Structural variation

(A story of surprise → frustration → hope)

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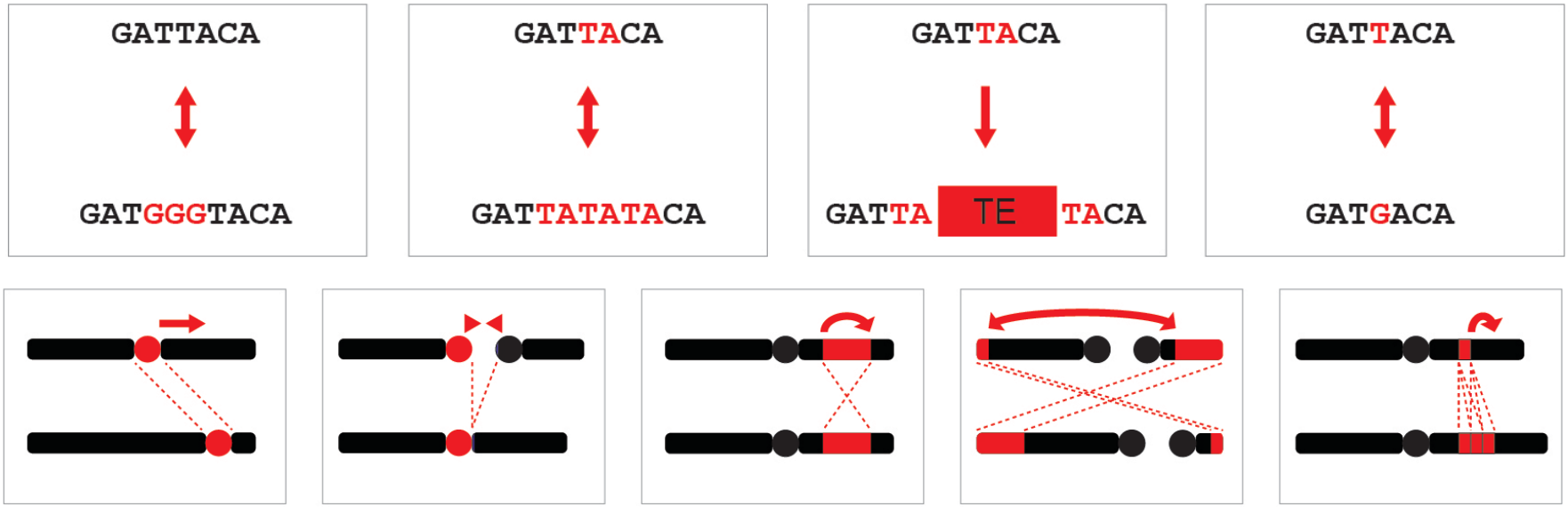
What is structural variation?

Structural variant (SV): genomic variation between individuals affecting the presence, abundance, position, and/or direction of a nucleotide sequence

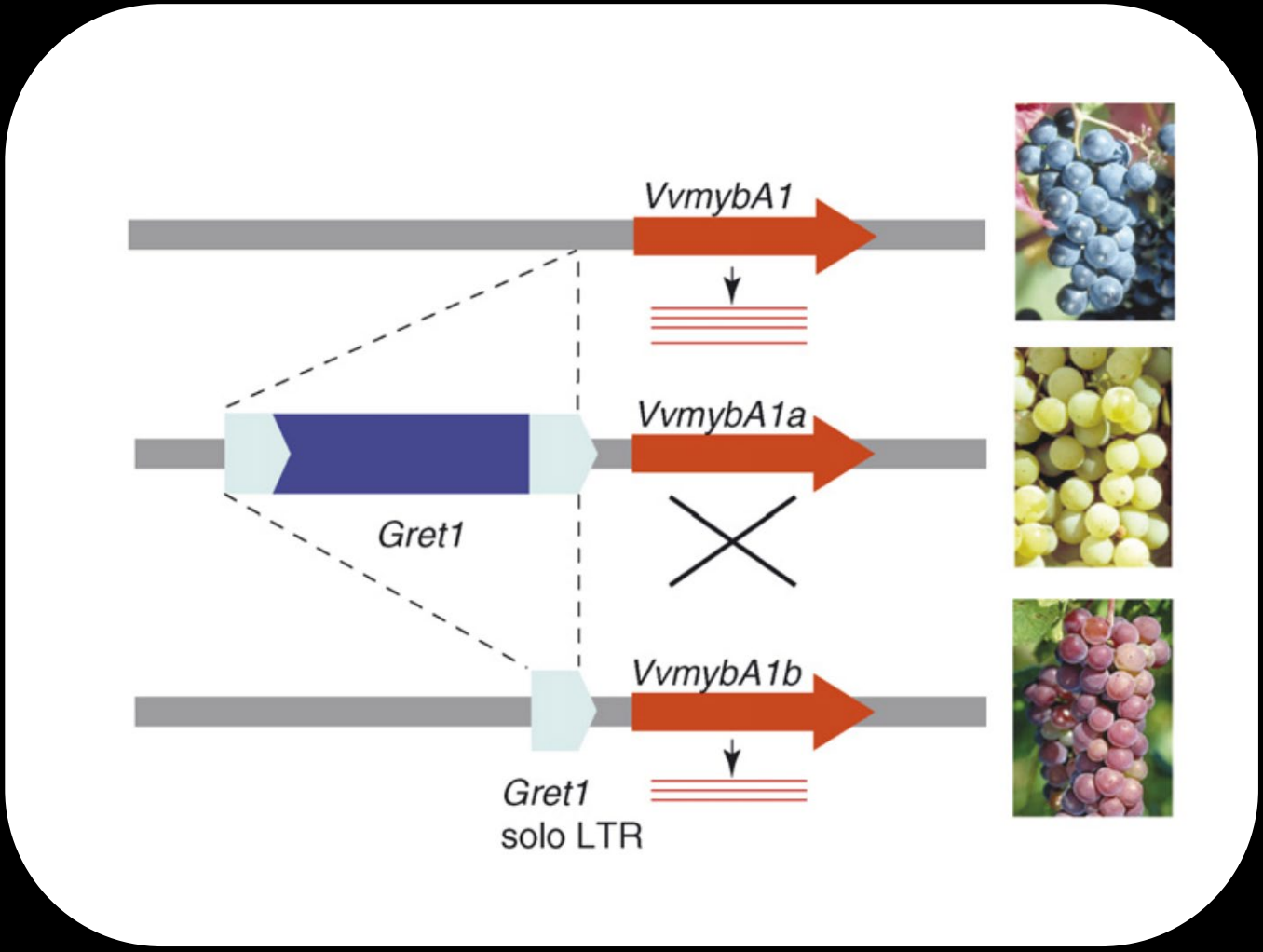
Mérot et al. 2020, *Trends Genet.*

Some key mutation types



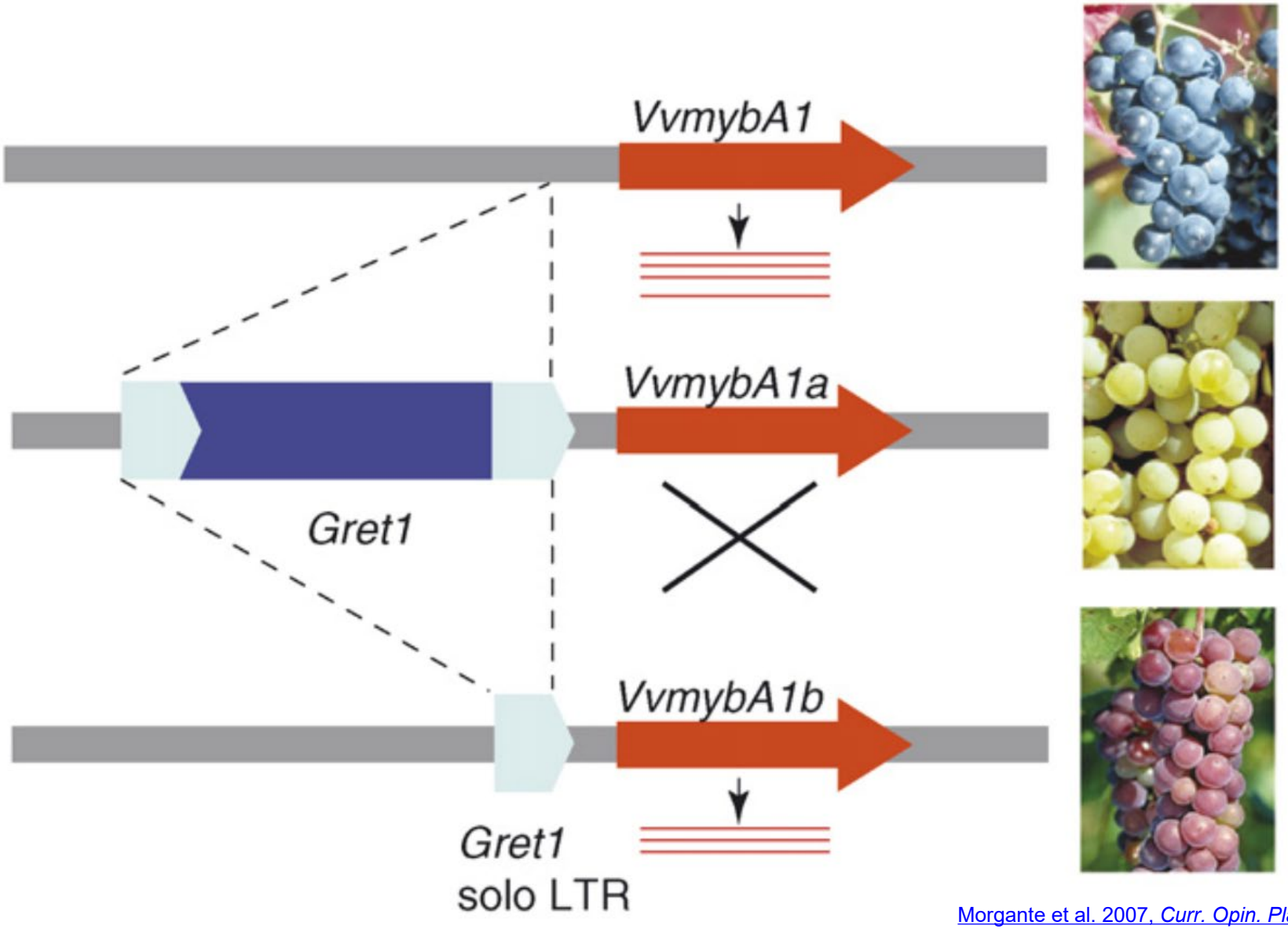
Berdan et al. 2021, *Mol. Ecol.*

Part 1: Surprise



A) It's not a SNP!

Delicious effects of SVs



Morgante et al. 2007, *Curr. Opin. Plant. Biol.*

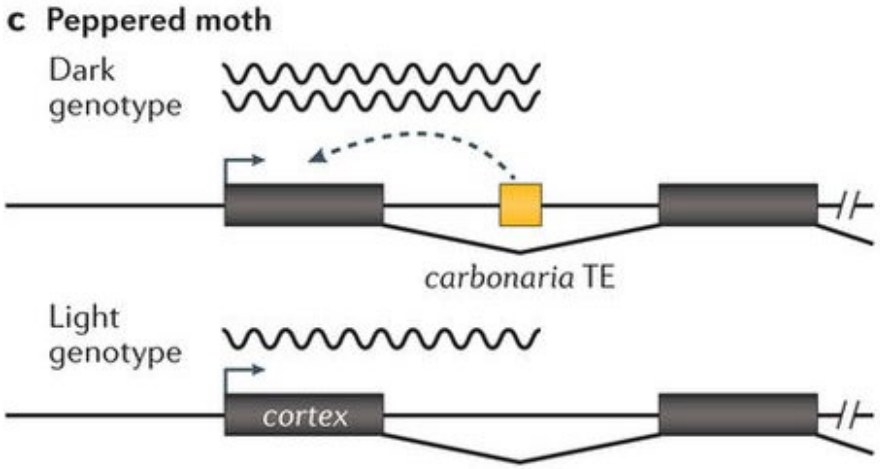
Discovery of gene regulation in 1940s

Barbara McClintock (Nobel Prize in Physiology or Medicine 1983)

Transposon Day: Barbara McClintock's 120th birthday is this week (June 16), check out: https://twitter.com/search?q=%23TransposonDay2022

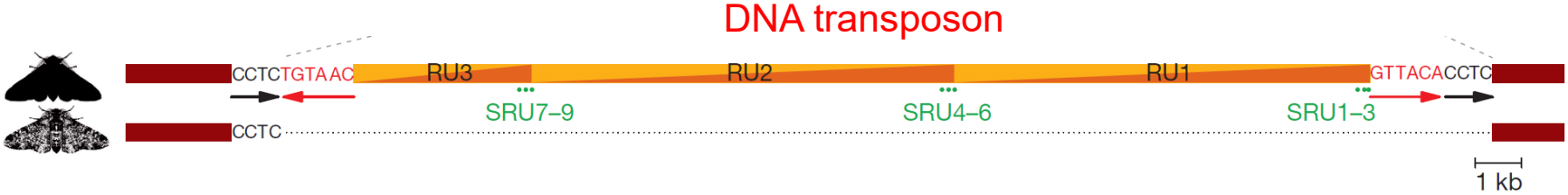
TE-induced rapid adaptation

The industrial melanism of the peppered moth is probably the most famous textbook example for adaptation (in only a few decades)!



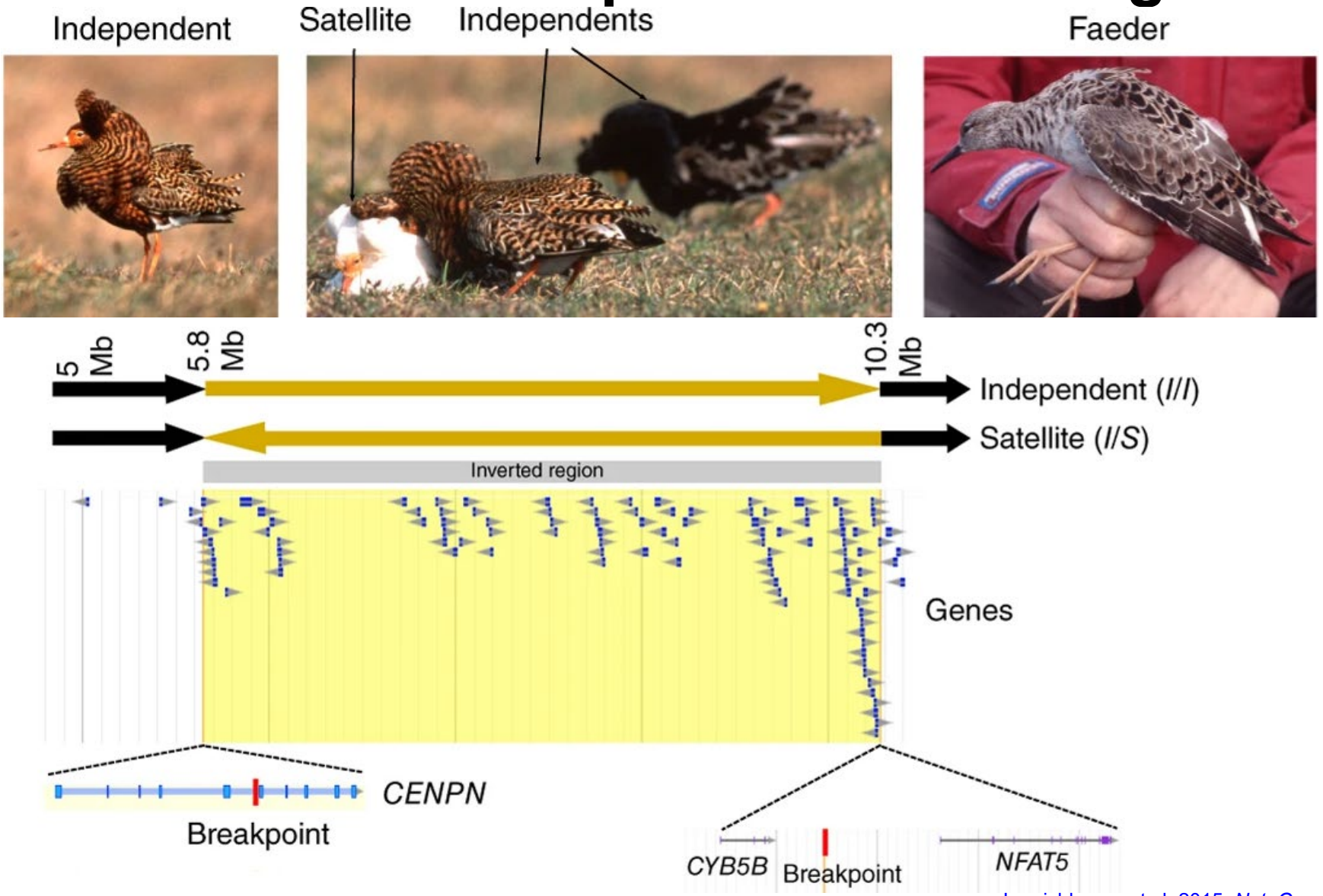
Upregulates cortex, resulting in increased darker coloration

Chuong et al. 2017 *Nat. Rev. Genet.*



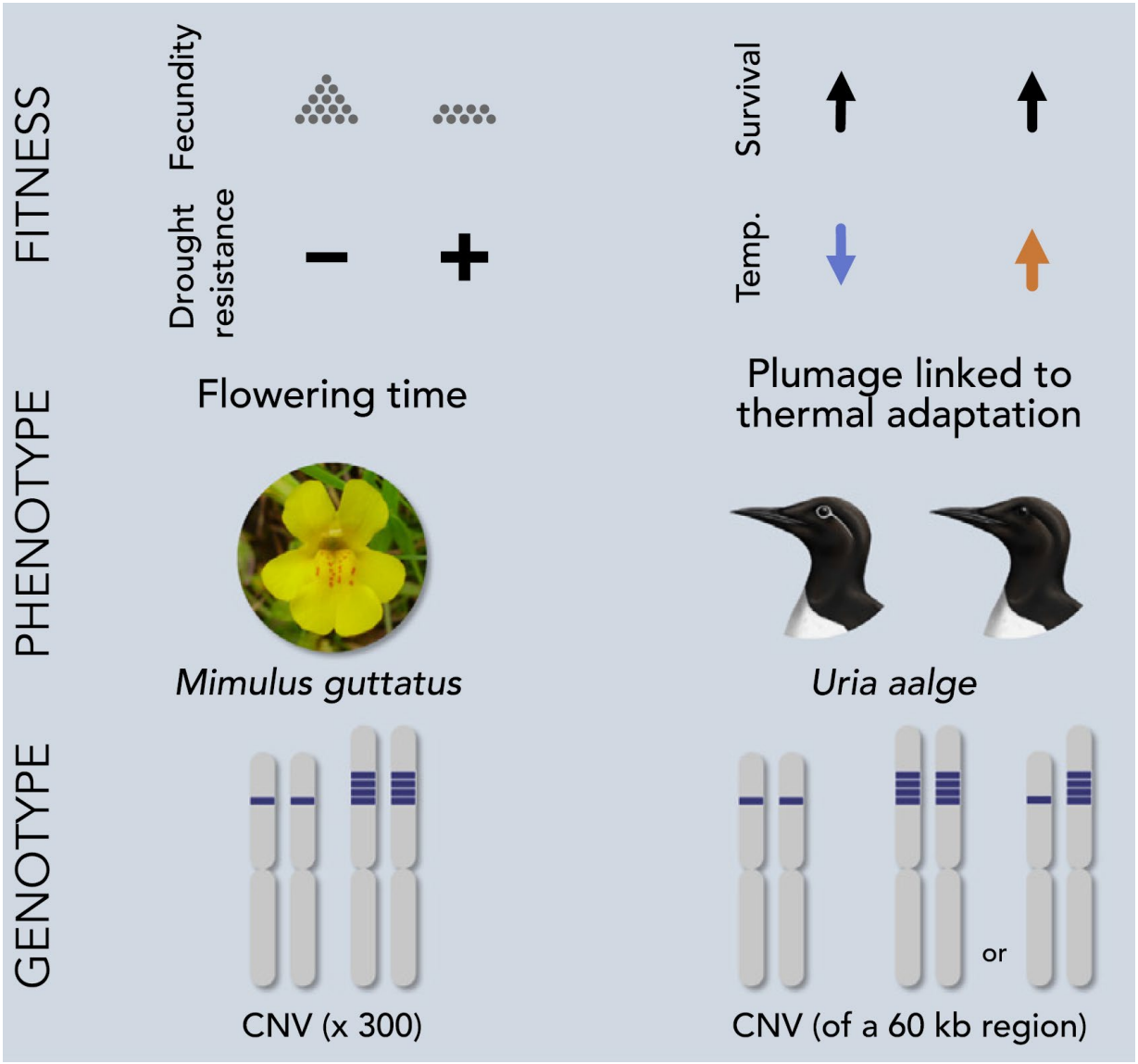
Van't Hof et al. 2016, *Nature*

Inversions in ruff reproductive strategies



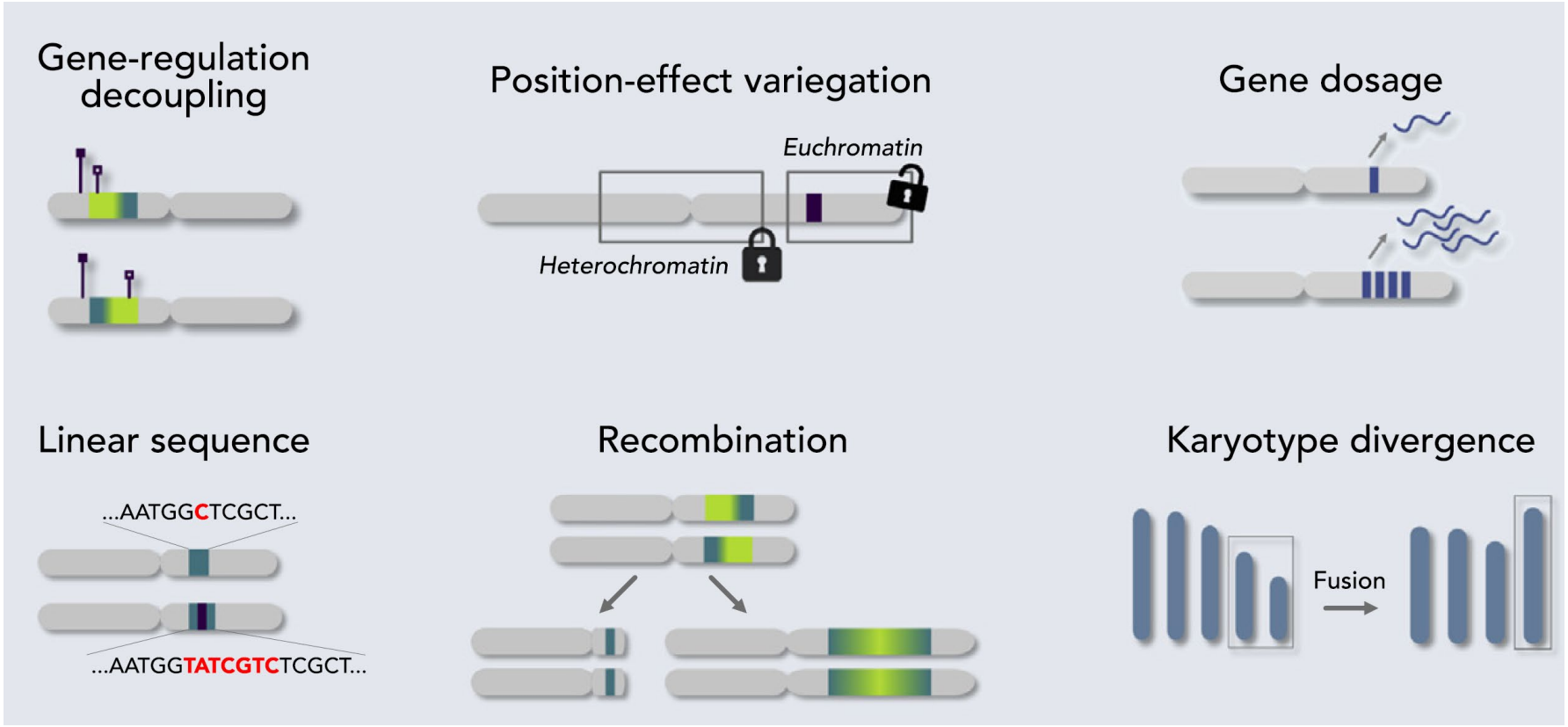
Lamichhaney et al. 2015, *Nat. Genet.*

Duplications



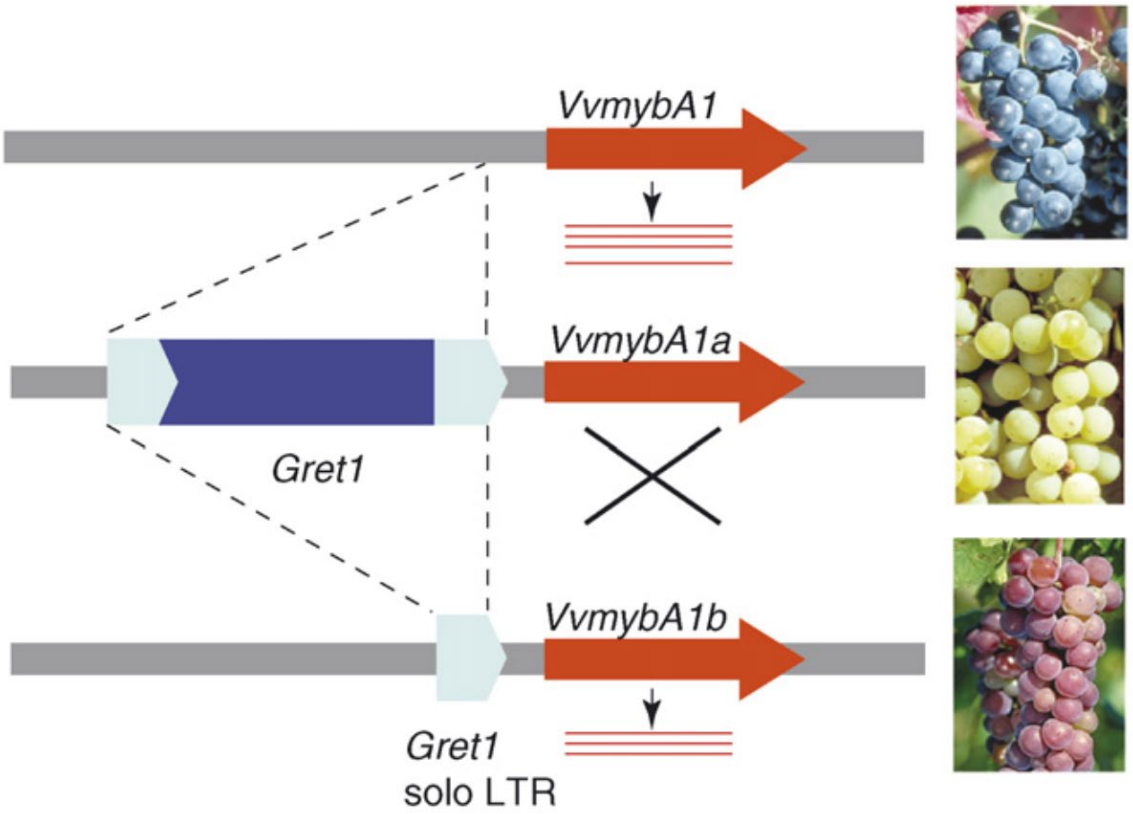
Mérot et al. 2020, *Trends Genet.*

High diversity of possible effects



Mérot et al. 2020, *Trends Genet.*

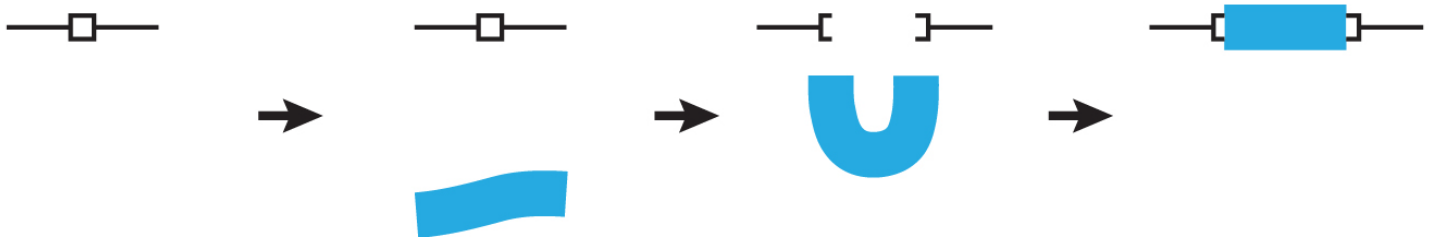
Part 1: Surprise



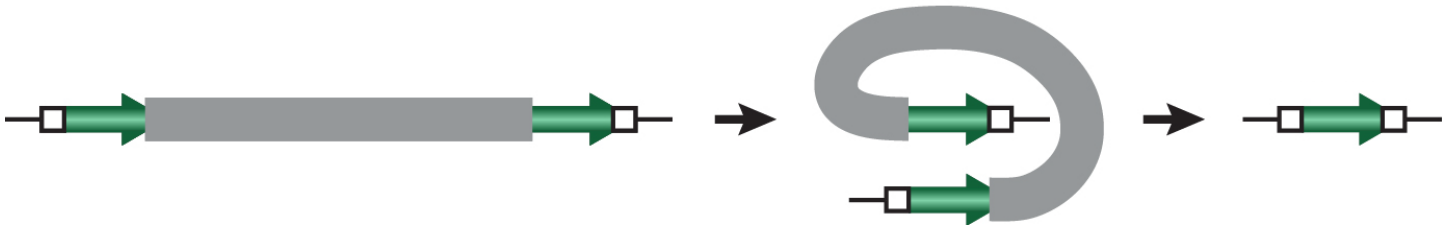
B) Covariation

Two key mechanisms of structural change

Non-homologous end joining (**NHEJ**)
(requires double-strand DNA breaks)

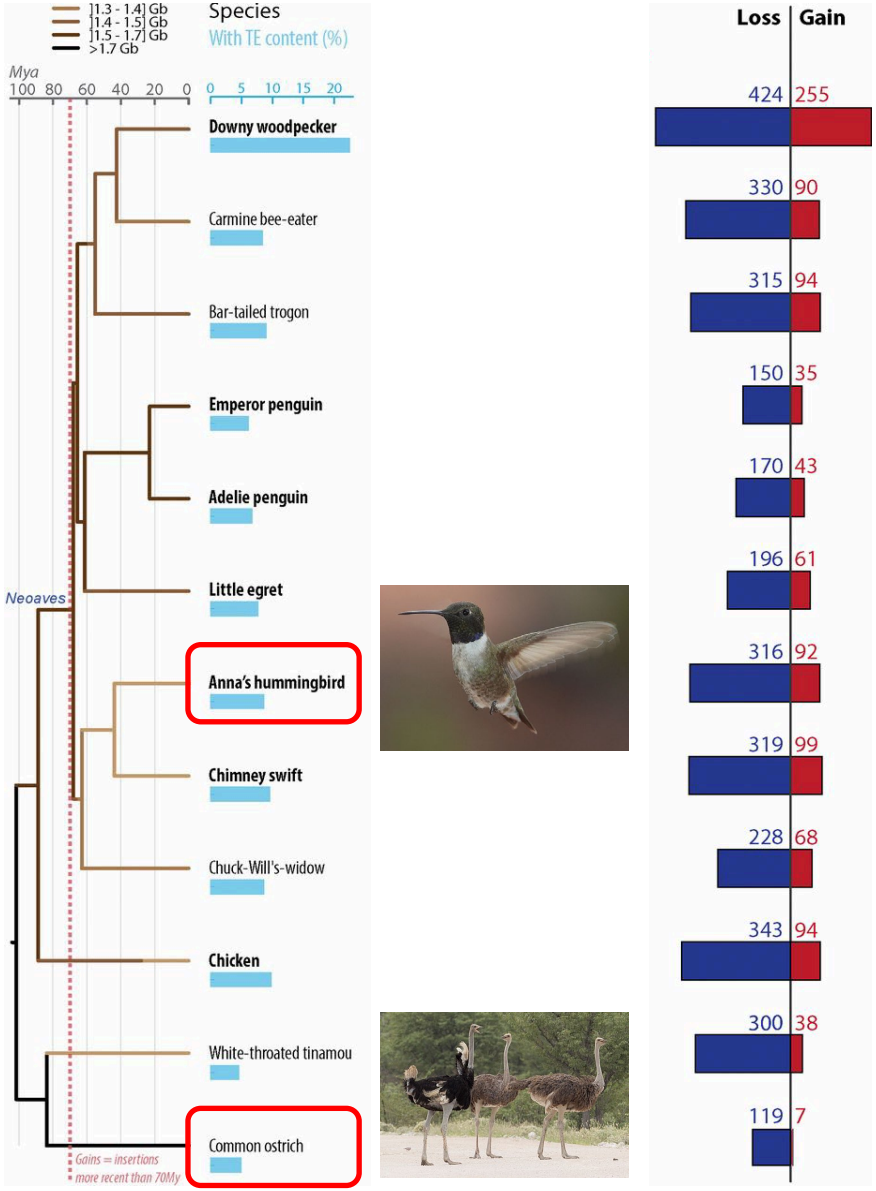


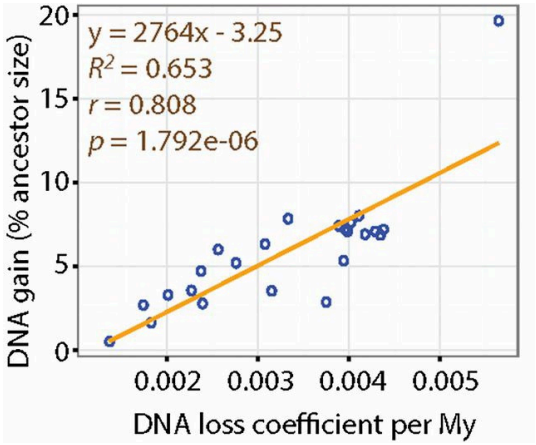
Non-allelic homologous recombination (**NAHR**)
(requires sequence homology)



NHEJ correlates with frequency of DNA damage, NAHR correlates with frequency of (identical, large) repeats

Genome shrinking despite more TEs





Accordion model

Consider not only host popgen, but also TE popgen!

Kapusta et al. 2017, *PNAS*

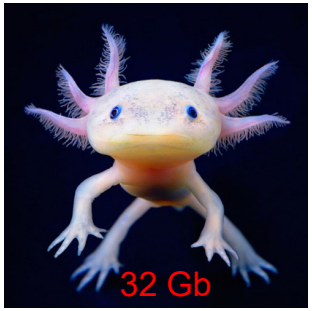
Genome size and life history traits

Dynamic genome
(more TEs, fast shrinking)

Static genome
(fewer TEs, slow shrinking)

Adaptive processes are often invoked but remain difficult to prove
(few high-quality genome assemblies and lack of popgen data)!

20 Gb



32 Gb

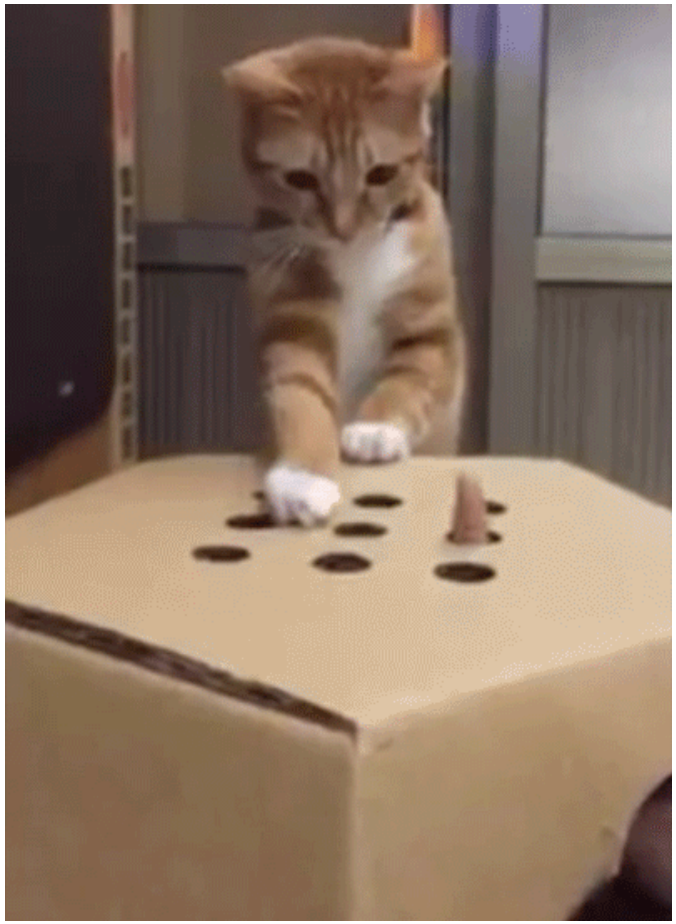
3.2 Gb

133 Gb

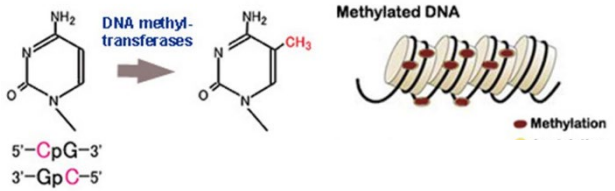
More context in Suh 2021 TE lecture 5

Non-adaptive processes likely contribute to a large or very large degree!

Genomes: whack-a-transposon

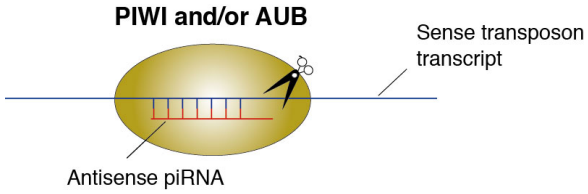


DNA methylation



http://helicase.pbworks.com/w/page/17605615/DNA%20Methylation

piRNA pathway



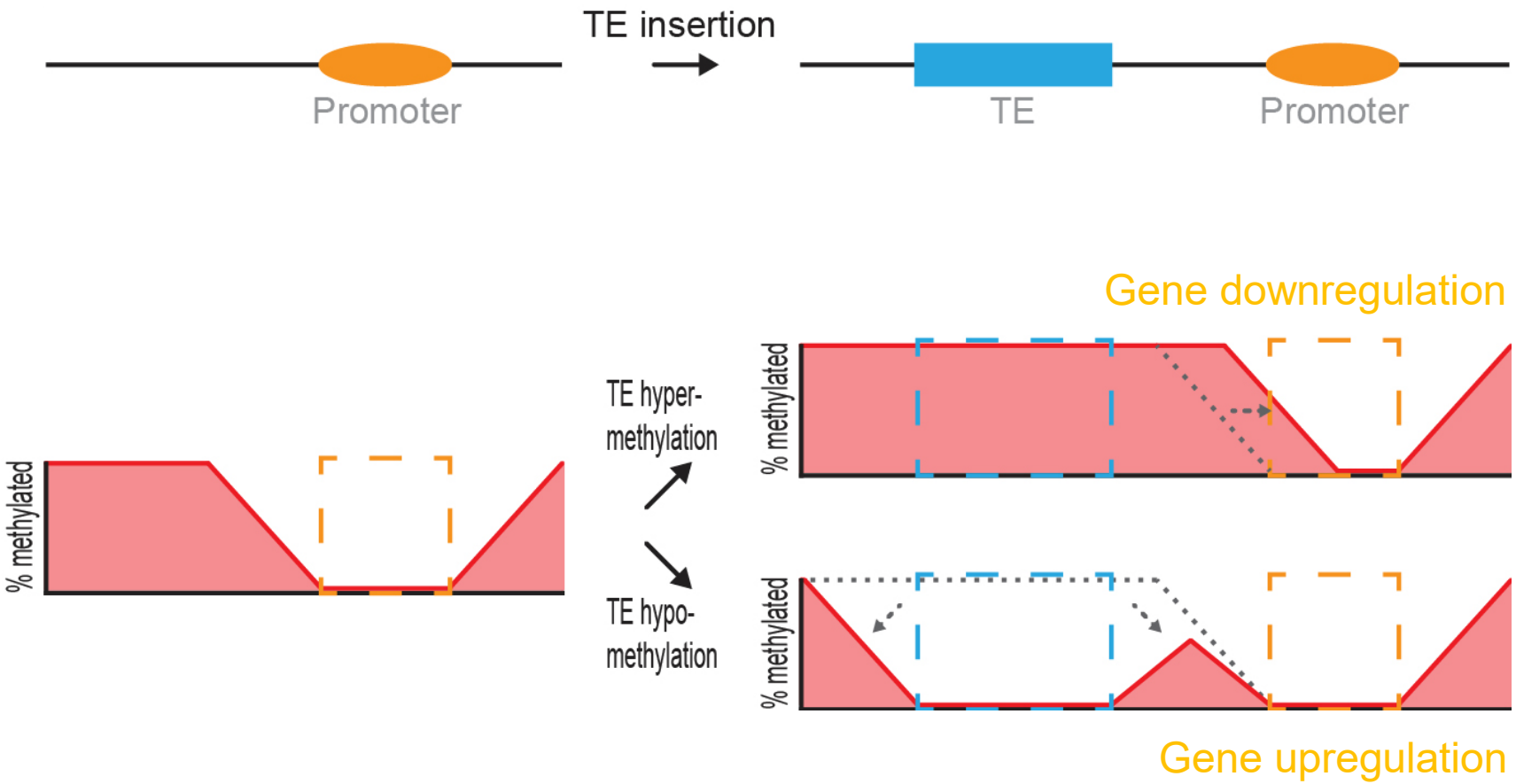
http://ruo.mbl.co.jp/bio/g/product/epigenetics/RNAworld.html

KRAB zinc-finger genes

Feschotte & Gilbert 2012, *Nat. Rev. Genet.*

More context in Suh 2021 TE lecture 6

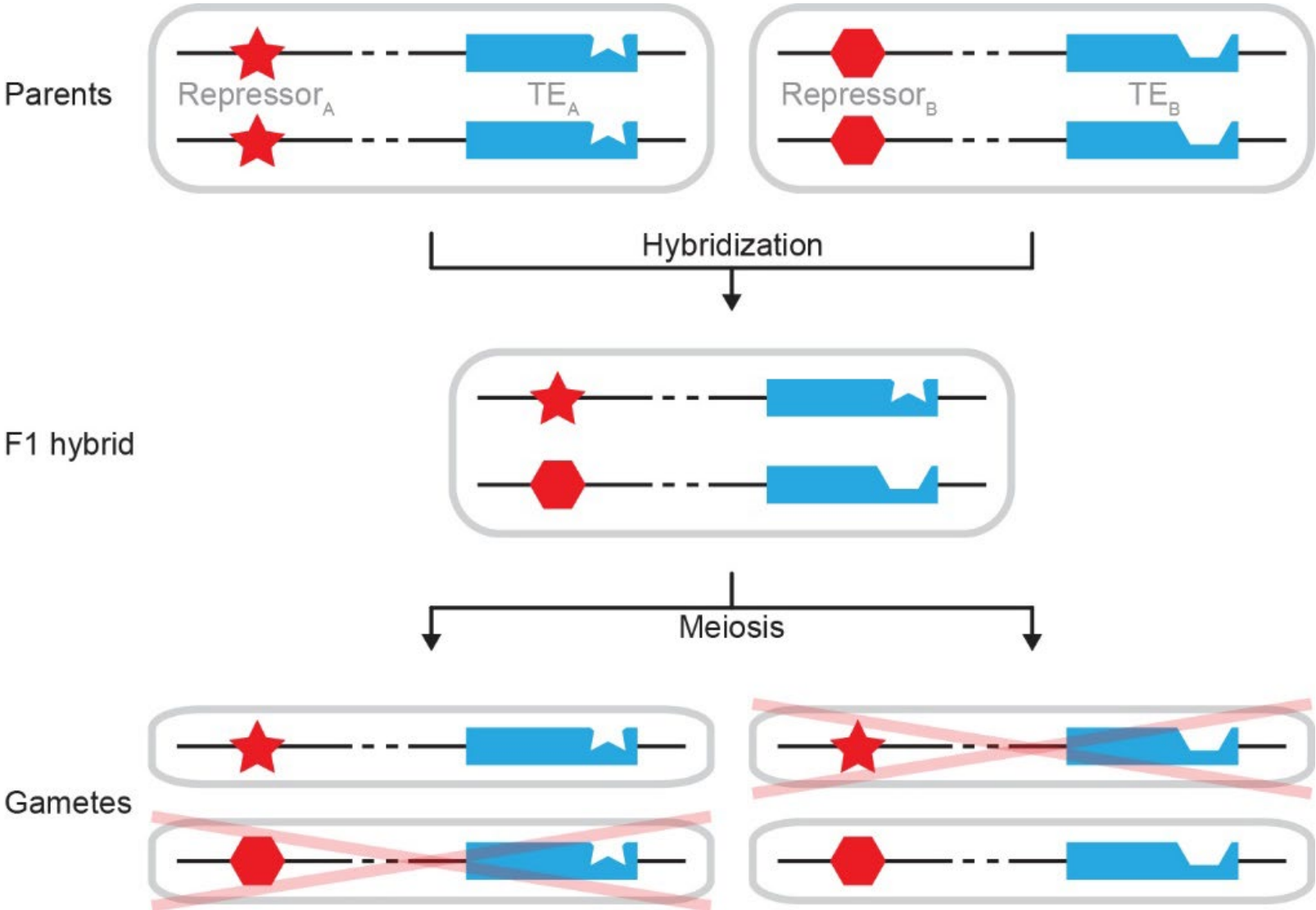
Covariation between (epi)mutation types



Spillover of DNA methylation and/or histone modifications from new TE insertions to nearby genes!

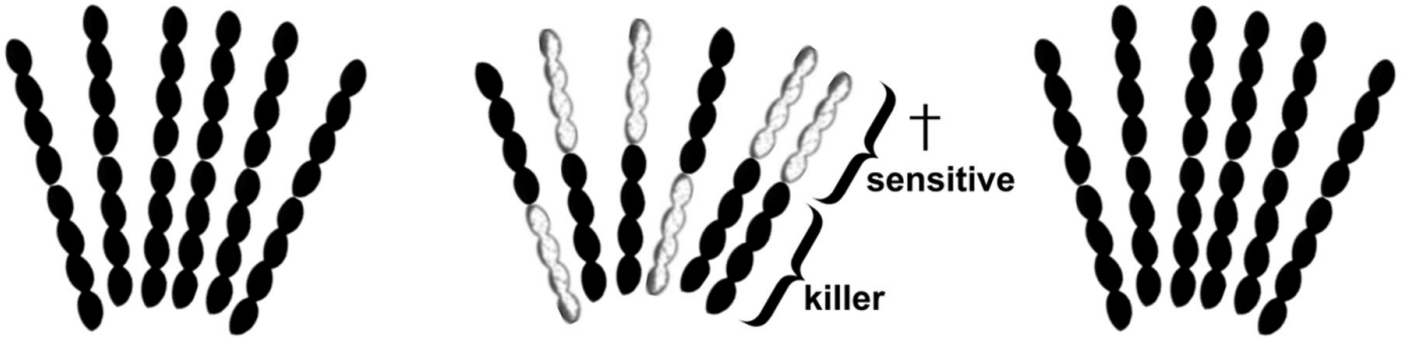
Weissensteiner & Suh 2019 in *Avian Genomics* book

Host–TE conflict and reproductive isolation



Weissensteiner & Suh 2019 in *Avian Genomics* book

Spore/sperm killing of some SVs

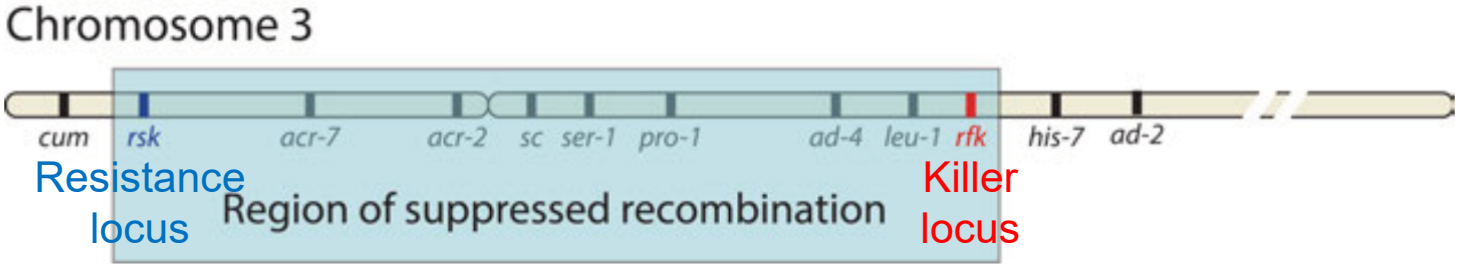


sensitive x sensitive

killer x sensitive

killer x killer

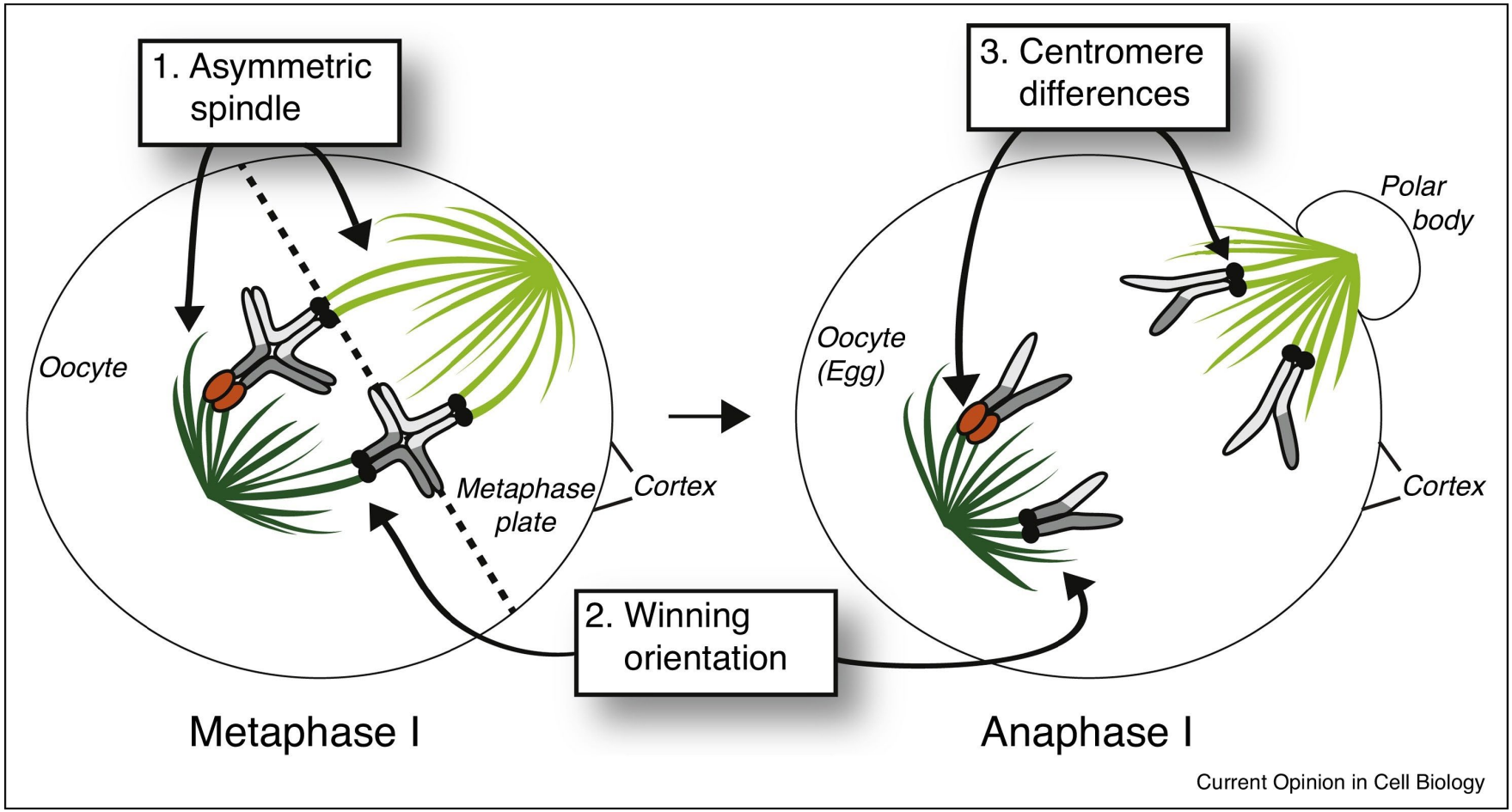
Spore sacs of red bread mold *Neurospora crassa*
(8 spores after meiosis and one mitotic division)



If an inversion or duplication leads to gene truncations, a toxin/antitoxin system can evolve to distort its transmission!

Svedberg 2017 PhD thesis

Centromere drive of some SVs



If a pericentric inversion or a centromere shift leads to a stronger centromere, it can distort its own transmission!

Kursel & Malik 2018, *Curr. Opin. Cell Biol.*

Questions?

Part 2: Frustration

A) Concepts and methods

What this lecture will not cover

1. Genome assembly: What is (not) assembled?
   Primers: Peona et al. 2018, Peona et al. 2021, Rhie et al. 2021, Nurk et al. 2022

2. Gene and repeat annotation: What is (not) annotated?
   Primers: Yandell & Ence 2012, Suh 2021 TE lecture 4, Goubert et al. 2022

3. Within-individual or germline/soma genome differences
   Primers: Smith et al. 2021, Suh & Dion-Côté 2021, Borodin et al. 2022

4. All SVs, all processes, all effects, all methods, all limitations. Talk to Valentina and me until 10 pm today!

2p – 5p	Alexander Suh	Structural variation	Egon Schiele
7p – 10p	Valentina Peona	Structural variation activity	Prelate

Valentina Peona

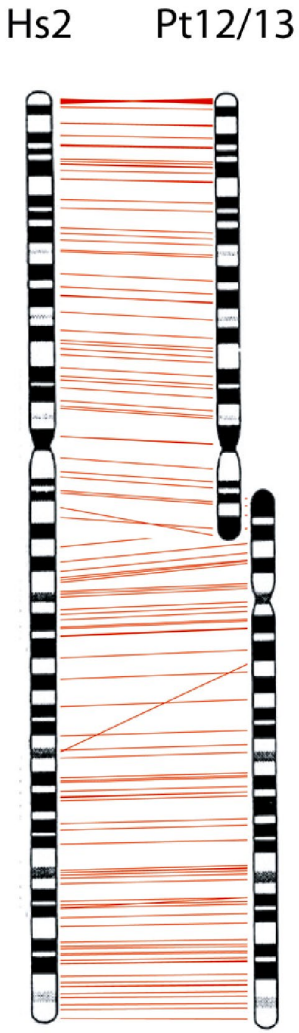
Awareness of biology and technology

How can we make sure that what we see in our data is what we think it is?

Did we account for biological patterns/processes and technological limitations?

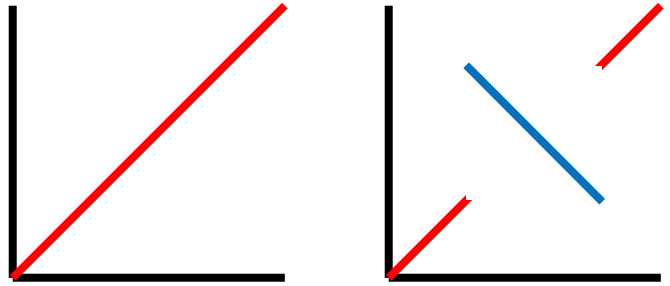
Terminology

Synteny vs. collinearity

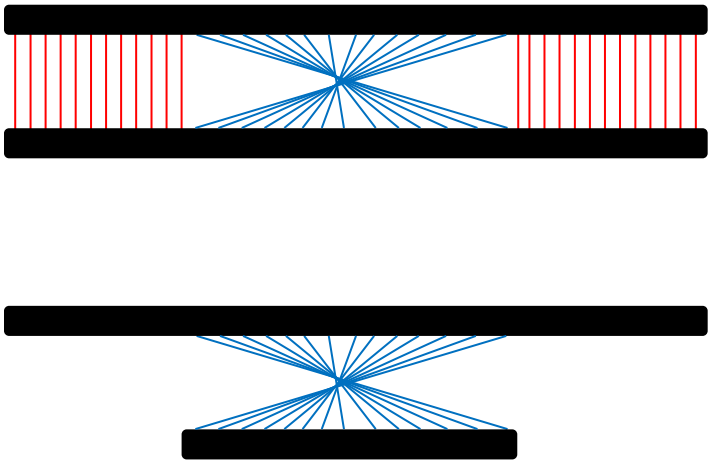


Feuk et al. 2005, *PLoS Genet.*

Dot plot



Pattern vs. process



Beware of waves

My SNP explains everything!

My inversion explains everything!

My TE explains everything!

Each of these statements can be true, but what if there is covariation with other mutation types?

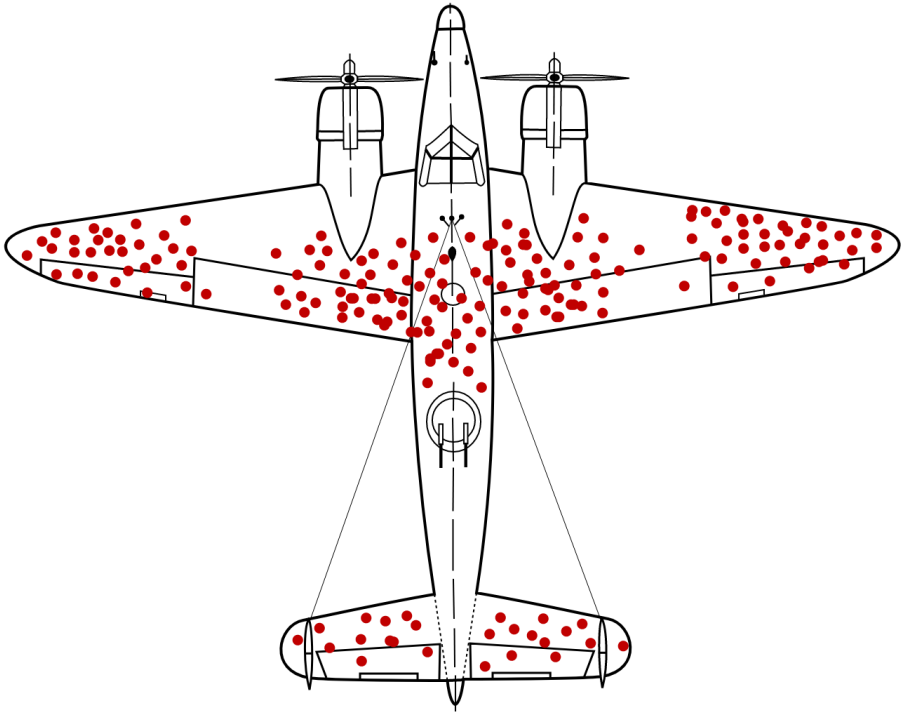
Taxon X is not known to have mutation type Y

We did not look for mutation type Y in taxon X

Reflection on biases

Confirmation bias

Survivorship bias



My own biases: I like transposable elements, centromere shifts, and simple answers to complicated questions!

Ultimate vs. proximate causes

Proximate: This TE is beneficial for the host

Ultimate: ~~TEs jump to be beneficial for the host~~
TEs jump because they can

Proximate: This asteroid caused diversification

Ultimate: ~~Asteroids land to cause diversification~~
Asteroids land eventually

What is the null hypothis?

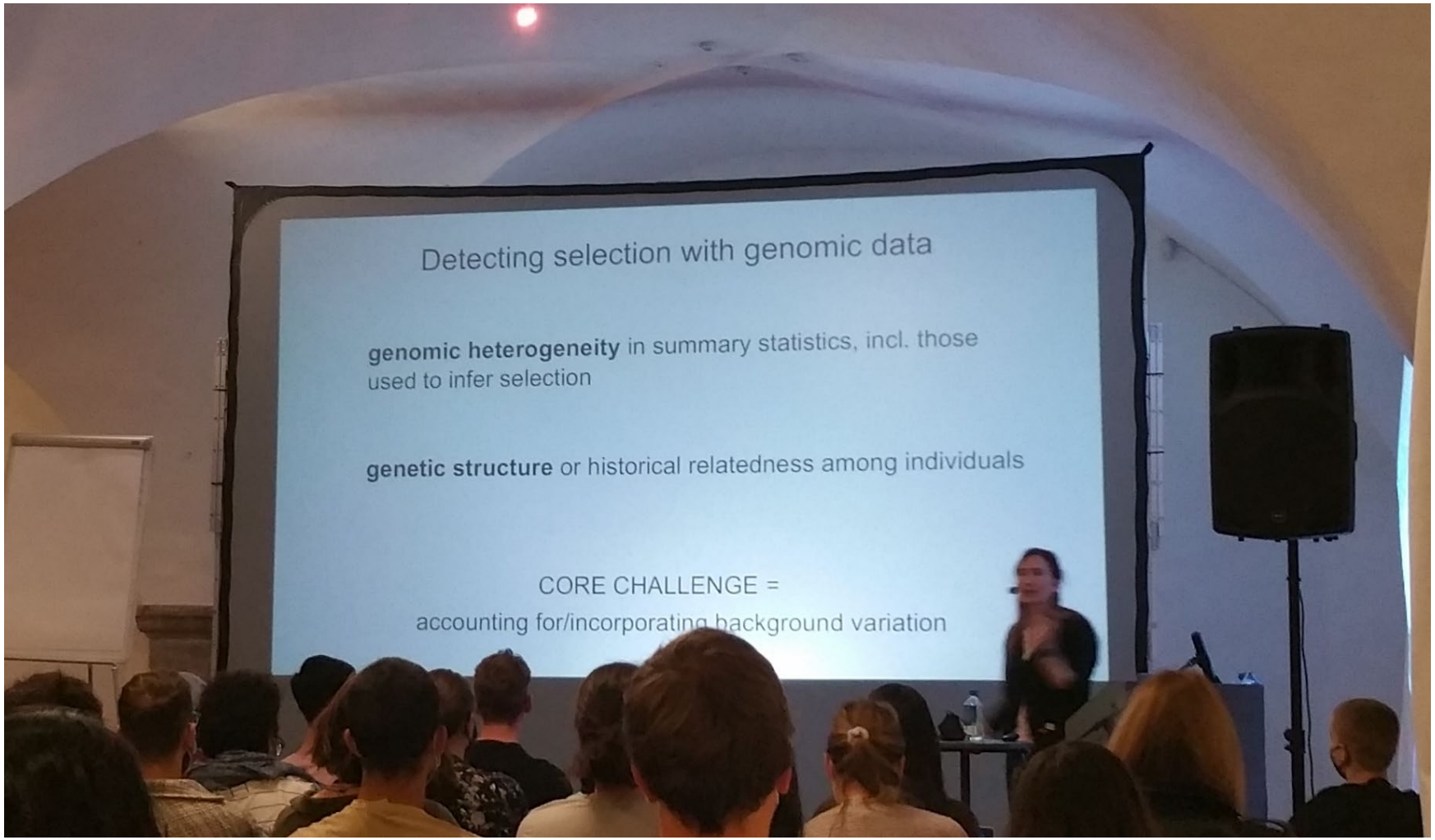
~~Guilty until proven innocent~~

Innocent until proven guilty

~~Absence of evidence~~

Evidence of absence

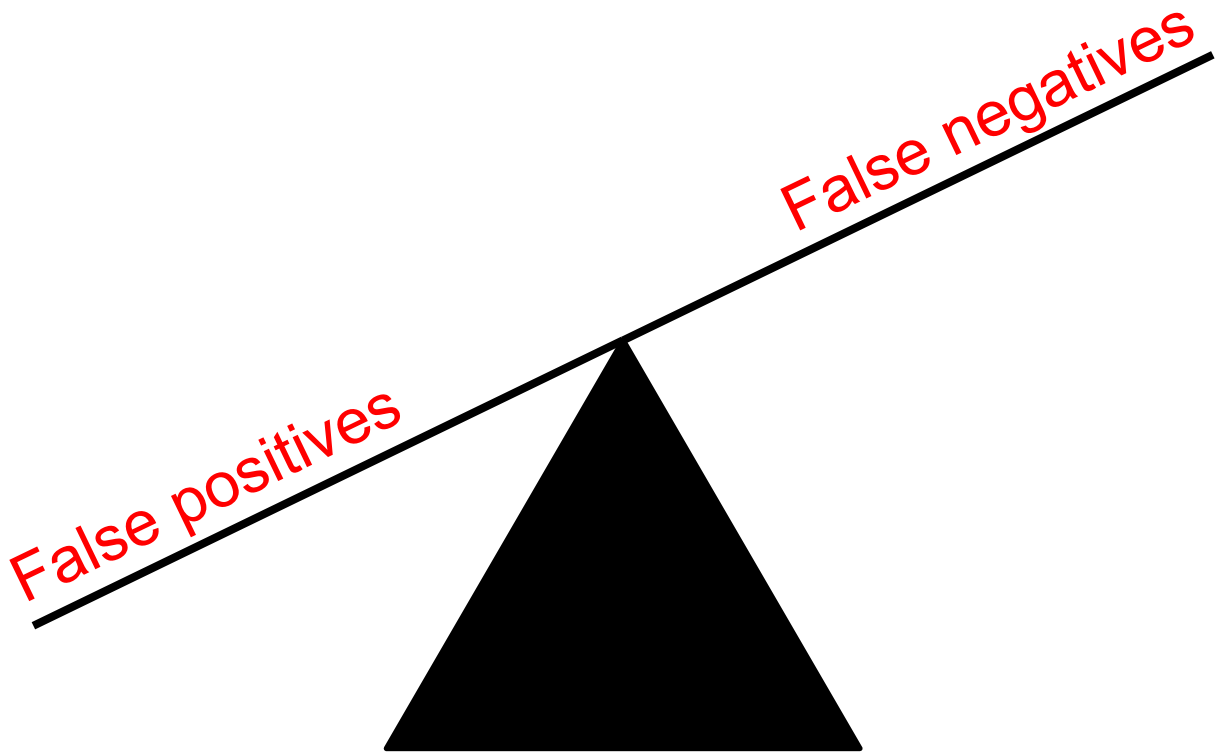
Theory applies to SNPs and to SVs



Background variation: What SNPs and SVs are there?

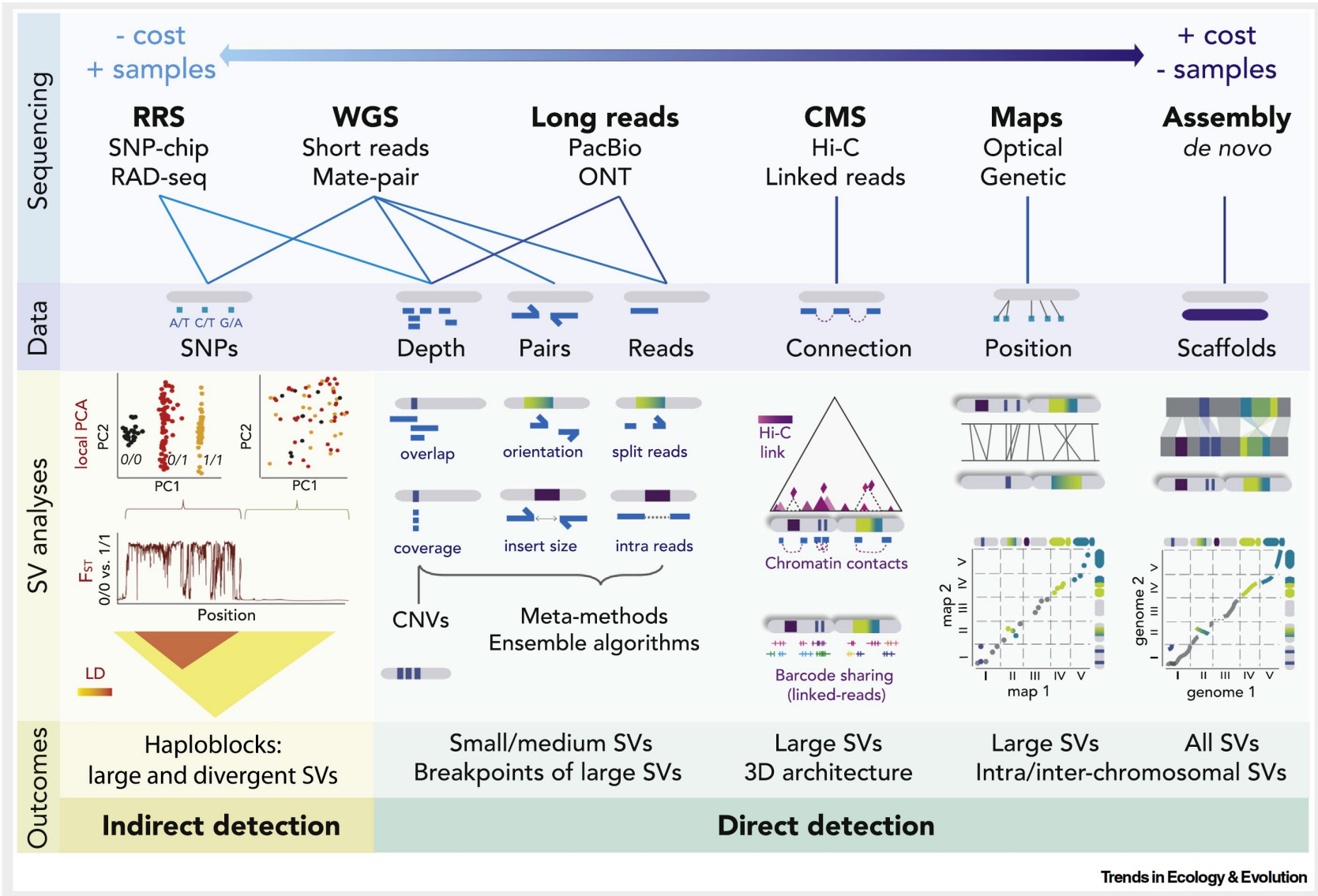
http://evomics.org/2022-workshop-on-population-and-speciation-genomics-cesky-krumlov/

SVs are nowhere as established as SNPs



Problem: Reliable SV genotyping (cf. SNP activies in this workshop) + accounting for covariation with other SVs (cf. this lecture) is essential but the SV field is not there yet.

One approach to find them all?



Mérot et al. 2020, *Trends Genet.*

How to pick a tool for finding SVs?

Repeat tools

Description

This page compiles a list of software for the detection, annotation, analysis, simulation and visualization of repetitive, mobile and selfish DNA and related entities.

It is maintained by Tyler A. Elliott and a more metadata rich form of the data can be found here. It was initiated with the help of Elizabeth Smikle and Miduna Rahulan, formerly and currently at the Centre for Biodiversity Genomics at the University of Guelph. Suggestions, updates and error corrections are welcome. Please feel free to add missing tools into the table, that would help a lot!

We encourage the authors of these tools to create pages for them on TE Hub, so that they can provide more information about their work, and link it back to this table. Please find a template software sheet here.

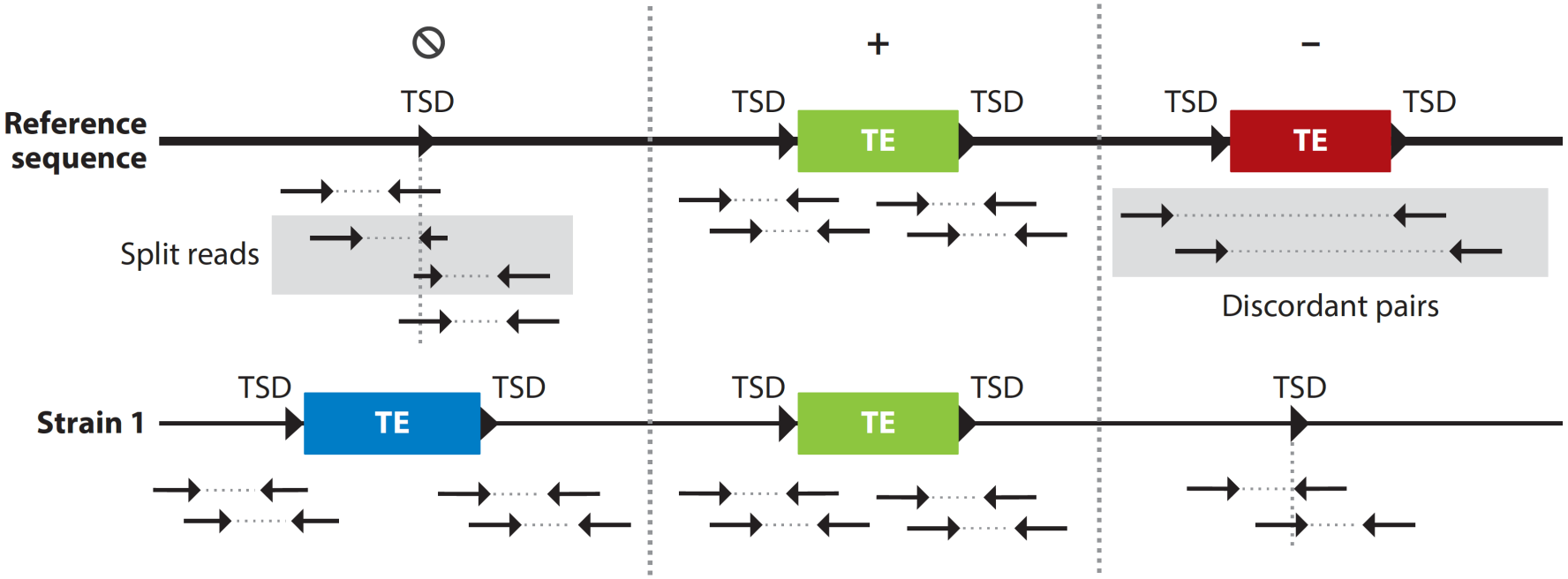
Overview of tools for repeat analysis

Tool ↕ Find...	DOI ↕ Find...	Alternate URL ↕ Find...	Keywords ↓ Polymorphism
AluMine	https://doi.org/10.1101/588434		Alu, SINE, Genotype, Polymorphism, NGS/HTS
alu-detect	https://doi.org/10.1093/nar/gkt612		Alu, SINE, Genotype, Polymorphism, NGS/HTS, Paired-End

88 tools listed for TE insertion polymorphism analysis!

https://tehub.org/en/resources/repeat_tools; The TE Hub Consortium 2021, *Mobile DNA*

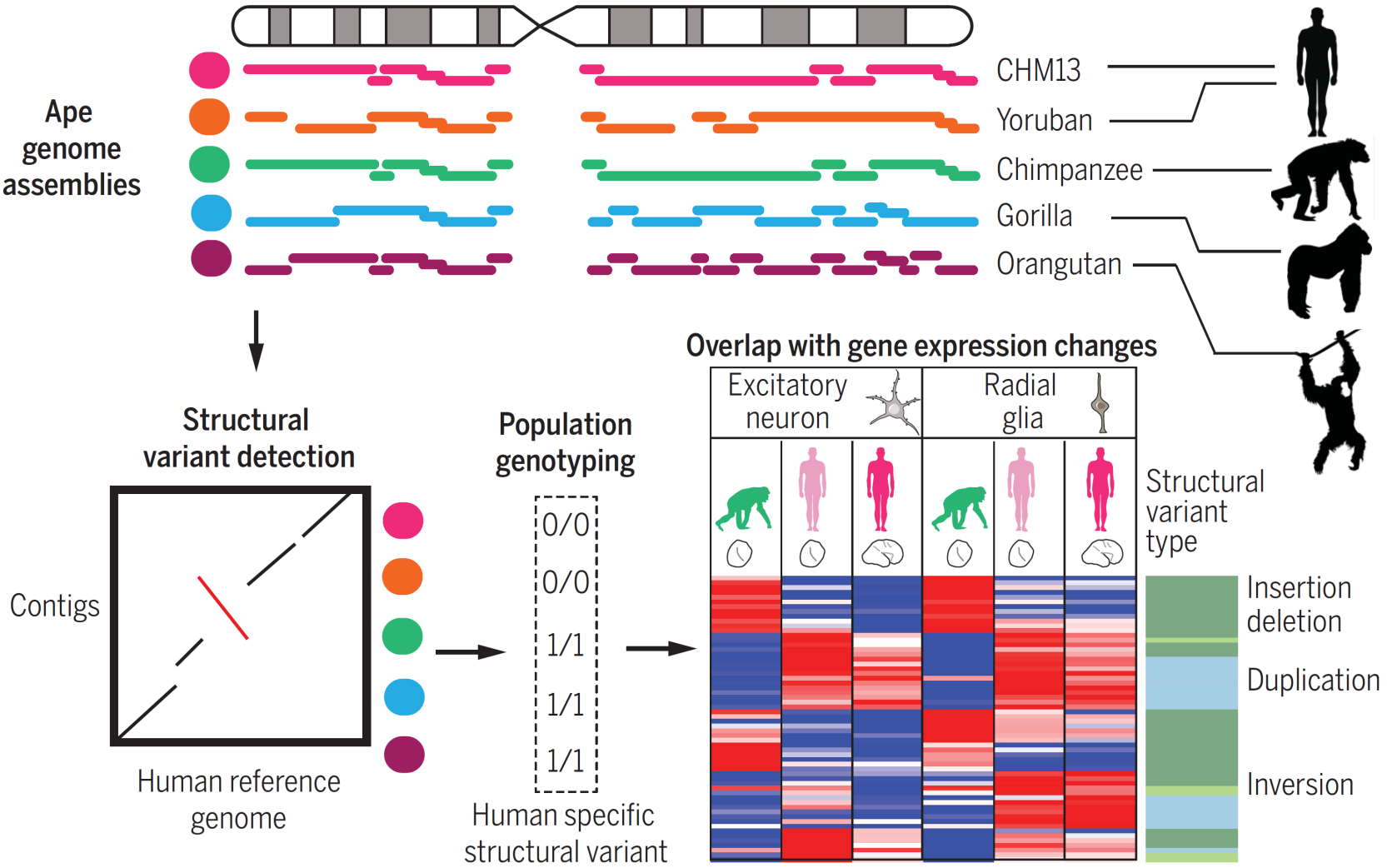
Read-based SV detection



Reliable read mapping and SV scoring is difficult near (other) repeats, near gaps, at misassemblies …

Kronenberg et al. 2018, *Science*

Assembly-based SV detection



Reliable genome alignment and SV scoring is difficult in highly repetitive regions (if assembled …)

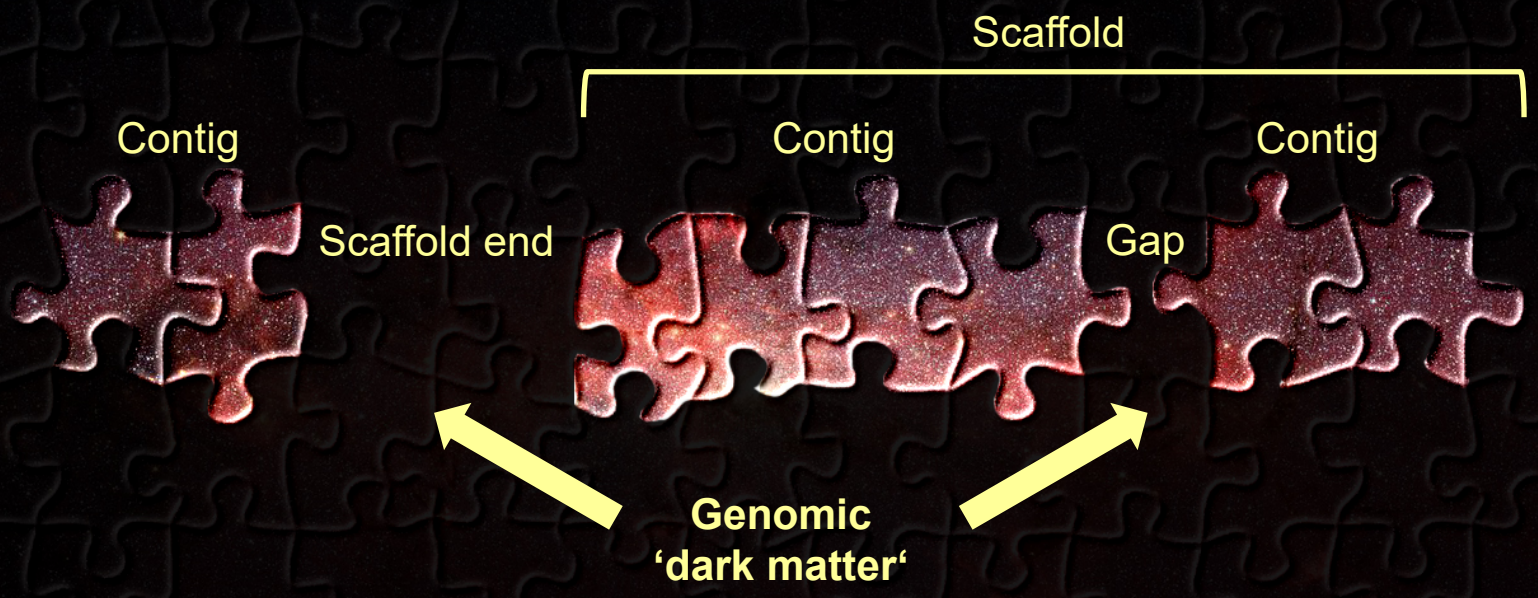
Barrón et al. 2014, *Annu. Rev. Genet.*

It could all be so easy

(if it wasn‘t for technological limitations)

Karyogram of a human male (Wikipedia)

Genomics: a big and messy puzzle

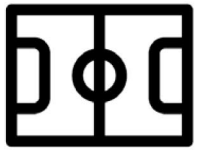


CCATAGTC

TATGCGTACACACGGT**NNNN**ATCGACATACT

Various sequencing technologies

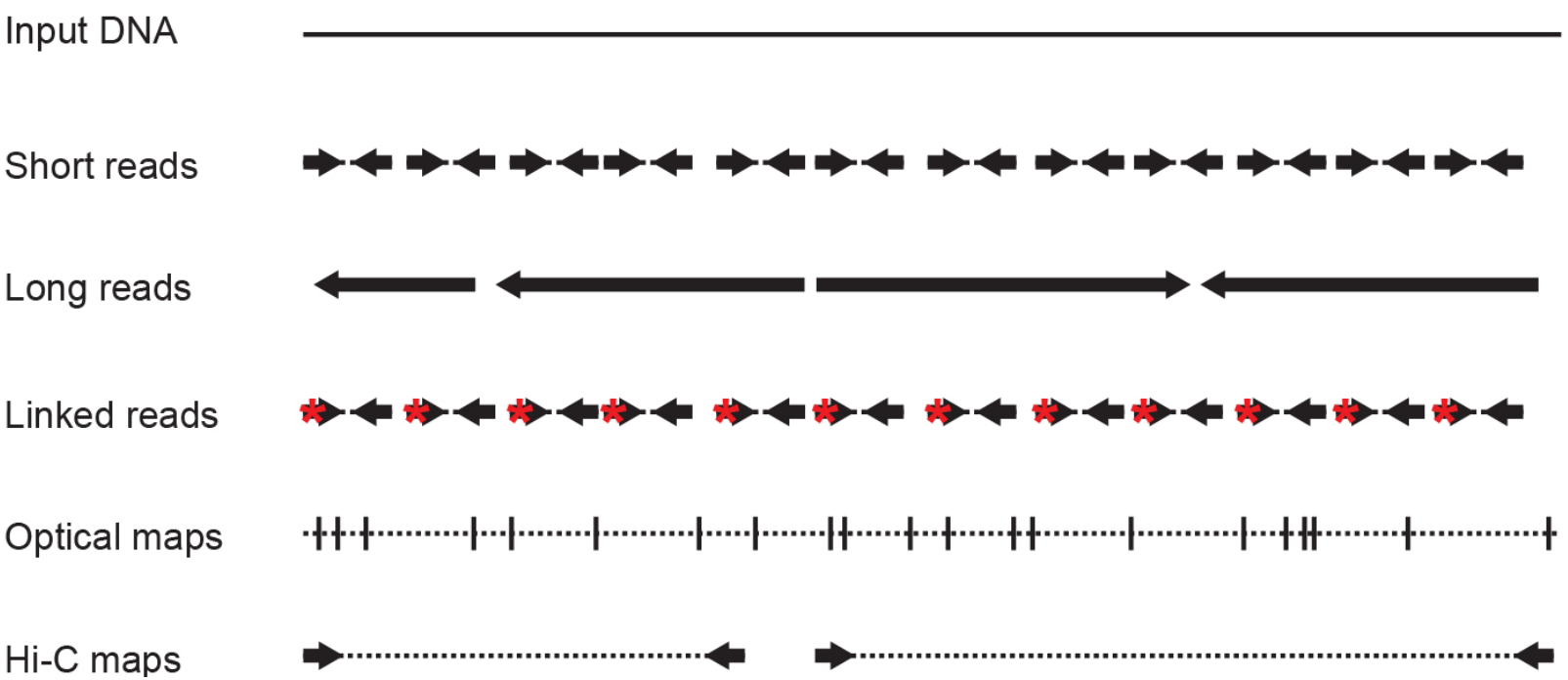
Distance Rome-Paris
(avian genome)
1,100,000,000 bp



Football field
(OM, LRC, Hi-C)
150,000 bp

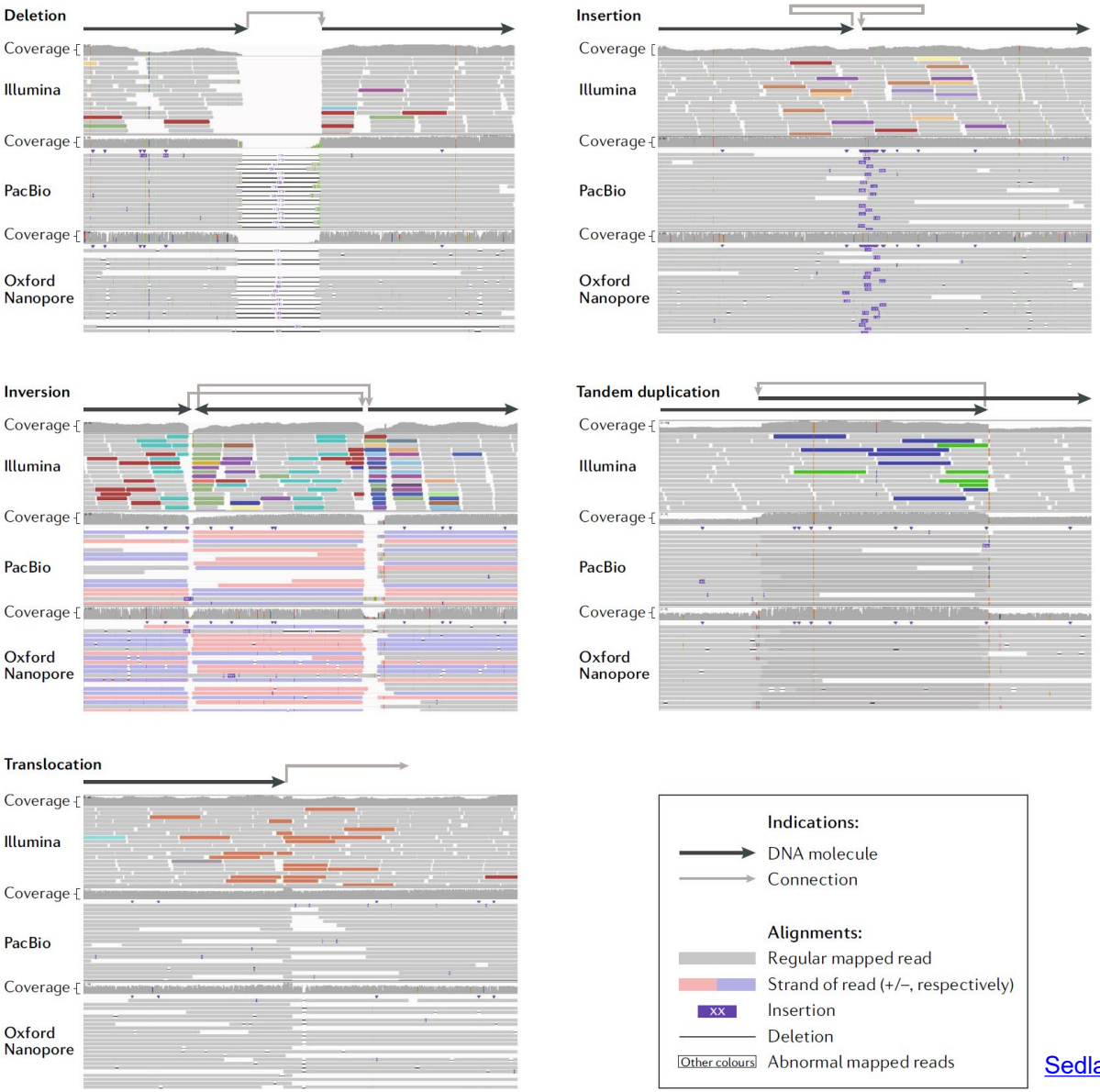
Autobus
(long reads)
15,000 bp

Smartphone
(short reads)
150 bp



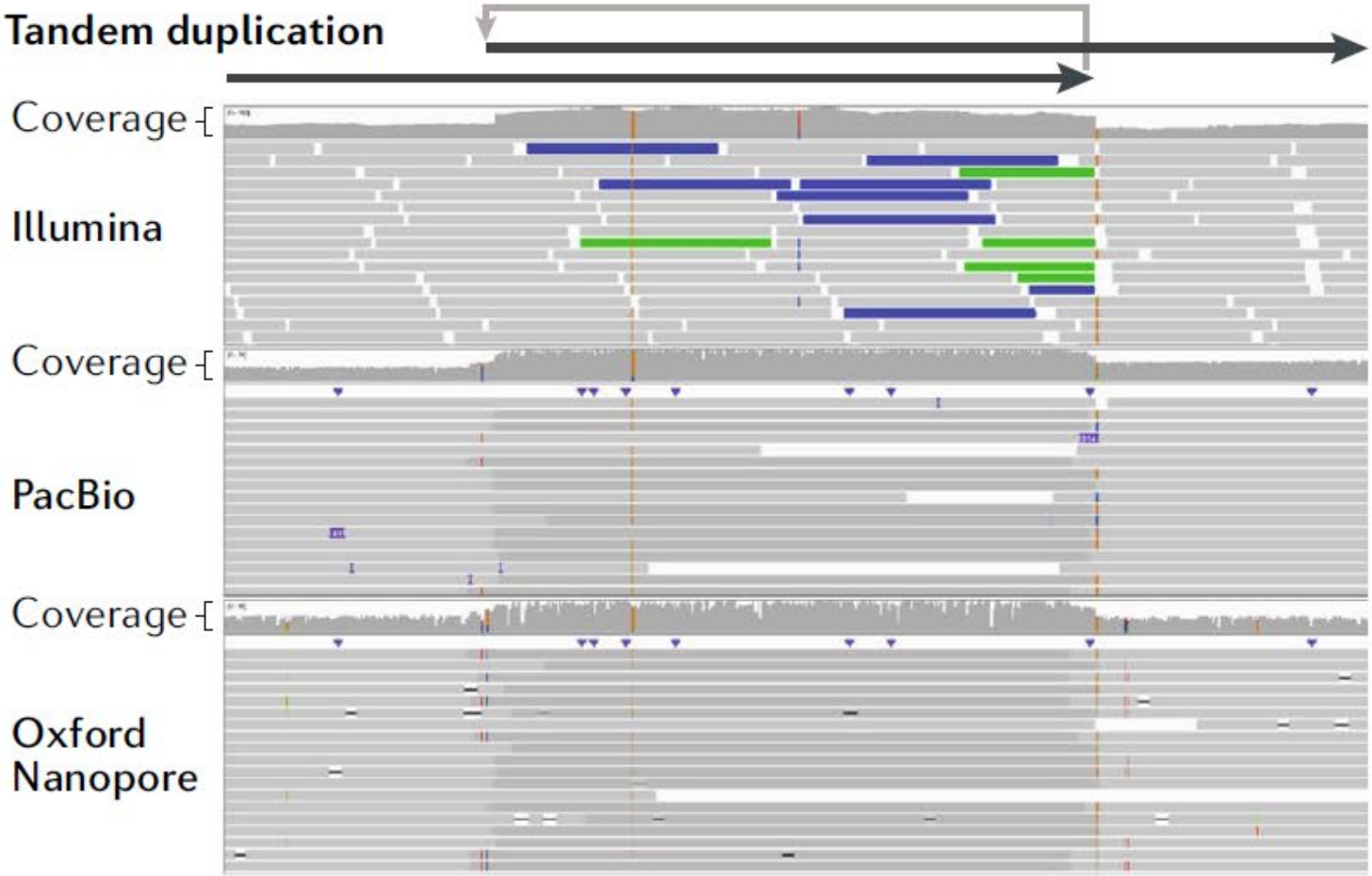
Peona et al. 2018, *Mol. Ecol. Res.*

SV mapping with longer and longer reads



Sedlazeck et al. 2018 *Nat. Rev. Genet.*

What does coverage variation tell us?

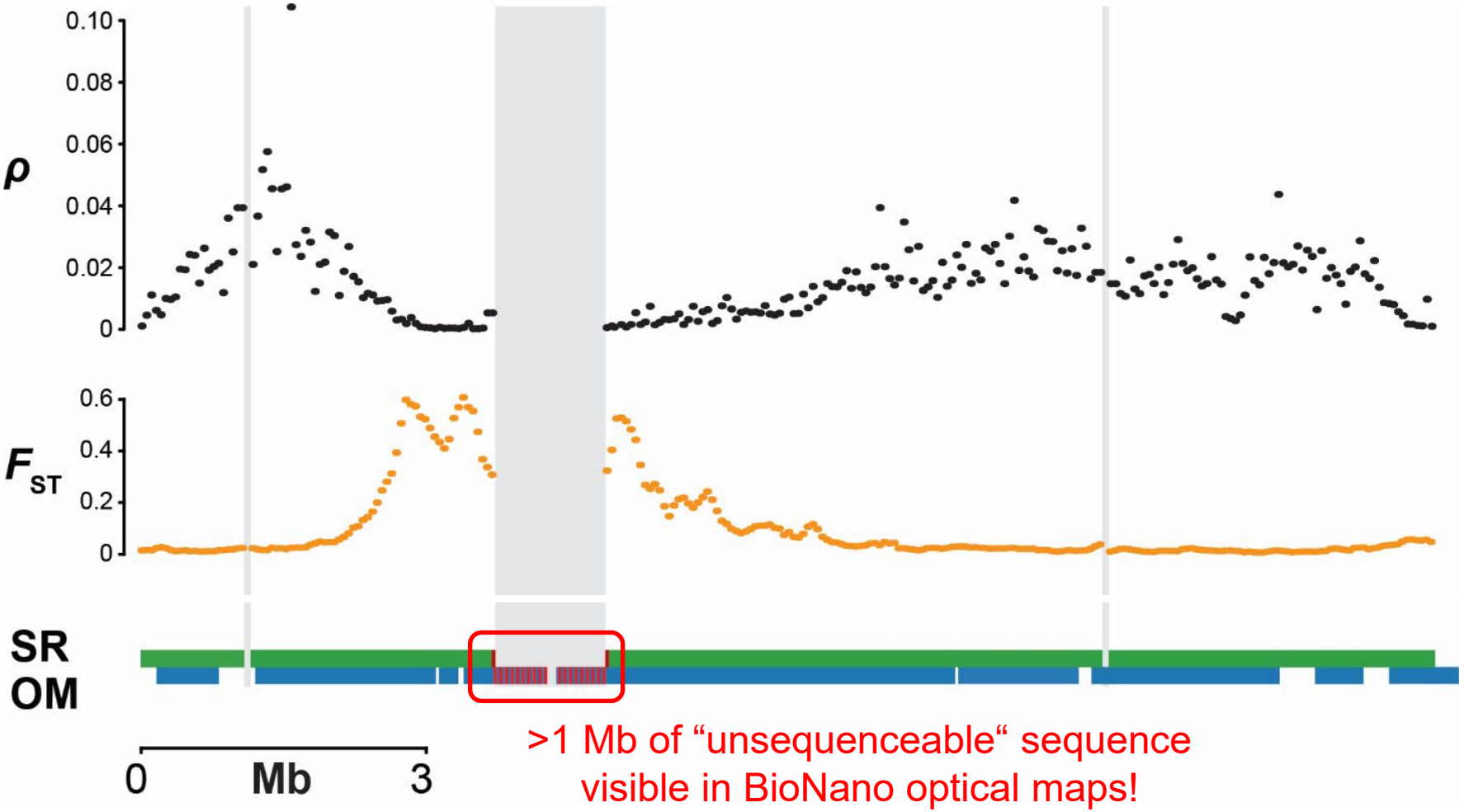


Tandem duplications are (usually) collapsed in assemblies!

Sedlazeck et al. 2018 *Nat. Rev. Genet.*

Not all gaps are equal

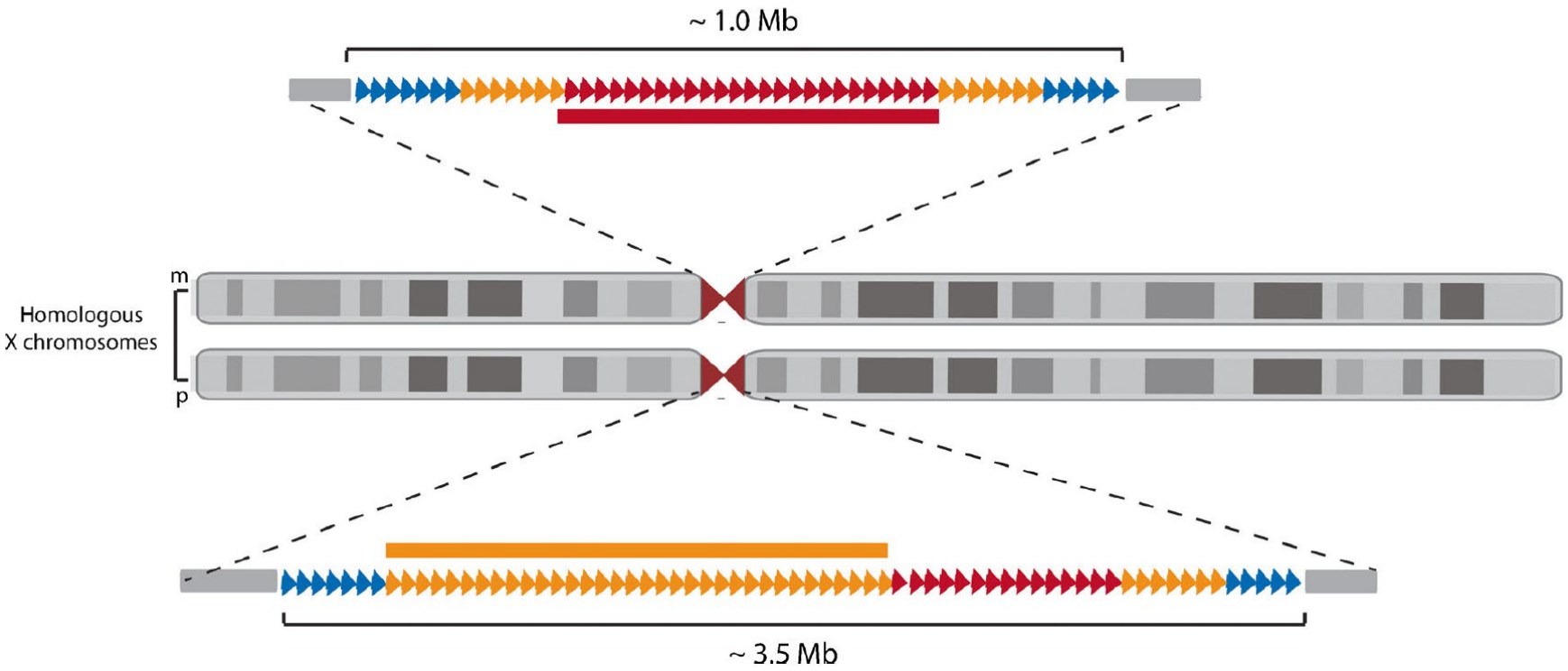
Chromosome 18 of hooded/carrion crow



>1 Mb of “unsequenceable“ sequence visible in BioNano optical maps!

Weissensteiner et al. 2017, *Genome Res.*

Centromeres are very, very repetitive



Rule of thumb: centromeres are not *in* assemblies but in gaps within or between scaffolds!

Miga 2015, *Chromosome Res.*

Questions?

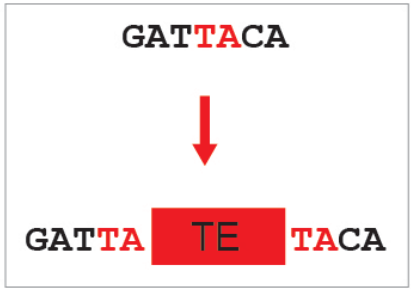
Coffee break (10 minutes)

Task: Form random groups of 3 and discuss what resources (assembly quality, gene/repeat annotation) there are for your respective study system.

Part 2: Frustration

B) Biology and more concepts

Transposable elements are very diverse



Classification		Structure	TSD	Code	Occurrence
Order	**Superfamily**				
Class I (retrotransposons)					
LTR	*Copia*	GAG AP INT RT RH	4–6	RLC	P, M, F, O
	Gypsy	GAG AP RT RH INT	4–6	RLG	P, M, F, O
	Bel–Pao	GAG AP RT RH INT	4–6	RLB	M
	Retrovirus	GAG AP RT RH INT ENV	4–6	RLR	M
	ERV	GAG AP RT RH INT ENV	4–6	RLE	M
DIRS	*DIRS*	GAG AP RT RH YR	0	RYD	P, M, F, O
	Ngaro	GAG AP RT RH YR	0	RYN	M, F
	VIPER	GAG AP RT RH YR	0	RYV	O
PLE	*Penelope*	RT EN	Variable	RPP	P, M, F, O
LINE	*R2*	RT EN	Variable	RIR	M
	RTE	APE RT	Variable	RIT	M
	Jockey	ORF1 APE RT	Variable	RIJ	M
	L1	ORF1 APE RT	Variable	RIL	P, M, F, O
	I	ORF1 APE RT RH	Variable	RII	P, M, F
SINE	*tRNA*		Variable	RST	P, M, F
	7SL		Variable	RSL	P, M, F
	5S		Variable	RSS	M, O
Class II (DNA transposons) - Subclass 1					
TIR	*Tc1–Mariner*	Tase*	TA	DTT	P, M, F, O
	hAT	Tase*	8	DTA	P, M, F, O
	Mutator	Tase*	9–11	DTM	P, M, F, O
	Merlin	Tase*	8–9	DTE	M, O
	Transib	Tase*	5	DTR	M, F
	P	Tase	8	DTP	P, M
	PiggyBac	Tase	TTAA	DTB	M, O
	PIF–Harbinger	Tase* ORF2	3	DTH	P, M, F, O
	CACTA	Tase ORF2	2–3	DTC	P, M, F
Crypton	*Crypton*	YR	0	DYC	F
Class II (DNA transposons) - Subclass 2					
Helitron	*Helitron*	RPA Y2 HEL	0	DHH	P, M, F
Maverick	*Maverick*	C-INT ATP CYP POL B	6	DMM	M, F, O

Structural features

Long terminal repeats; Terminal inverted repeats; Coding region; Non-coding region; Diagnostic feature in non-coding region; Region that can contain one or more additional ORFs

Protein coding domains

AP, Aspartic proteinase; APE, Apurinic endonuclease; ATP, Packaging ATPase; C-INT, C-integrase; CYP, Cysteine protease; EN, Endonuclease; ENV, Envelope protein; GAG, Capsid protein; HEL, Helicase; INT, Integrase; ORF, Open reading frame of unknown function; POL B, DNA polymerase B; RH, RNase H; RPA, Replication protein A (found only in plants); RT, Reverse transcriptase; Tase, Transposase (* with DDE motif); YR, Tyrosine recombinase; Y2, YR with YY motif

Species groups

P, Plants; M, Metazoans; F, Fungi; O, Others

Nature Reviews | Genetics

Wicker et al. 2008, *Nat. Rev. Genet.*

Today's focus: LINE, SINE, LTR, TIR

Weirder TEs in Suh 2021 TE lecture 1

Class I: LINE retrotransposons

Classification		Structure	TSD	Code	Occurrence
Order	Superfamily				
Class I (retrotransposons)					
PLE	*Penelope*	RT EN	Variable	RPP	P, M, F, O
LINE	*R2*	RT EN	Variable	RIR	M
	RTE	APE RT	Variable	RIT	M
	Jockey	ORF1 APE RT	Variable	RIJ	M
	L1	ORF1 APE RT	Variable	RIL	P, M, F, O
	I	ORF1 APE RT RH	Variable	RII	P, M, F

Dear RNA polymerase II,

if you read this,
transcribe me
into RNA

Dear ribosome,

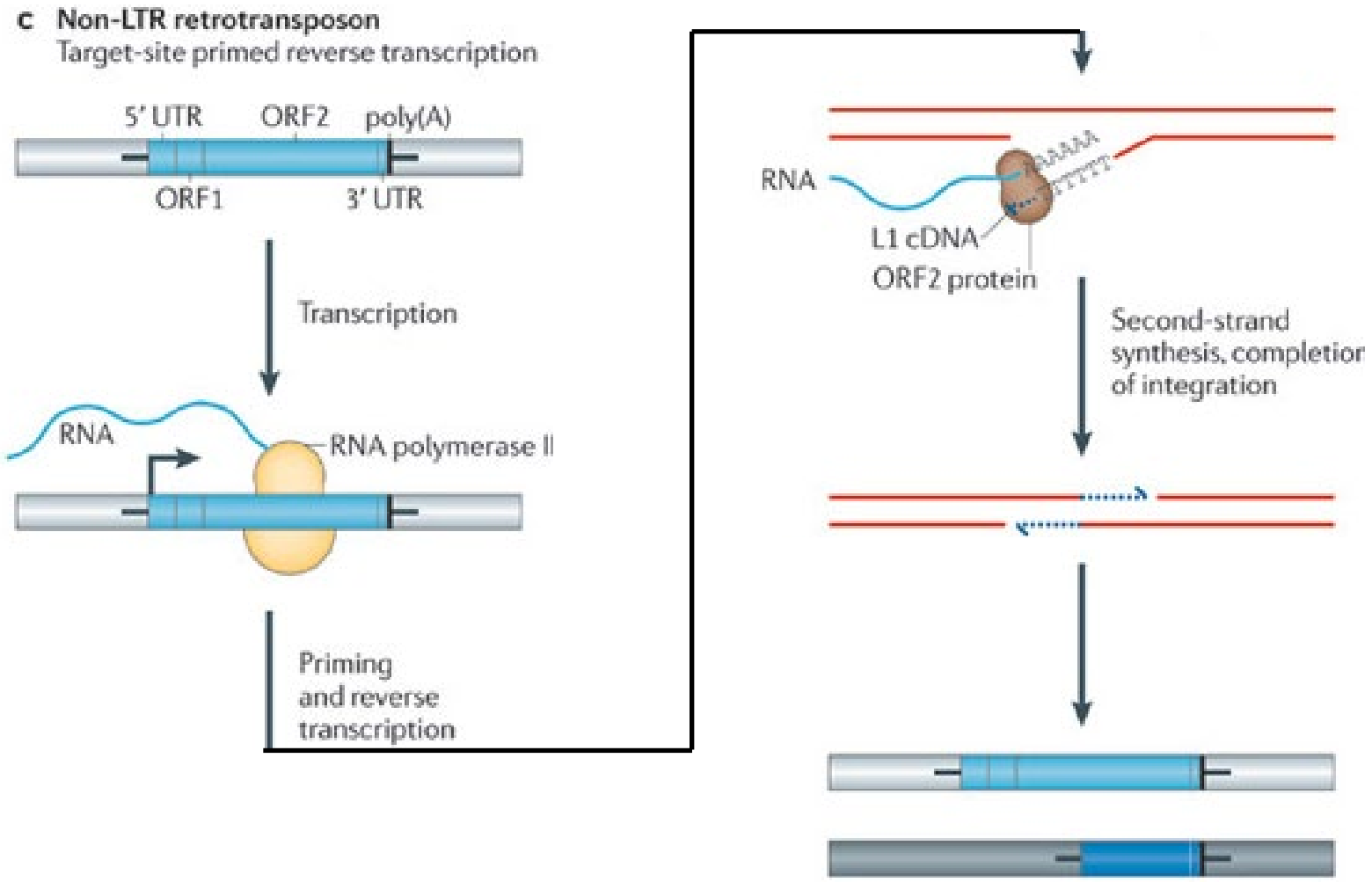
if you read this,
translate me into a
reverse transcriptase

Dear reverse transcriptase,

if you read this,
retropose me somewhere
in the genome

Wicker et al. 2008, *Nat. Rev. Genet.*

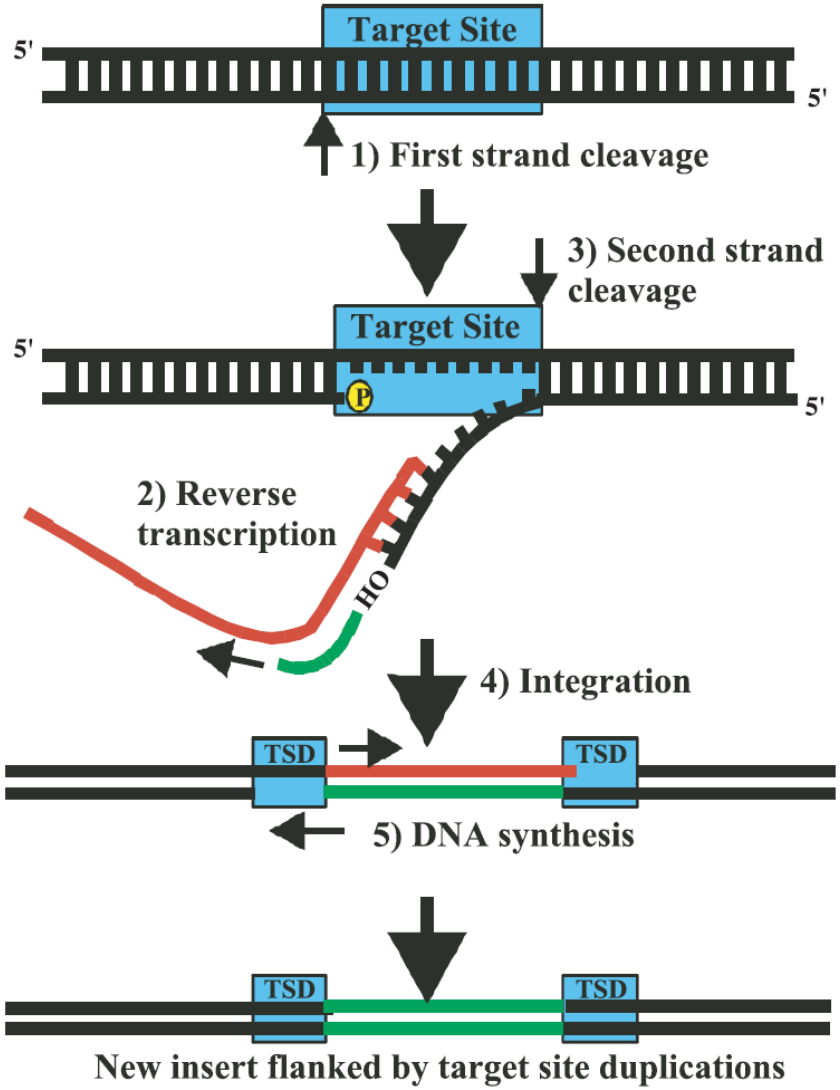
Target-primed reverse transcription (TPRT)



TPRT frequently undergoes premature termination (5‘ truncation)

Levin & Moran 2011, *Nat. Rev. Genet.*

Target site duplication (TSD)



TSDs are a hallmark of nearly all (retro)transposition mechanisms!

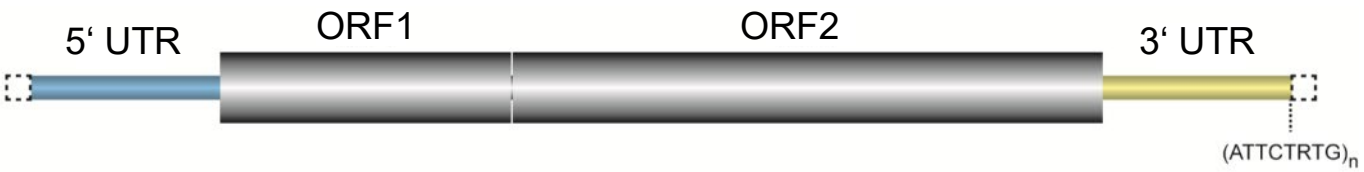
Kazazian 2004, *Science*

Class I: SINE retrotransposons

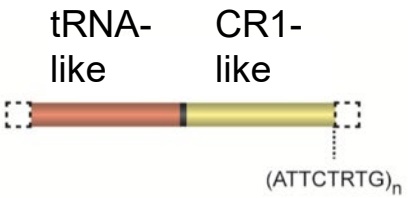
Classification		Structure	TSD	Code	Occurrence
Order	Superfamily				
Class I (retrotransposons)					
SINE	*tRNA*		Variable	RST	P, M, F
	7SL		Variable	RSL	P, M, F
	5S		Variable	RSS	M, O

SINEs are parasites of LINEs! *Trans*-mobilization via LINE enzymes.

CR1



TguSINE1



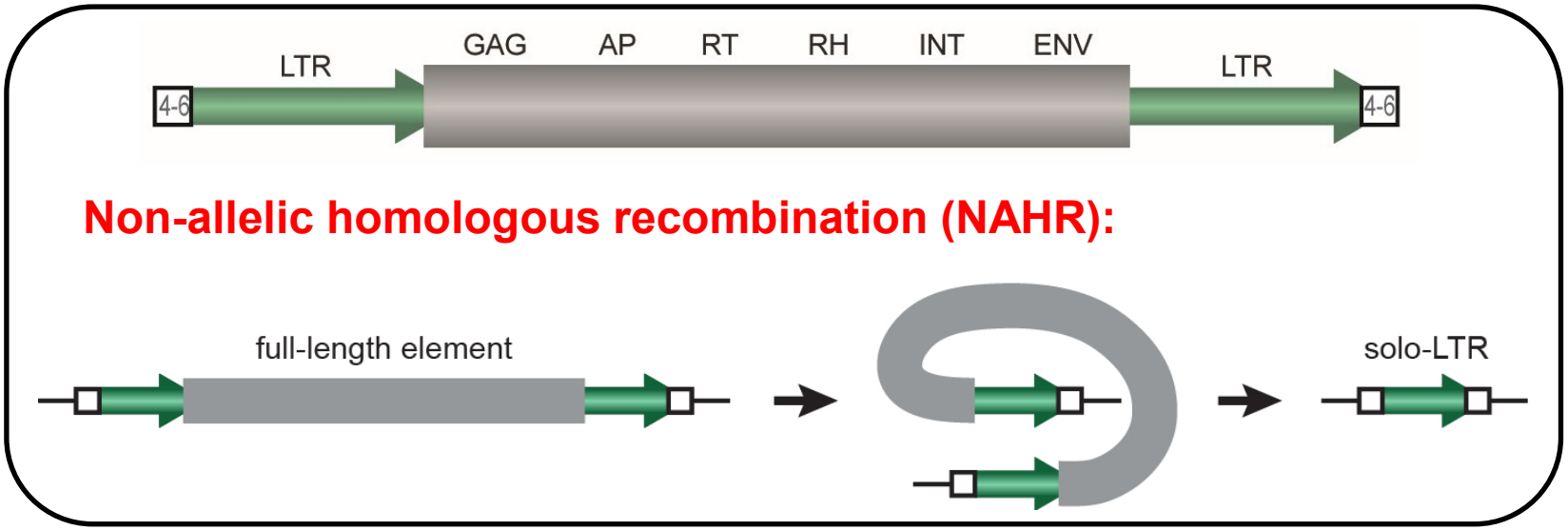
SINEs contain RNA polymerase III promoters, i.e., technically they are selfish small RNAs!

Note: In theory, any small RNA gene (pol III) can become a SINE!

Wicker et al. 2008, *Nat. Rev. Genet.*

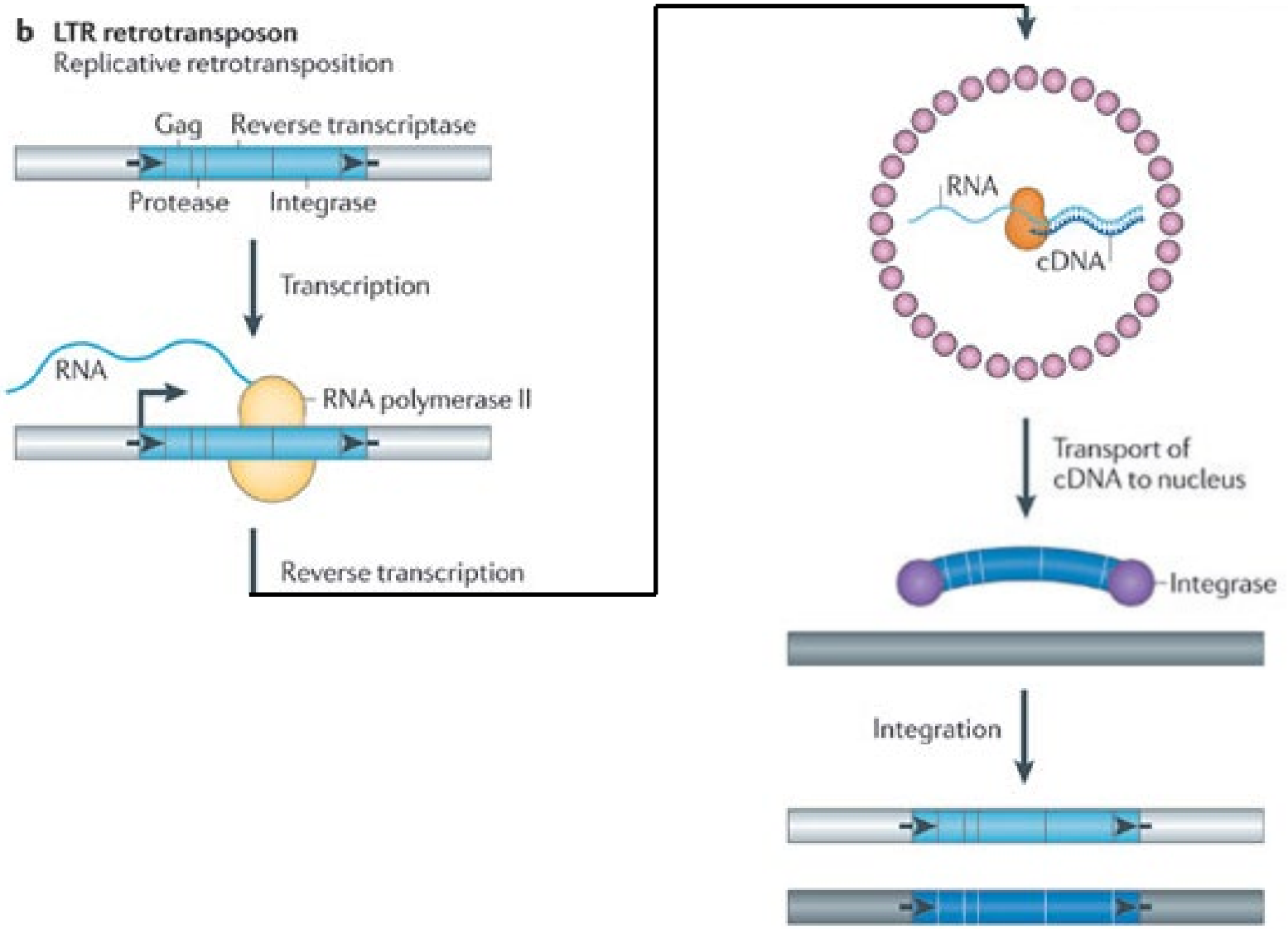
Class I: LTR retrotransposons

Classification		Structure	TSD	Code	Occurrence
Order	Superfamily				
Class I (retrotransposons)					
LTR	*Copia*	GAG AP INT RT RH	4–6	RLC	P, M, F, O
	Gypsy	GAG AP RT RH INT	4–6	RLG	P, M, F, O
	Bel–Pao	GAG AP RT RH INT	4–6	RLB	M
	Retrovirus	GAG AP RT RH INT ENV	4–6	RLR	M
	ERV	GAG AP RT RH INT ENV	4–6	RLE	M
DIRS	*DIRS*	GAG AP RT RH YR	0	RYD	P, M, F, O
	Ngaro	GAG AP RT RH YR	0	RYN	M, F
	VIPER	GAG AP RT RH YR	0	RYV	O



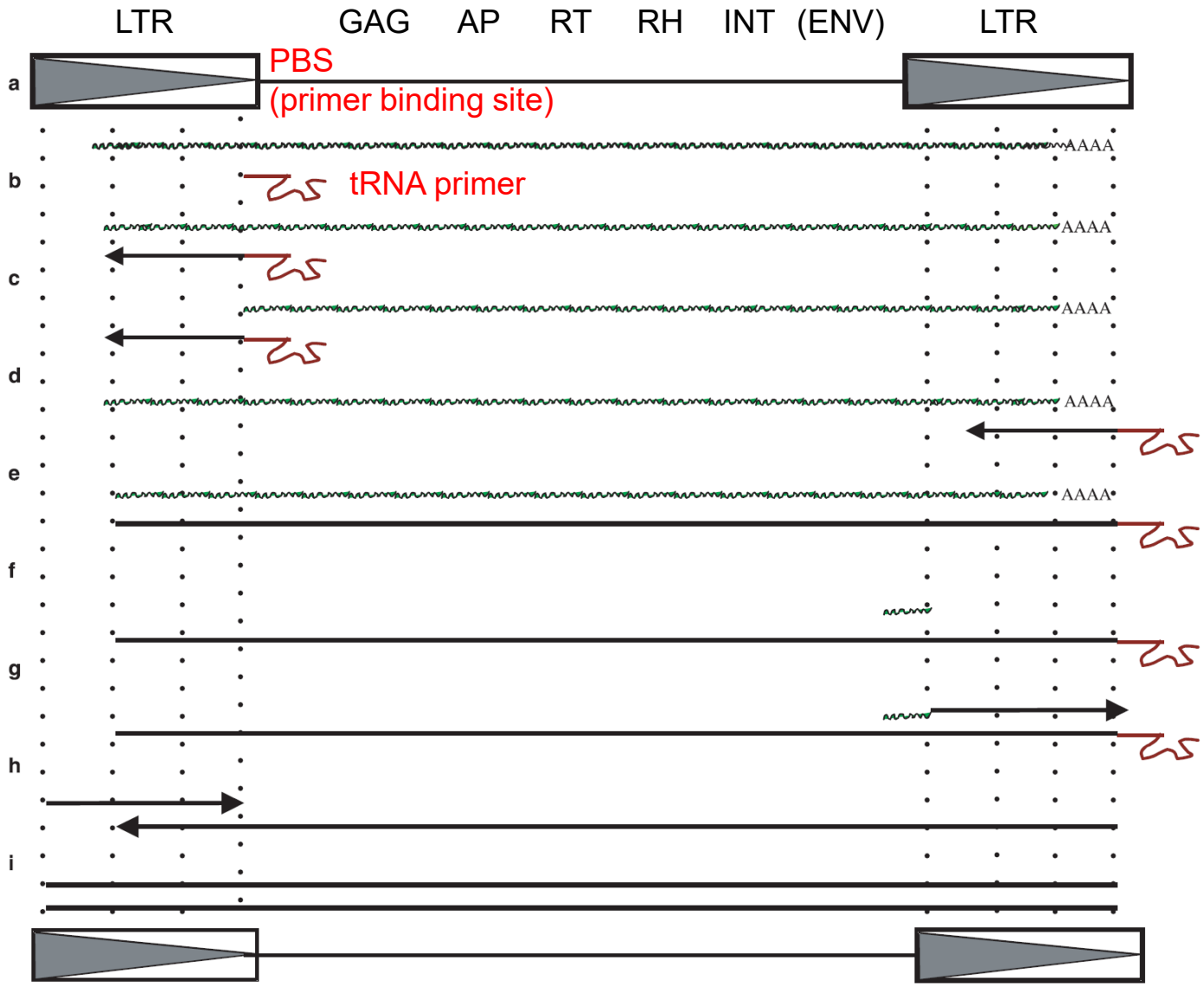
Wicker et al. 2008, *Nat. Rev. Genet.*

Replicative retrotransposition



Levin & Moran 2011, *Nat. Rev. Genet.*

Why LTR retrotransposons have LTRs



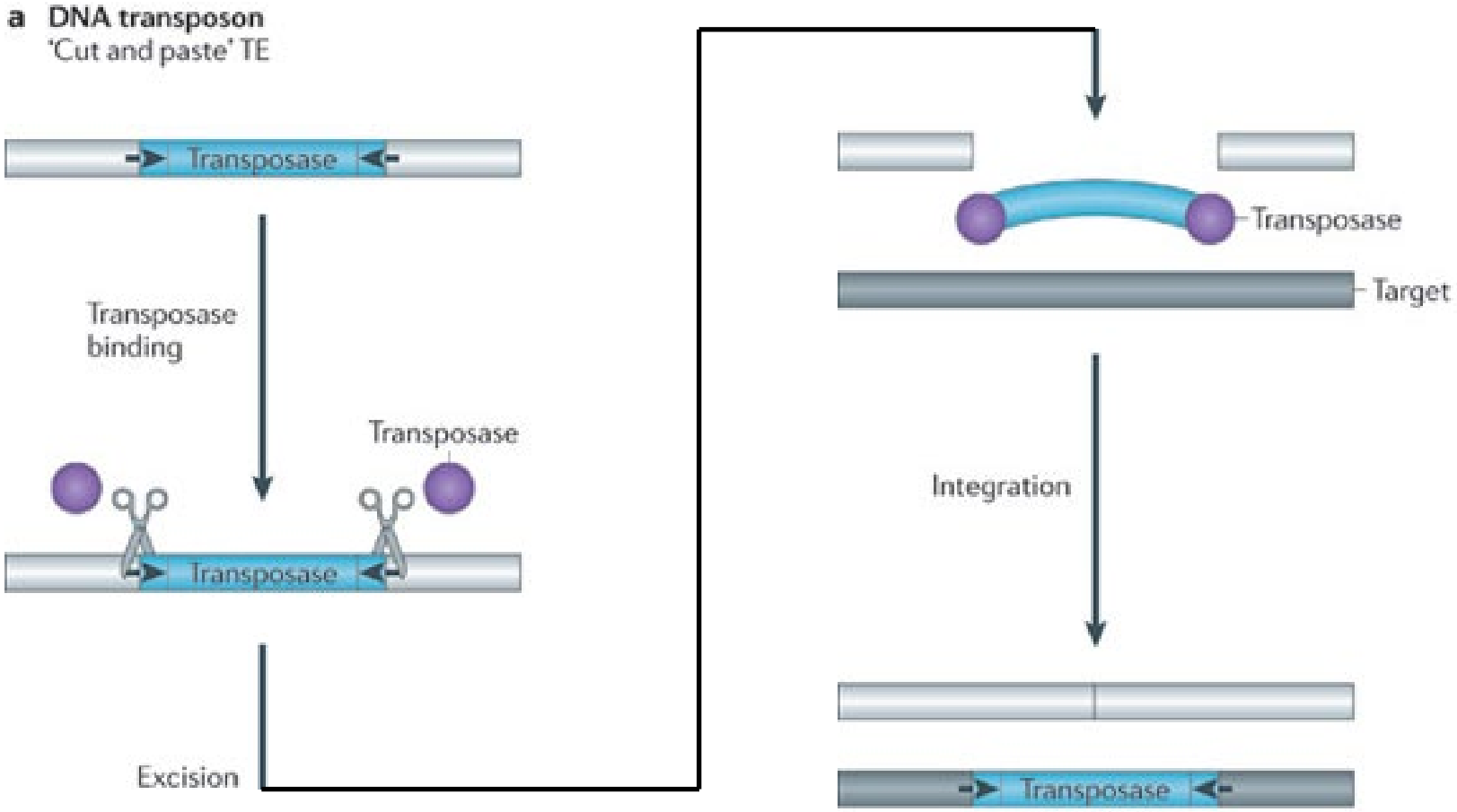
Kazazian 2004, *Science*

Class II: DNA transposons

Classification		Structure	TSD	Code	Occurrence
Order	Superfamily				
Class II (DNA transposons) - Subclass 1					
TIR	*Tc1–Mariner*	Tase*	TA	DTT	P, M, F, O
	hAT	Tase*	8	DTA	P, M, F, O
	Mutator	Tase*	9–11	DTM	P, M, F, O
	Merlin	Tase*	8–9	DTE	M, O
	Transib	Tase*	5	DTR	M, F
	P	Tase	8	DTP	P, M
	PiggyBac	Tase	TTAA	DTB	M, O
	PIF–Harbinger	Tase* ORF2	3	DTH	P, M, F, O
	CACTA	Tase ORF2	2–3	DTC	P, M, F
Crypton	*Crypton*	YR	0	DYC	F

Wicker et al. 2008, *Nat. Rev. Genet.*

Cut-and-paste transposition (TIR)



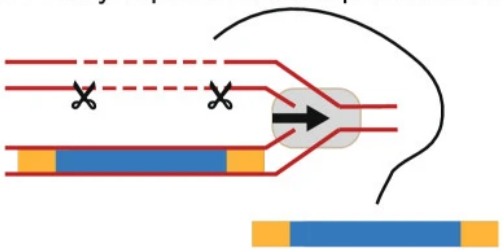
Mobile DNA

Levin & Moran 2011, *Nat. Rev. Genet.*

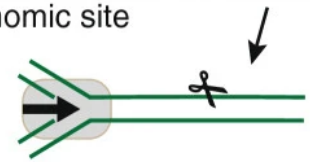
How to increase in copy number?

I. DNA replication fork passes transposon

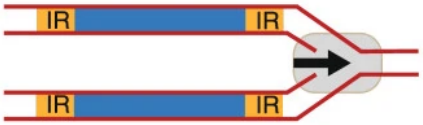
II. Newly replicated transposon is cut out...



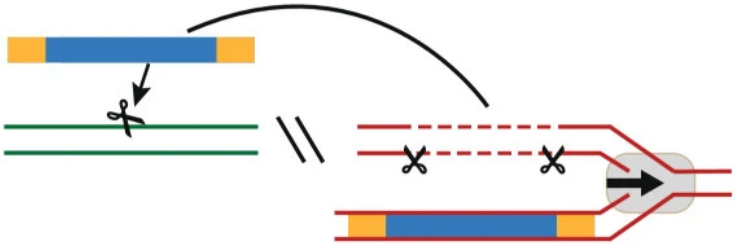
III. ...and inserted into a not-yet replicated genomic site



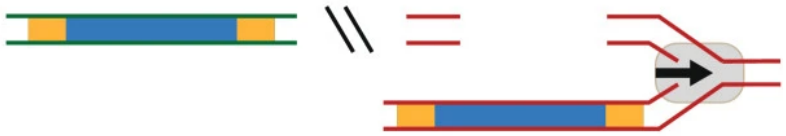
IIII. DNA replication fork passes insertion site



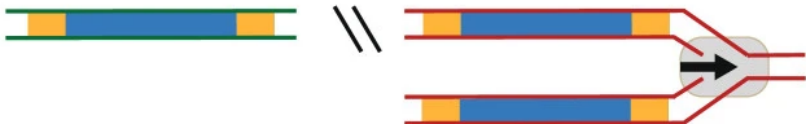
I. Newly replicated transposon is cut out...



II. ...and transposed into a new locus



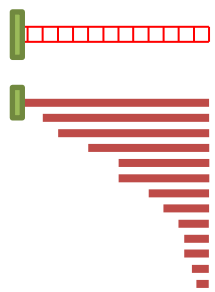
III. Following transposition, the double-stranded break is repaired by homology-dependent DNA repair



Skipper et al. 2013, *J. Biomed. Sci.*

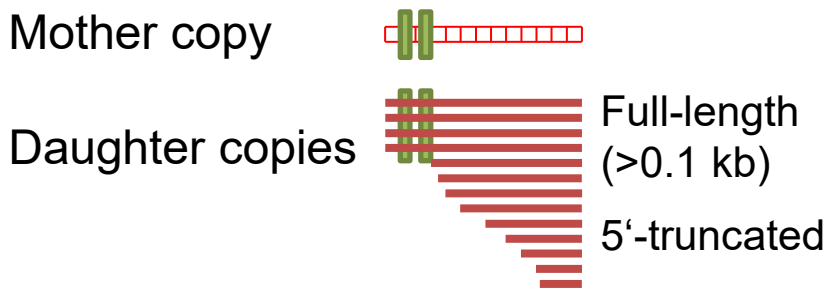
TE ≠ TE

LINE



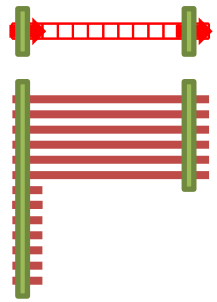
5‘ truncation during insertion

SINE



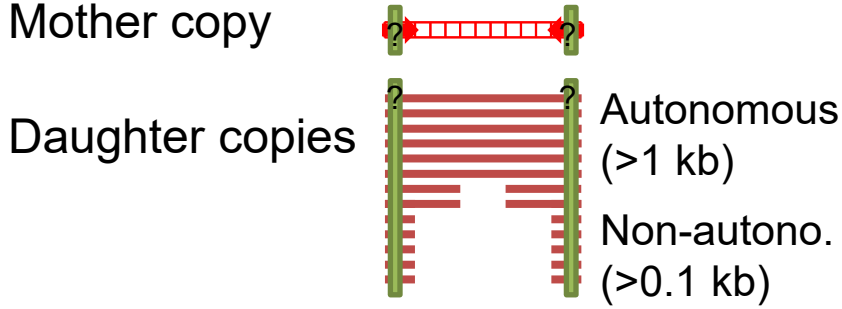
5‘ truncation during insertion

LTR



NAHR after insertion

TIR

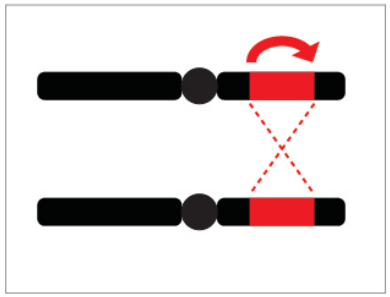


Deletion after insertion

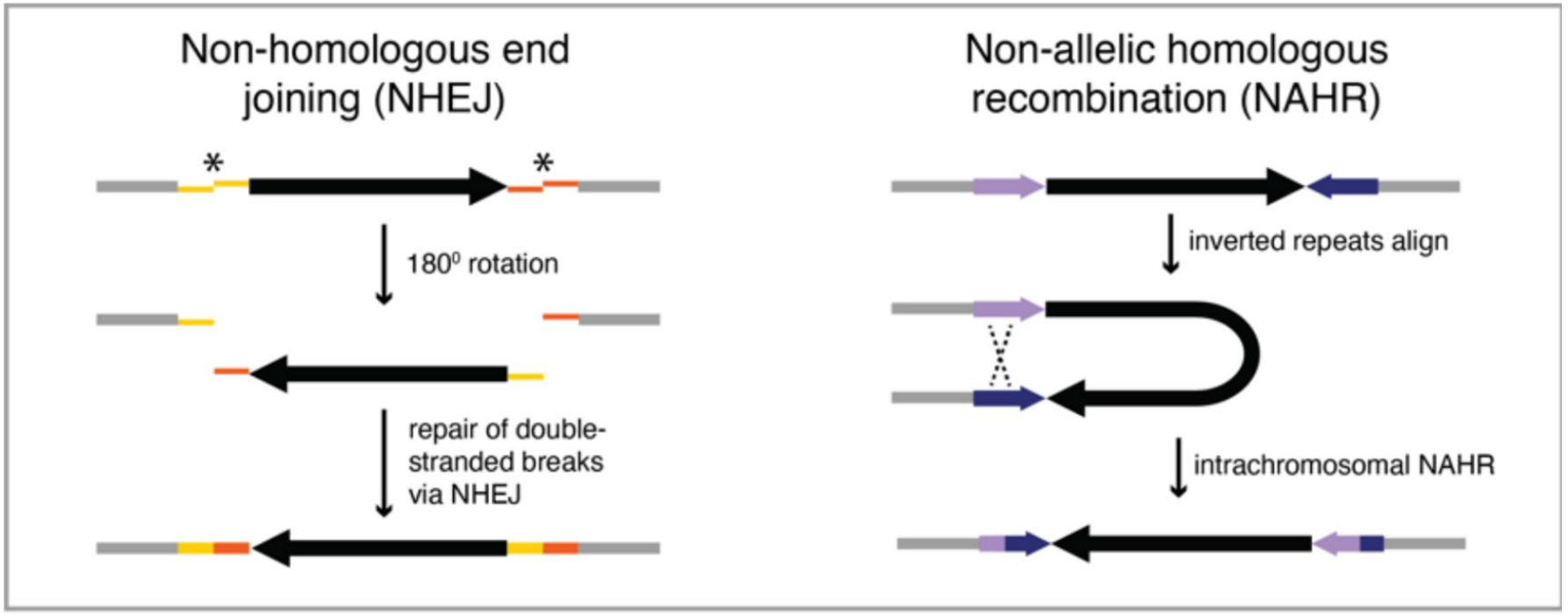
Some TE copies contain regulatory elements, some don‘t.

More context in Suh 2021 TE lecture 2

Inversion formation



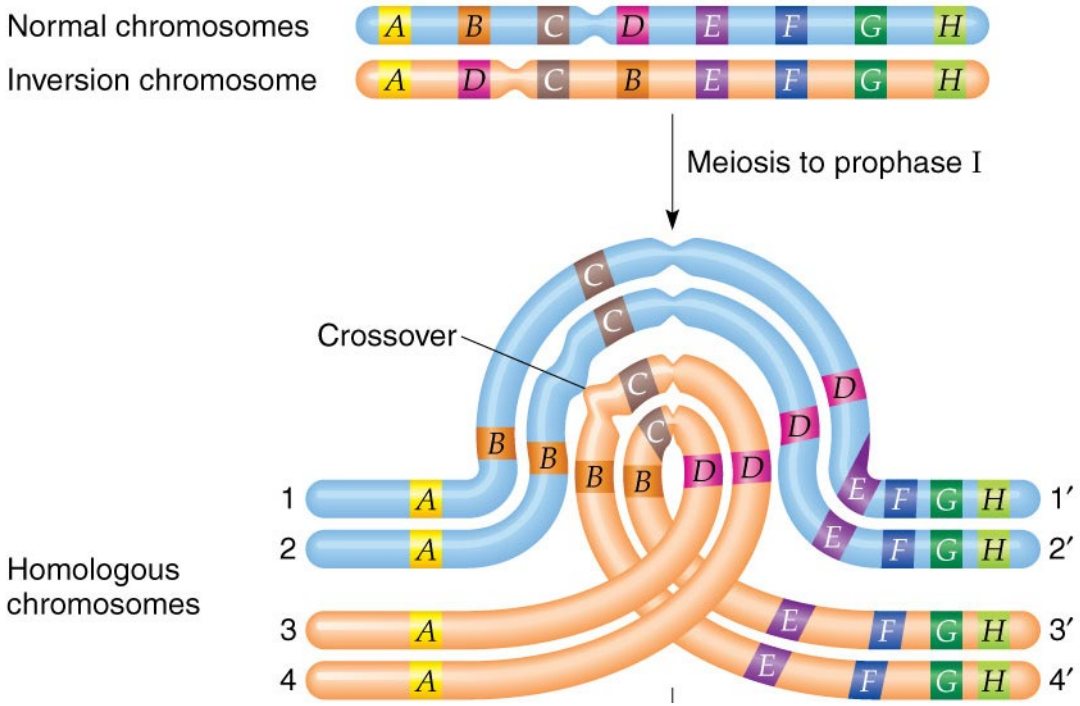
"*We found that inversion breakpoints frequently occur in centromeric and telomeric regions and are often flanked by long inverted repeats (0.5-50 kb)*"



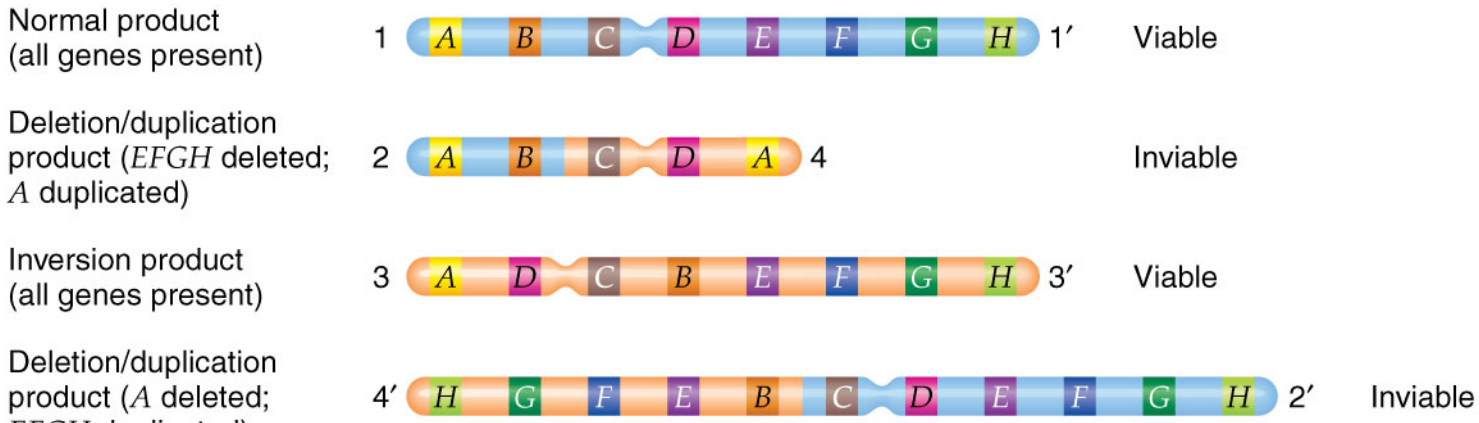
Assembling or mapping inversion breakpoints is difficult!

Harringmeyer & Hoekstra 2022, *bioRxiv*

Inversions reduce recombination

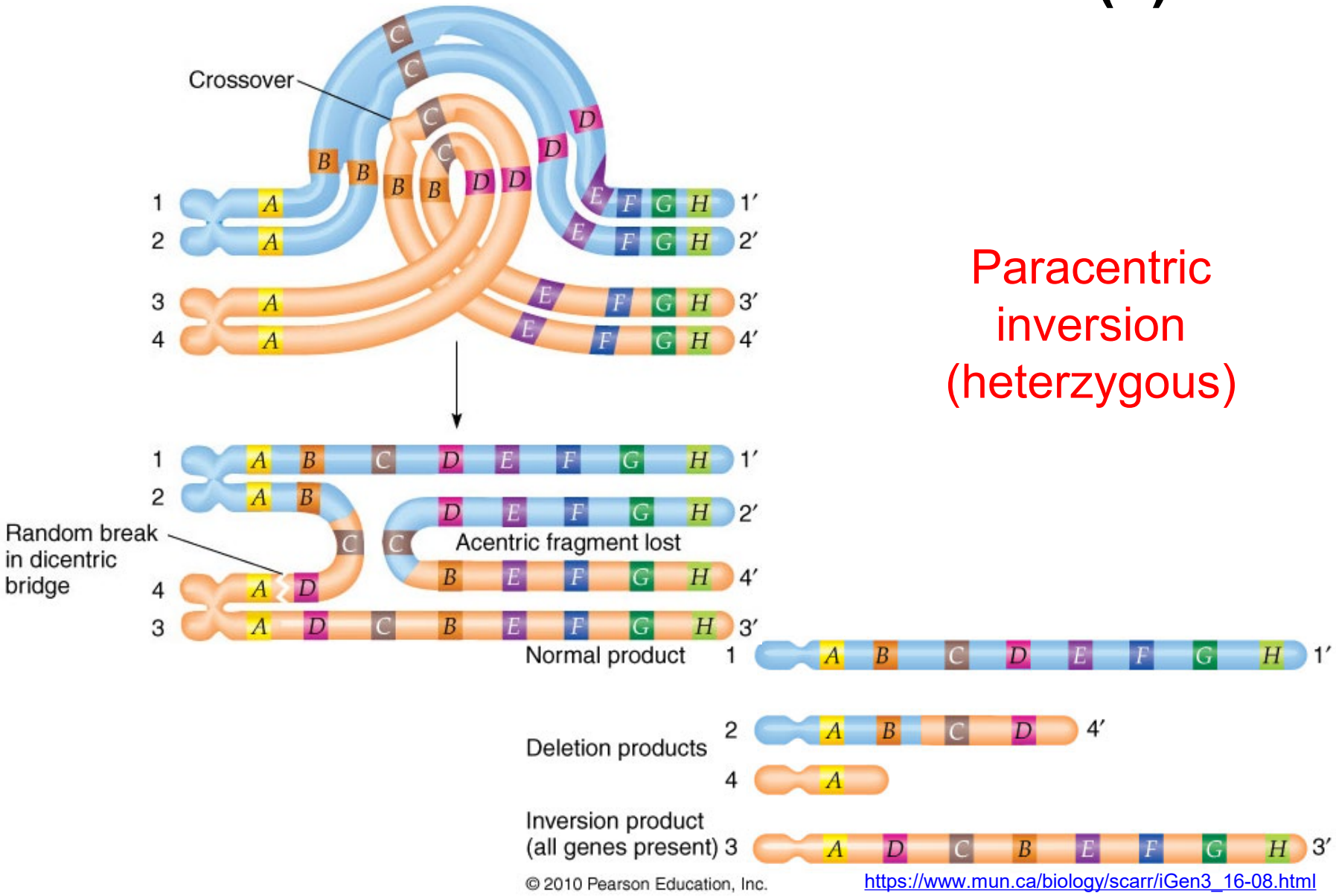


Pericentric inversion (heterzygous)



https://www.mun.ca/biology/scarr/iGen3_16-08.html

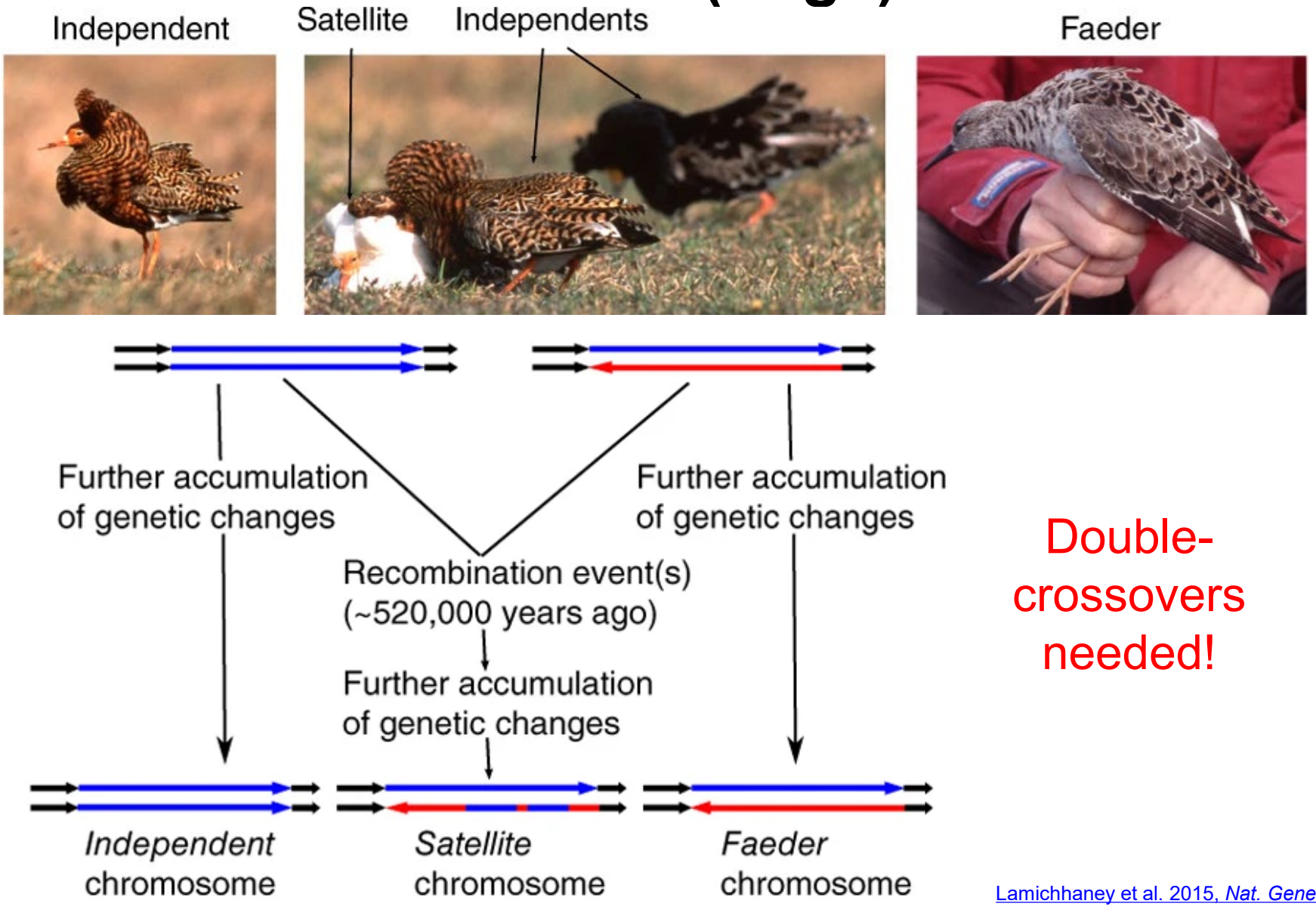
Inversions reduce recombination (2)



Paracentric inversion (heterzygous)

https://www.mun.ca/biology/scarr/iGen3_16-08.html

Rare recombination in (large) inversions

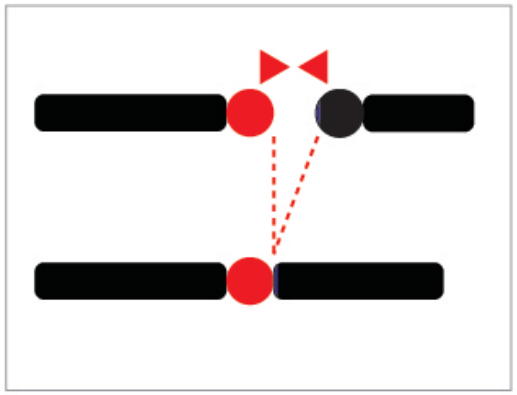


Double-crossovers needed!

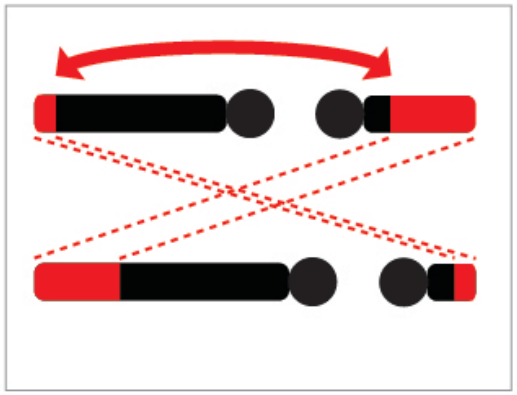
Lamichhaney et al. 2015, *Nat. Genet.*

More cases of NAHR

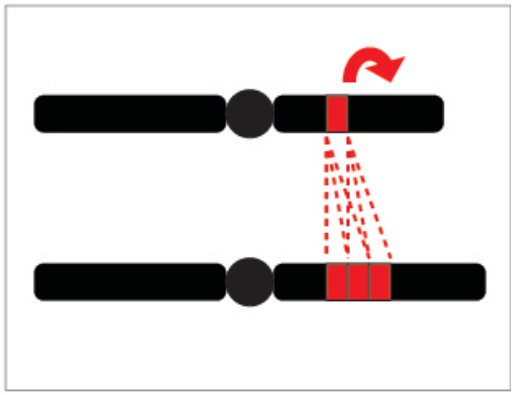
Fusion/fission



Translocation



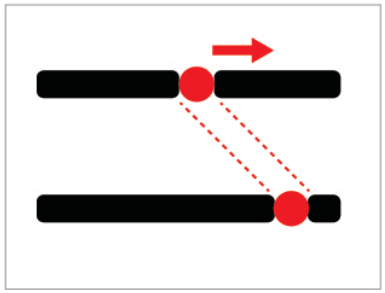
Duplication



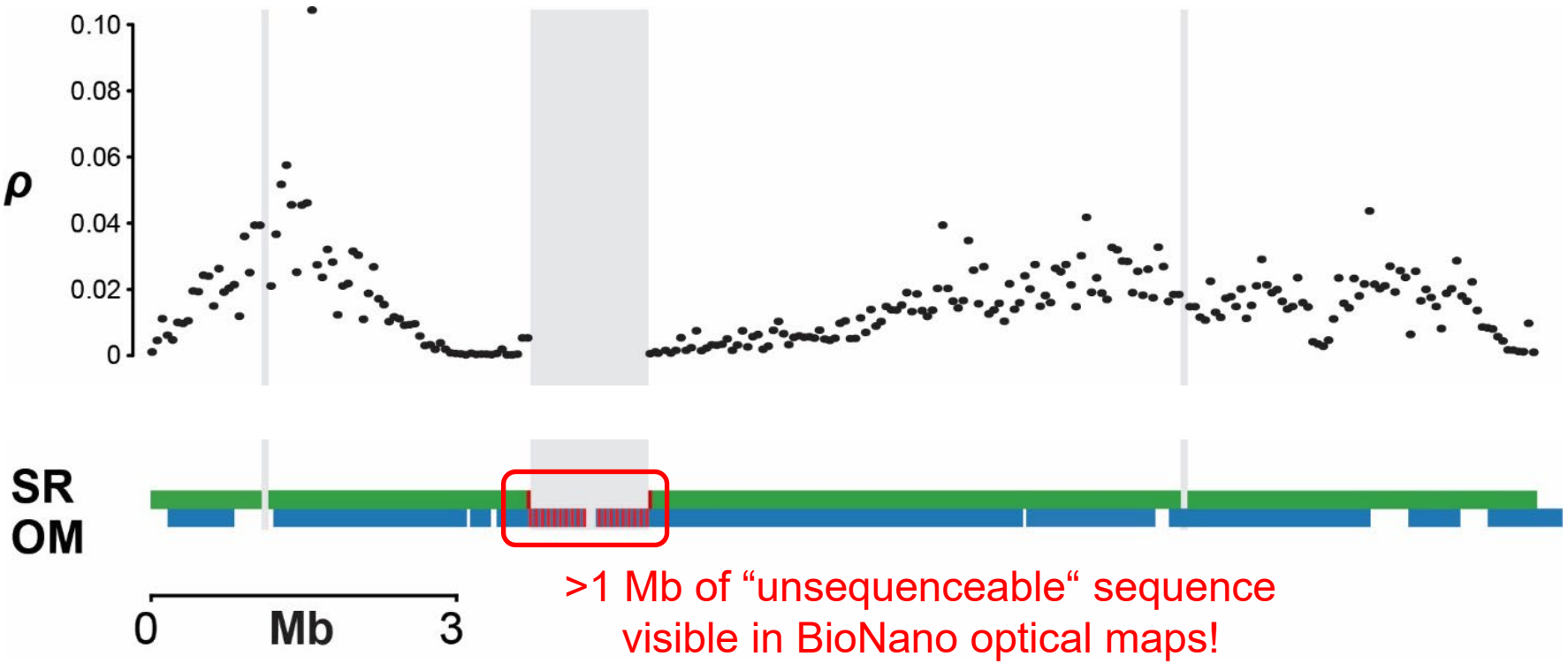
Fusions/fissions/translocations can decrease (new proximity to centromere) or increase (new proximity to telomere) recombination rates

Duplications can increase the chance of further non-allelic homologous recombination (NAHR)

Centromere shifts



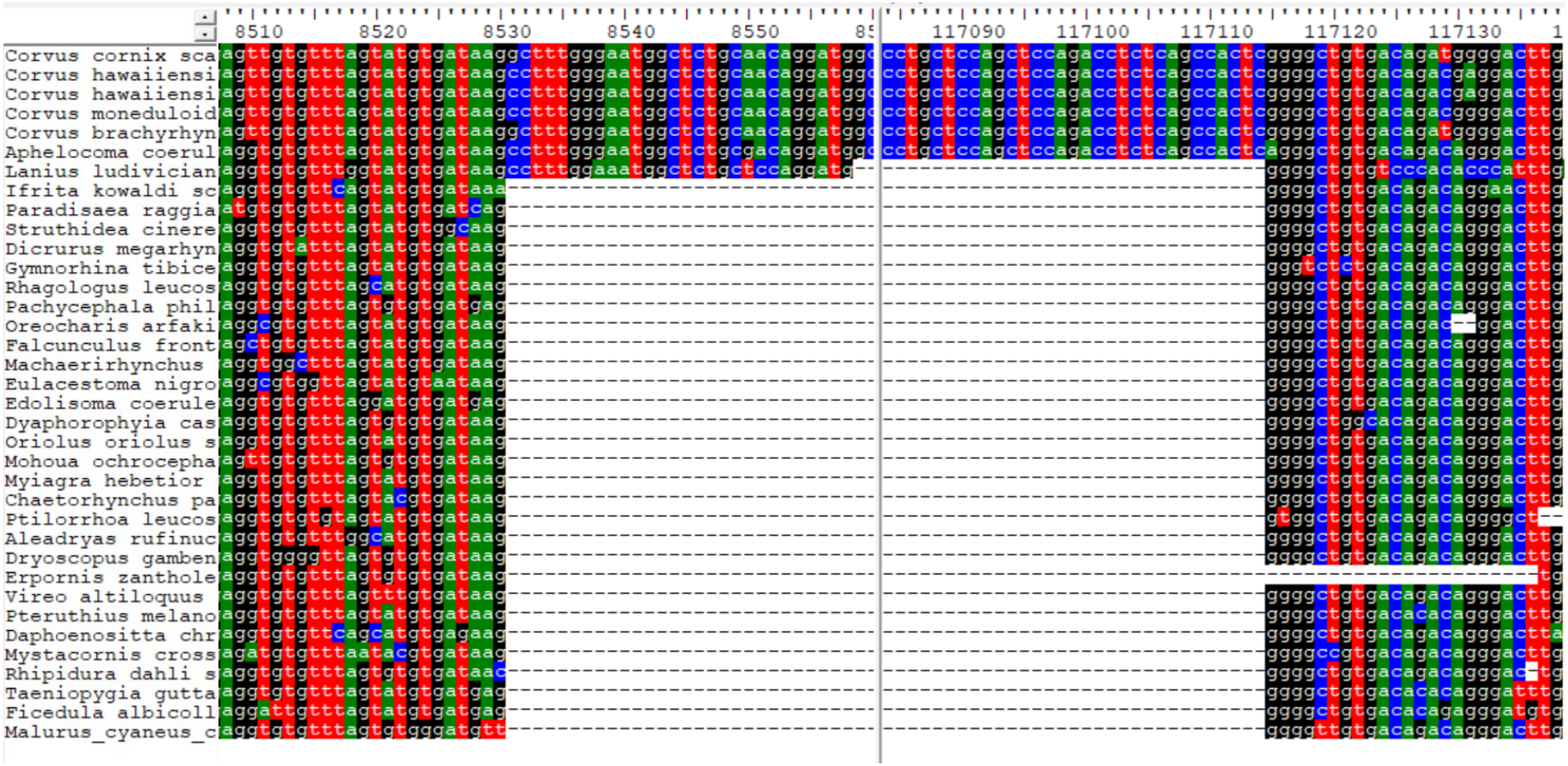
Chromosome 18 of hooded/carrion crow



>1 Mb of “unsequenceable“ sequence visible in BioNano optical maps!

Weissensteiner et al. 2017, *Genome Res.*

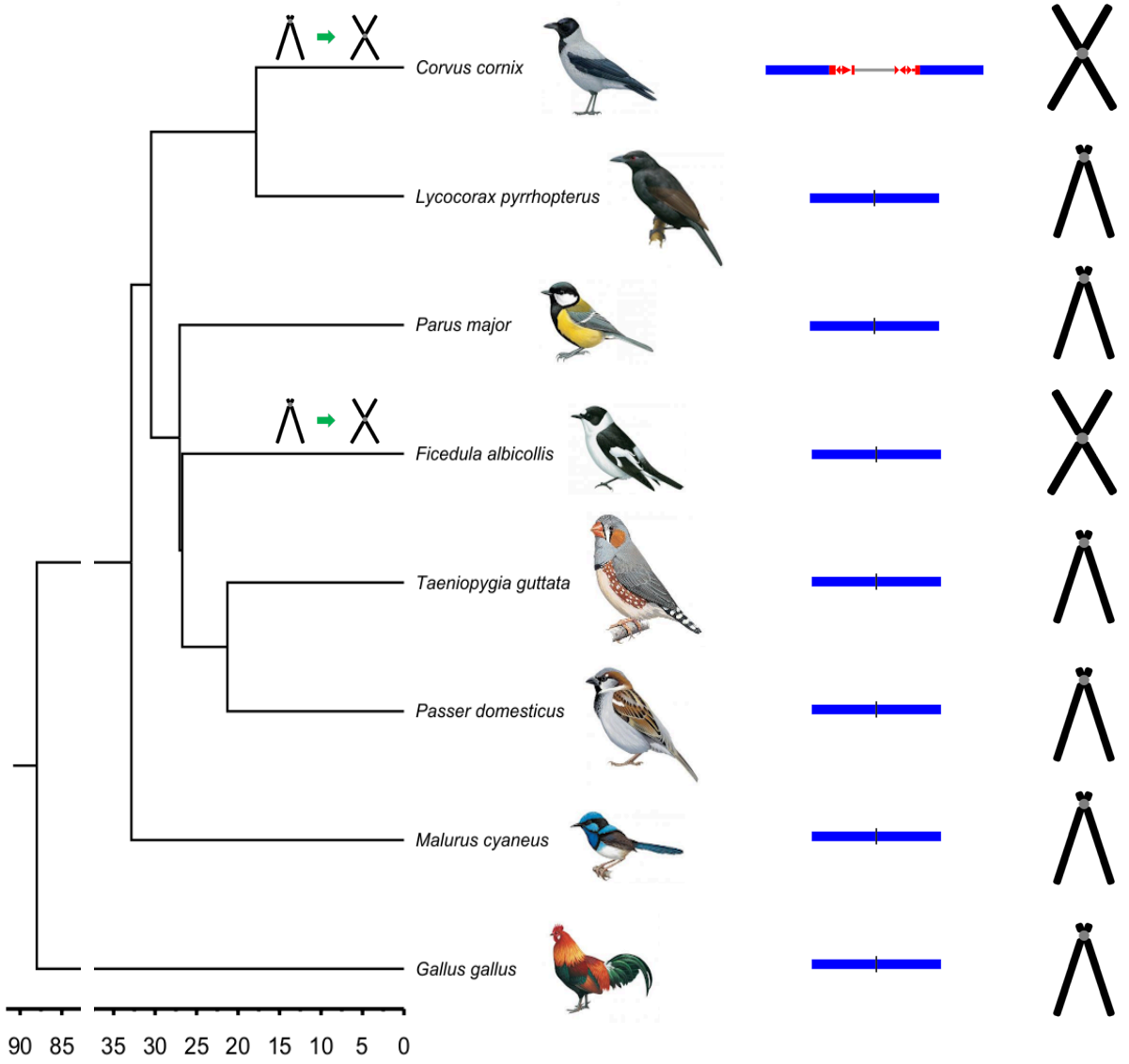
Centromere shifts across songbirds



>1 Mb satellite DNA array inserted in a formerly 5-kb intergenic region!

Westerberg et al., *in prep.*

Centromere shifts across songbirds



Metacentric

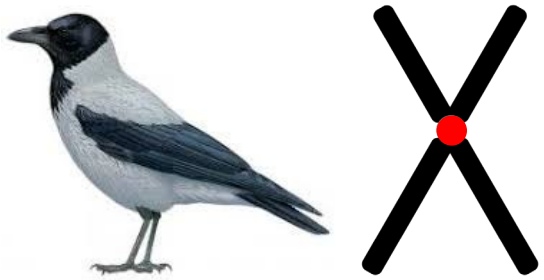
Metacentric

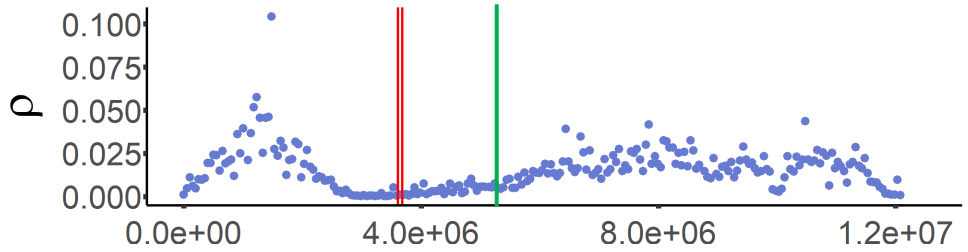
Acrocentric
(verified flanking sequences;
Knief & Forstmeier 2015)

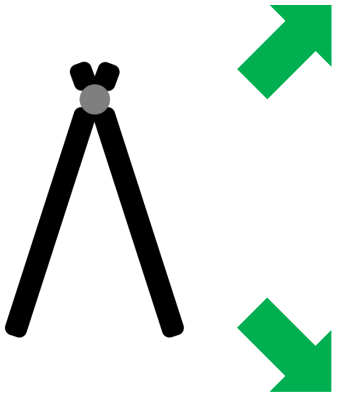
Acrocentric
(ChIP-seq of CENP-A;
Shang et al. 2010)

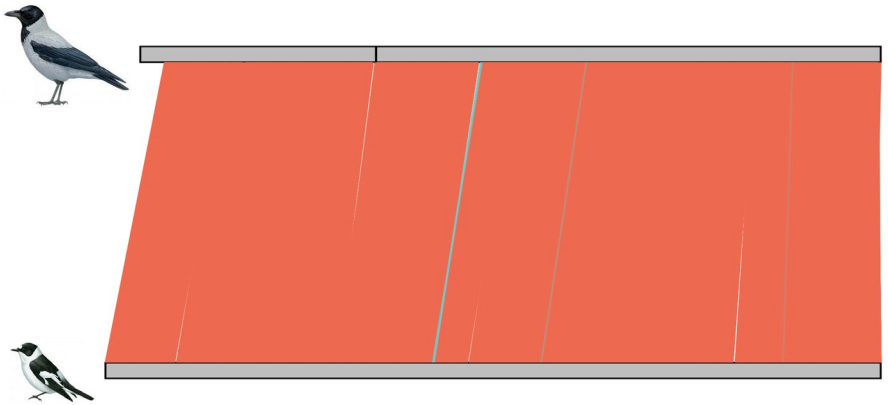
Westerberg et al., *in prep.*

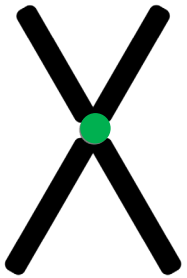
Not so stable chromosomes after all?

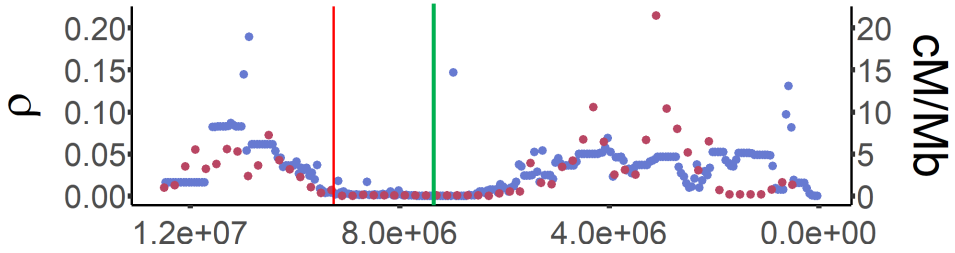












Westerberg et al., *in prep.*

Am I stuck in confirmation bias?

Centromere shifts: frequency independent recombination reduction (unlike inversions)

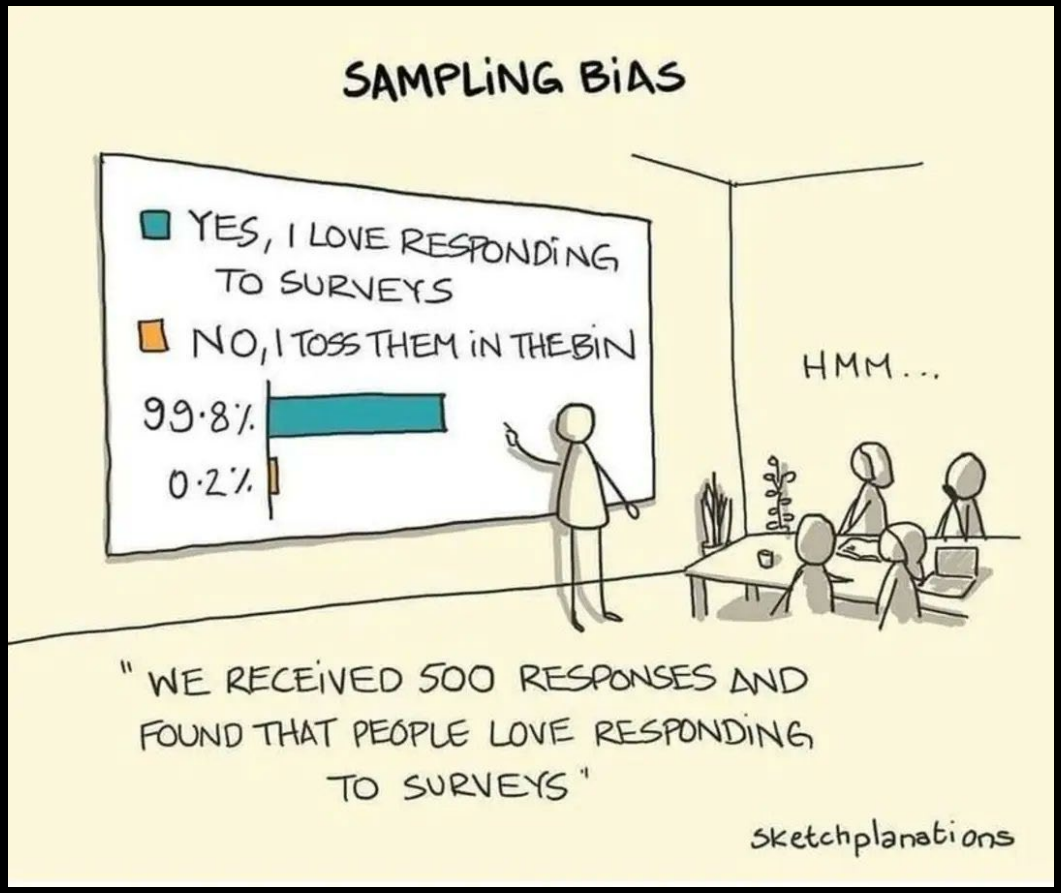
Have centromere shifts been proposed as alternatives to inversions in speciation literature?

Are some variants that were interpreted as inversions actually centromere shifts?

Can centromere shifts fix more frequently than inversions because of meiotic drive?

Talk to me or email me (alexander.suh@ebc.uu.se)
if you have references and/or criticism!
PS: Manuscript in preparation about this model.

Coffee break (20 minutes)



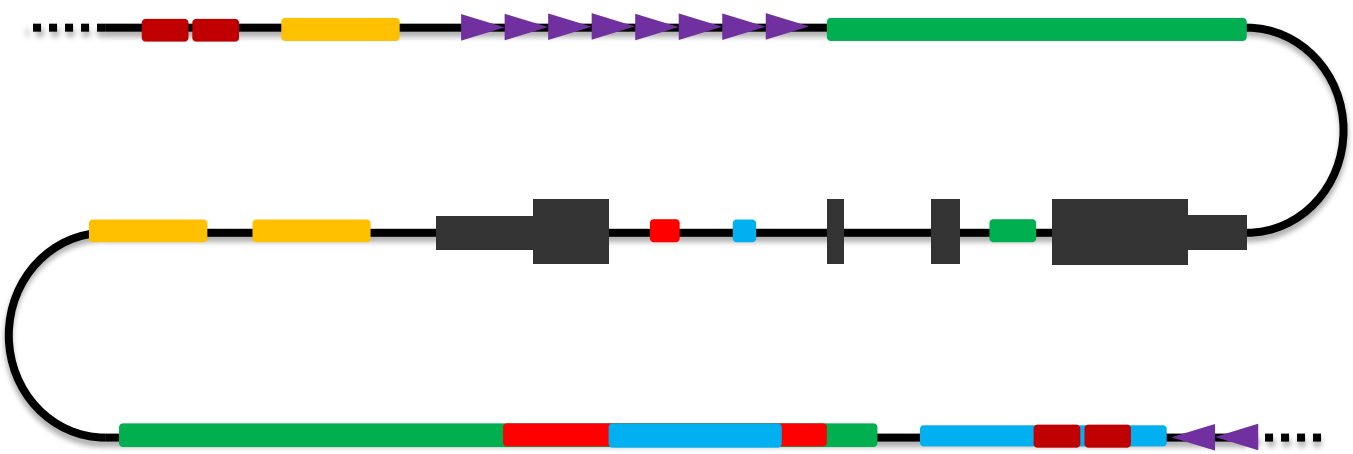
Task: Gather in same groups of 3 and discuss 1) what SVs you want to study, 2) what SVs you can study, and 3) what data you need to be less frustrated.

Part 3: Hope

How frustrated are you?

- What types of SVs do you want to study?
- What types of SVs can you study?
- What data do you need to be less frustrated?

Genomes: ecosystems of selfish genes



Interspersed repeats

- Retrotransposons
- DNA transposons
- Endogenous viruses

Tandem repeats

- Satellites
- Minisatellites
- Microsatellites

Biodiversity inside each genome!

Cellular organisms
Phylum
Class
Order
Family
Genus
Species
Individual

Transposable elements
Class
Subclass
Order
Superfamily
Family
Subfamily
Copy

More context in Suh 2021 TE lecture 3

Too much TE data, too few TEologists

Repetitive elements in the era of biodiversity genomics: insights from 600+ insect genomes

John S. Sproul, Scott Hotaling, Jacqueline Heckenhauer, Ashlyn Powell, Amanda M. Larracuente, Joanna L. Kelley, Steffen U. Pauls, Paul B. Frandsen

doi: https://doi.org/10.1101/2022.06.02.494618

Posted June 03, 2022.

Our findings suggest this RE-annotation bottleneck, driven largely by uneven taxonomic representation in RE reference databases, is worsening. Although the diversity of available insect genomes has rapidly expanded, the rate of community contributions to RE databases (essential for RE annotation) has not kept pace, preventing high resolution study of REs in most groups. We highlight the tremendous opportunity and need for the field of biodiversity genomics to embrace REs and suggest collective steps for making progress towards this goal.

Sproul et al. 2022, *bioRxiv*

Complete human genome in April 2022

- Nearly 200 million bp more than the previous human reference (GRCh38) with 1956 new genes (99 protein-coding) and 0 assembly gaps!

- Homozygous cell line sequenced with: 120x coverage of Oxford Nanopore ultra-long reads, 70x PacBio CLR long reads, 30x PacBio HiFi long reads, 50x 10X Genomics linked reads, BioNano DLS optical maps, Arima Genomics Hi-C maps.

TELOMERE-TO-TELOMERE CONSORTIUM

Money is less of a limitation now than sample amount + quality + repetitiveness!

Nurk et al. 2022, *Science*

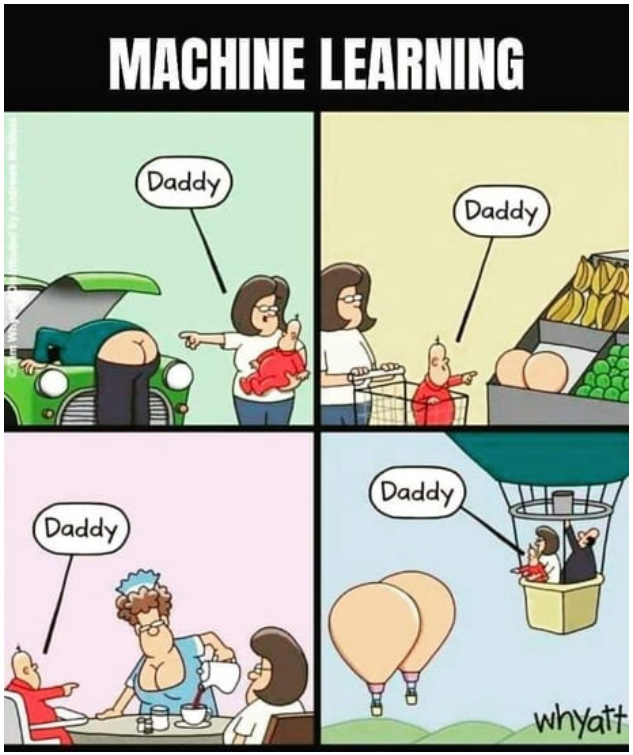
What's next: Machine learning?

DeepTE: a computational method for de novo classification of transposons with convolutional neural network

https://github.com/LiLabAtVT/DeepTE, Yan et al. 2020 *Bioinformatics*

TransposonUltimate: software for transposon classification, annotation and detection

https://github.com/DerKevinRiehl/TransposonUltimate, Riehl et al. 2022 *Nucl. Acids Res.*



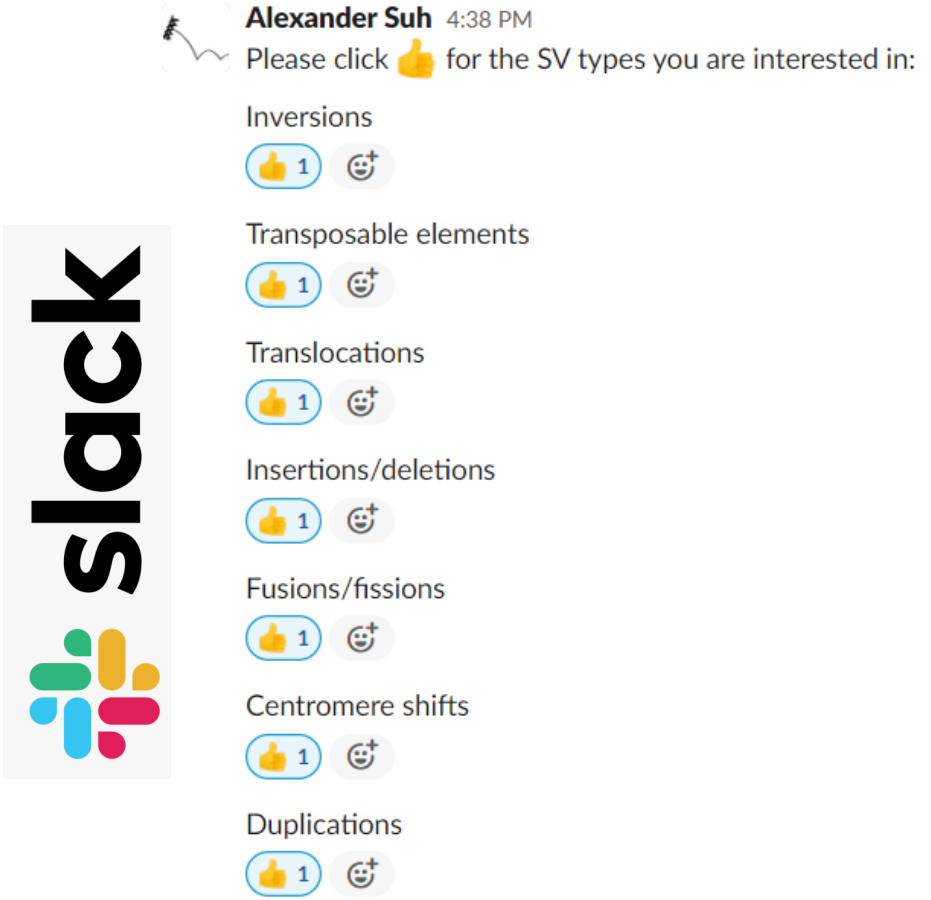
Prediction: AI training (cf. SV biology and curation) will be a key bottleneck for evaluating machine learning results!

More community initiatives needed

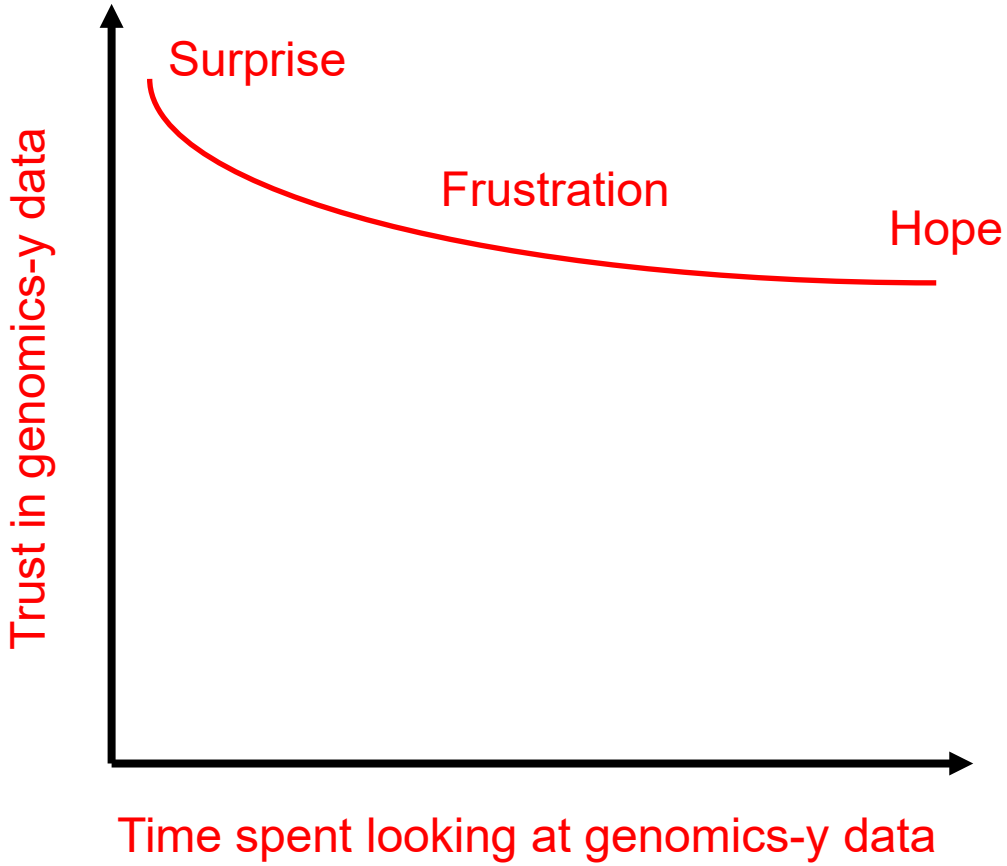
TE Hub website

TE Worldwide Slack
#te-hub channel

Let‘s keep in touch in the WPSG 2022 Slack channel #structural_variation!
(https://wpsg2022participants.slack.com)



Conclusion: Genomics is no silver bullet



Genomics + cytogenetics = cytogenomics

Karyogram of a human male (Wikipedia)

What to take with a grain of salt

1. How can we declare something as absent in a genome (evidence of absence vs. absence of evidence)?
2. How can we study unassembled or underassembled regions (multicopy genes, GC-rich genes, TEs)?
3. How can we compare species with different assembly qualities, data types, or annotation efforts?
4. How can we account for unknown peculiarities (sex chromosomes, B chromosomes, …)?

The transposition goes on!

From 01 April 2023:
Professor at University of Bonn and Head of the
Centre for Molecular Biodiversity Research
in Bonn/Hamburg, Germany

Talk to me or email me (alexander.suh@ebc.uu.se) if interested in developing cytogenomics and/or genome annotation/curation for scaling across animals

PhD/postdoc/researcher positions available!

Questions?

Thank you, Český Krumlov!