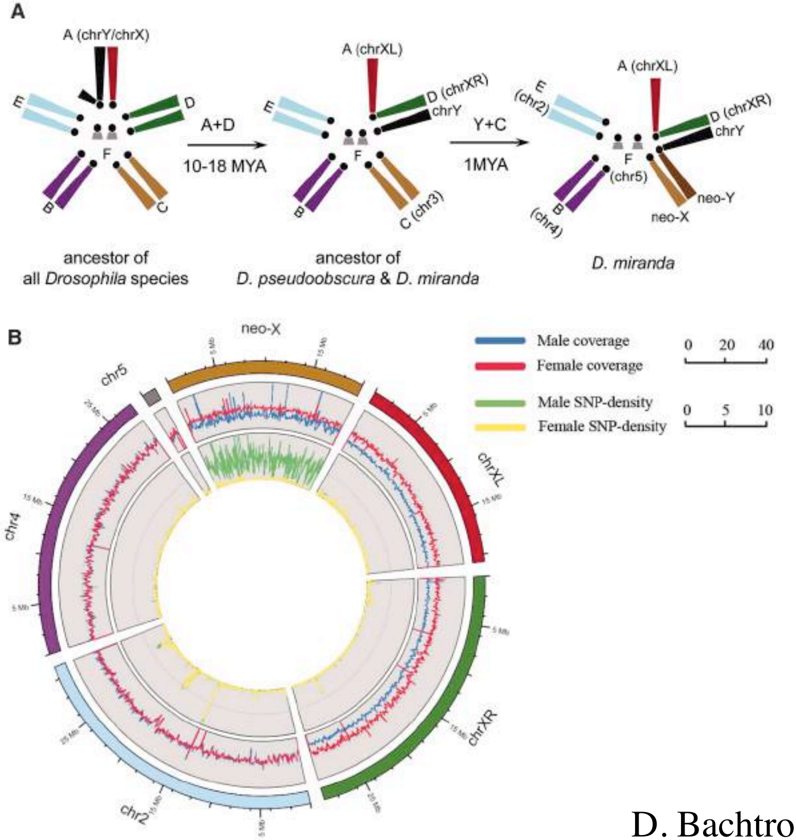


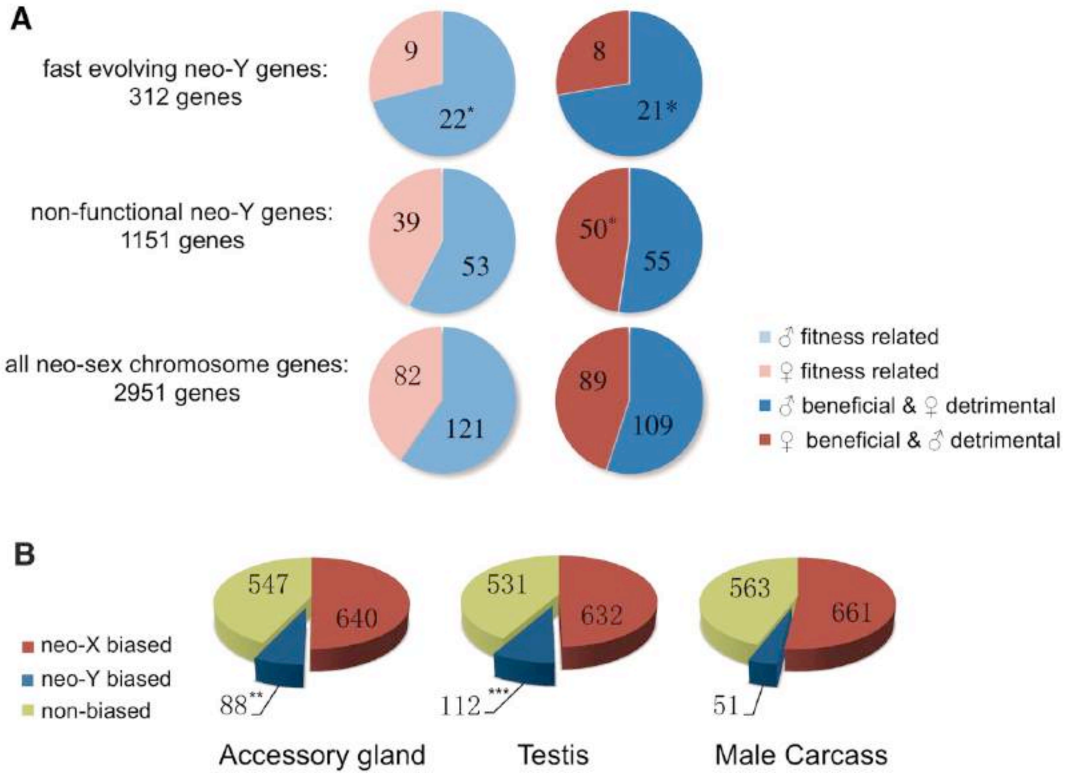
Neo-sex chromosomes (in green) are formed by fusions of autosomes with the ancestral sex chromosomes (in grey), and the neo-X and neo-Y carry identical gene sets at the time of their origin (that is, 0 million years).

D. Bachtrog, NRG 2013

Watching the evolution of sex chromosomes

- Drosophila miranda: neo-Y chromosome originated only approximately 1 million years ago.
- Whole-genome and transcriptome analysis reveals massive degeneration of the neo-Y
- Male-beneficial genes on the neo-Y are more likely to undergo accelerated protein evolution,
- Neo-Y genes evolve biased expression toward male-specific tissues
- Shrinking gene content of the neo-Y becomes masculinized.
- Although older X chromosomes show a paucity of genes expressed in male tissues, neo-X genes highly expressed in male-specific tissues undergo increased rates of protein evolution if haploid in males.
- Thus, the response to sex-specific selection can shift at different stages of X differentiation, resulting in masculinization or demasculinization of the X-chromosomal gene content.





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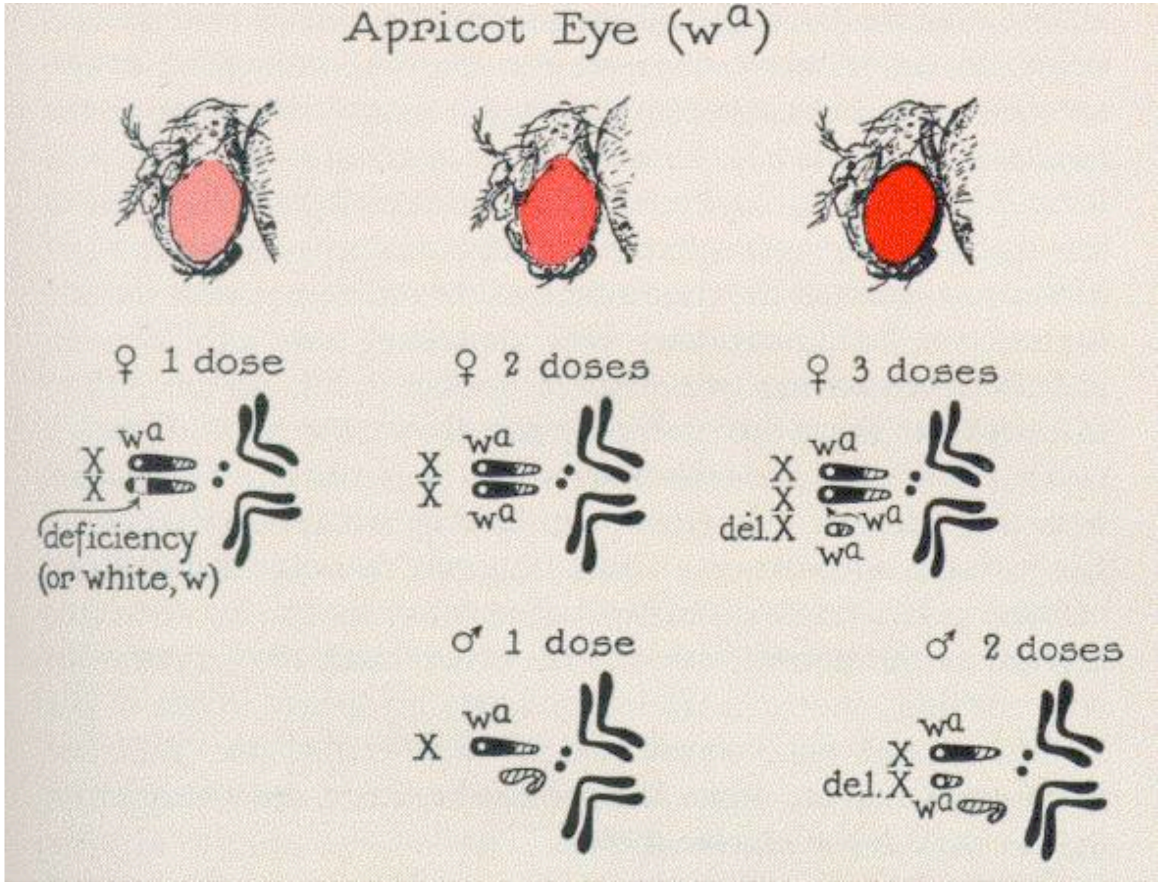
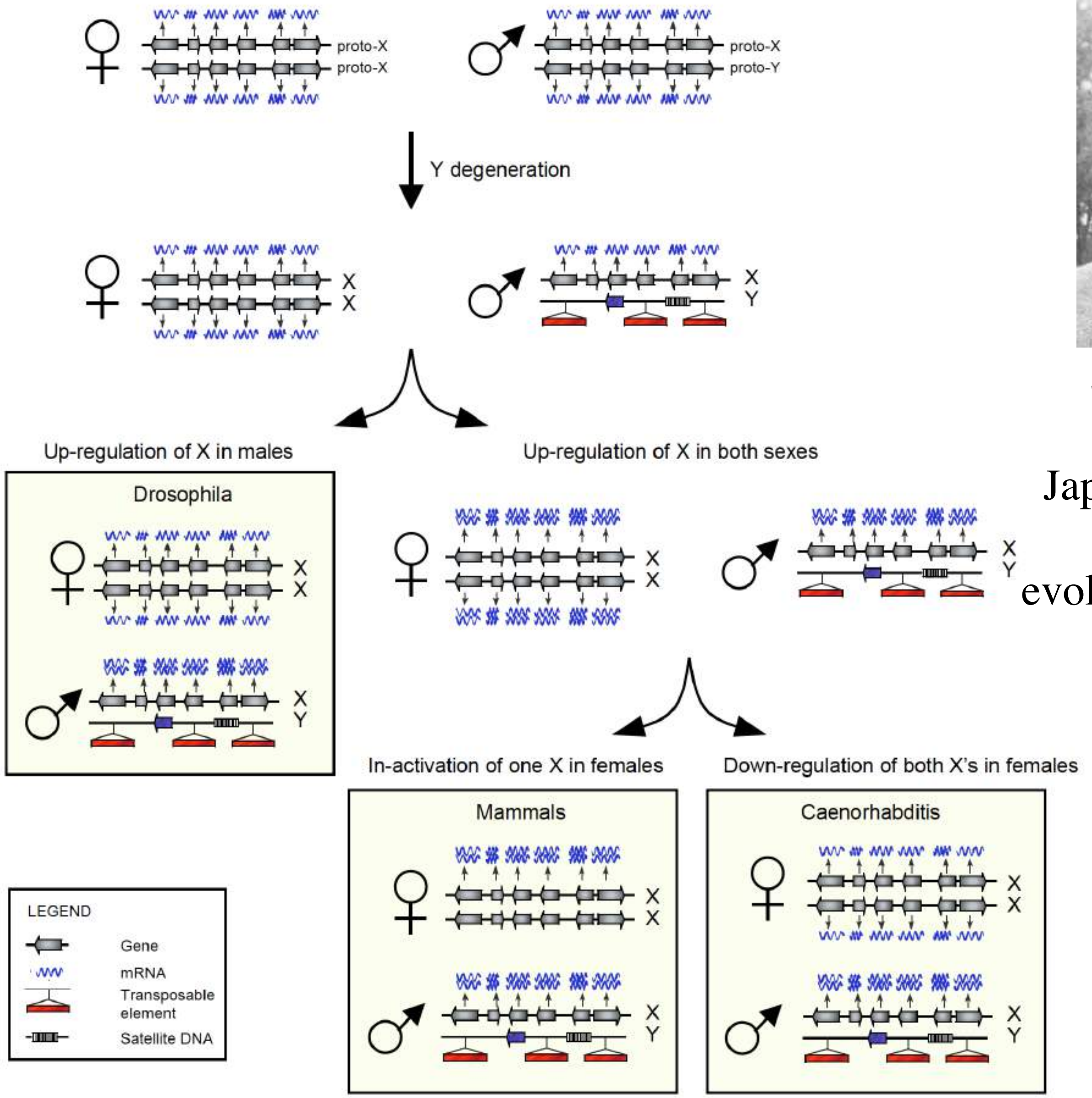
D. Bachtrog, NRG 2013

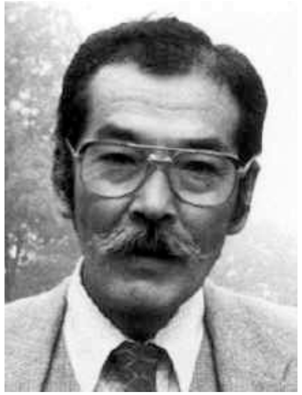
Sex Chromosomes and Gene Dosage?

Sex Chromosome dosage compensation - first described by Muller:
"Effects of dosage changes of sex-linked genes, and the compensatory effects of the gene differences between male and female" (Muller, et al., 1931)



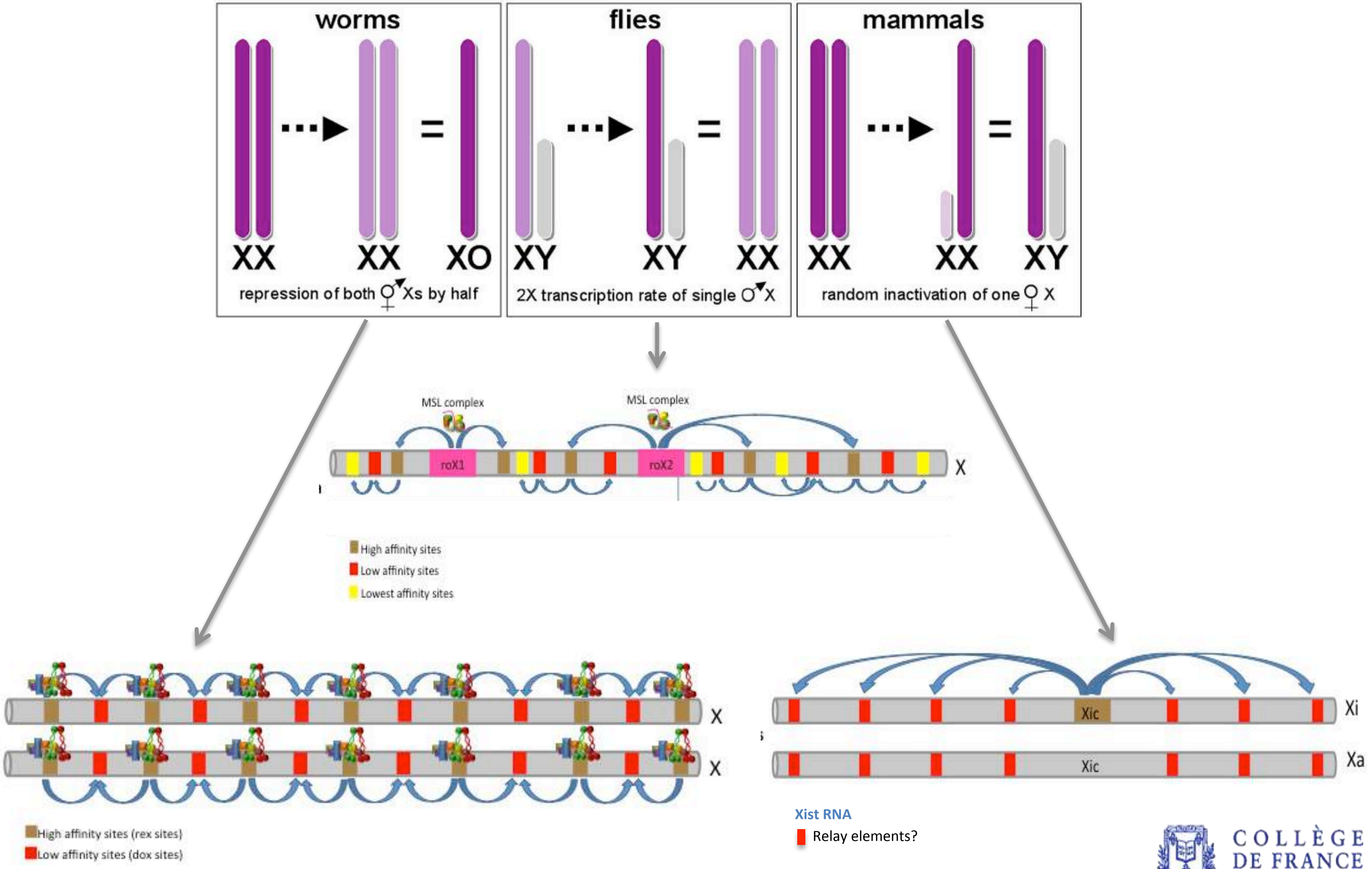
Evolution of dosage compensation in flies, mammals & worms



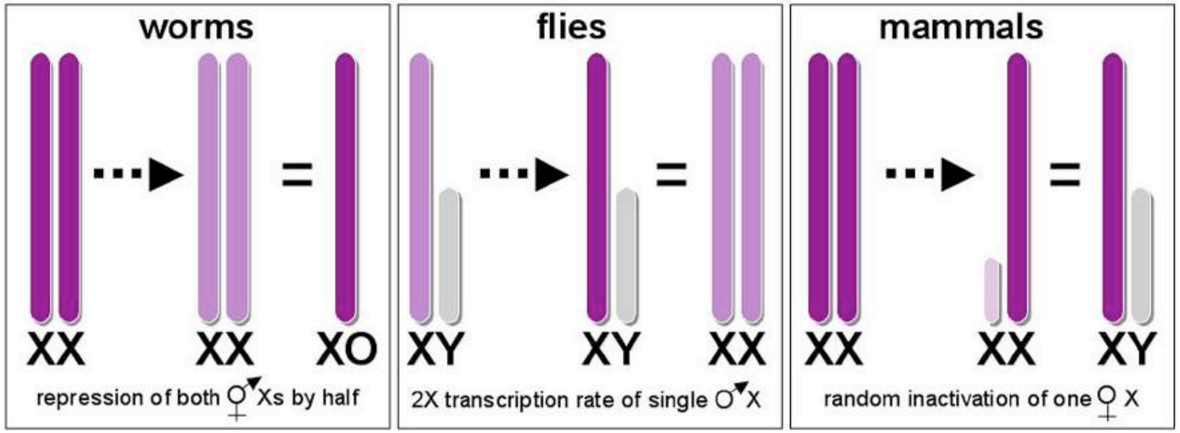


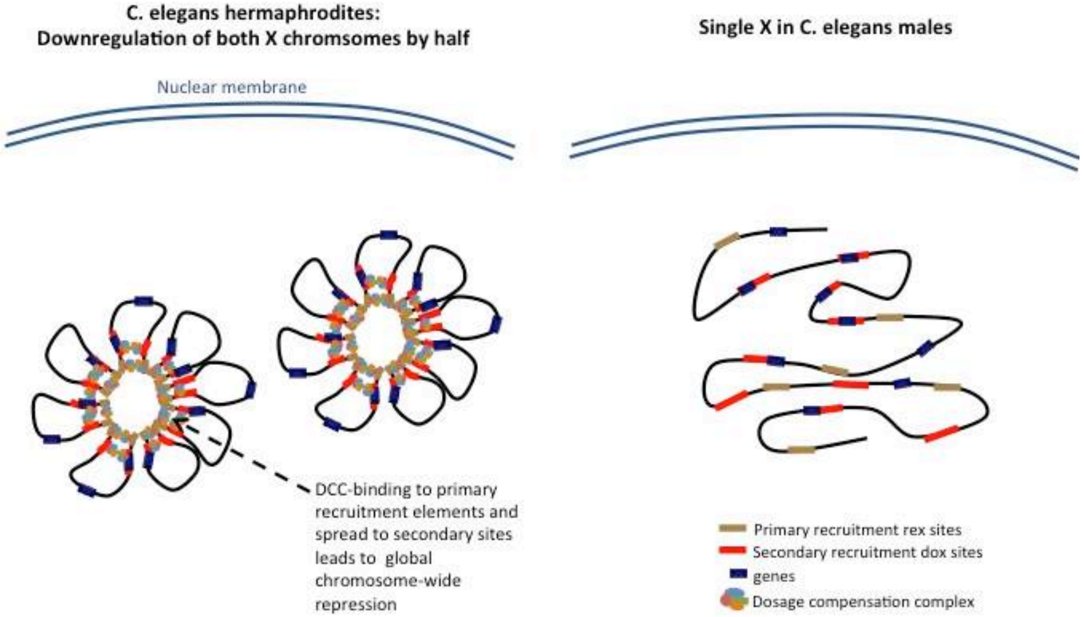
Susumu Ohno
(1928-2000)
Japanese-American
Geneticist,
evolutionary biologist

Sex Chromosome Dosage Compensation

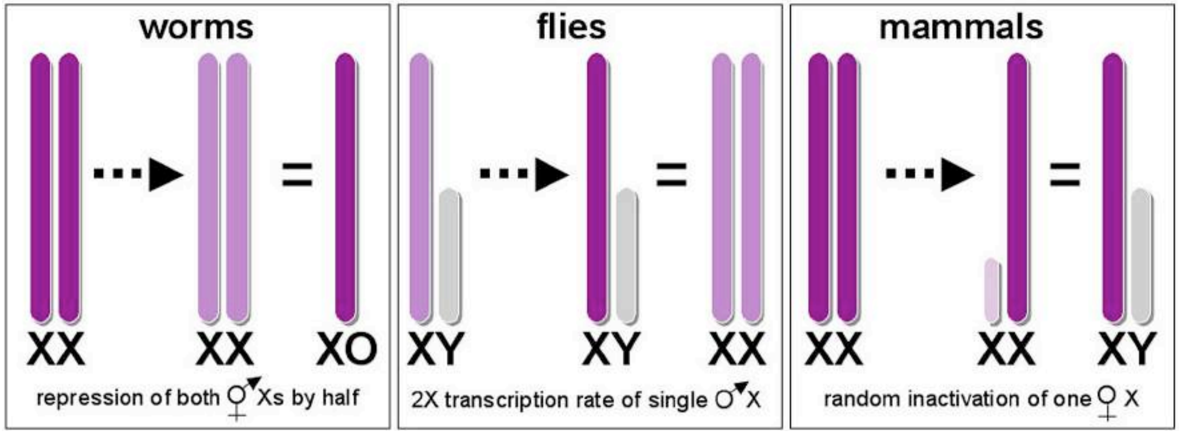


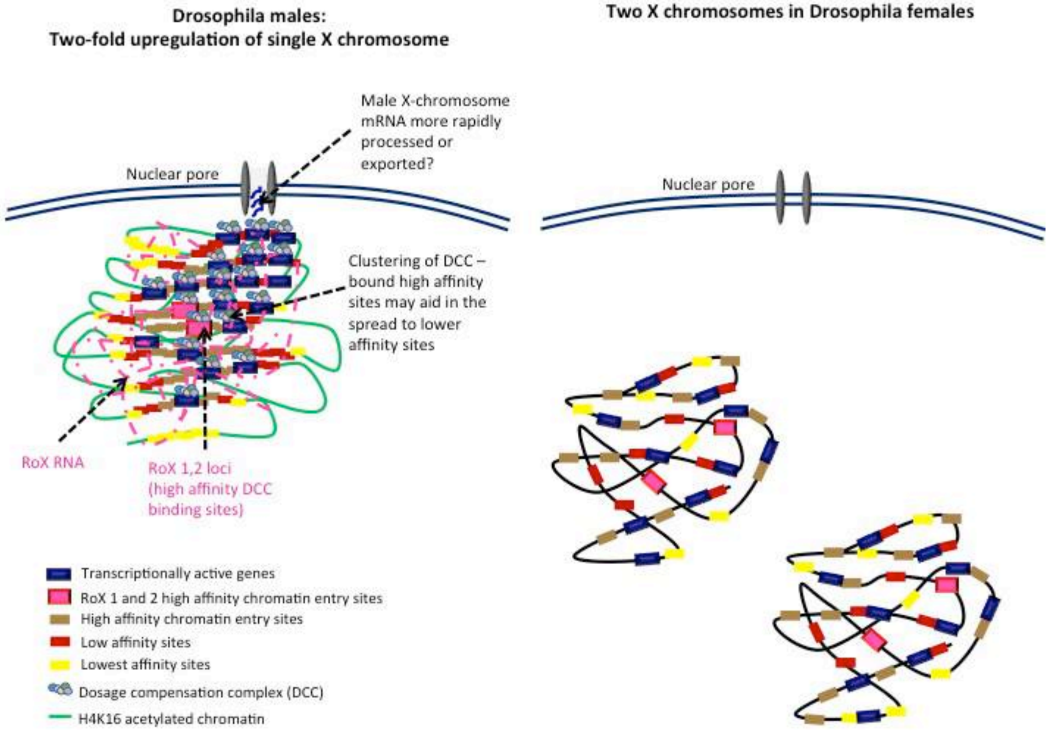
Sex Chromosome Dosage Compensation



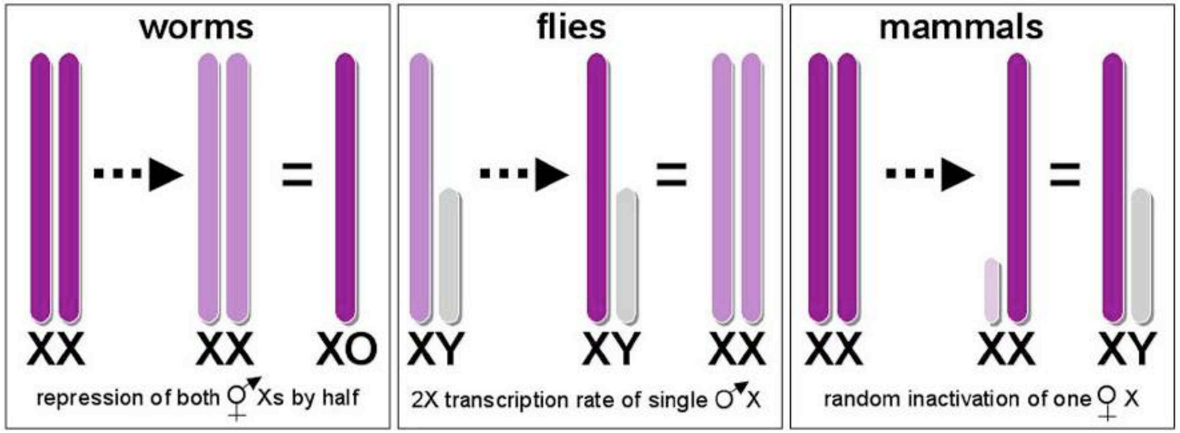


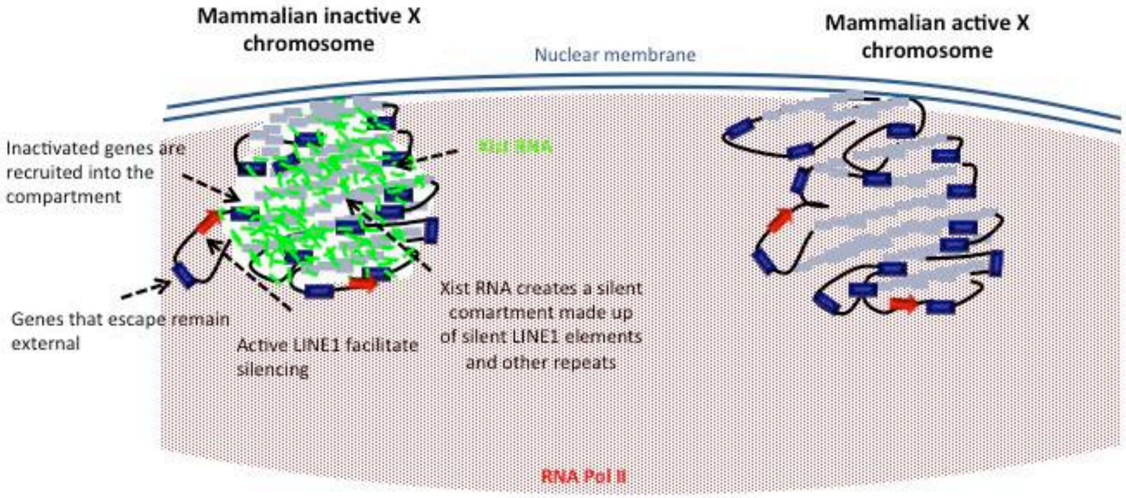
Sex Chromosome Dosage Compensation





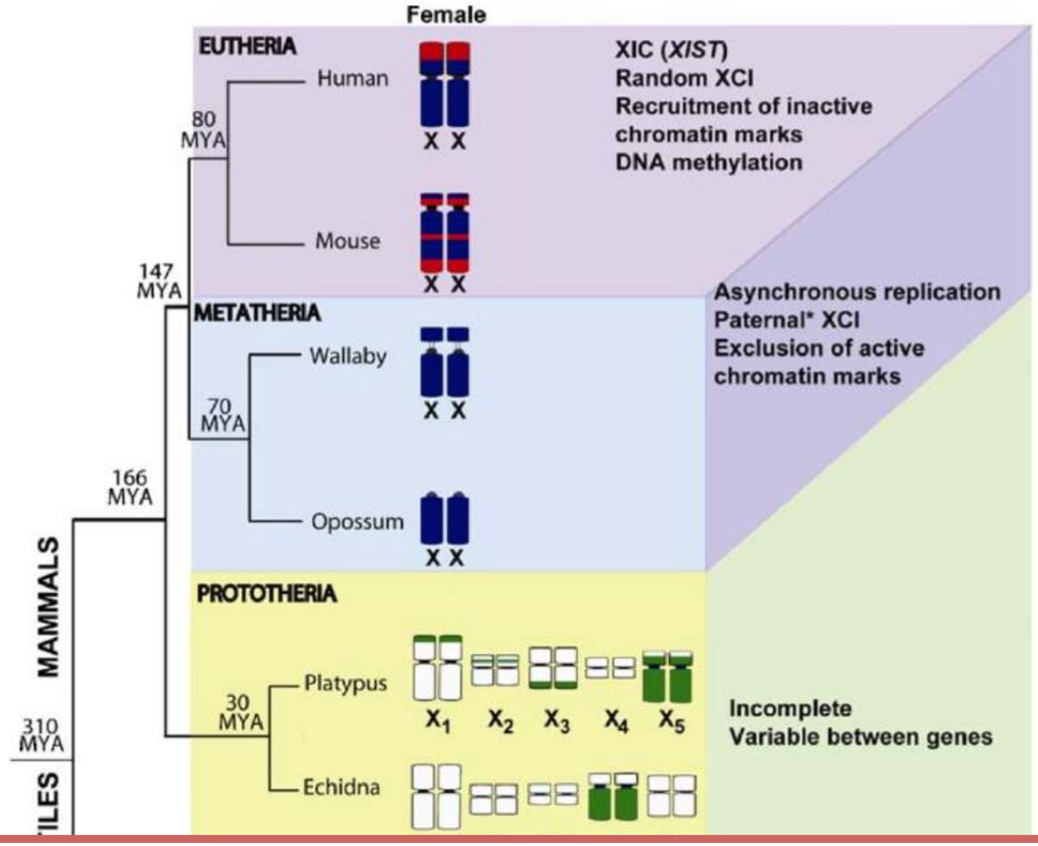
Sex Chromosome Dosage Compensation





The role of Epigenetics in differential gene expression output from the X chromosome: Next Week

Chromosome-wide Dosage Compensation may be the exception rather than the rule…



Ancestral dosage compensation may be "gene by gene"
Recent superposition of chromosome-wide strategies
eg by long non-coding RNAs…
(COURS II + III)

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2017-2018 :
"Le chromosome X -
paradigme de la génétique et l'épigénetique"

5 février, 2018

Cours II

Régulation génétique et épigénétique du chromosome X inactif

Genetic and Epigenetic Regulation of the Inactive X chromosome

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