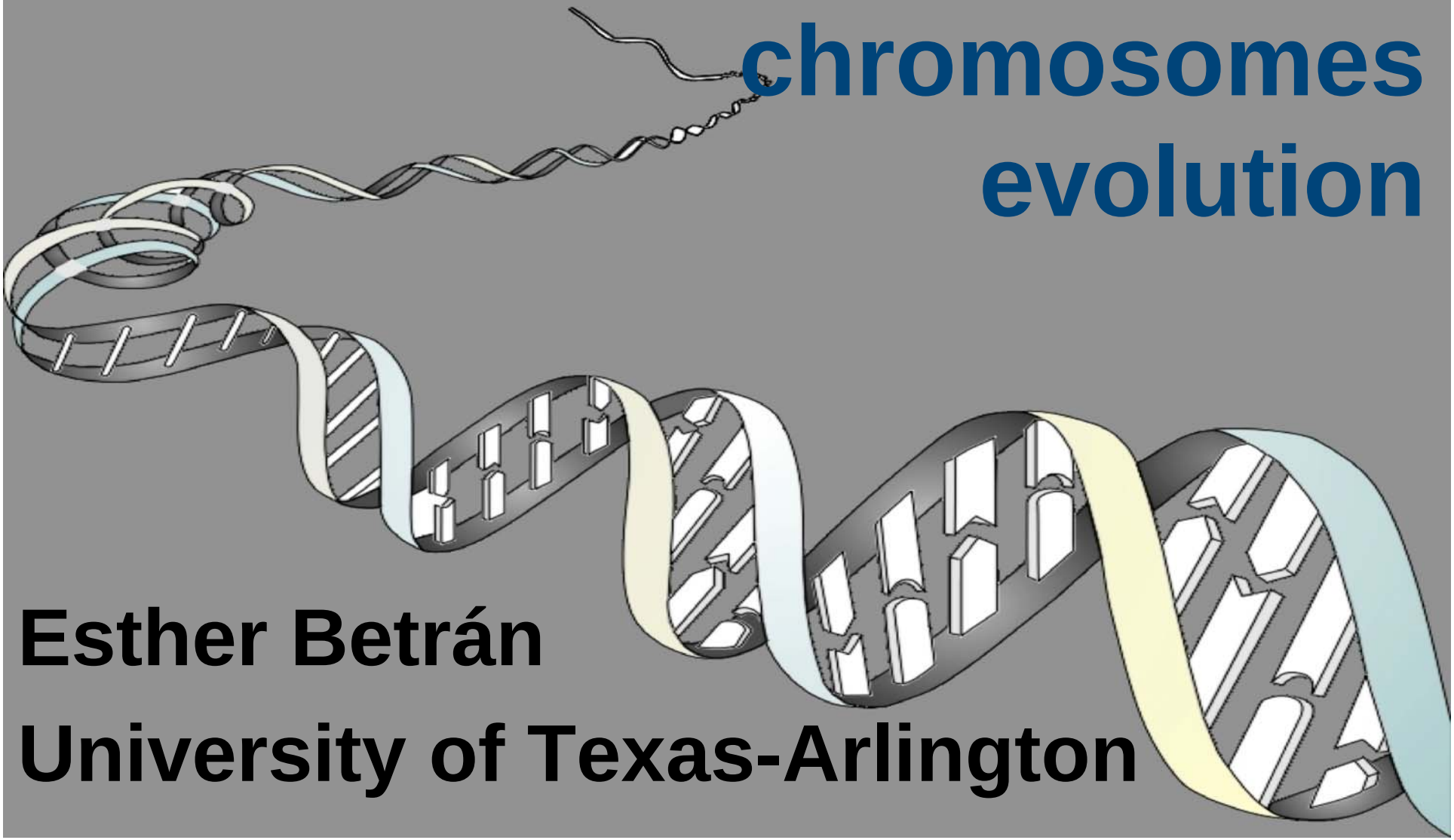
Patterns of gene duplication and sex chromosomes evolution



Esther Betrán

University of Texas-Arlington

Outline:

Introduction :

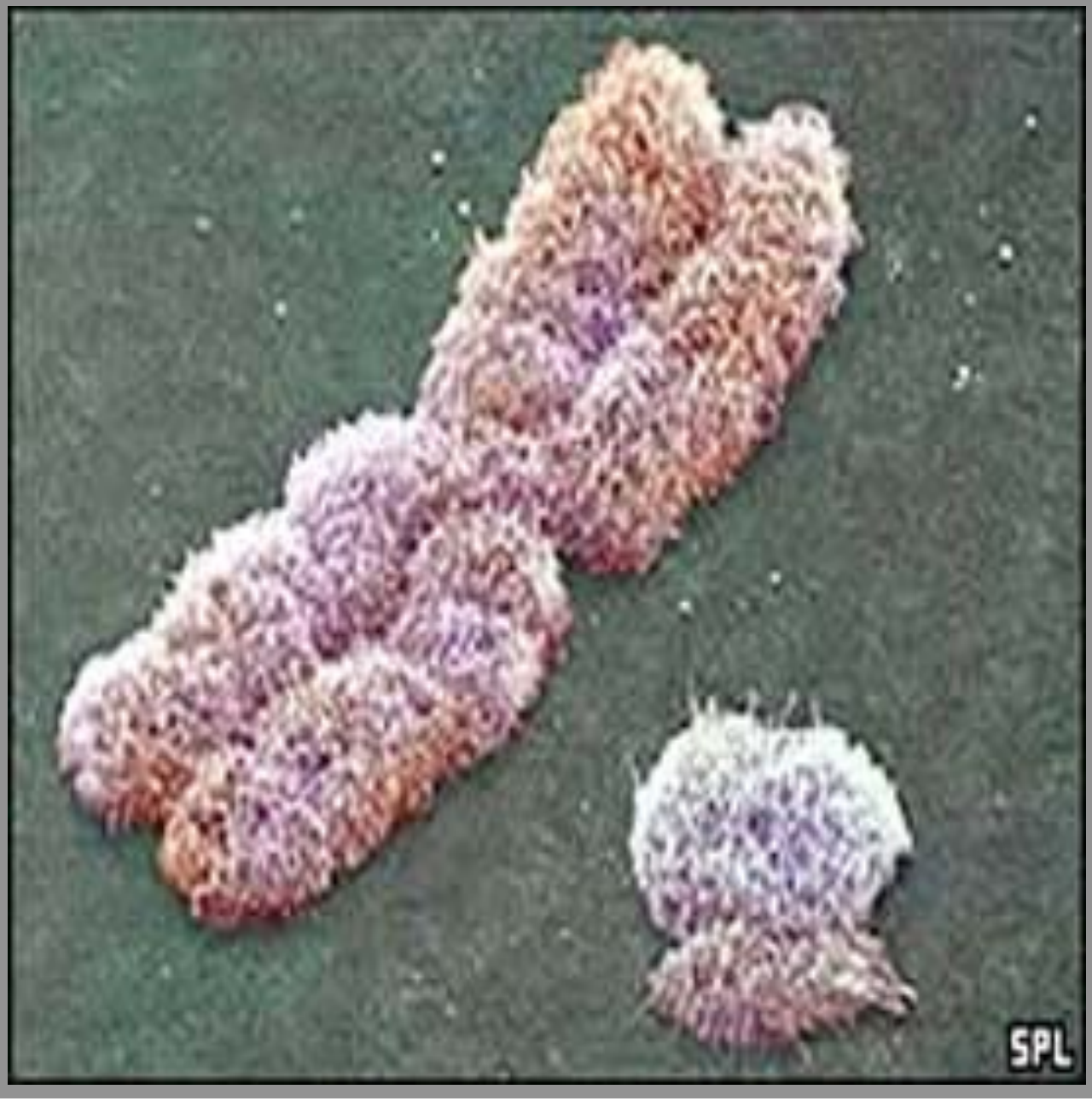
- Sex chromosomes evolution
- Retroposition as a gene duplication mechanism

Recent surprises:

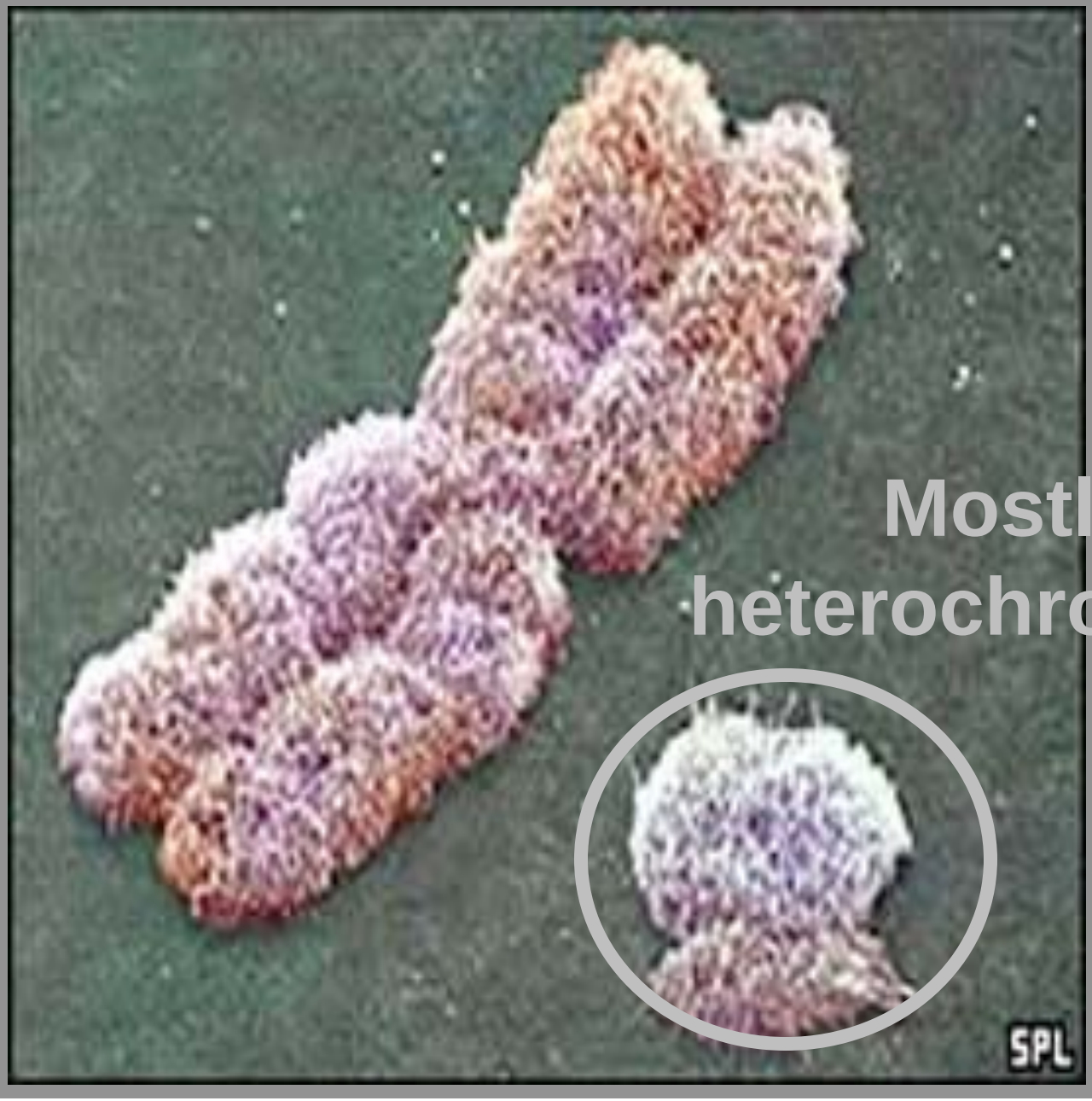
- Rates and patterns of gene duplication change the traditional view of X chromosome evolution
- Three hypotheses to explain the patterns
  - X inactivation
  - Sexual antagonism
  - Meiotic drive
- Some surprises also in the Y chromosome.

Summary

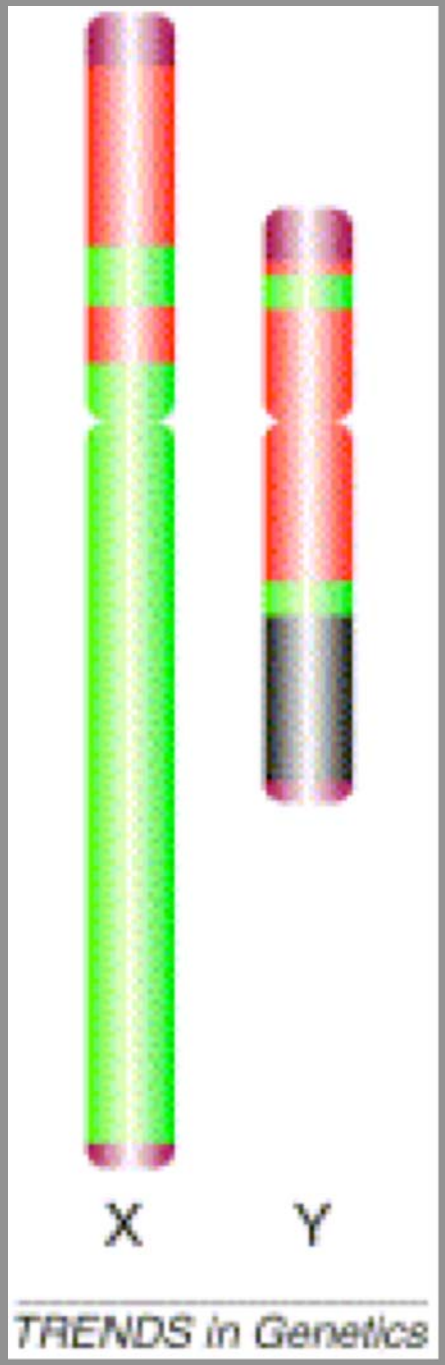
Human sex chromosomes



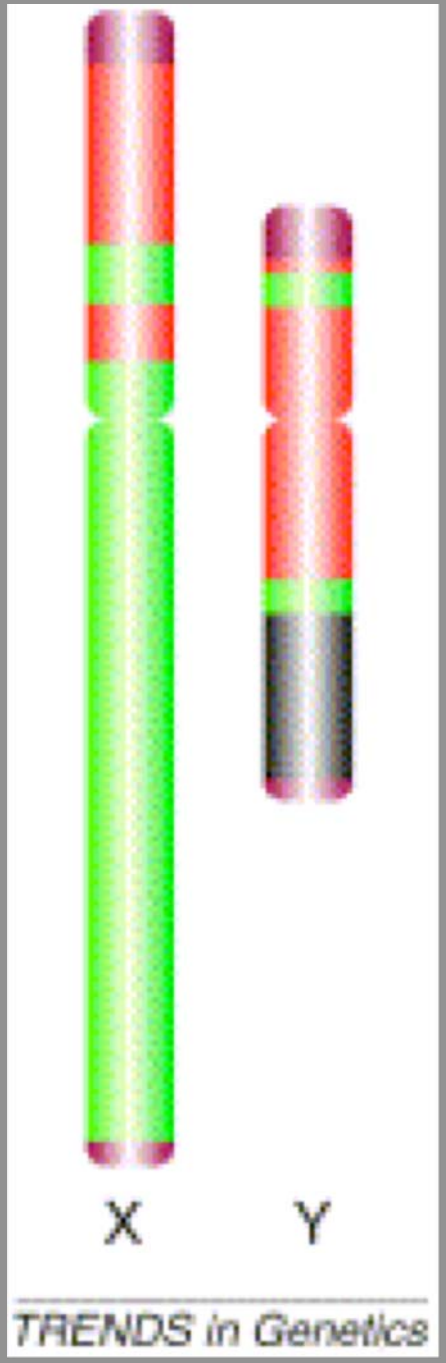
Human sex chromosomes

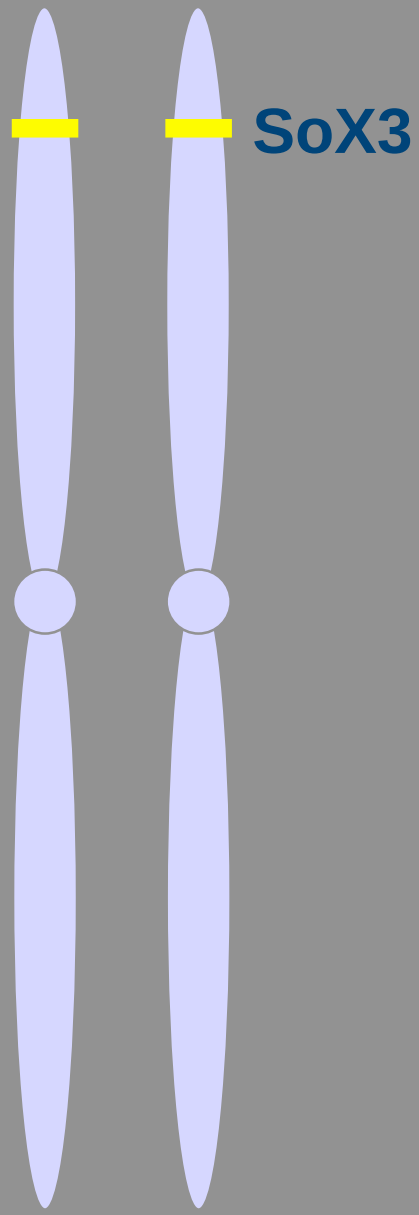


Human sex chromosomes X and Y are morphologically very different:
Y is small ~ 78 genes and X is big ~1200 genes

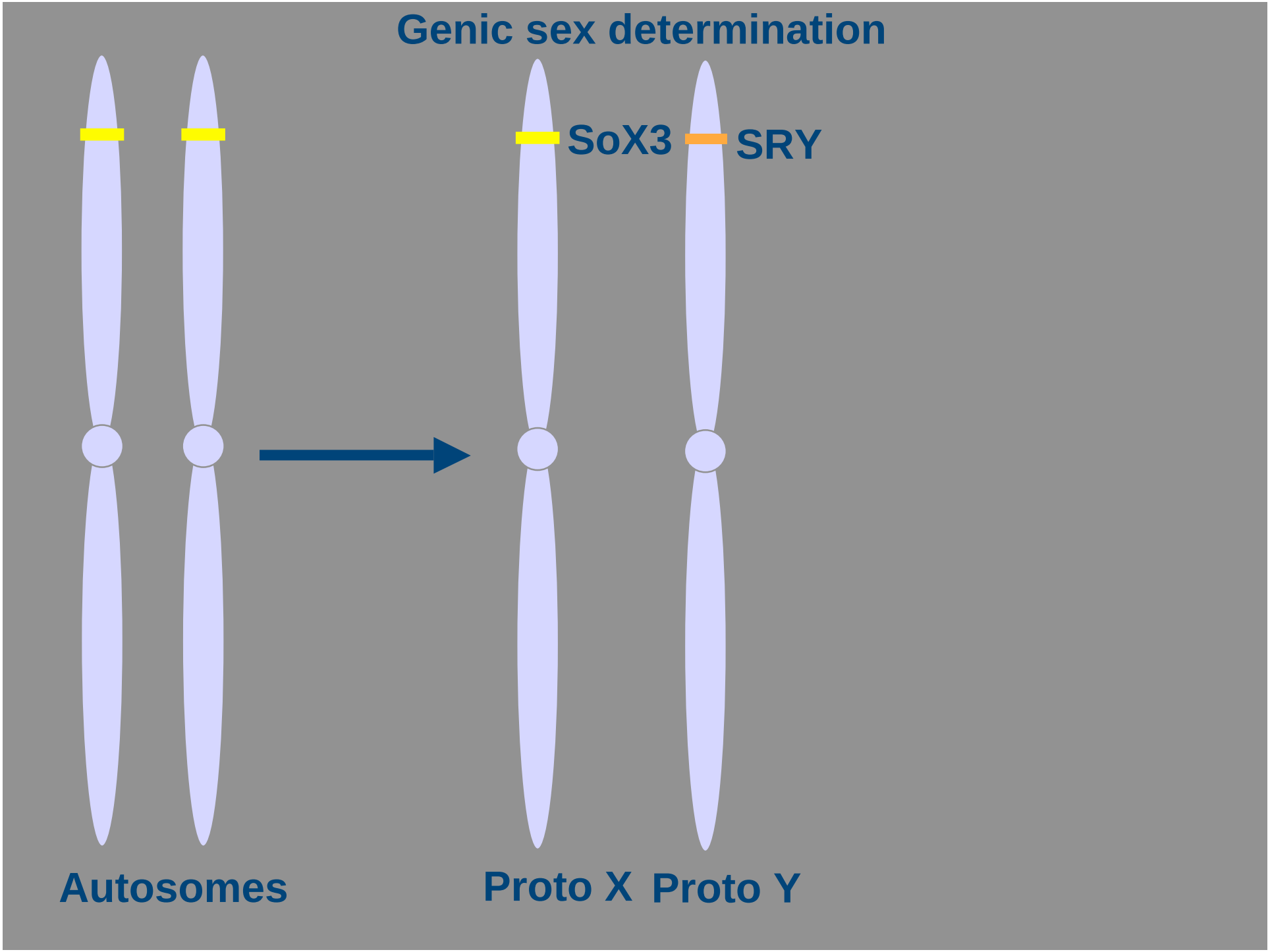


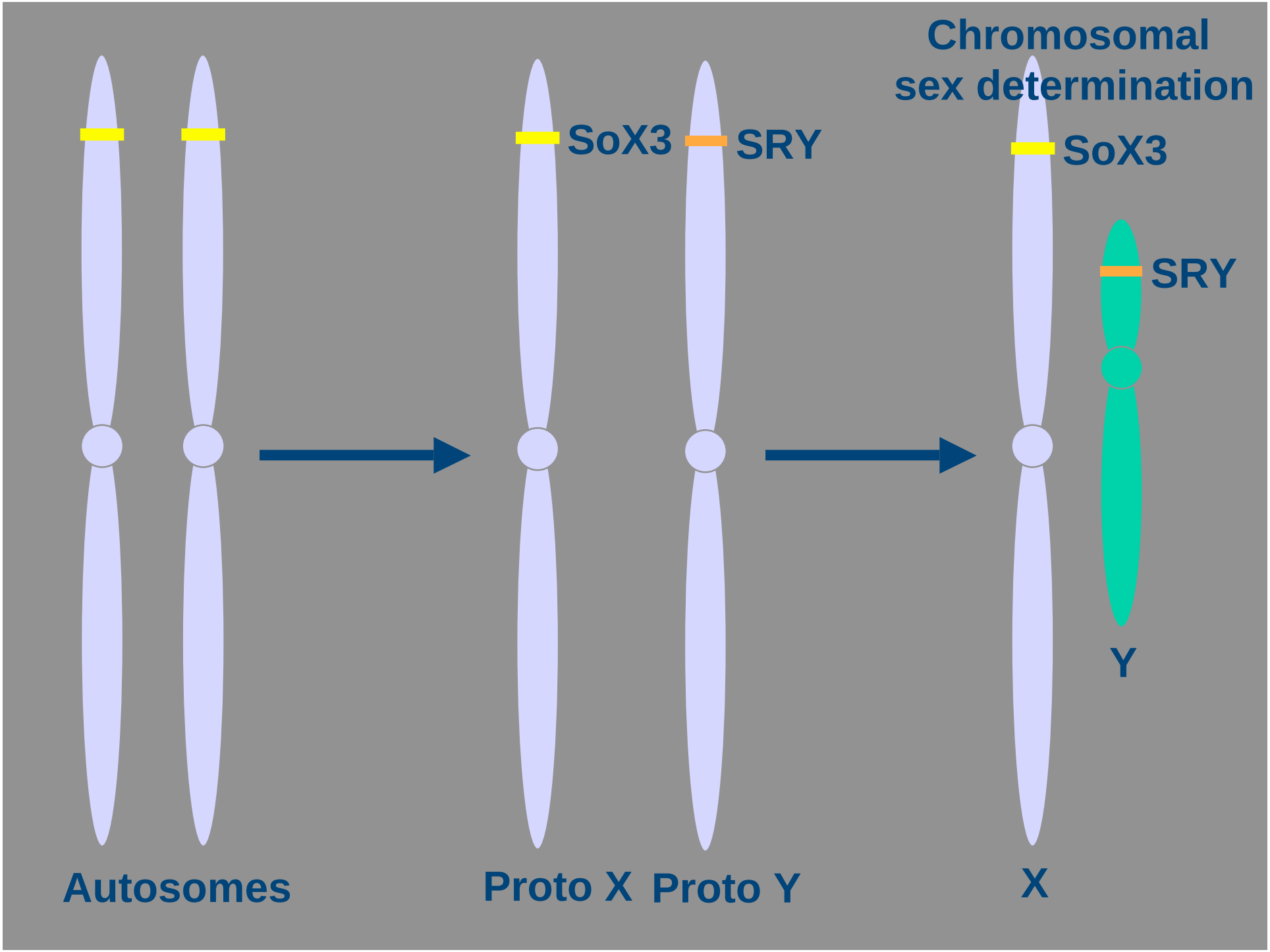
However they begun their journey as a normal pair of autosomes where an allele of a gene (SRY) evolved to have the sex determining role.

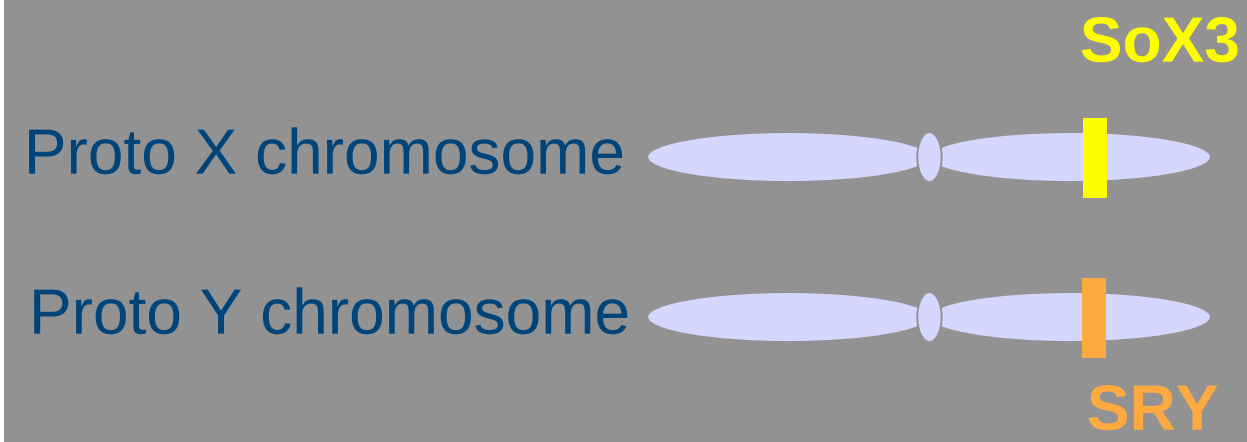


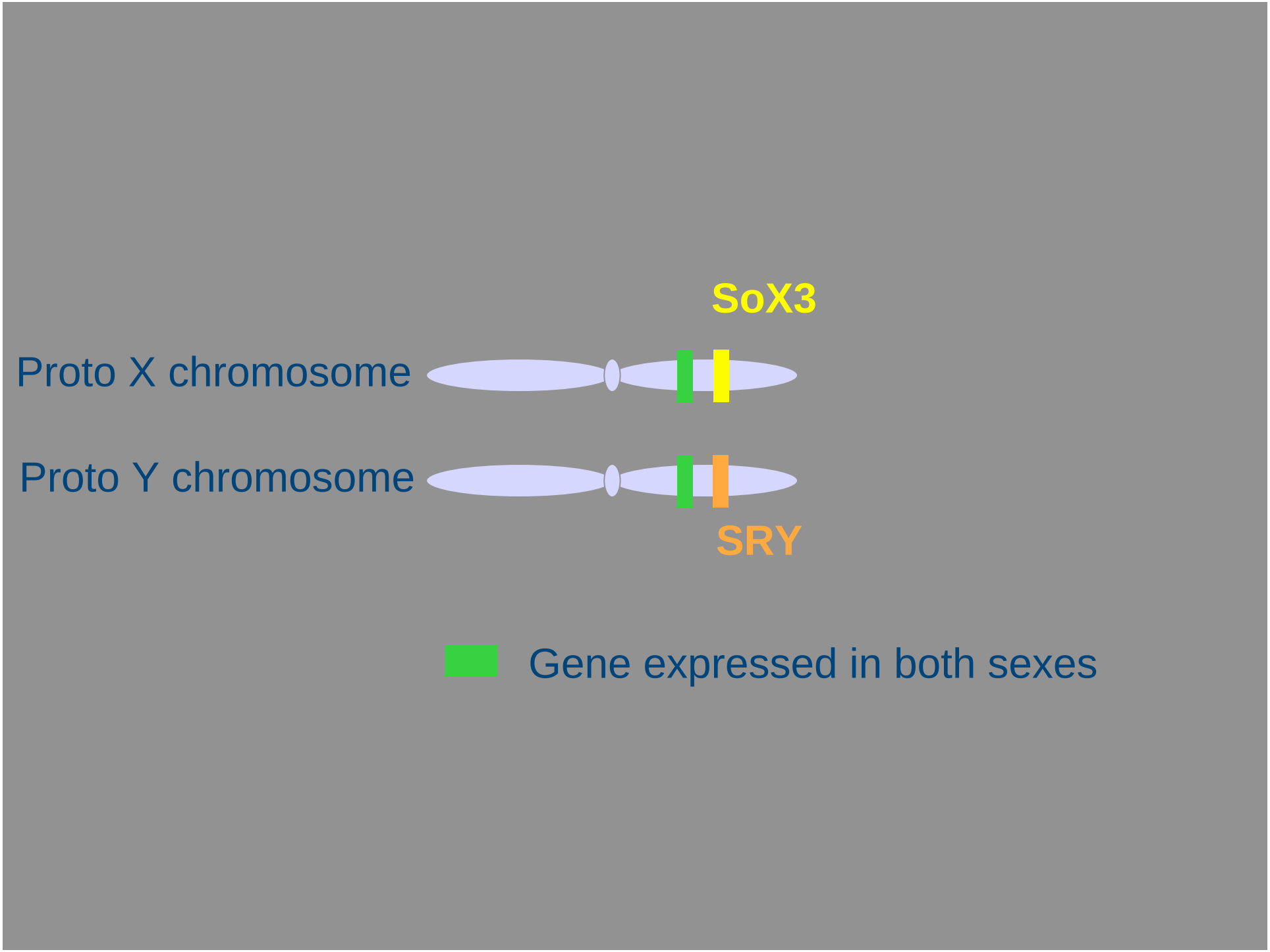


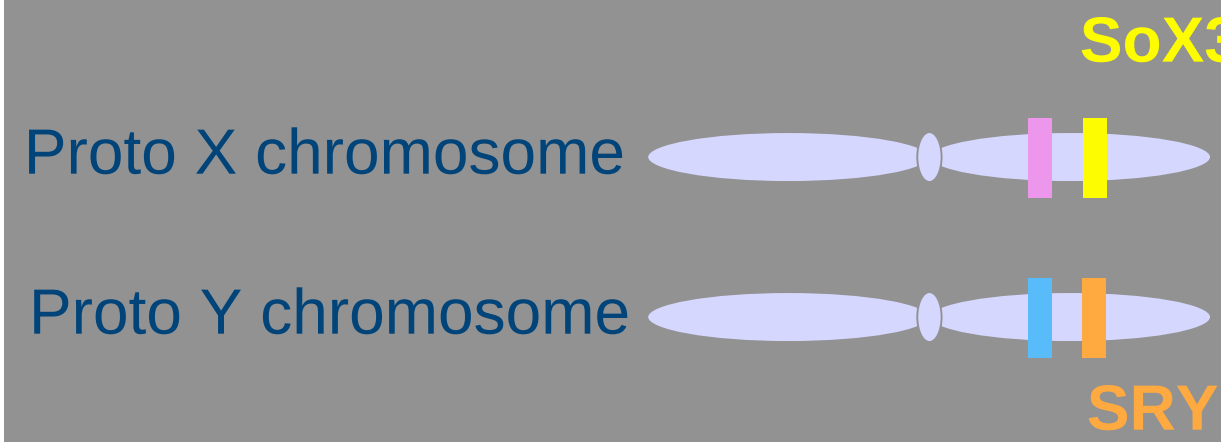
Autosomes


Genic sex determination
SoX3
SRY
Autosomes
Proto X
Proto Y


Chromosomal
sex determination
SoX3
SRY
SoX3
SRY
Y
Autosomes
Proto X
Proto Y
X

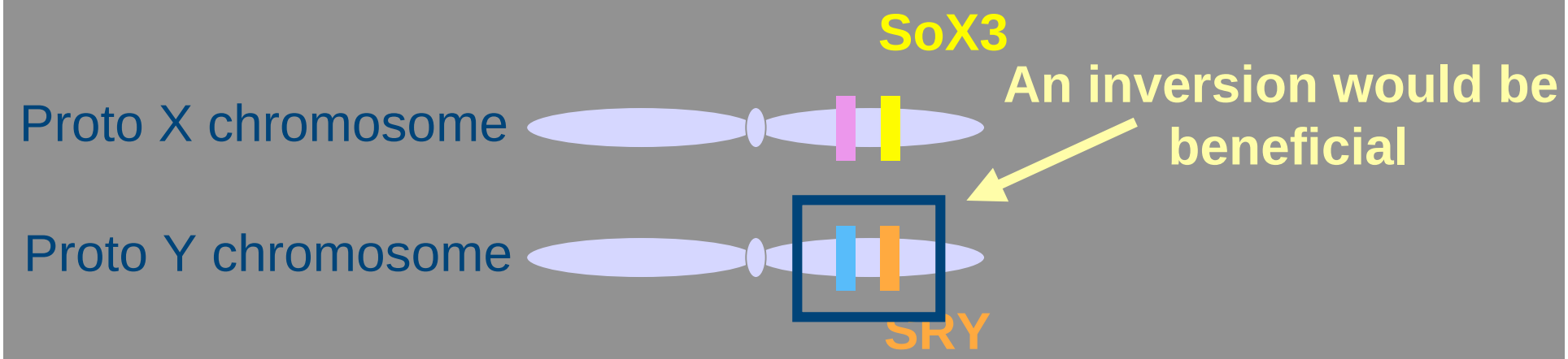

SoX3
Proto X chromosome
Proto Y chromosome
SRY


SoX3
Proto X chromosome
Proto Y chromosome
SRY
Gene expressed in both sexes



Allele that benefits the males but hurts the females

Allele that benefits the females but hurts the males



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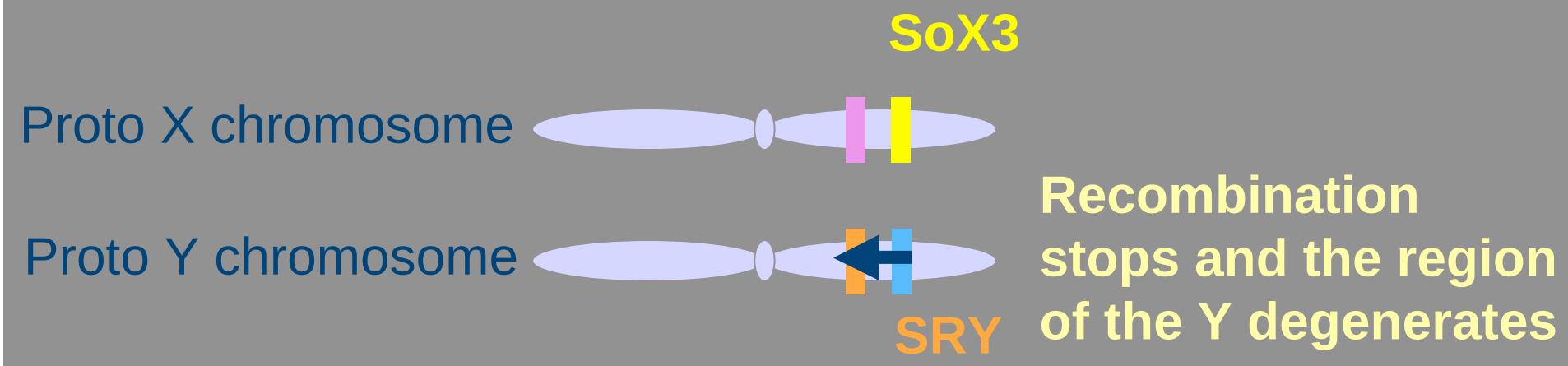
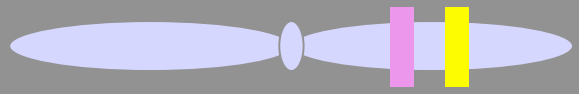


Allele that benefits the males but hurts the females

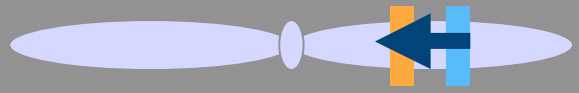
Allele that benefits the females but hurts the males

SoX3

Proto X chromosome



Proto Y chromosome



SRY

In addition the genes in that region begin evolving separately

Allele that benefits the males but hurts the females

Allele that benefits the females but hurts the males

Rice 1996 for a review

Degeneration of the Y chromosome

Several mechanisms related to the lack of recombination:

1. One process is deleterious mutation accumulation by Muller's ratchet, leading to an increasing number of deleterious mutations, which become fixed as the process continues and they cannot be recombined out.

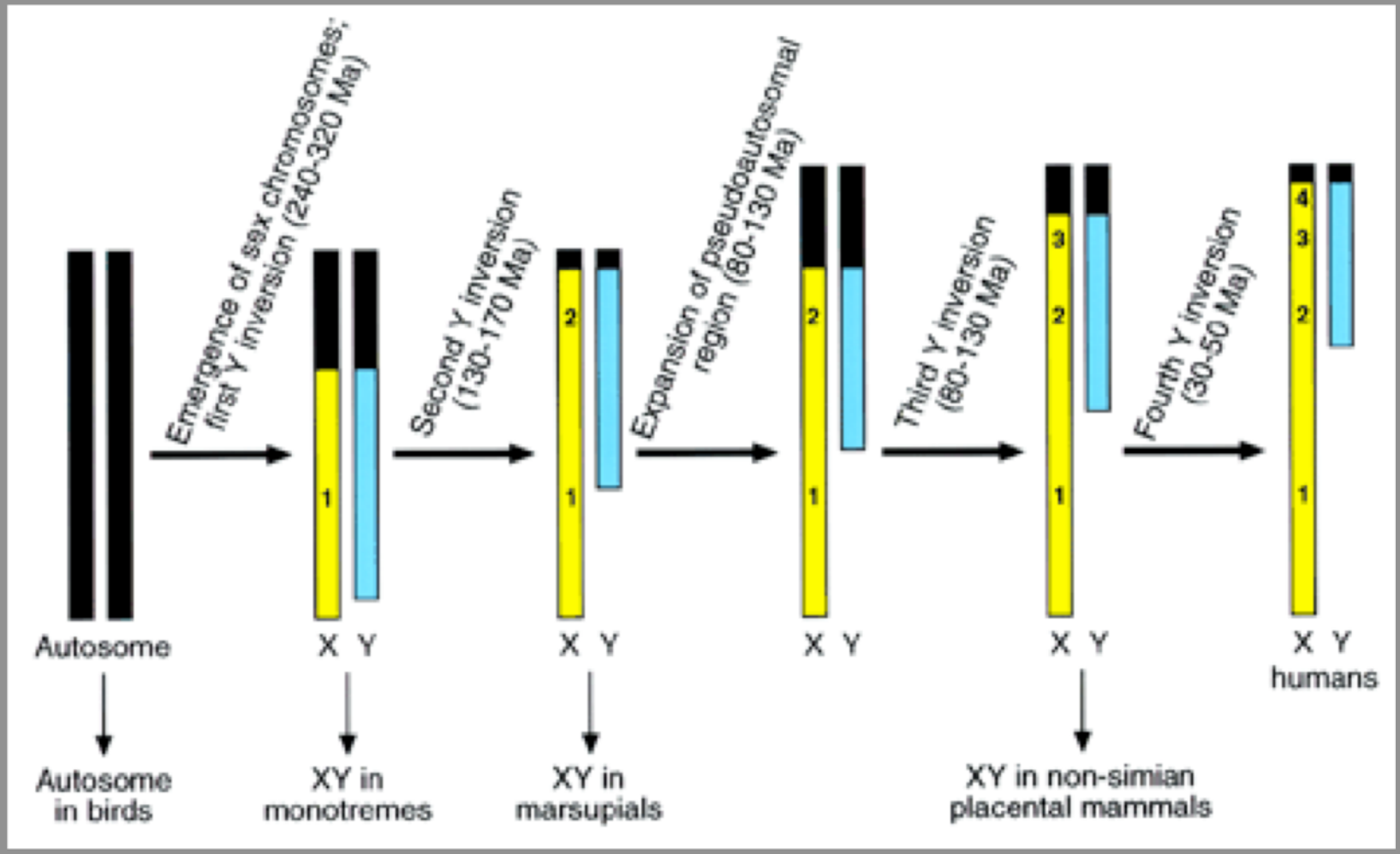
2. Another possibility is hitch-hiking: favorable mutant alleles arise on the proto-Y and rise in frequency to fixation, concomitantly fixing deleterious alleles on the same chromosome.

3. Background selection, selection against strongly deleterious mutations, will have the effect of reducing the population size. This accelerates the fixation of mildly deleterious mutations and reduces de chance of fixation of mildly advantageous mutations.

Charlesworth and Charlesworth 2000 for a review

In summary, the nonrecombining Y chromosome will accumulate deleterious mutations. A fraction of those will be caused by insertions of transposable elements (TE).

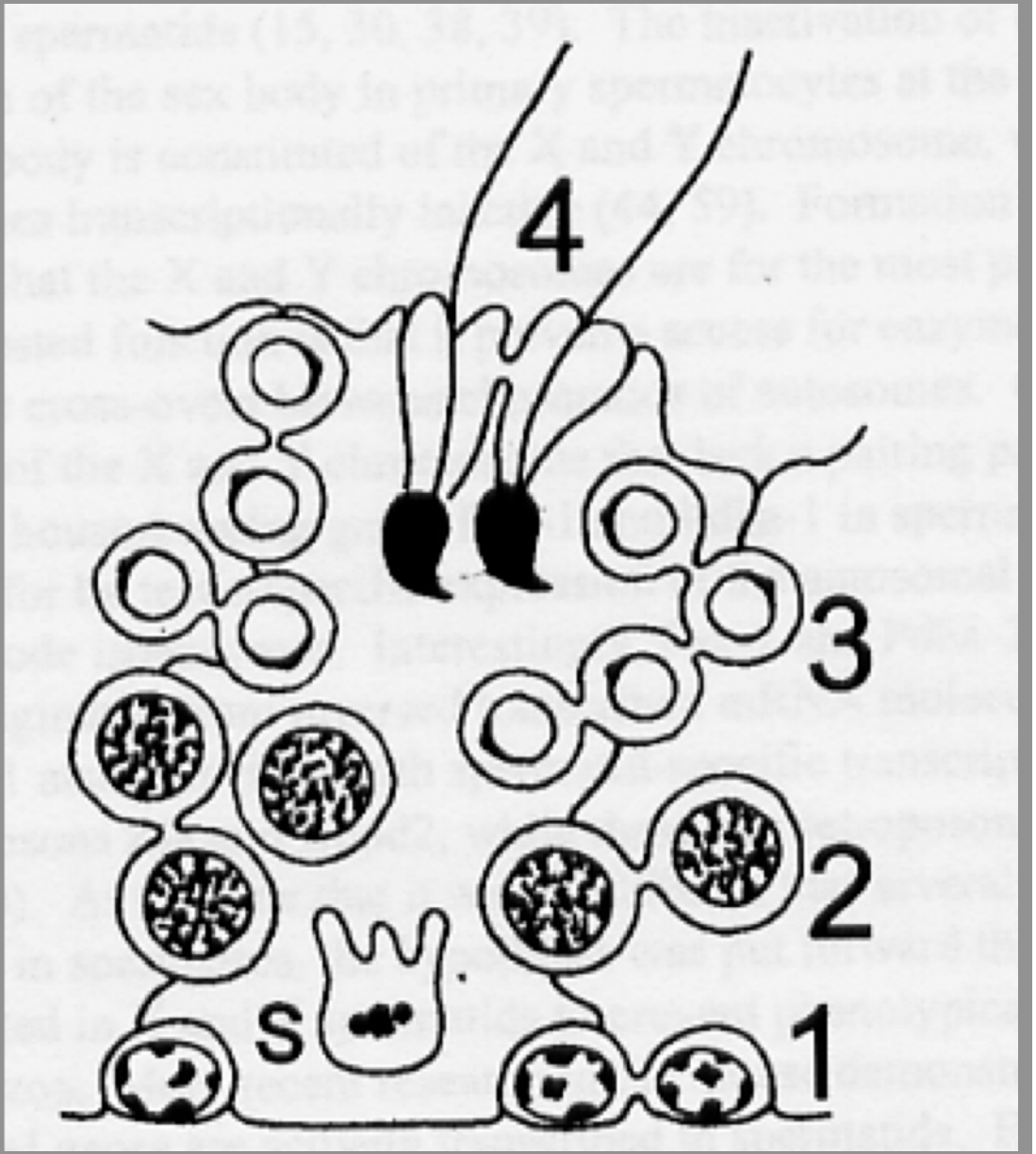
Four strata in the human Y chromosome



Lahn and Page 1999

At the end the non-recombining region of the Y chromosome is left with very few genes that are male-specific.

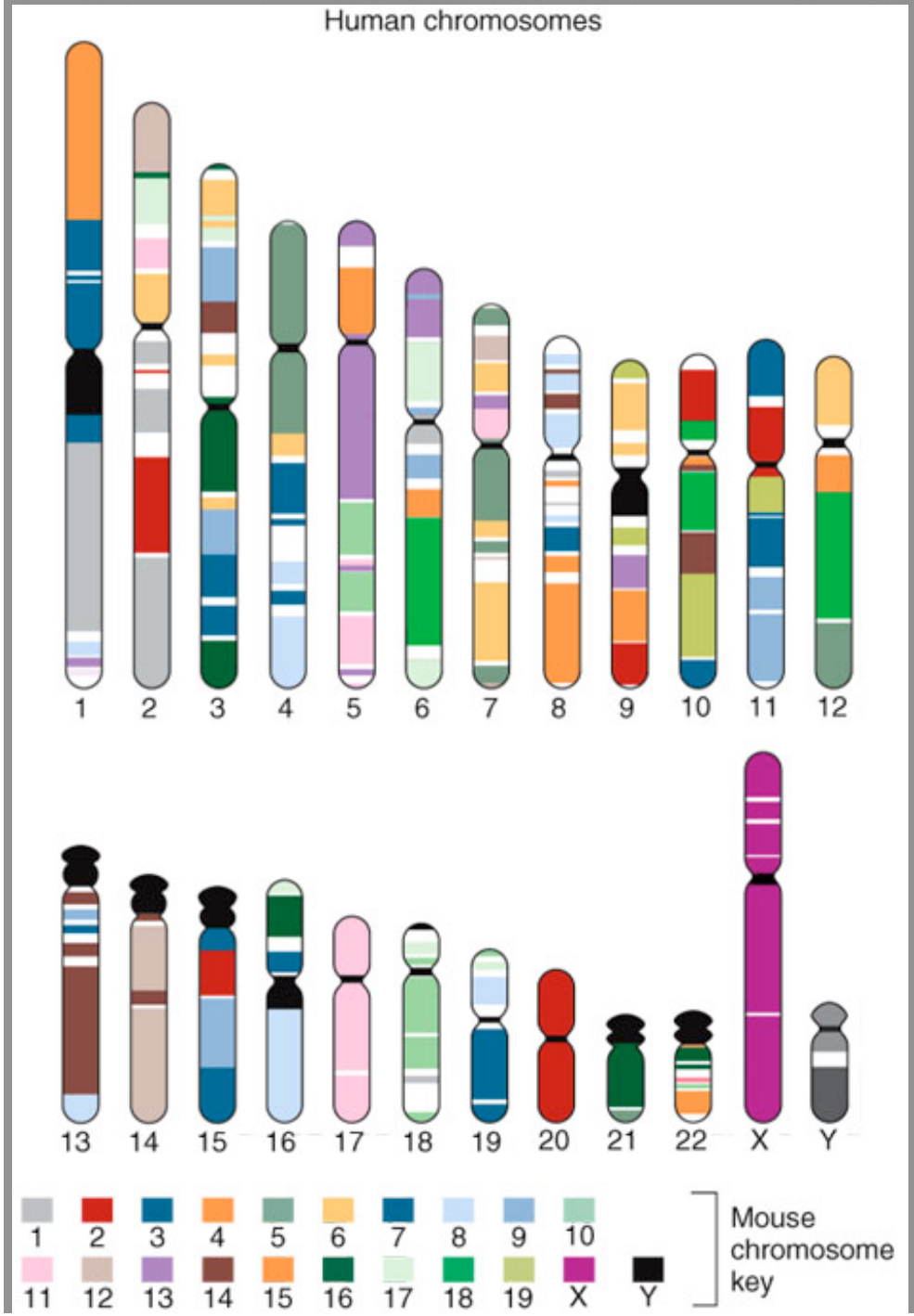
Y chromosome specialization



Dosage compensation is the mechanism by which the genes on the X chromosome express at the same level in male and female.

Females are XX

Males are XY



Traditional view:

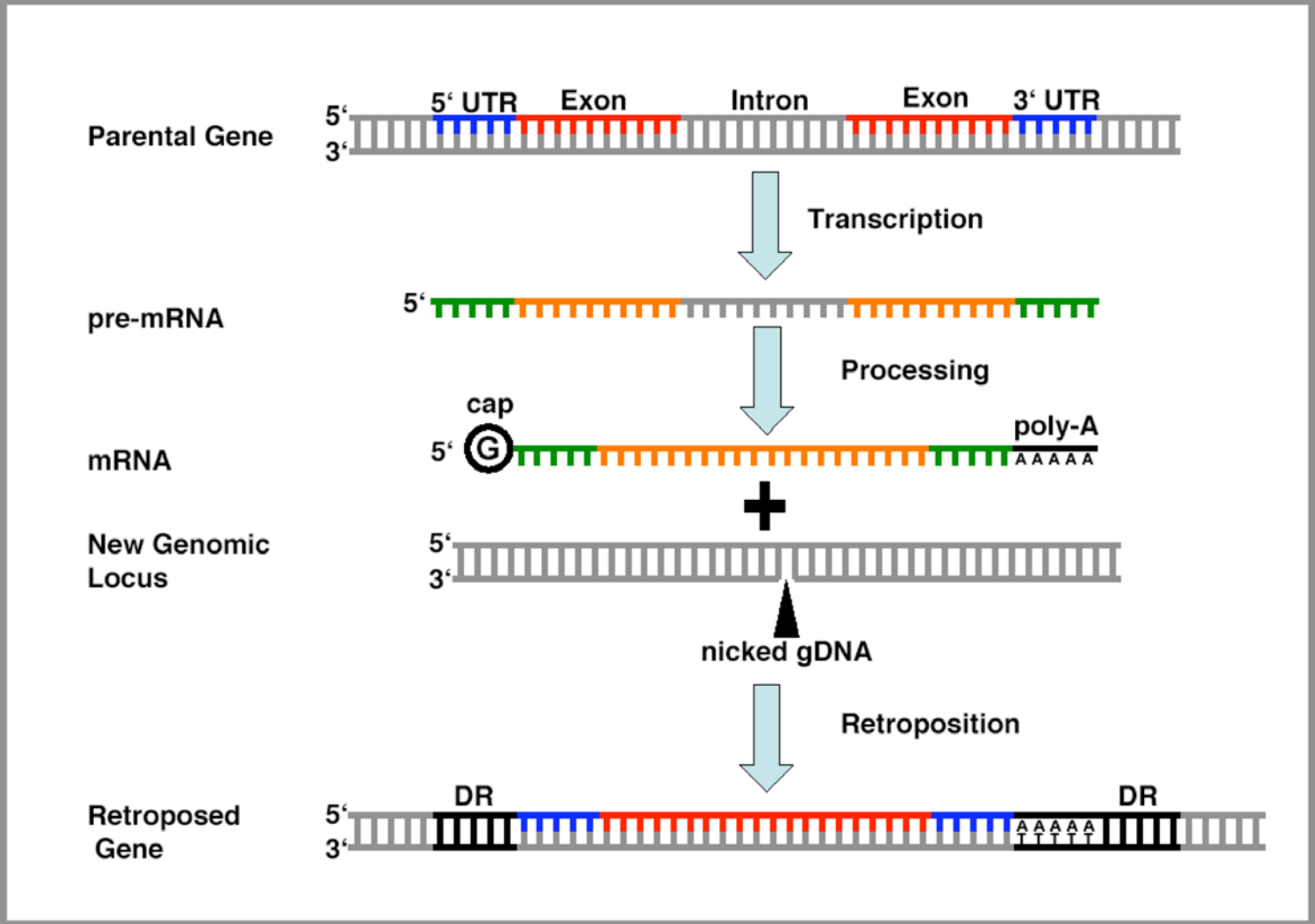
- Y chromosome degenerates and specializes
- X chromosome undergoes dosage compensation
- X chromosome conserved gene content
- favored location for male- and female-biased genes

Gene duplication:

a. genome duplication
b. segmental duplication
    -tandem duplication
    -transposition
c. retroposition

Mechanisms reviewed in:
Long et al. Nature Reviews Genetics 2003

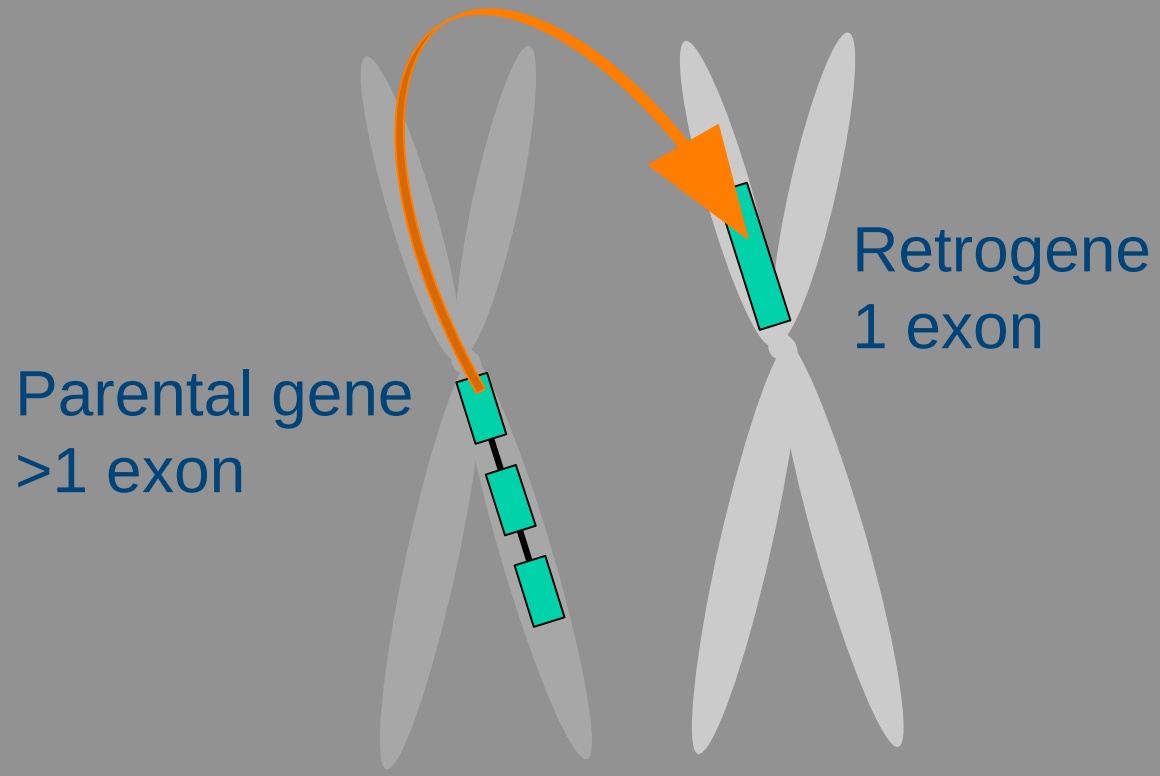
New gene formation by retroposition



Consequences of retroposition

- Hallmarks of retroposition:
  - intronless
  - poly-A tract
  - flanking direct repeats
- Parental and derived genes have different location
- Parental and derived genes share sequence similarity
- The retrogene usually lacks regulatory region at the time of insertion

Direction of copying is clear



e.g. X 3

We have studied retrogenes and patterns of duplication in:

Fly

(Betrán *et al.*Genome Research 2002;
Bai *et al.* Genome Biology 2007)

Human and Mouse

(Emerson *et al.* Science 2004)

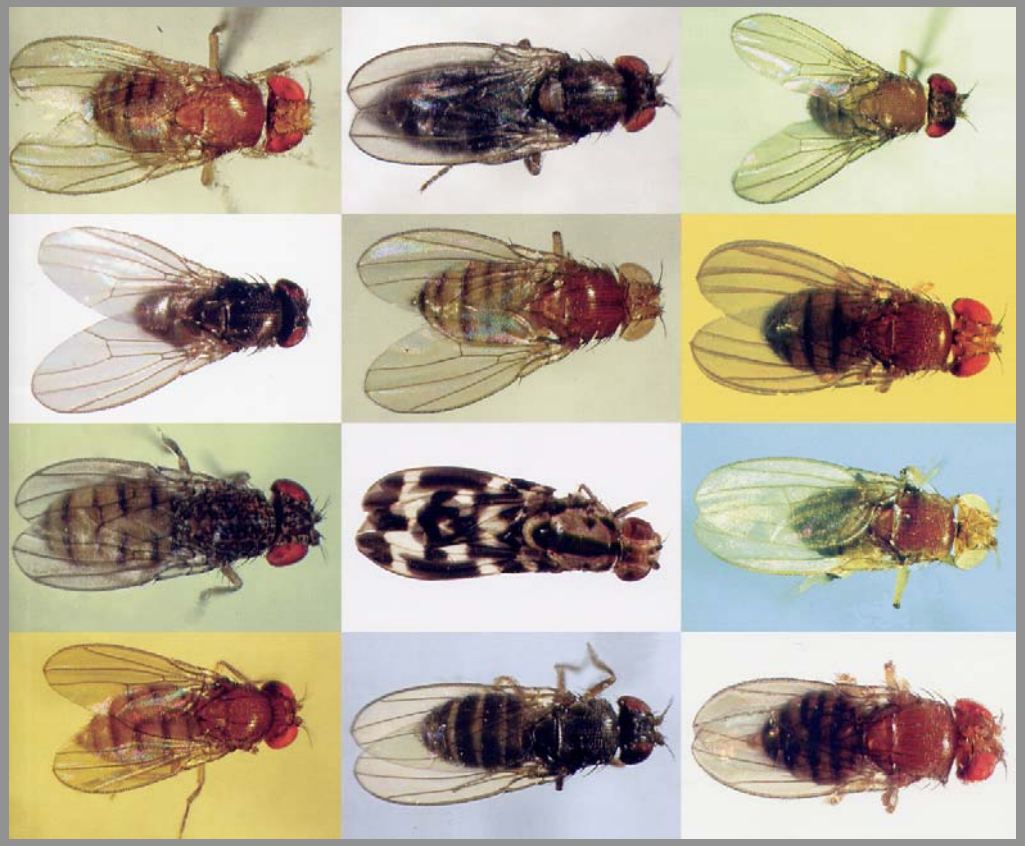
Chicken

(Hillier *et al.* Nature 2004)

Worm

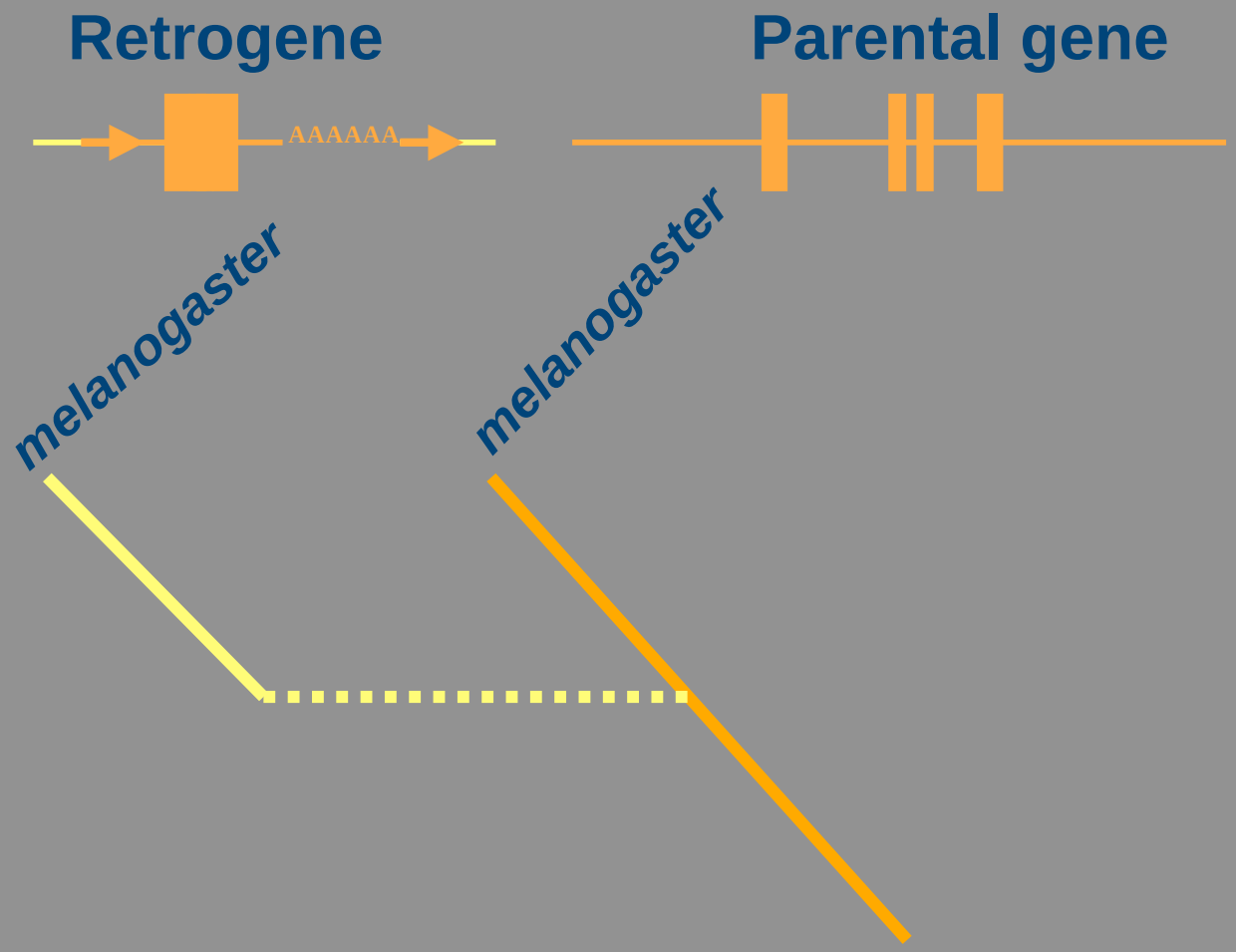
(In preparation)

Drosophila

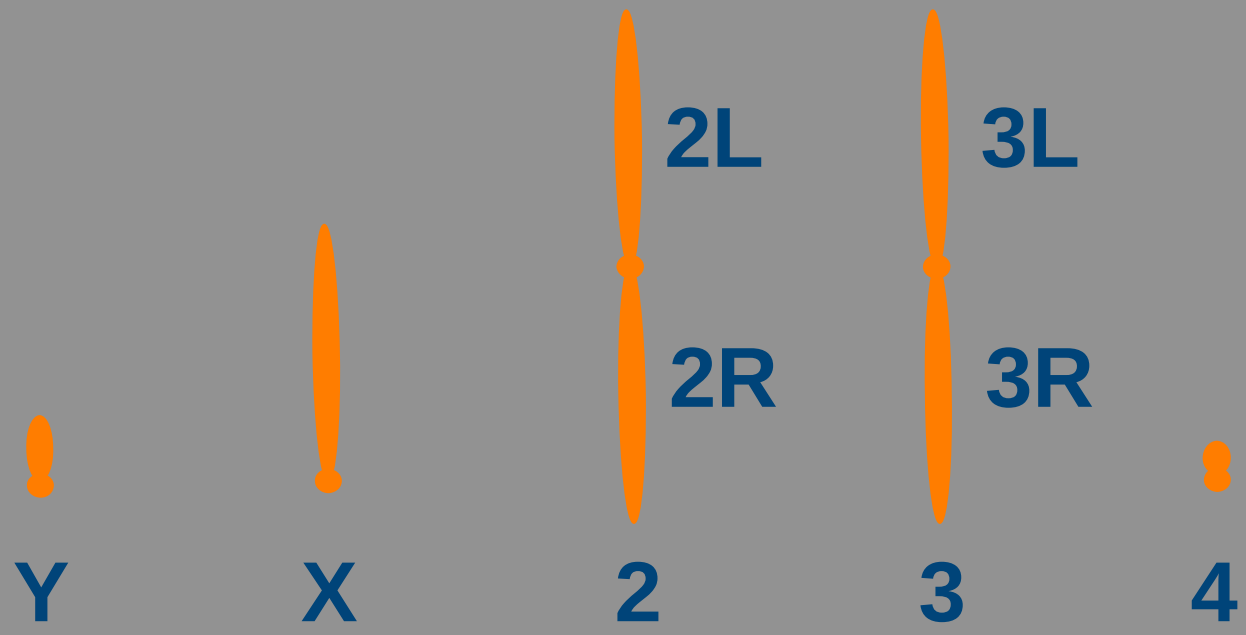


We have now 12 sequenced and annotated genomes of fruitflies and is serving as a good model system.

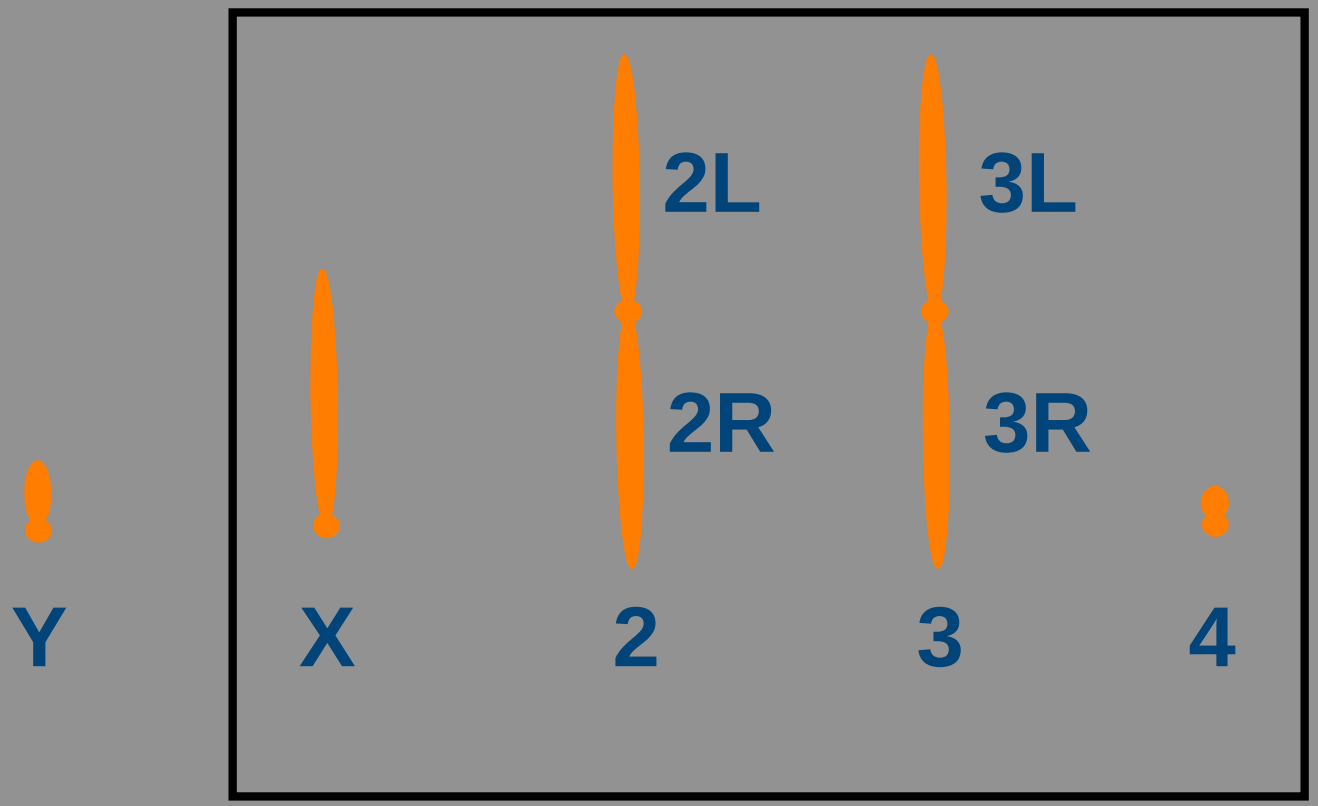
Identifying retrogenes in the *Drosophila* genome



D. melanogaster chromosomes



D. melanogaster chromosomes



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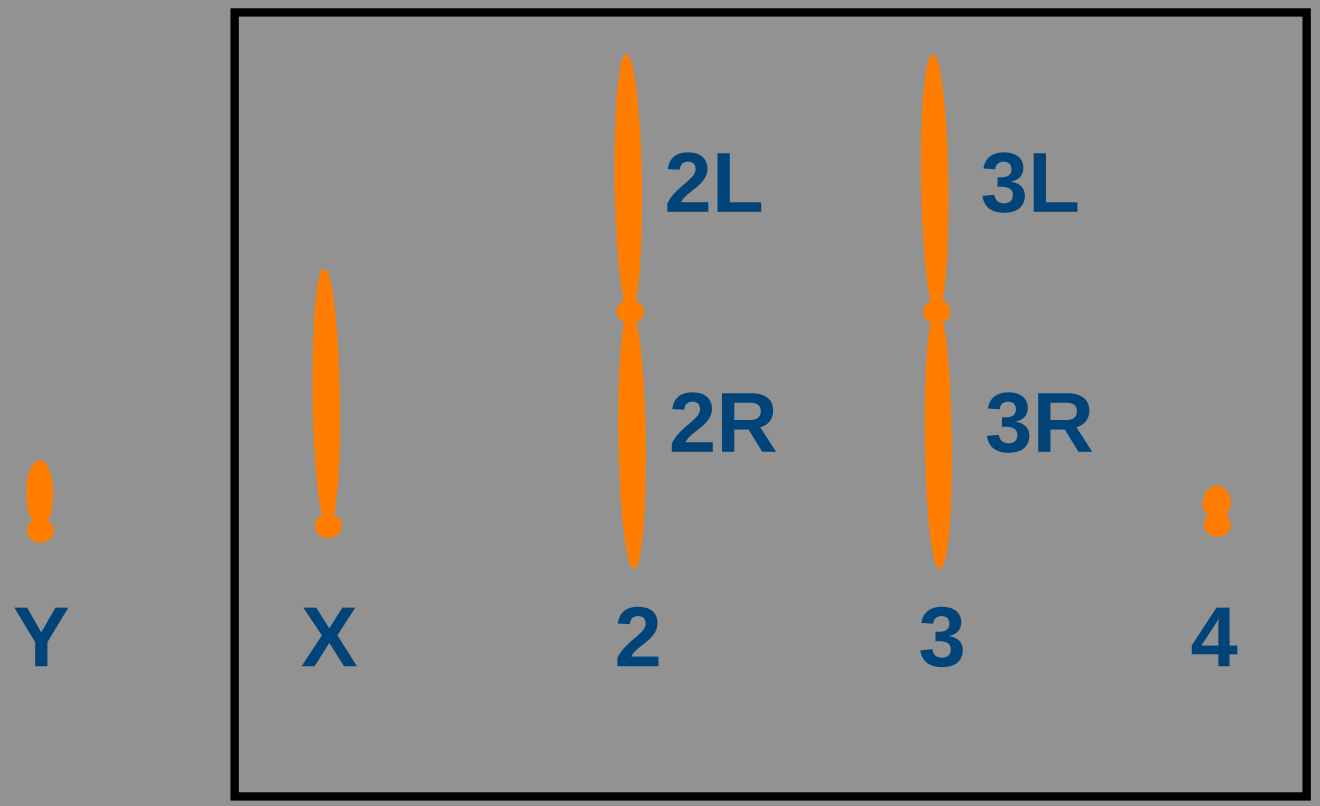
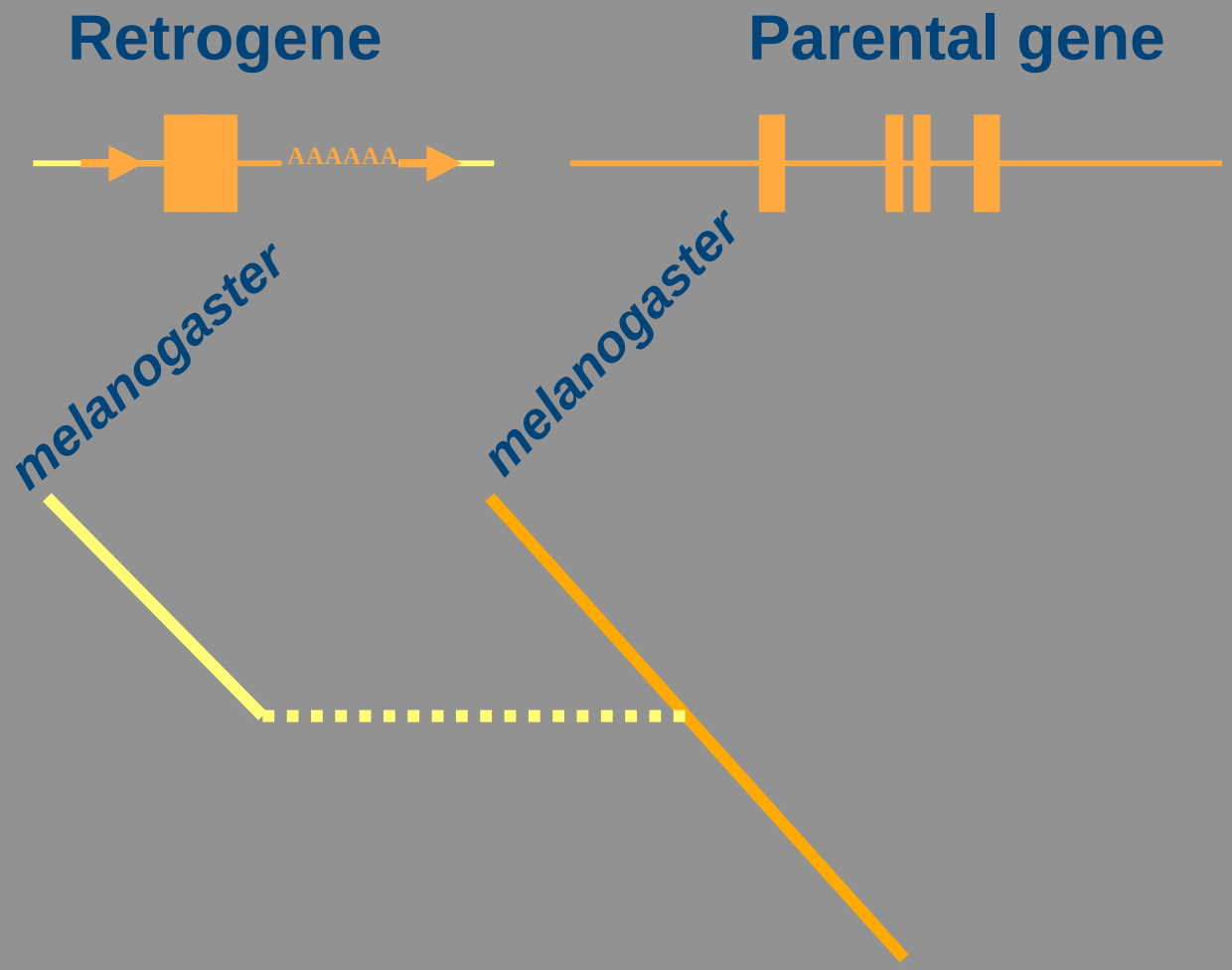
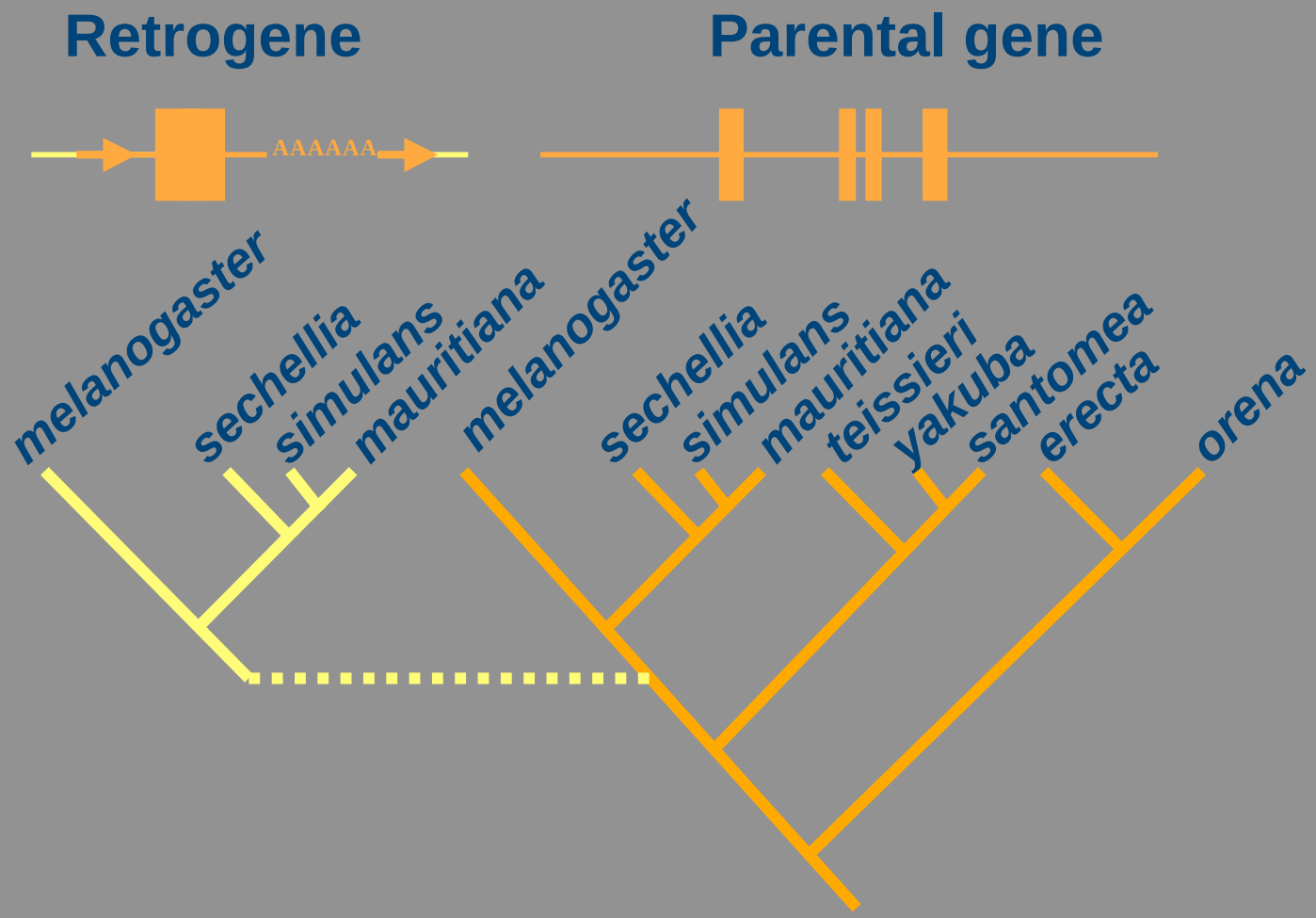


94 retroposition events

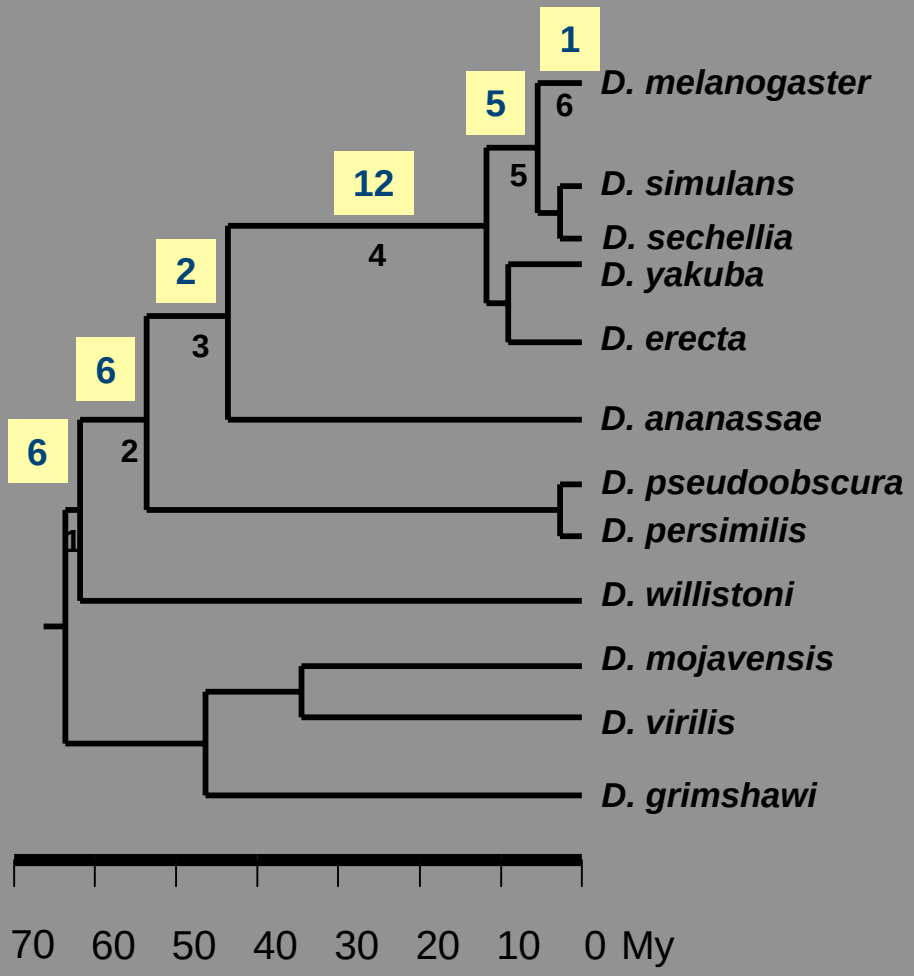
Rate of retroposition in the *Drosophila* genome



Rate of retroposition in the *Drosophila* genome



Rate of duplication

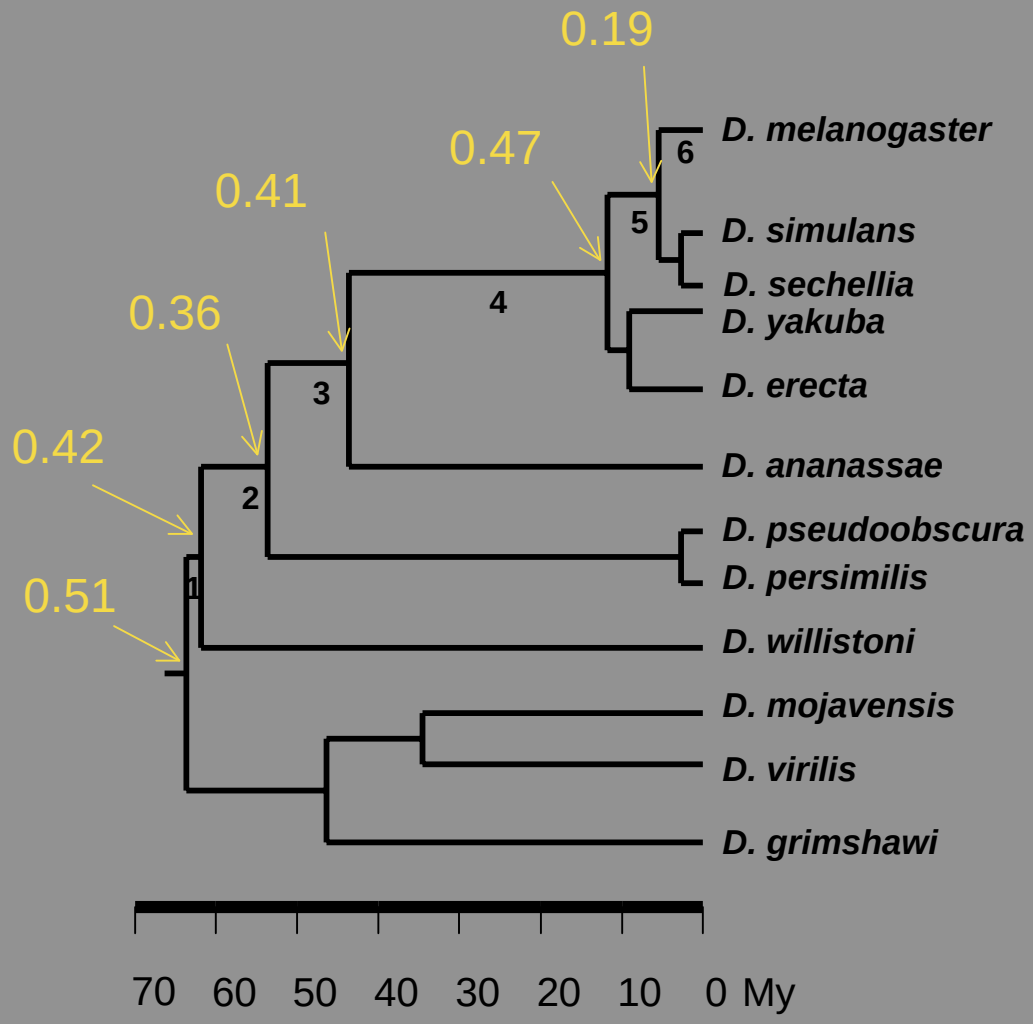


(Tree from Tamura et al. 2004)

- 32 retrogenes originated in the last 63 My

Bai *et al.* Genome Biology 2007

Rate of duplication



(Tree from Tamura et al. 2004)

- 32 retrogenes originated in the last 63 My
- In the *D. melanogaster* lineage, the rate is 1 gene every two My.
- The rate seems to be constant and ongoing
- Similar to human lineage; 1 retrogene per My (Marques *et al.* 2005)
- Small fraction (3%) of all duplications in Drosophila (17 genes per My; Hahn *et al.* 2007)

Bai *et al.* Genome Biology 2007

X chromosome exports excess of retrogenes in *Drosophila*

Table 1. Analysis of duplication between chromosomes. Expected values were calculated following Betrán et al. (2002)

Direction	Expectation		Observation
	%	No	
X → A	23.3	13.5	30
A → X	20.3	11.8	10
A → A	56.4	32.7	18
X^2= 27.0496; df =2; P=0.000001			58

X, X chromosome; A, Autosome.

Bai *et al.* Genome Biology 2007

TE distribution in the *D. melanogaster* euchromatin

Row	Factors	df	Coefficient Sign	*F*	*p*(*F*)	Variance Explained
a	Recombination	1	−	1,283.4	<0.001	17.4%
b	Intergenic or (introns + UTRs) length	1	+	1,156.6	<0.001	15.7%
c	Proportion of conserved sequences	1	−	140.1	<0.001	1.9%
d	X versus autosomes	1	−	22.2	<0.001	0.3%
e	Neighborhood	1	+	23.4	<0.001	0.3%
f	Germline- versus soma-expressed genes	1	−	0.9	0.92	0.0%
g	Intergenic regions versus genes	1	(−)	37.8	<0.001	0.5%
h	Neighborhood : germline versus soma	1	(+)	2.7	0.1	0.0%
i	Neighborhood : intergenic regions versus genes	1	−	8.5	<0.01	0.1%
j	Germline versus soma : intergenic regions versus genes	1	(−)	16.3	<0.001	0.2%
k	Neighborhood : germline versus soma: intergenic regions versus genes	1	+	5.0	<0.05	0.1%
	Total	15,674				36.5%

The variable "neighborhood" is the proportion of germline-expressed genes among the ten neighbors of a focal gene or intergenic region. Coefficient signs of the GLM indicate the sign of linear coefficients associated with the terms of the model and hence indicate the direction (positive or negative) in which the different factors affect the number of TE insertions. Parentheses around the sign indicate that the linear coefficients were not significantly different from zero in the model.

doi:10.1371/journal.pgen.0030210.t001

Fontanillas *et al.* 2007

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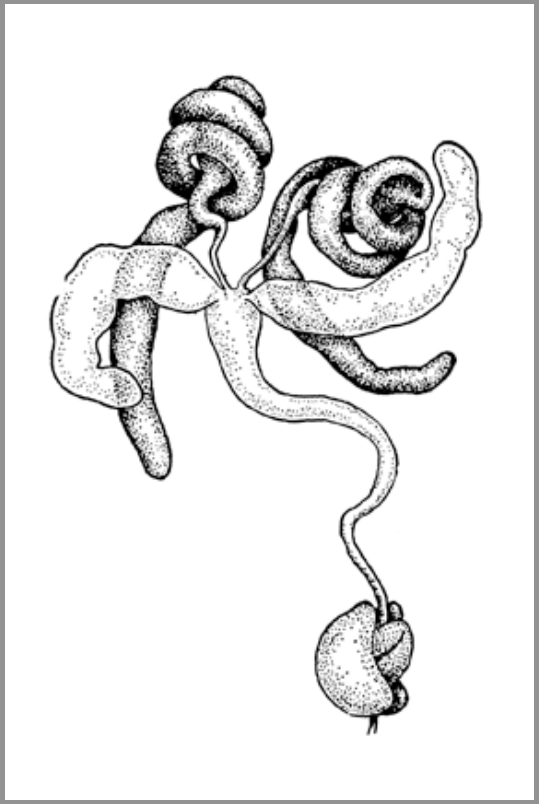
Fontanillas *et al.* 2007

Retrogenes express highly in testis

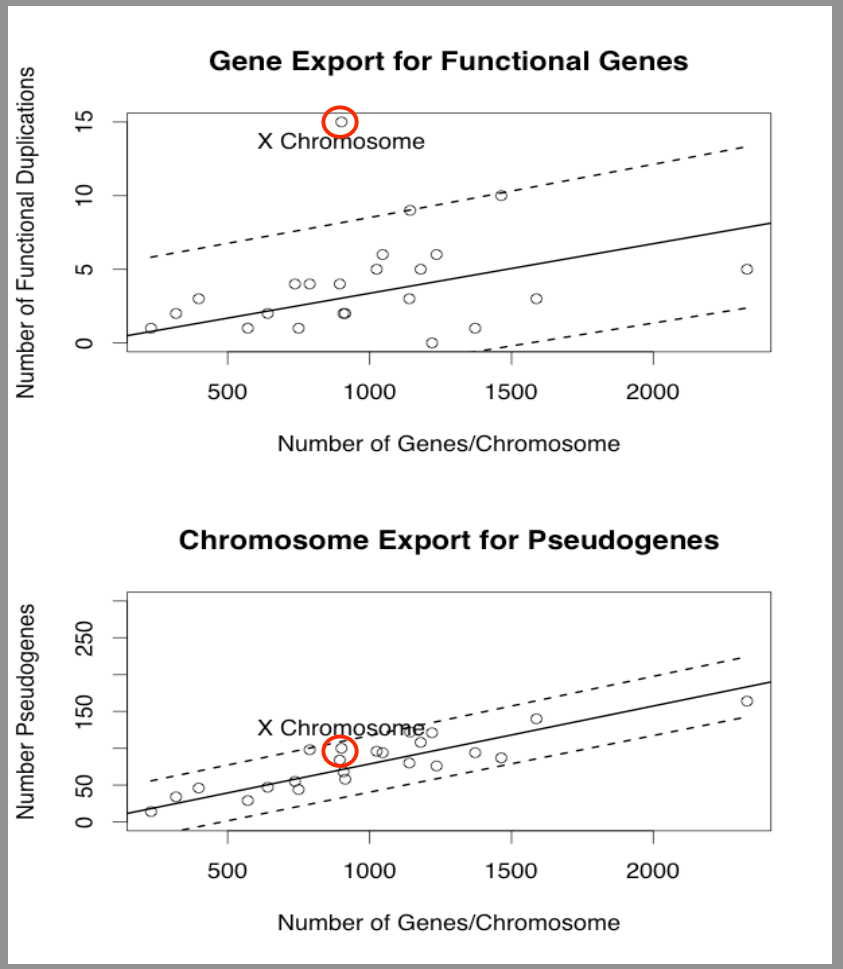


- **51% of retrogenes express predominantly in testis**
- **36% are uniquely expressed in testis**
- **Genome percentage of uniquely expressed in testis is 7%**

Bai *et al.* Genome Biology 2007
Bai *et al.* BMC Genomics 2008

Humans & Mouse

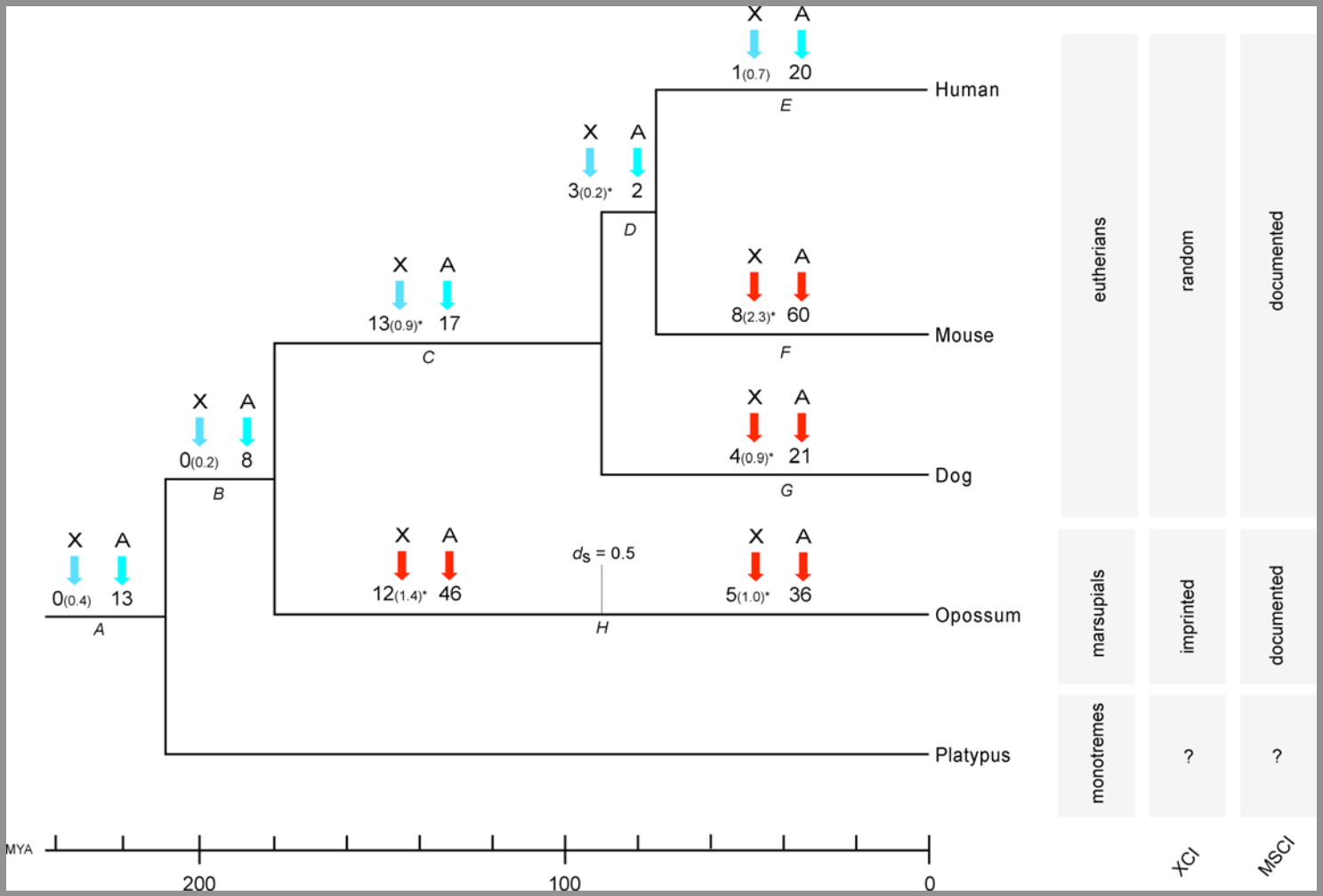
- Human and mouse are ideal because they have a lot of retrogenes and retropseudogenes
- There is a bias for male germline expression
- Ongoing duplication pattern



95% prediction interval ·····

Emerson *et al.* Science 2004

Export started with sex chromosomes birth

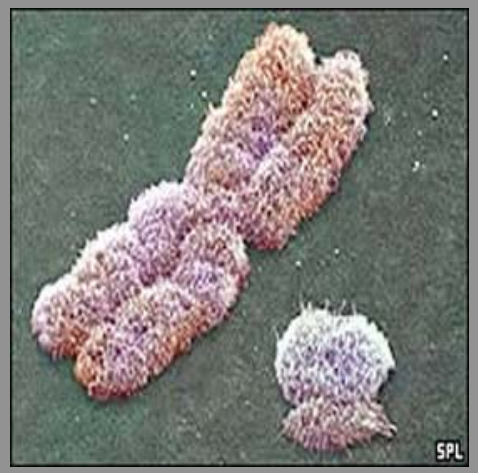


Potrzebowski et al 2008

Data changes previous believes

- In every genome where we have observed enough “genes going retro” we see an ongoing X chromosome export of male-biased genes

- This observation is against the traditional believe that male-biased genes should be on the X chromosome.



More dynamic view of X chromosome evolution.

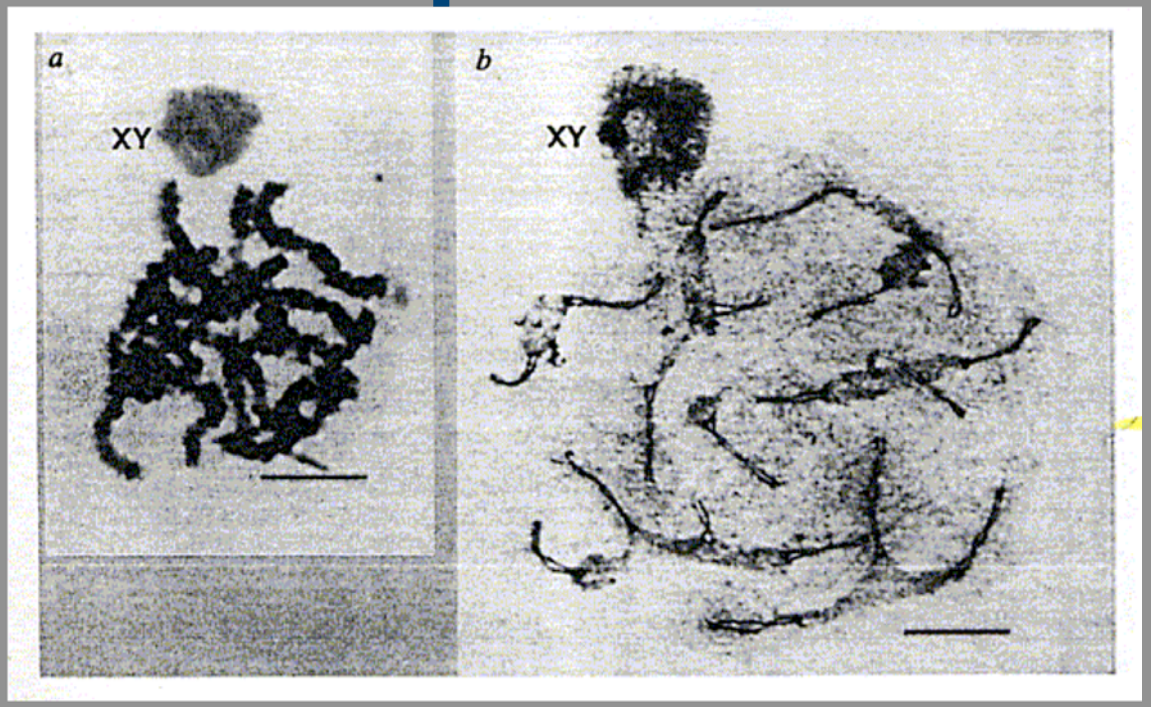
Why excess export from the X?

Hypothesis I: Avoidance of male meiotic X-inactivation

- Generating a copy elsewhere allows genes to avoid silencing during spermatogenesis
- Many of the genes that produce copies are essential genes and this avoidance could provide a selective advantage

Supported by X inactivation data: Lifschytz et al. 1972; Hoyle et al. 1995; Hense et al. 2007; Vibranovski et al. Submitted.

X inactivation reduces transcription in testis

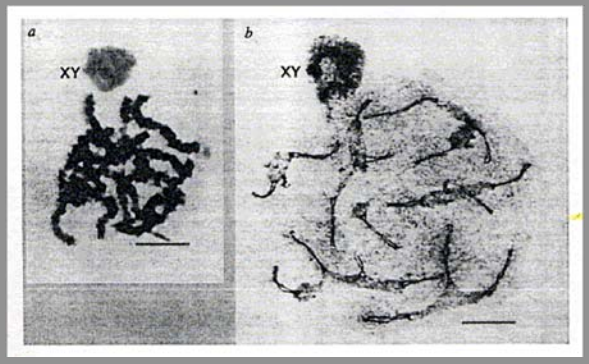


Believed to take place to protect unpaired sex chromosomes and/or suppress recombination between sex chromosomes

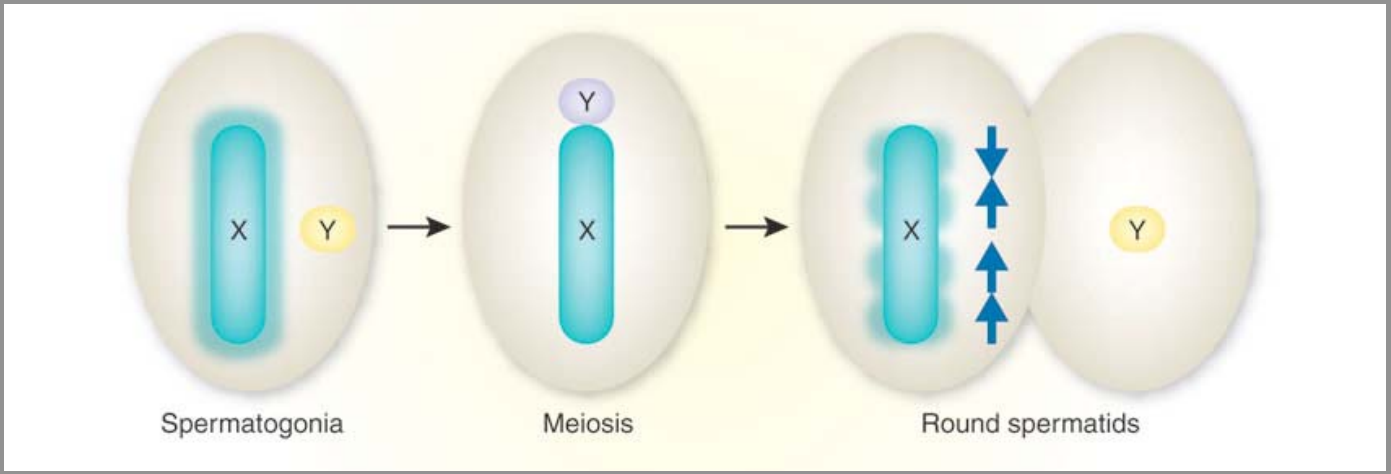
Richler et al. 1992 Nature Genetics

Predictions from X inactivation

- Intense selection for essential genes. A lot of pressure early on and less pressure now.
- It is a type of subfunctionalization (i.e. partition of the original pattern of expression)
- Genes should keep original function (i.e. be under quite strong purifying selection)
- Genes will transcribe during X inactivation and mutations will cause sterility



Mammalian male germline X postmeiotic reactivation



Single gene studies, and microarray and in situ hybridization of nascent transcripts in postmeiotic cells. Many multicopy genes are expressed from the X.

Wang *et al.* 2001; Mueller *et al.* 2008

Why excess export from the X?

Hypothesis II: Sexual antagonism

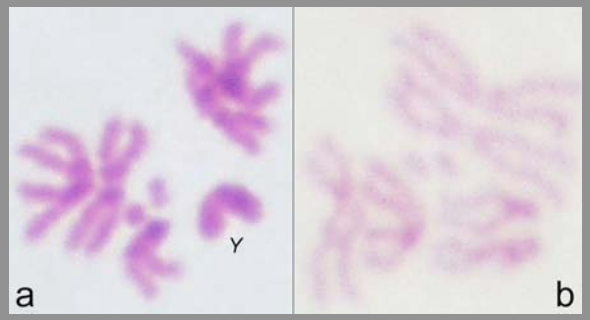
- Female can select for genes in the X chromosome because it spends 2/3 of the time in females
- Male-specific genes avoid X chromosome in general in male germline but also somatic tissues

Supported by the autosomal location of many male germline and male somatic genes: Parisi *et al.* 2003 and 2004; Sturgill et al. 2007; Zhang et al. 2007.

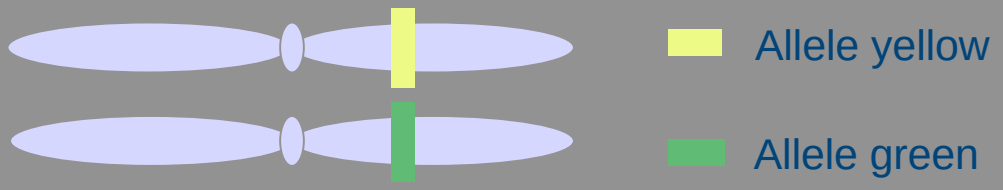
Reviewed in Betrán *et al.* Cell Cycle 2004

Genes under sexual antagonism?

Male and female have the same genome (i.e. very few genes are on the Y chromosome) but different morphology and deployment of that genome.

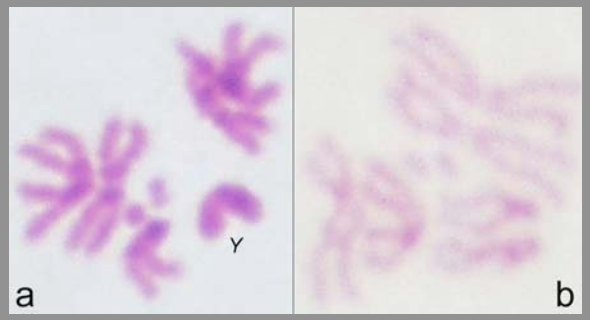


In antagonistic genes, there are allele/s that benefit the female but harm the male and allele/s that are better for the male but not good for the females. Selection acting on these alleles depends on their dominance, sex effect and chromosomal location.

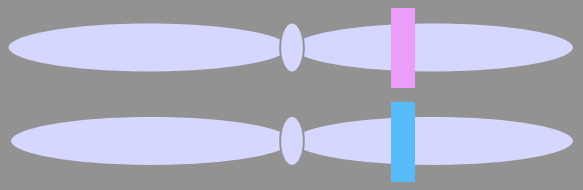


Genes under sexual antagonism?

Male and female have the same genome (i.e. very few genes are on the Y chromosome) but different morphology and deployment of that genome.



In antagonistic genes, there are allele/s that benefit the female but harm the male and allele/s that are better for the male but not good for the females. Selection acting on these alleles depends on their dominance, sex effect and chromosomal location.



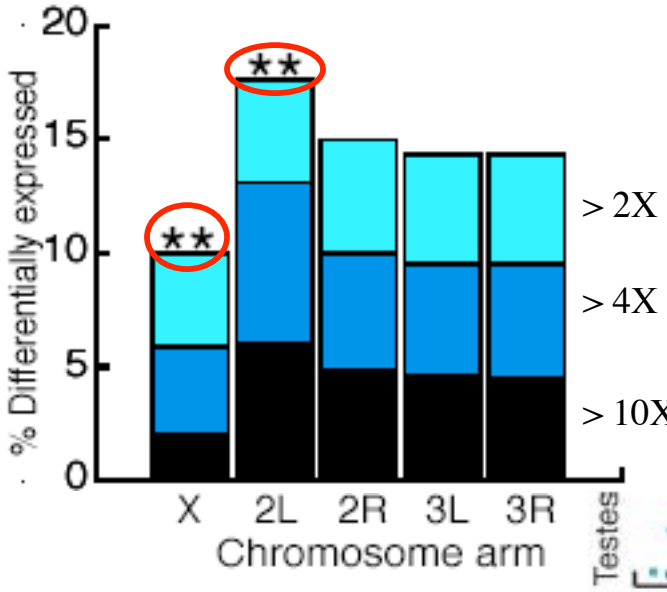
Allele that benefits the males but hurts the females

Allele that benefits the females but hurts the males

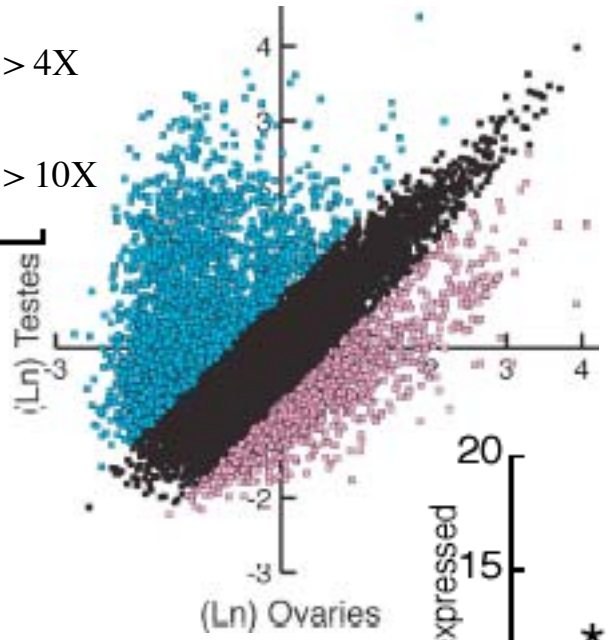
Predictions from sexual antagonism

- Intense selection for antagonistic genes (mostly on the X chromosome)
- It is a type of subfunctionalization but there should be specialization after duplication
- Genes should not exactly keep original function but similar
- X should be a disfavored location in male tissues at all times (all the time during meiosis and somatic cells)

Germline expression



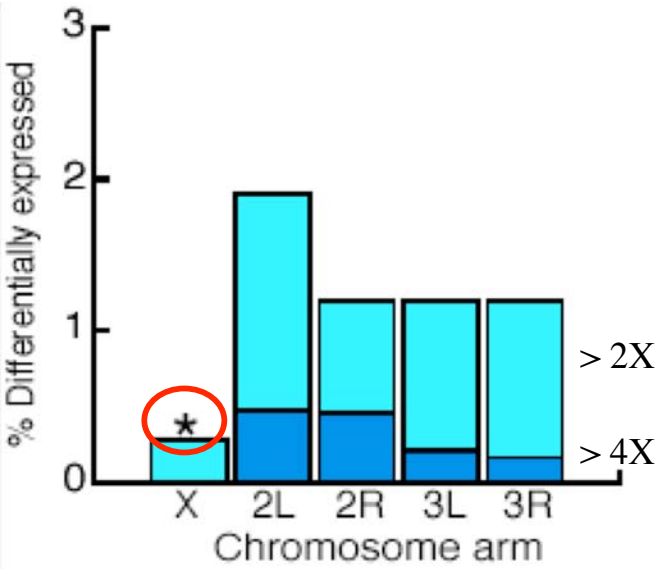
Lack of genes on the X-chromosome

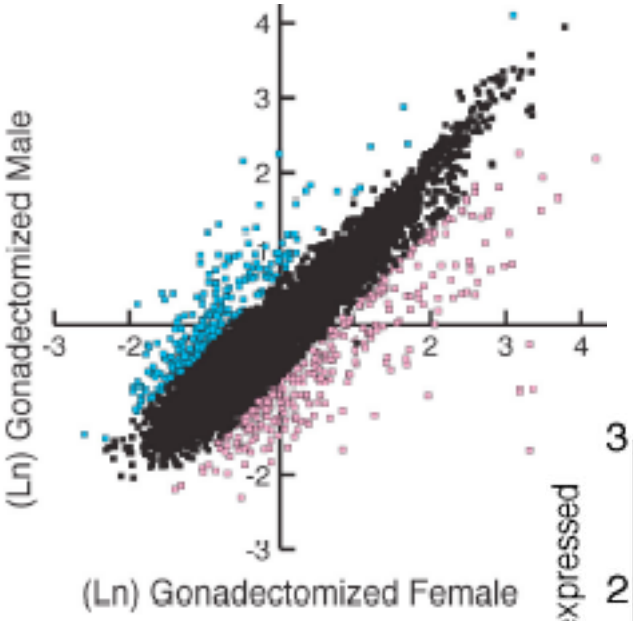


Excess of ovary biased genes on the X

Parisi et al. 2003

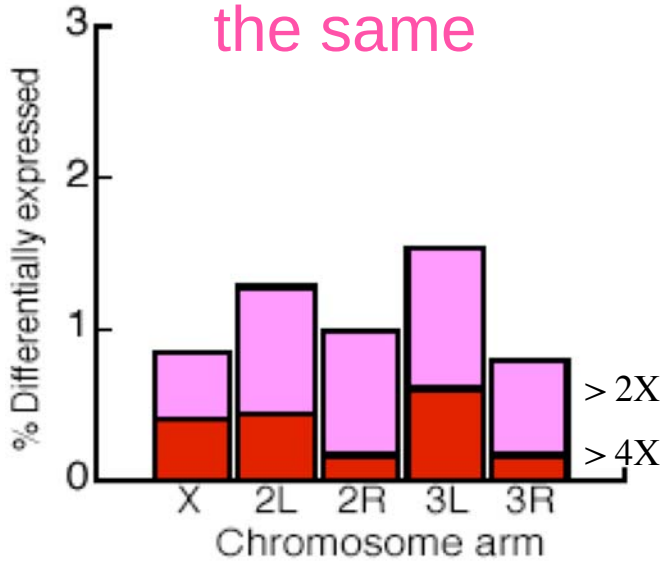
Soma expression





As before, lack of genes on the X-chromosome
X demasculinization

All arms the same

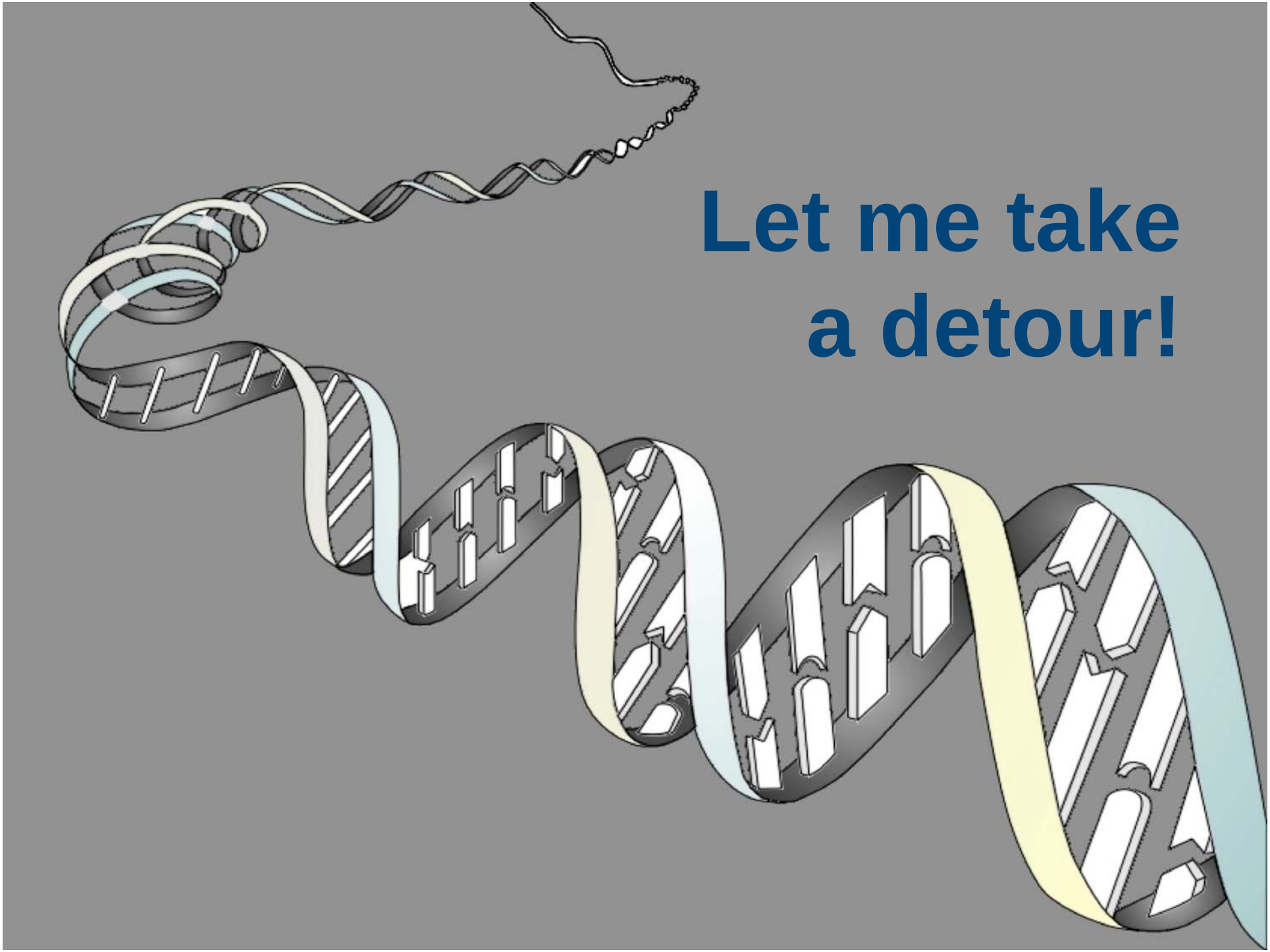


Parisi et al. 2003

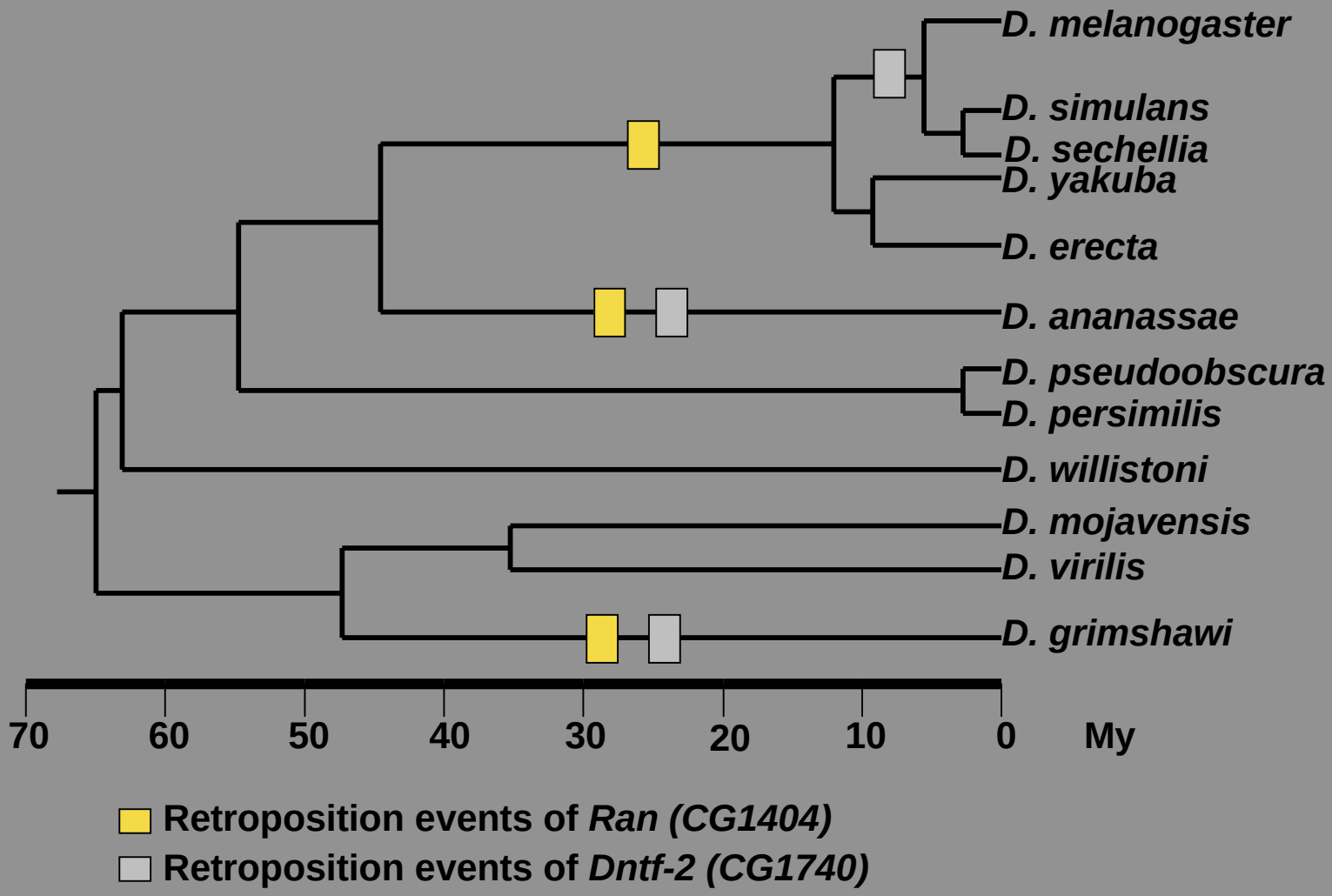
Male-biased genes in Drosophila

- Excess (7-14%) compare to female-biased (3-9%) genes in all lineages
- High birth and extinction rates
- Higher divergence
- Autosomal location and X chromosome demasculinization (30-43% less male-biased genes than expected under uniform distribution). Seen in neo-sex chromosomes in less than 12 My in *D. pseudoobscura* because of new male-biased genes in autosomes.

Parisi *et al.* 2003 and 2004; Sturgill et al. 2007; Zhang et al. 2007.

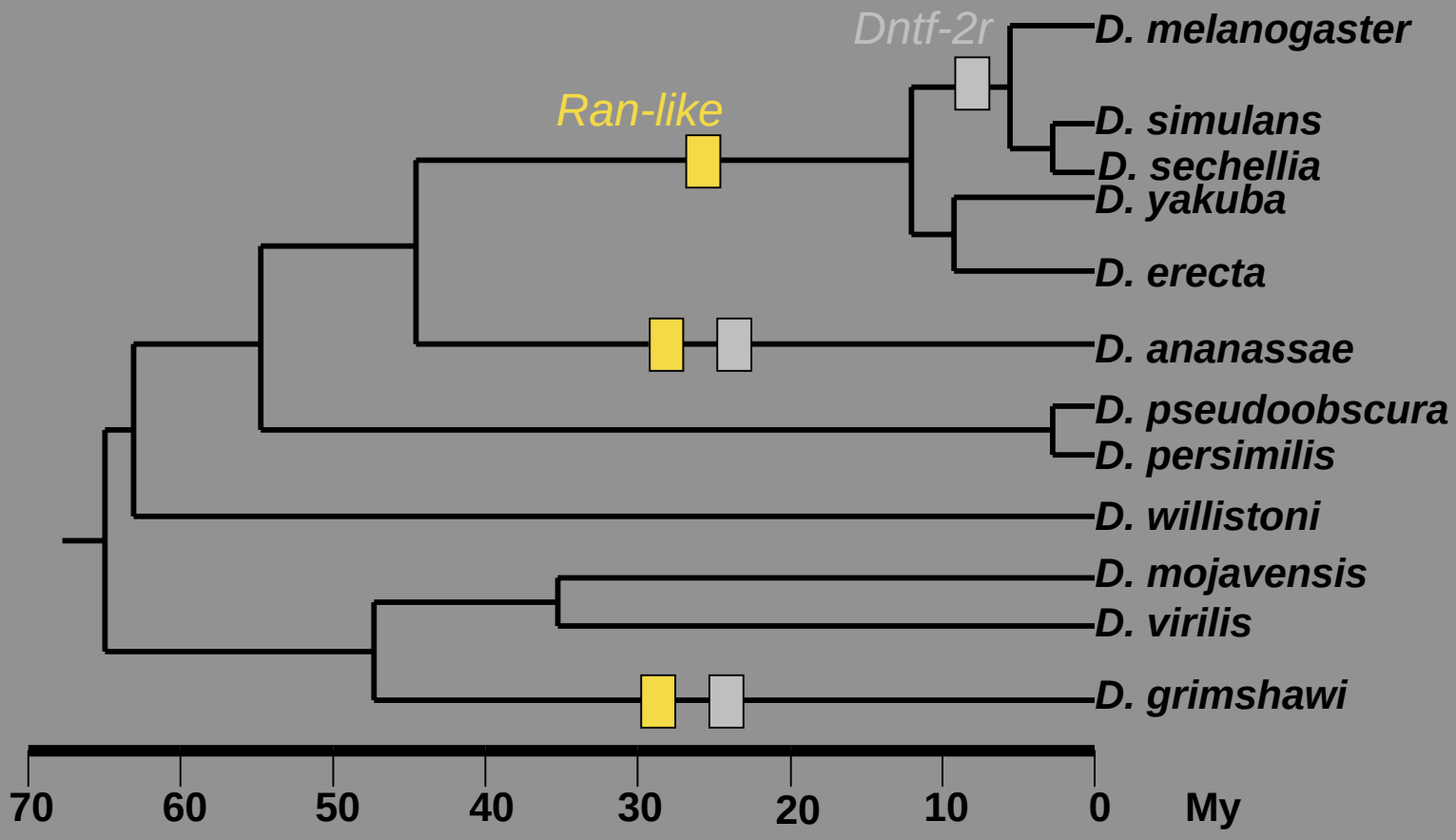

Let me take
a detour!

Recurrent retroposition events from X → A



Bai *et al.* Genome Biology 2007

Recurrent retroposition events from X → A



Bai *et al.* Genome Biology 2007

Nuclear transport overview

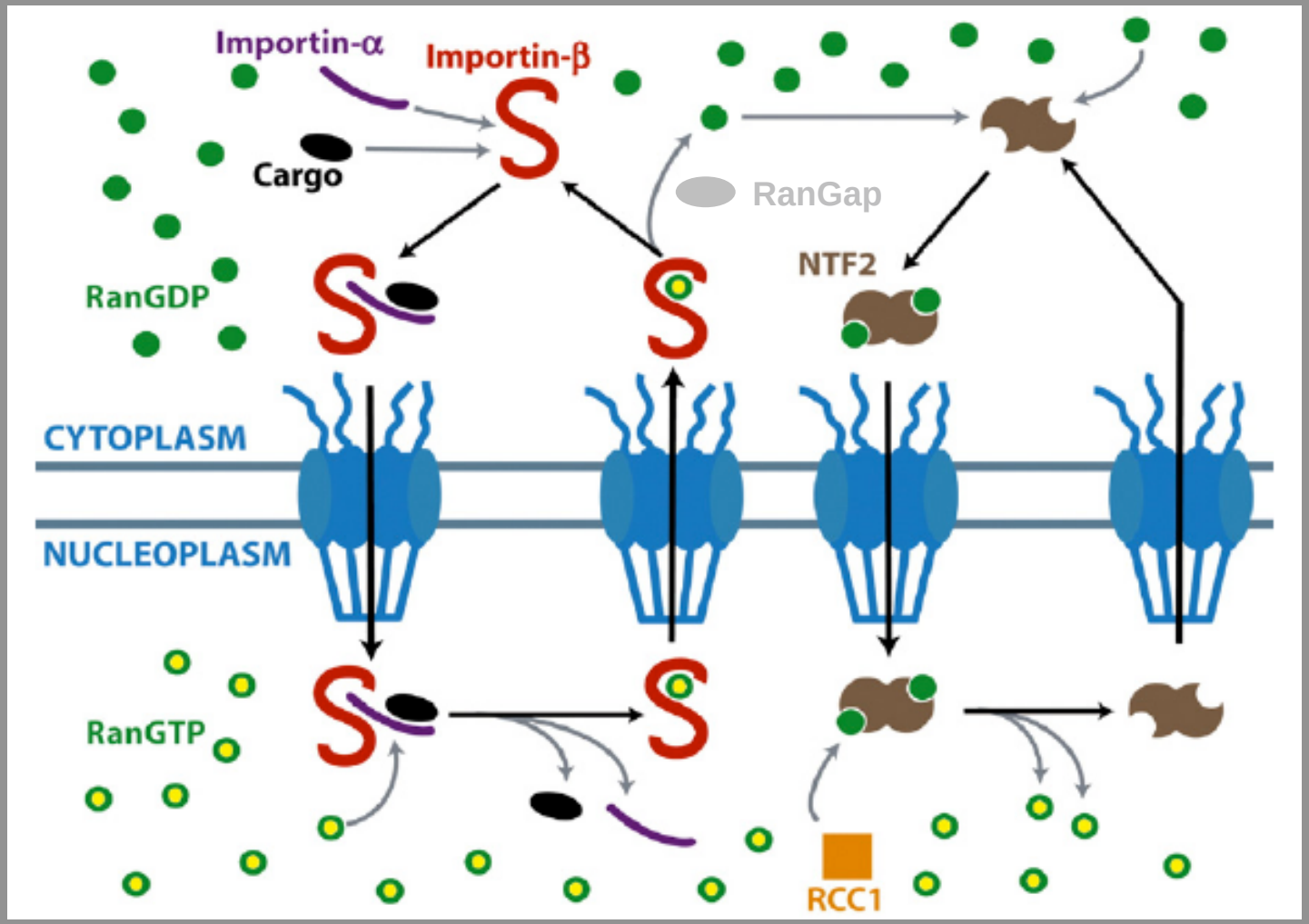
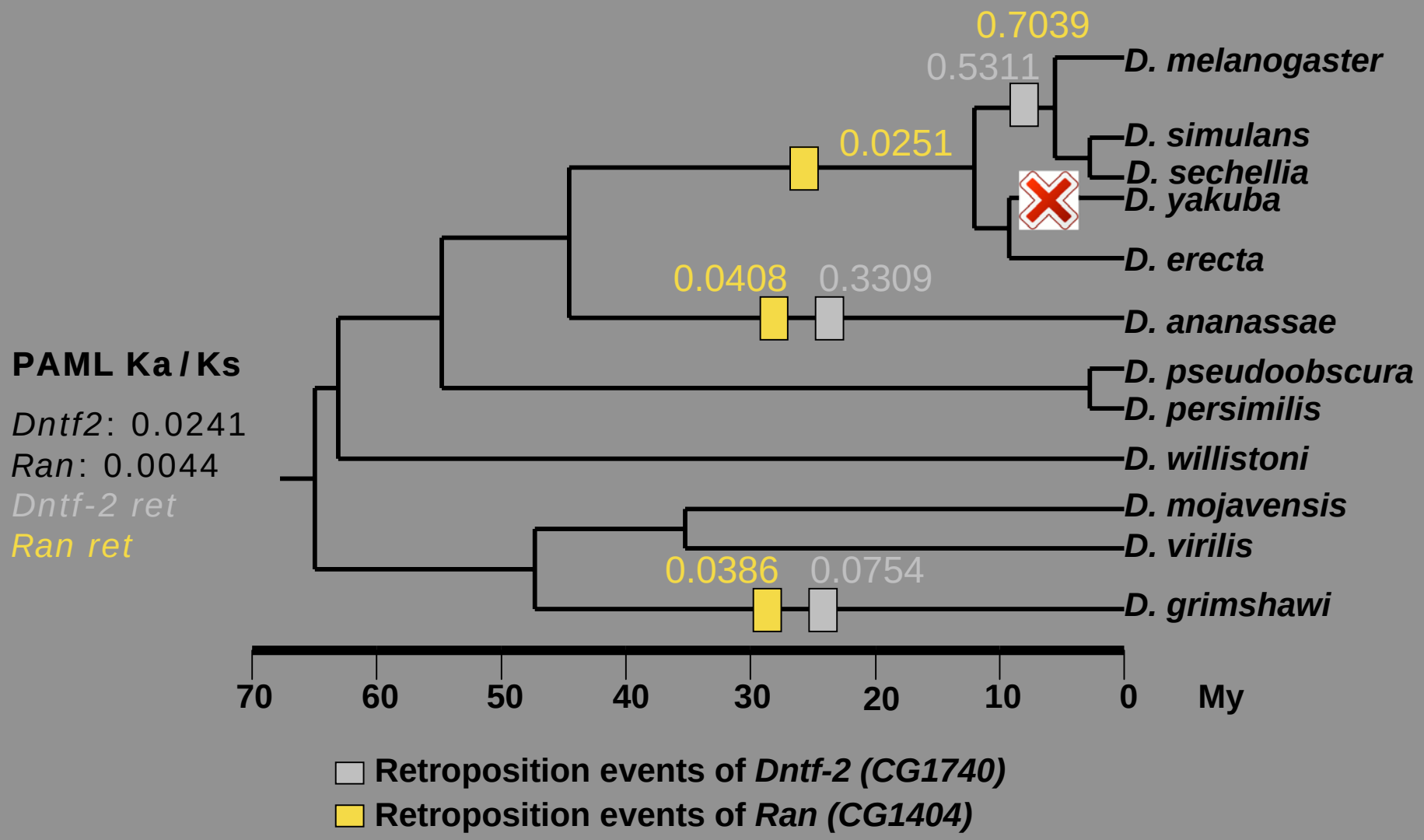


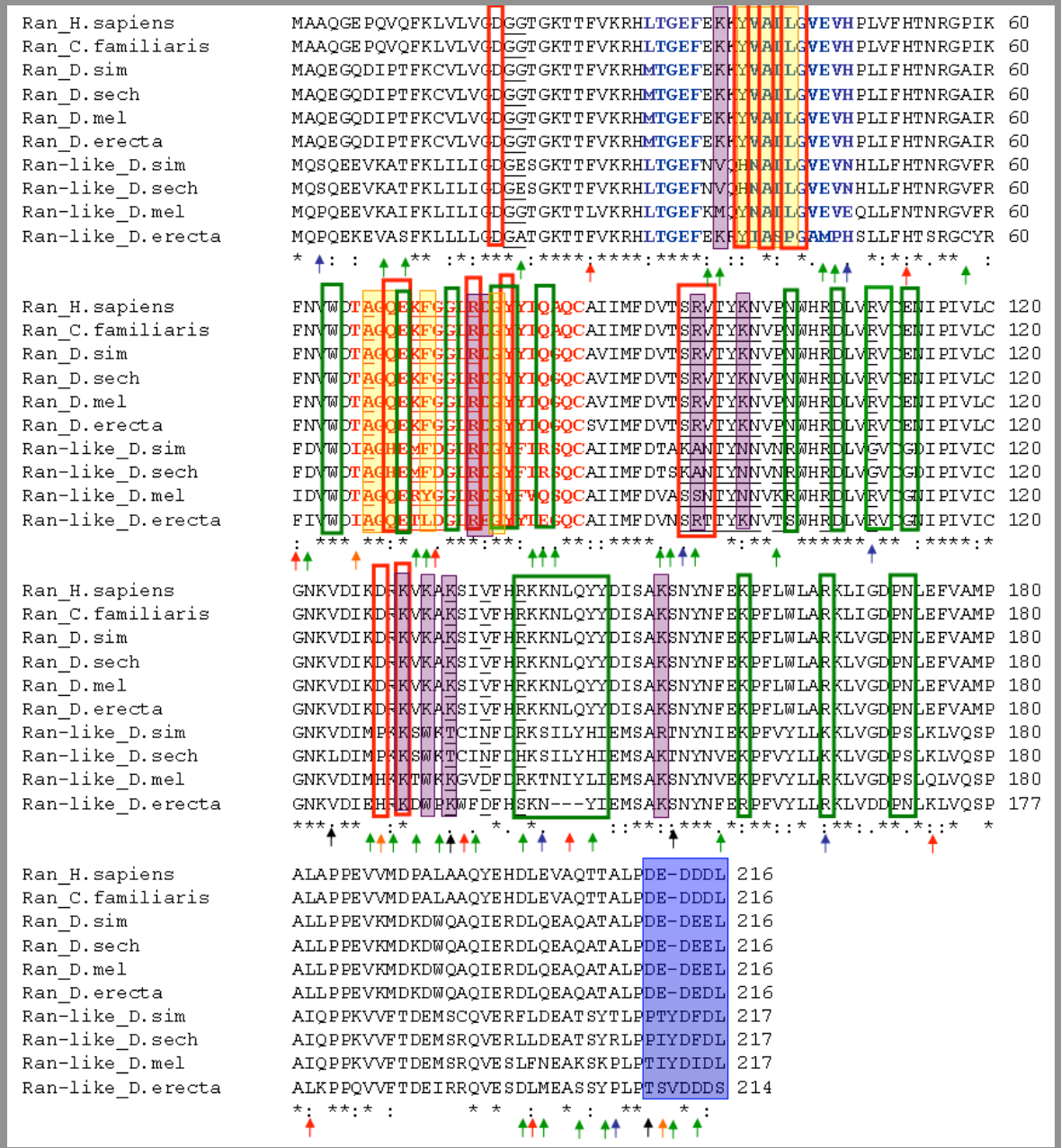
Figure from Isgro and Schulten, 2007

Rate of evolution



Tracy *et al.* In preparation

Ran-like interactions



KT Interaction with RCC1

KT Switch I

KT Switch II

Interaction with Dntf-2

Interaction with RanGap

Interaction with exportins

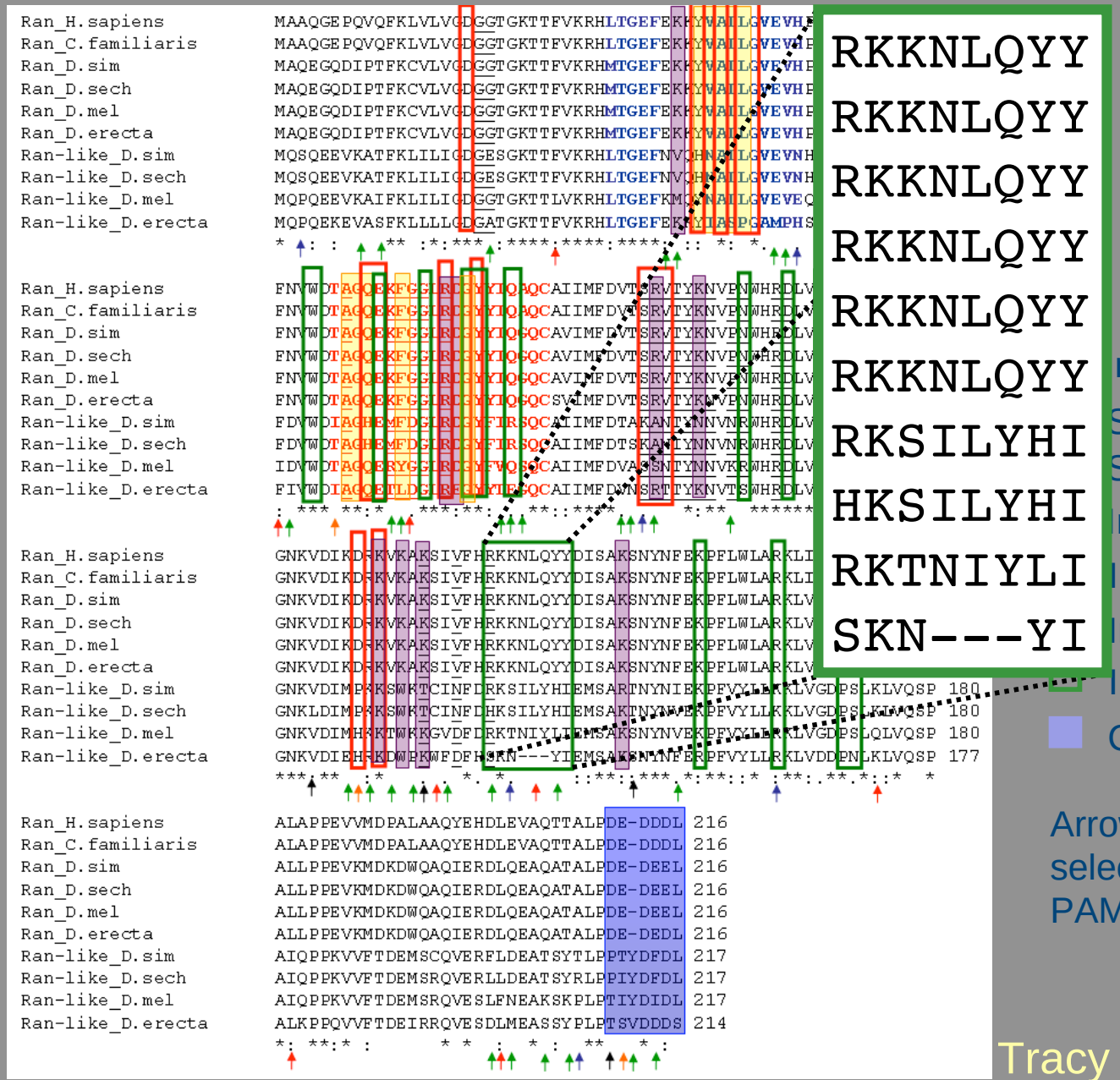
Interaction with Importin β

C terminal end interactions

Arrows show positively selected sites inferred using PAML

Tracy *et al.* In preparation

Ran-like interactions



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Tracy *et al.* In preparation

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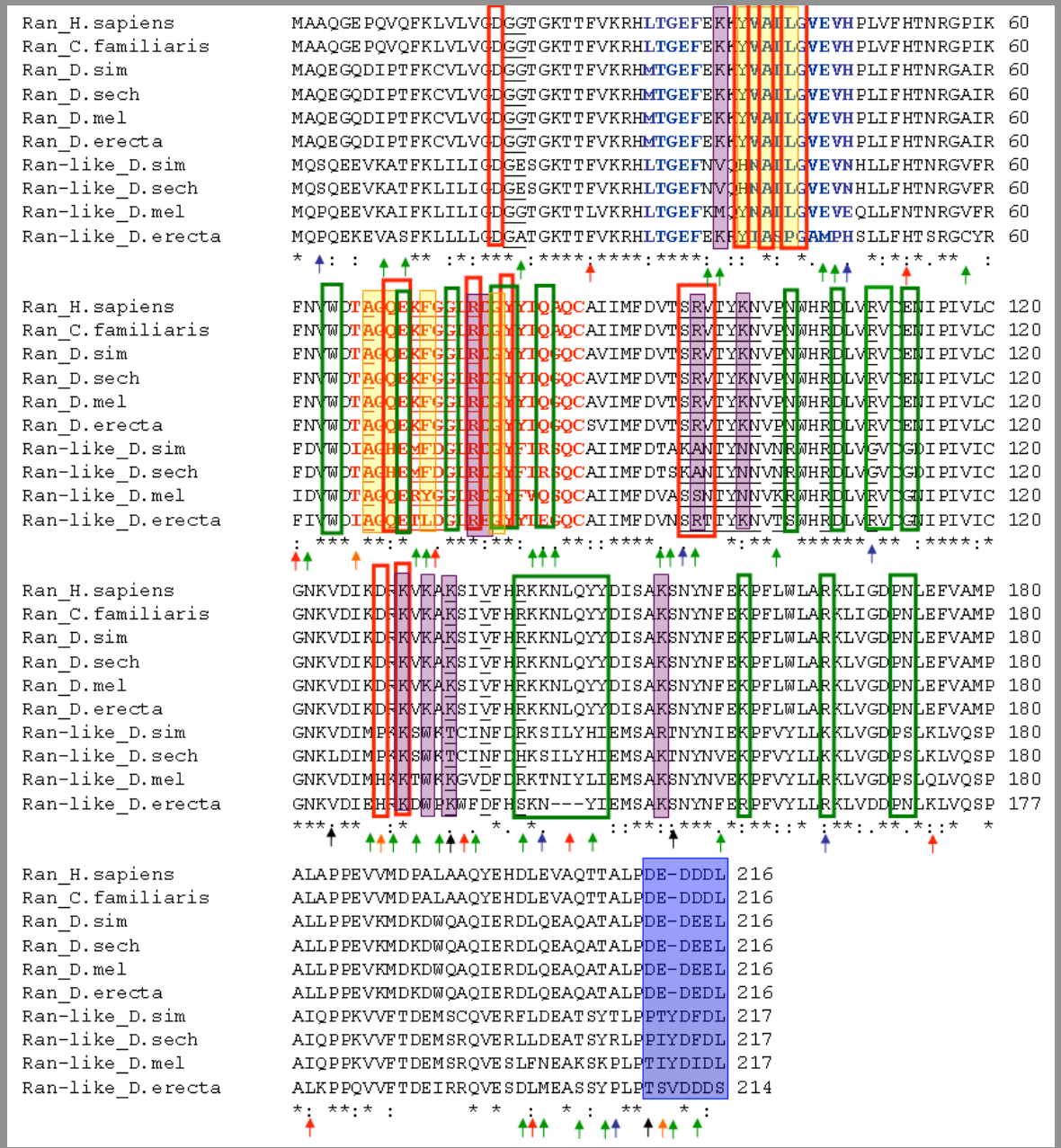

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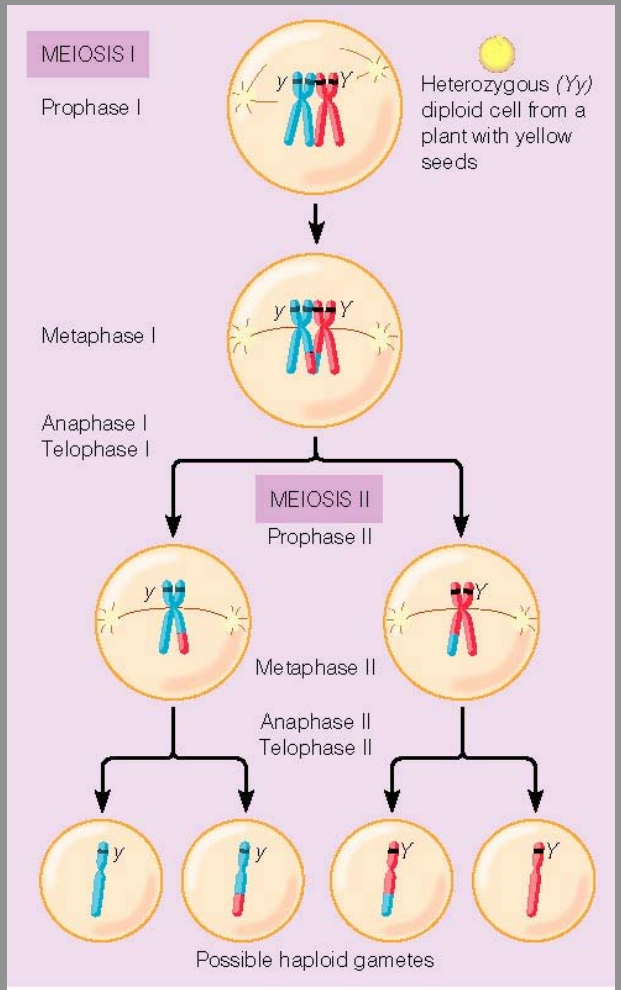
Tracy *et al.* In preparation

What is meiotic drive?

Meiotic drive (also called segregation distortion) is any process which causes one gametic type to be over-represented in the gametes formed during meiosis, and hence in the next generation.



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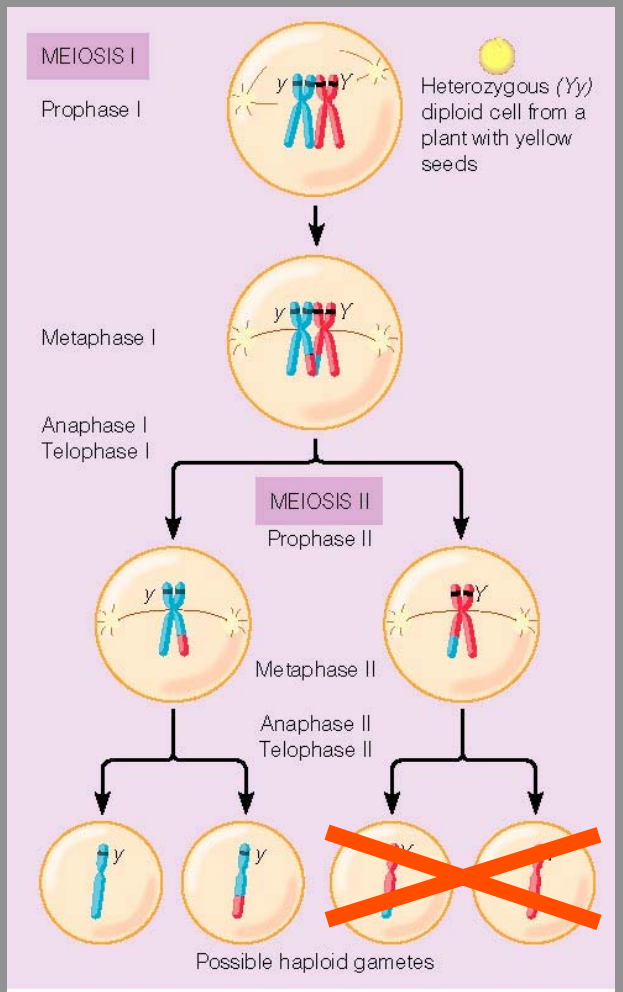
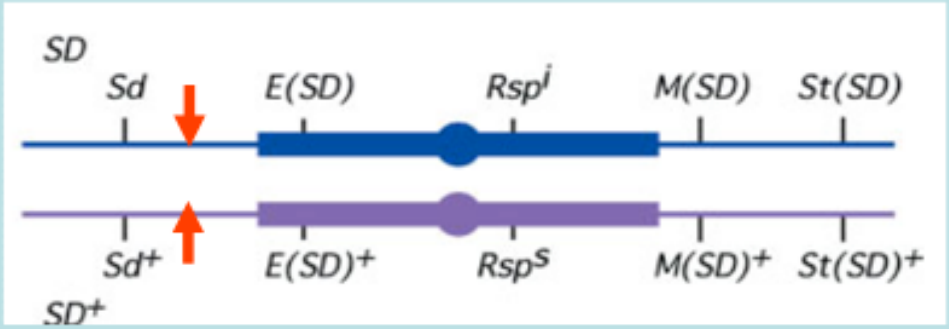


SD system in *D. melanogaster*

The SD system in *Drosophila*



SD Chromosome showing distorted transmission

Sd Segregation distorter gene

E(SD) Enhancer of SD

M(SD) Modifier of SD

St(SD) Stabilizer of SD

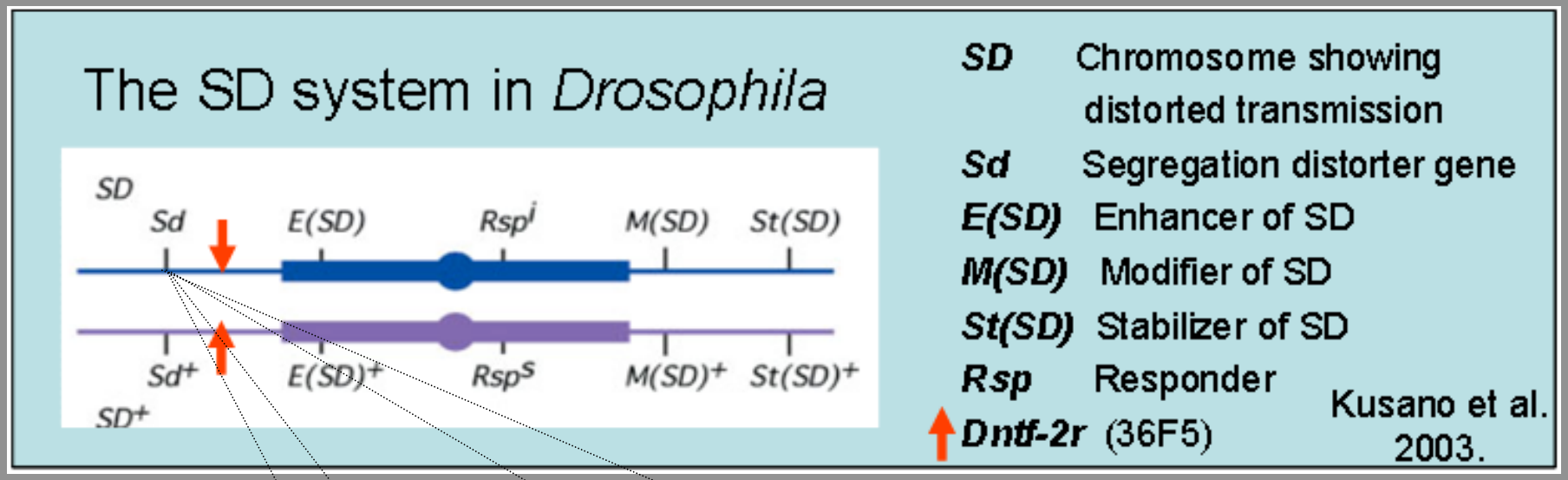
Rsp Responder

Dntf-2r (36F5)

Kusano et al. 2003.

- Only heterozygous males show distortion
- SD chromosome present in 99% of progeny

SD system in *D. melanogaster*



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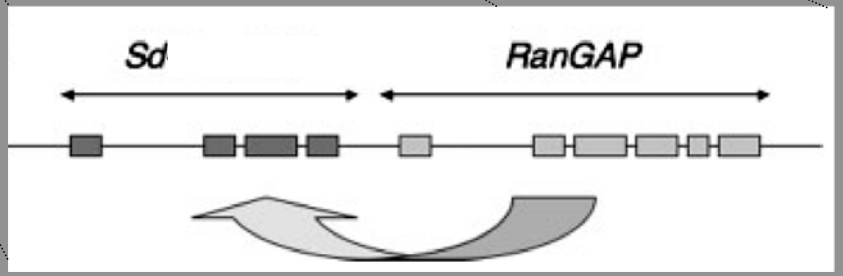


SD system in *D. melanogaster*

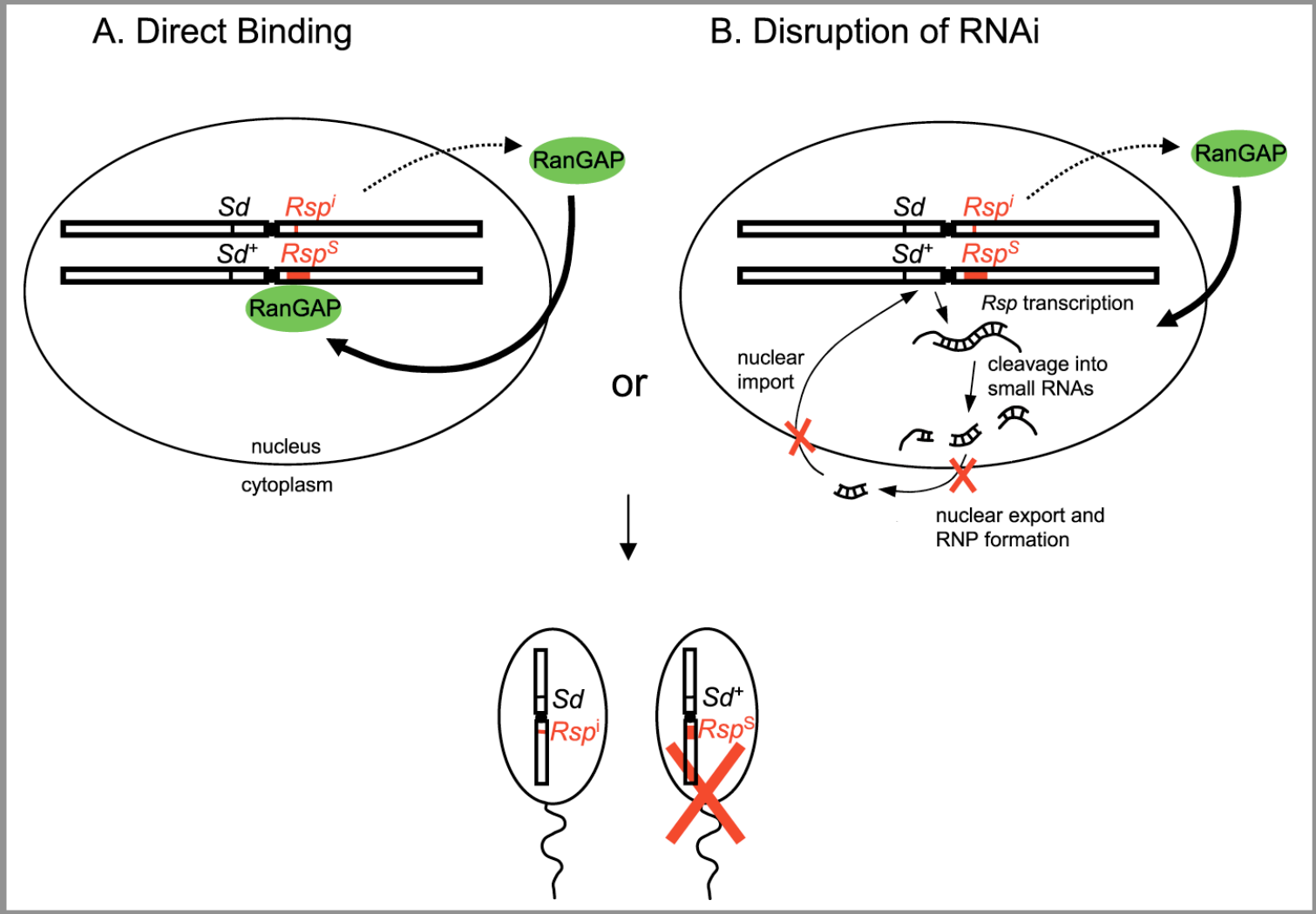


Figure from Ferree and Barbash, 2007

Segregation distortion in *Dntf-2r* knock down

Test for the sensitivity of Rsp^{ins} cn bw *chromosomes. The cross is:*
(A) SD-i/Rsp^{ins}-j cn bw ♂♂ × cn bw ♀♀ *and (B) the reciprocal cross*

Genotype of parent	Type of cross	Phenotype of progeny* +	*cn bw*	*k*†
SD-5/cn bw	A	2181	8	0.99
	B	1465	1358	

Ganetzkyz, Genetics **86: 321-355** June. 1977

SD-5/16658	a	1434	419	0.77
	b	82	68	

k values are the proportion of SD-bearing progeny among the total offspring

- 0.99 is significantly different from 0.77 (Fisher's Exact Test $P<10^{-7}$)
- 82/68 is not significantly different from 75/75 ($X^2=1.3067$; d.f.=1; P=0.2530)
- No obvious fertility effects of *Dntf-2r* knockout

Why recurrent recruitment of Ntf-2 and Ran?

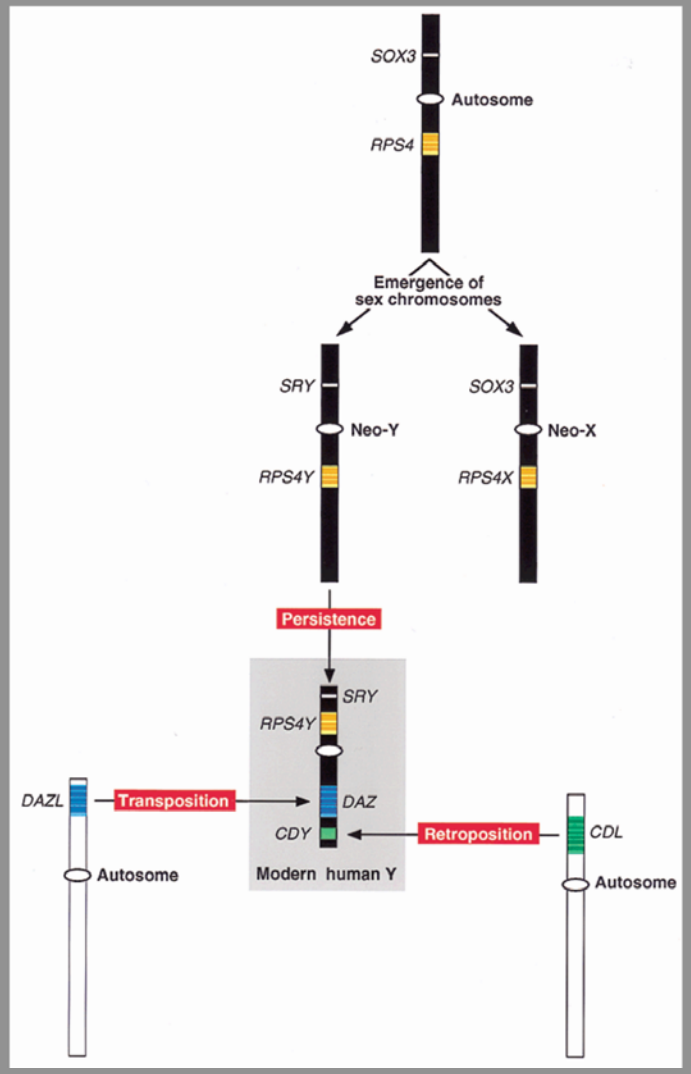
Hypothesis III: Meiotic drive role

- Selfish meiotic drive systems evolve all the time and these genes might have a role as drivers or suppressors
- I also like to speculate that they might also have an interplay with sexual antagonism

Supported by loss of new retrogenes, loss of functions of the new retrogenes, and lack of infertility effects of null alleles of *Dntf-2r* (Tracy *et al.* In preparation) and high turnover of species restricted genes with male biased expression (Zhang et al. 2007)

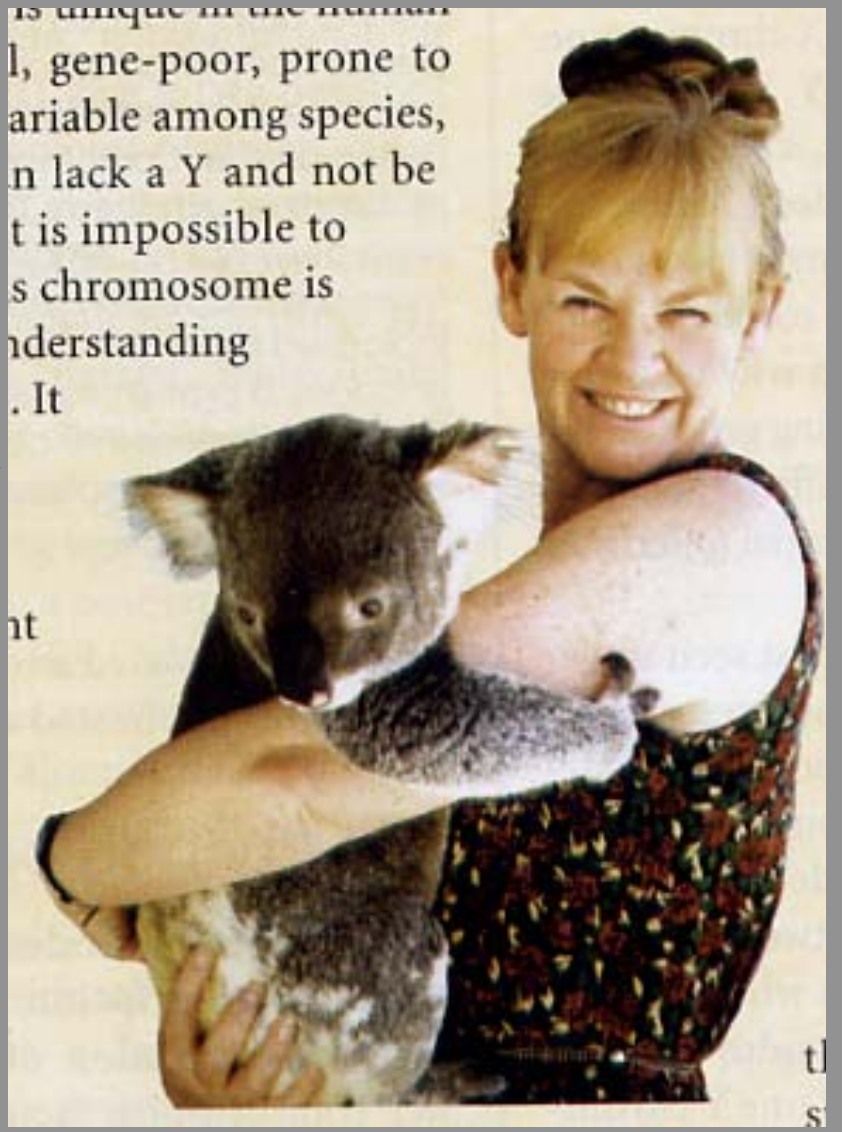
Y chromosome and gene duplication

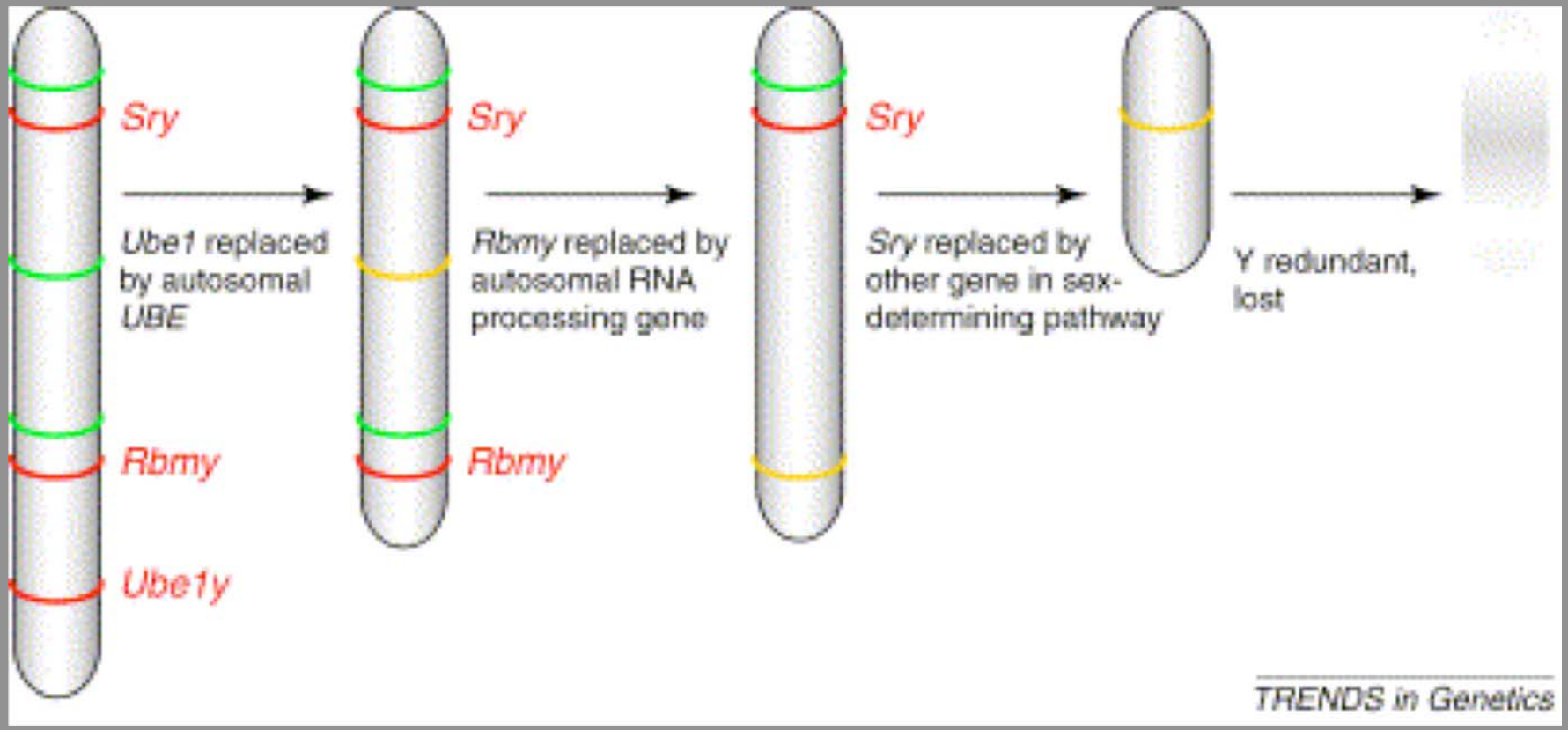
At the end the non-recombining region of the Y chromosome is left with very few genes that are male-specific.



The rise and fall of the human Y chromosome

Jennifer A. Marshall-Graves
Australian National University





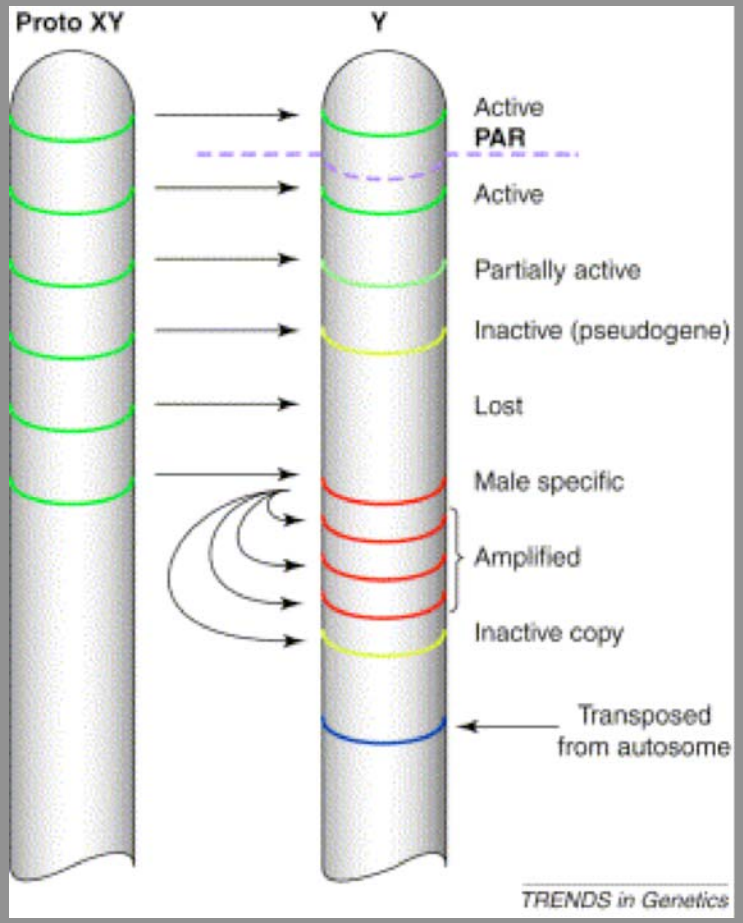
Marshall-Graves 2002

The sequencing of the Y chromosome: rethinking the rotting Y chromosome

David Page

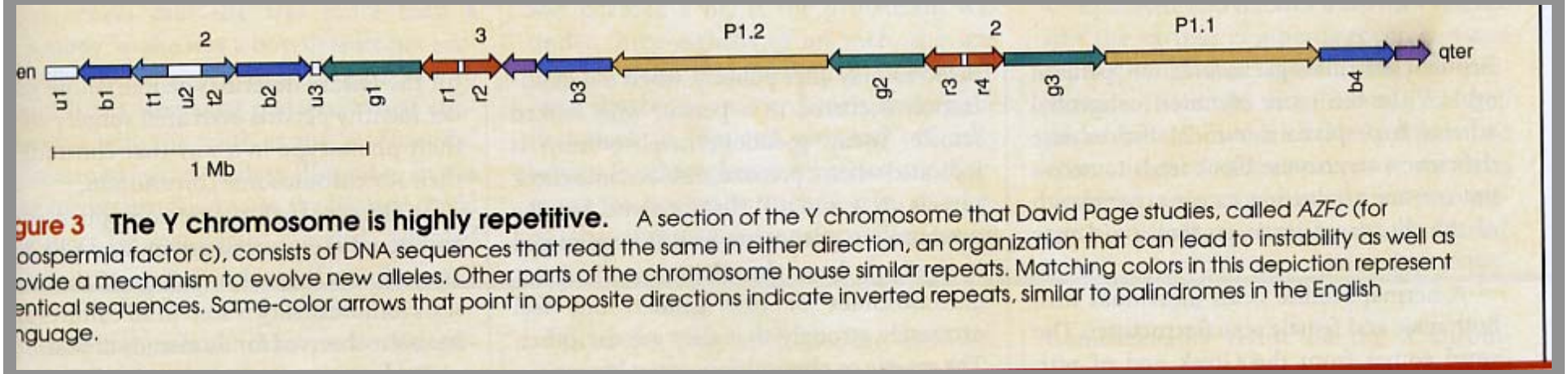
Associate Director of Science, Whitehead Institute
Professor of Biology, MIT
Investigator of the Howard Hughes Medical Institute

Determining the sequence of the human Y chromosome presented a daunting challenge. But the task is now done and the secrets revealed justify the effort.



Skaletsky et al. 2003; Willard 2003

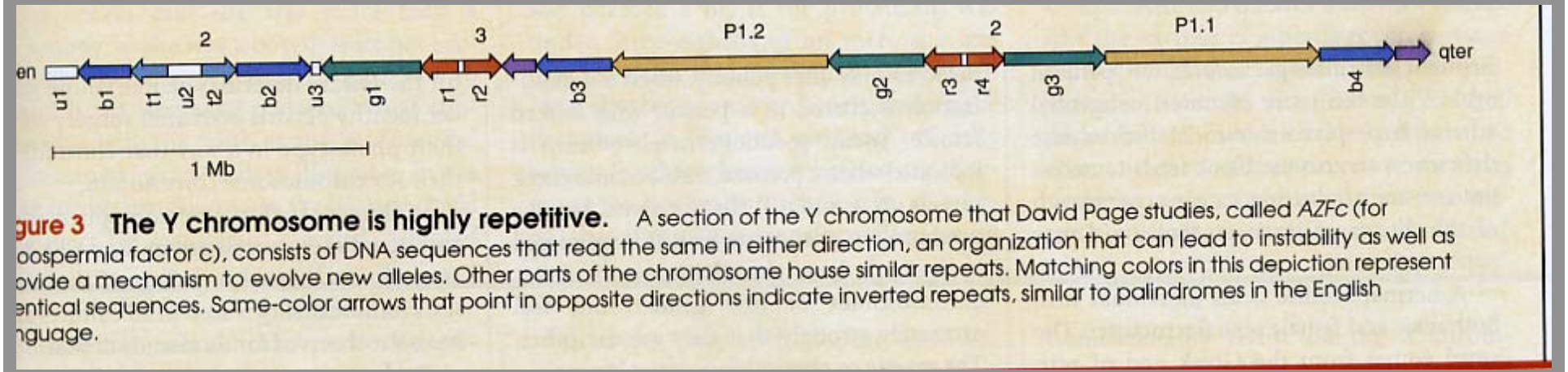
Eight palindromes comprise one-quarter of the euchromatic region of the Y chromosome Male Specific Region (MSY; previously named NRY or non-recombining region)



gure 3 The Y chromosome is highly repetitive. A section of the Y chromosome that David Page studies, called *AZFc* (for oospermia factor c), consists of DNA sequences that read the same in either direction, an organization that can lead to instability as well as ovide a mechanism to evolve new alleles. Other parts of the chromosome house similar repeats. Matching colors in this depiction represent entical sequences. Same-color arrows that point in opposite directions indicate inverted repeats, similar to palindromes in the English nguage.

Skaletsky et al. 2003; Rozen et al. 2003

This came as an incredible surprise. There are no regions in the genome organized this way.



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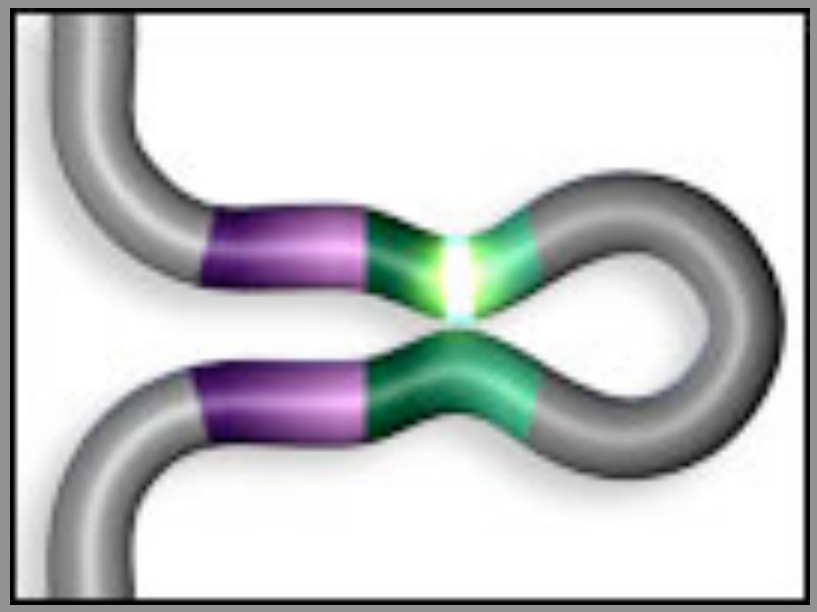
Abundant gene conversion between the arms of palindromes in human and ape Y chromosomes



Rozen et al. 2003

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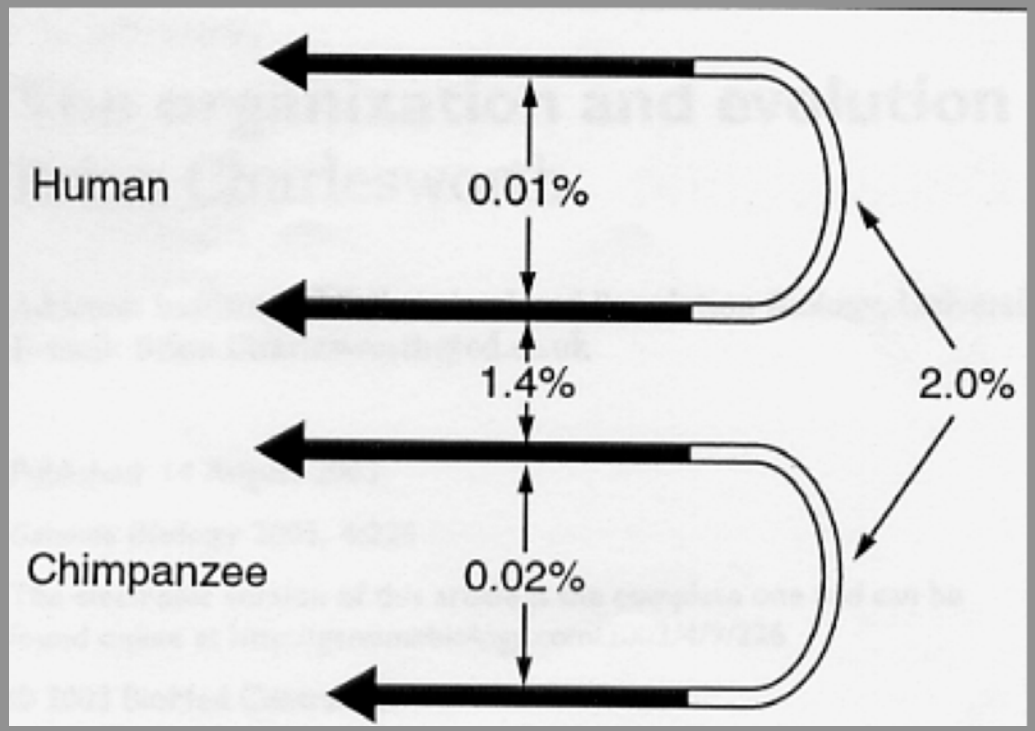
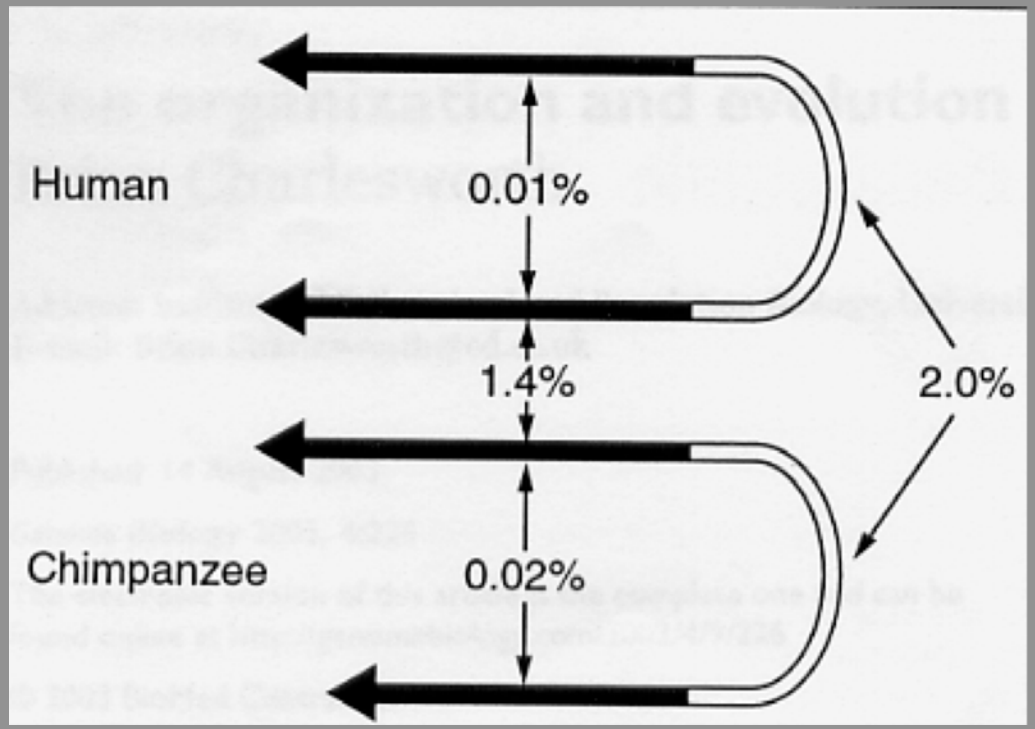


Rozen et al. 2003

Concerted evolution between the arms of palindromes in human and ape Y chromosomes



Rozen et al. 2003

Sex chromosomes evolution: a genomic make over

A lot of aspects of molecular evolution can be exemplified with sex chromosomes evolution:

1. **Whole chromosome gene expression changes/ Dosage compensation.**
2. **Chromosome degeneration and specialization**
3. **Effects of the lack of recombination**
4. **Chromosome reorganizations: inversions and translocations**
5. **Duplication into the Y, in the Y, out of the X and into the X**
6. **Accumulation of TE elements**
7. **Positive selection**

Current and future directions

- How do retrogenes recruit new promoters?
- What are the functions of the young retrogenes in *Drosophila*? Are some of them involved in meiotic drive? What about in other organisms?
- How different are the mitochondria and the proteasome during spermatogenesis?
- When does the export begin?
- Does it hold for other types of duplicates?
- Is there a pattern of duplication in other organisms?
- Is the X inactivated in *Drosophila*? Cytological approach
- Transposable element protein domestication
- Duplicated genes at the breakpoints of inversions

Lab members















Research Assistant:

- Javier Rio

Postdocs:

- Claudio Casola
- Miguel Gallach
- Jorge E. Quezada-Diaz

Graduate students:

- Yongsheng Bai
- Susana Domingues
- Aditi Bhardwaj
- Mansi Motiwale
- Taniya Muliyil
- Mehran Sorourian
- Daniel Szalay
- Charles Tracy

Undergraduate students

- Sarah Cole
- Jamie Dunlap
- Anton Mare
- Peter Pelache

Support: R01 from NIH and UTA (REP grant and startup funds)

Collaborators

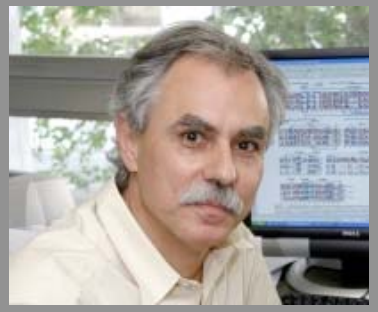
- Chitra Chandrasekaran
- Ying Chen
- Shawn Christensen
- Isabelle Dupanloup
- J.J. Emerson
- Cédric Feschotte
- Henrik Kaessmann
- Manyuan Long
- Alexandre Reymond
- Alfredo Ruiz
- Kevin Thornton











University of Chicago, University of Lausanne,

Wesleyan University and UTA