

A fluorescence microscopy image of human chromosomes. The chromosomes are stained blue. Several centromeres are marked with red fluorescent spots. Some p arms of acrocentric chromosomes are marked with green fluorescent spots. The background is black.

Formation and transmission of human Robertsonian chromosomes

Andrea Guarracino and Jennifer Gerton

UTHSC and Stowers Institute

Centromeres

p arms acrocentrics



Phillippy team



Sergey Koren (NHGRI)



Adam Phillippy (NHGRI)

Arang Rhie
Steven Solar
Brian Walenz
Gerry Bouffard
Brandon Pickett
Shelise Brooks
Juyun Crawford
Alice Young

Gerton team



Tamara Potapova



Leonardo Gomes de Lima

Chris Seidel
Sean McKinney
Kate Hall
Michael Peterson

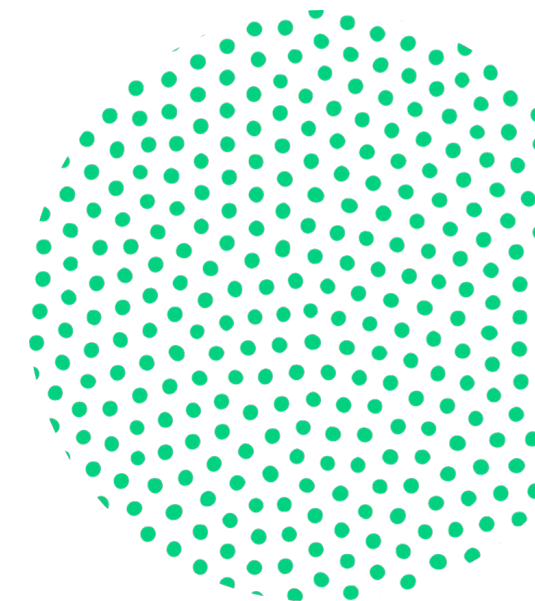
Garrison team



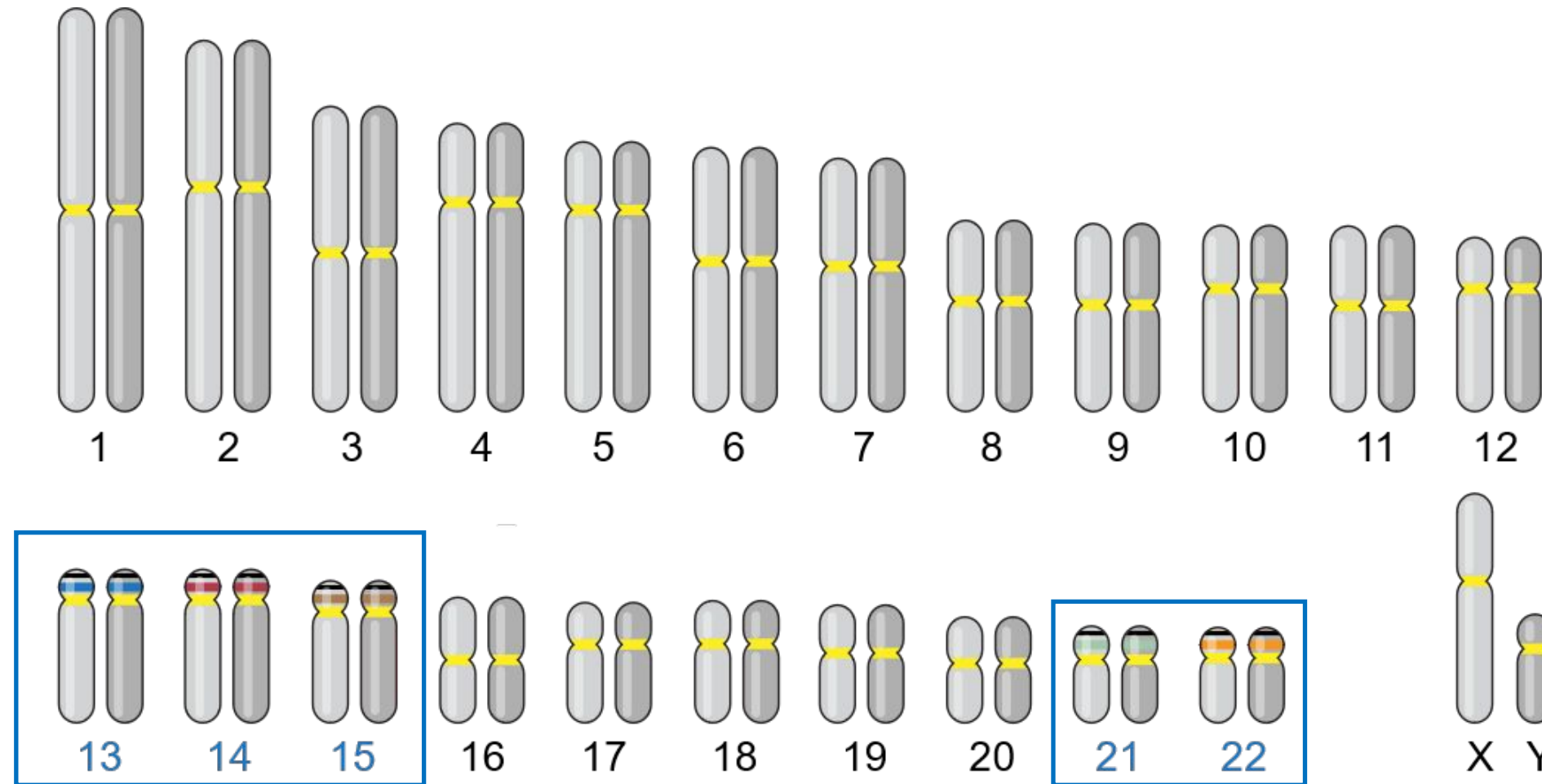
Erik Garrison (UTHSC)



Andrea Guaracino (UTHSC)

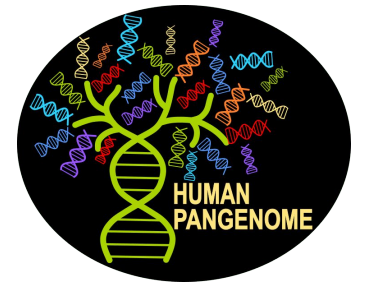


Human acrocentric chromosome short arms, assembled 2022

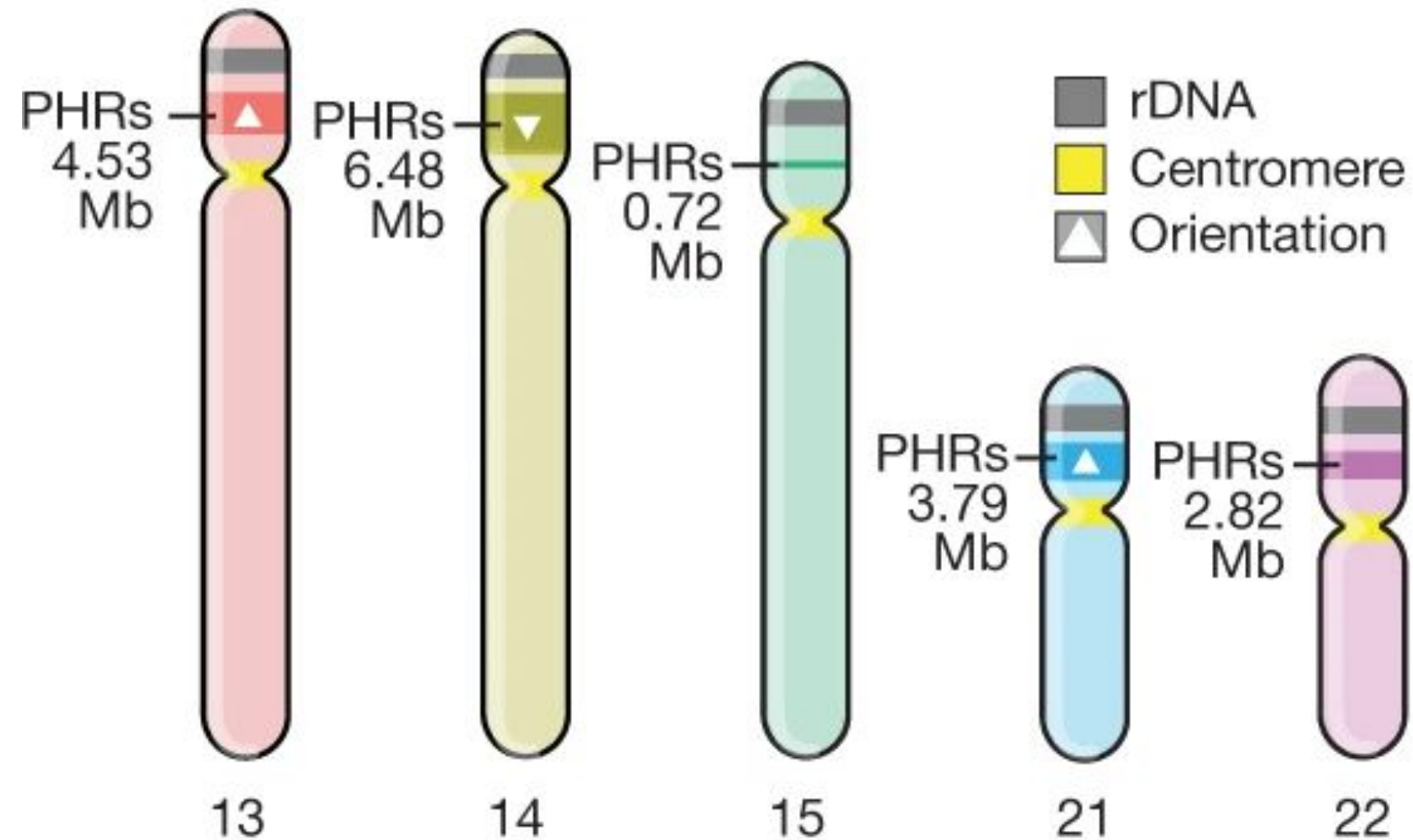


Guarracino et al, 2023, Pangenome acrocentrics, *Nature*

Nurk et al, 2022, CHM13 genome (acro p arms), *Science*



Pseudohomolog regions in acrocentric chromosomes



Andrea Guarracino Erik Garrison

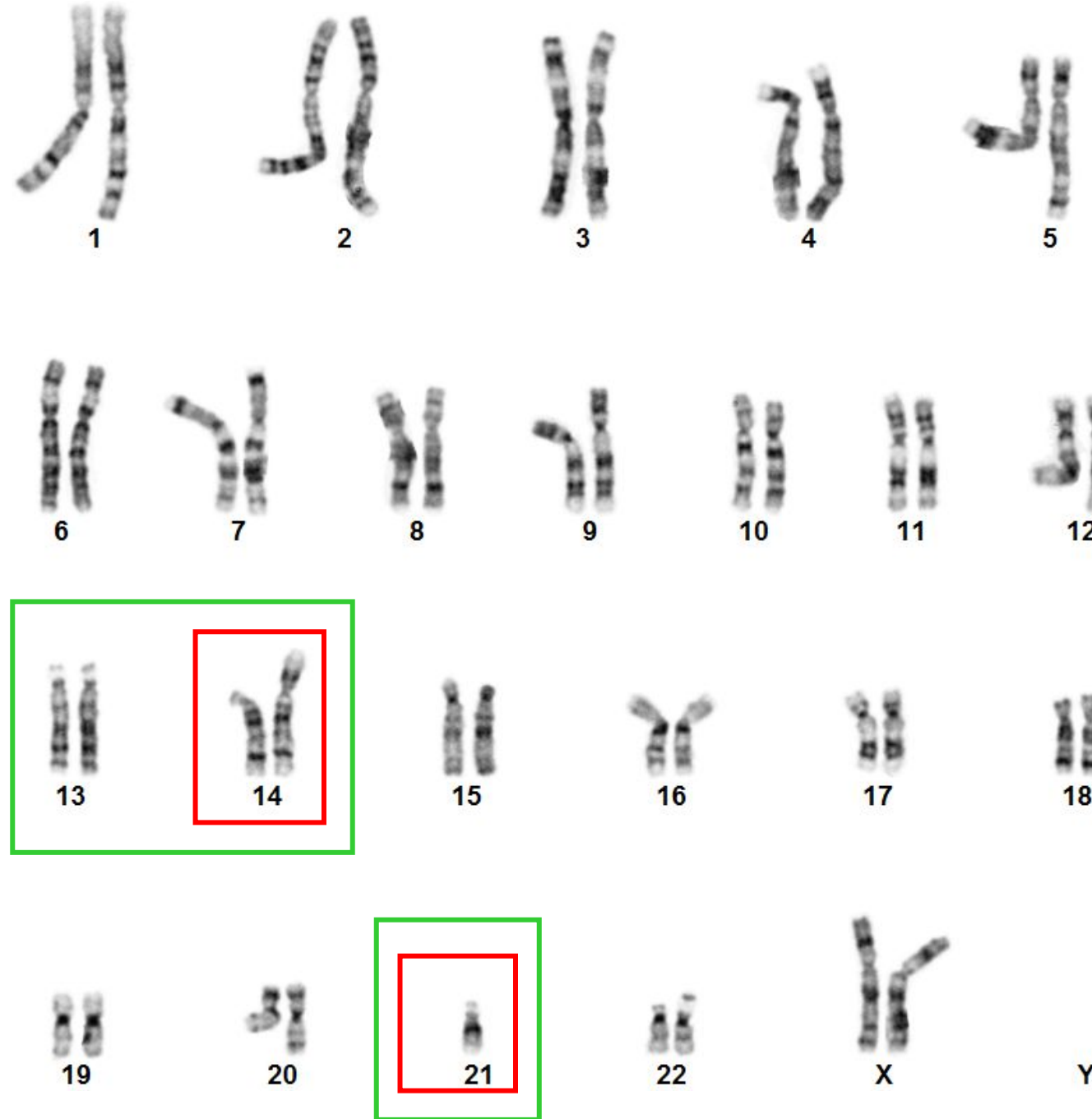


Guarracino et al., *Nature*, 2023

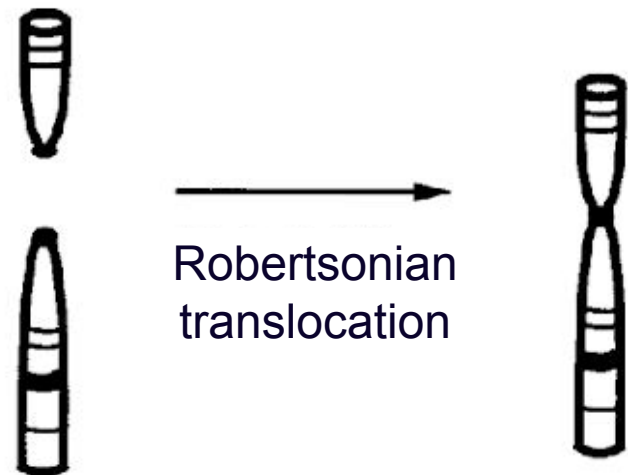
Jarmuz-Szymczak et al., 2014

Robertsonian chromosomes are common in nature-WHY?

William Rees Brebner Robertson 1881- 1941
American zoologist and early cytogeneticist

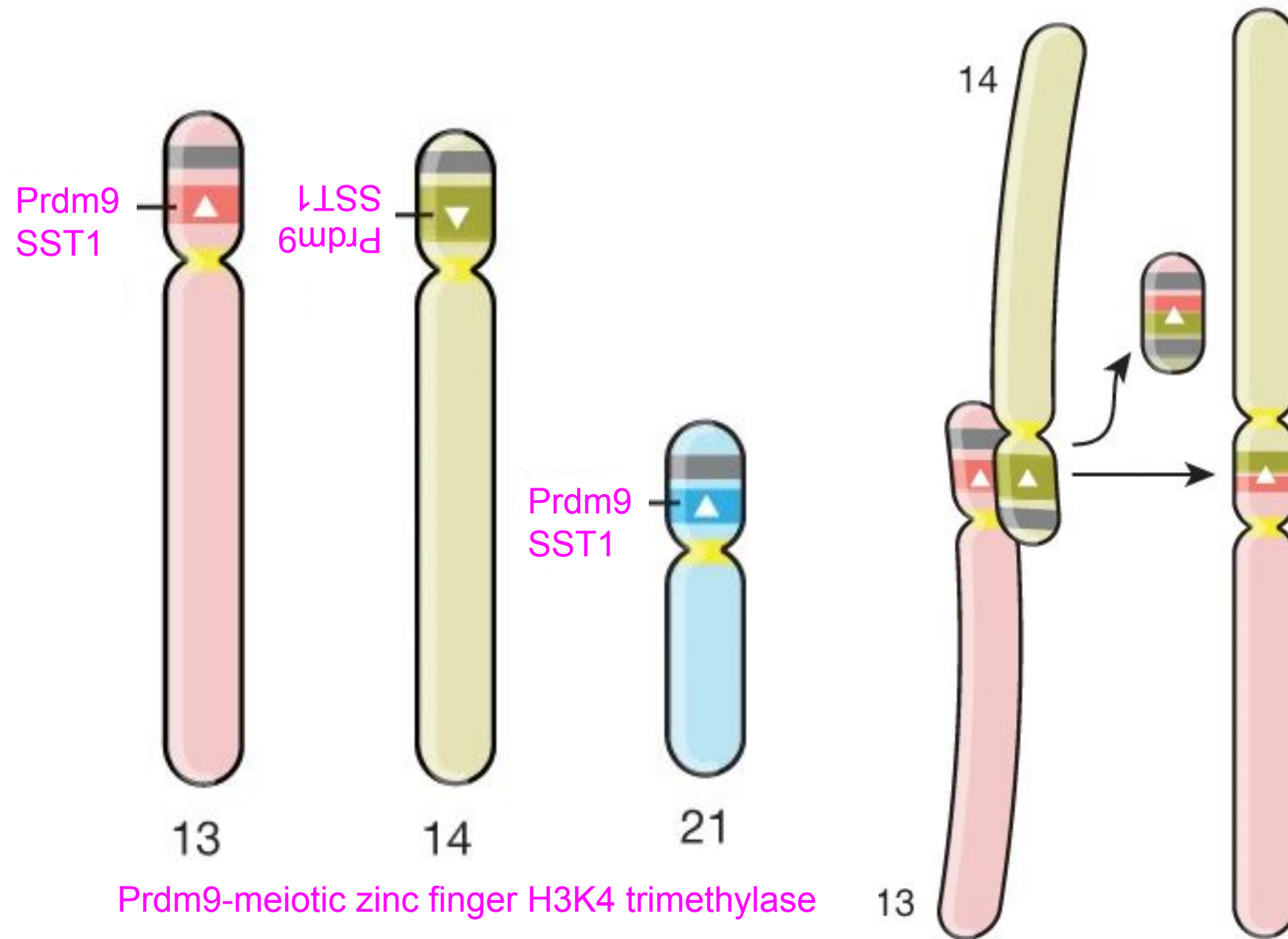


- 85% involve 14
- Female meiosis
- 1 in 800
- Sub/infertility
- Aneuploidy
- Cancer Incidence



- Karyotype evolution
- Speciation

Recombination between acrocentric chromosomes



Prdm9-meiotic zinc finger H3K4 trimethylase

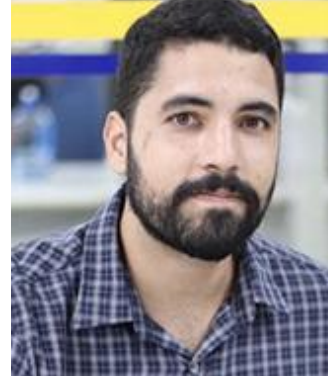
Baudat et al., 2010, Myers et al., 2010, Parvanov et al., 2010
Altemose et al., 2017

Robertsonian
Translocation

Andrea Guarracino

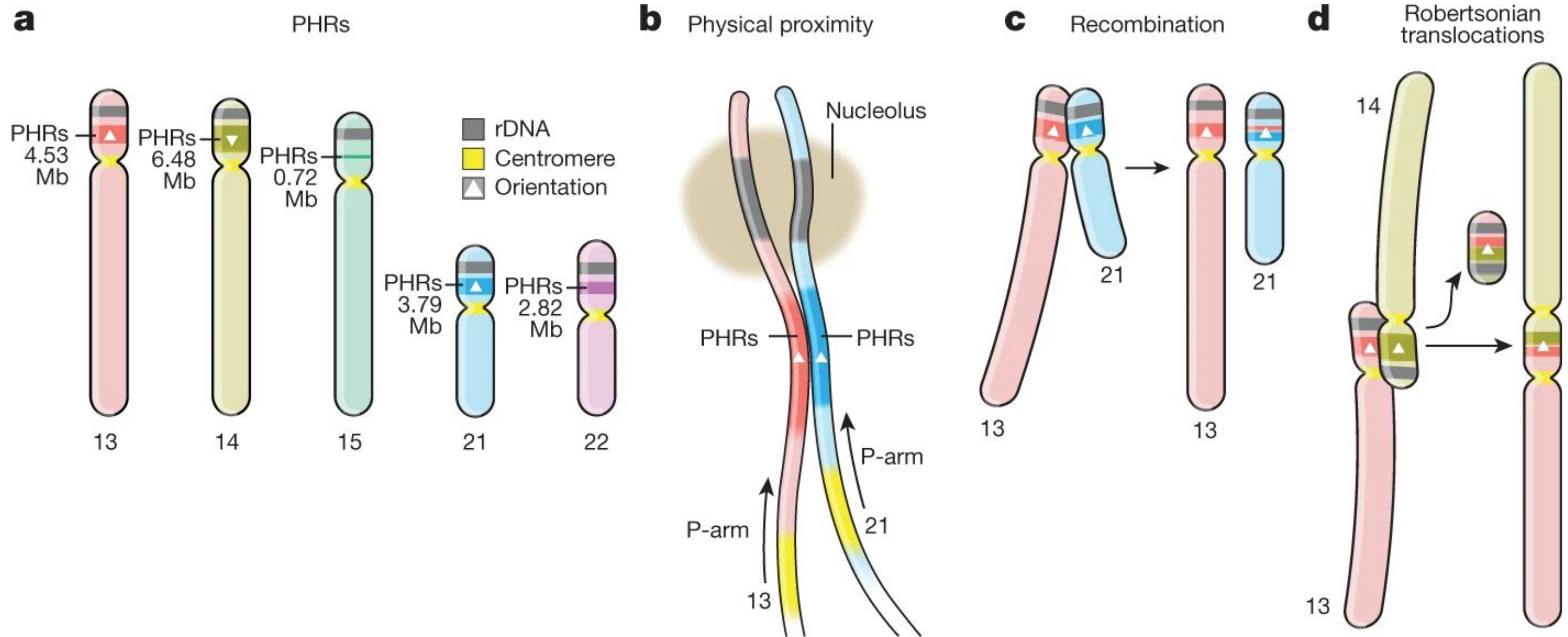


Leo Gomes de Lima



Guarracino et al., *Nature*, 2023

Model for the formation of Robertsonian translocations



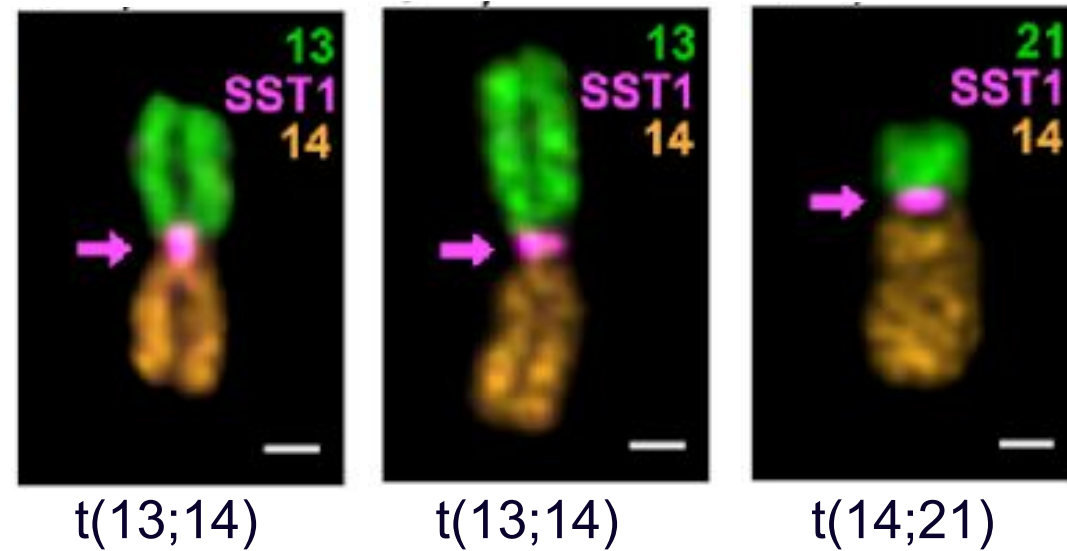
Guarracino et al., *Nature*, 2023

Gerton, *JCS*, 2024

Illustrations by Mark Miller

Robertsonian chromosomes-three predictions

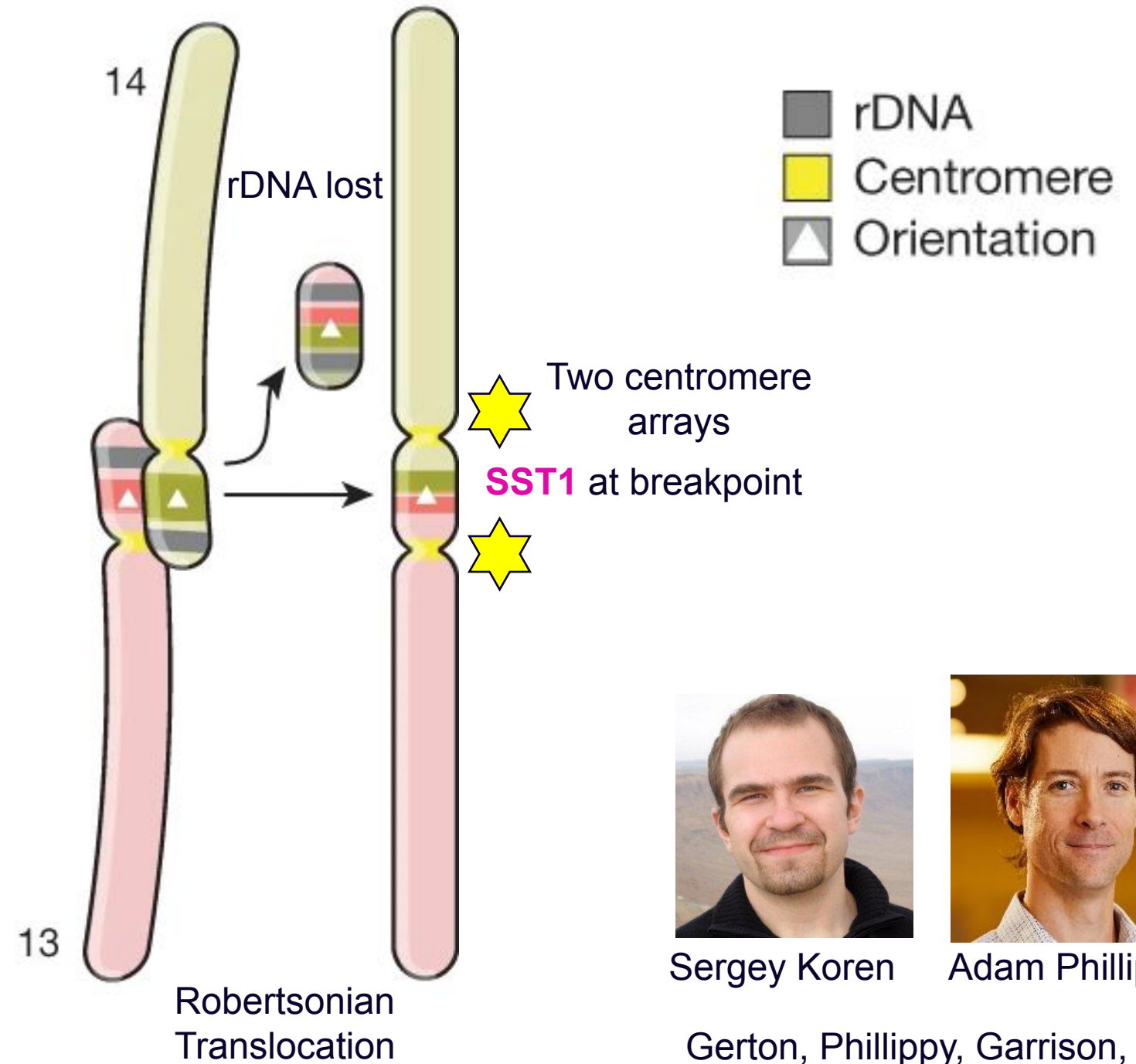
3 ROB lines



T. Potapova



- ONT, PacBio HiFi, HiC
- DNA methylation
- Cytogenetics
- Super-resolution imaging
- Phylogenetics



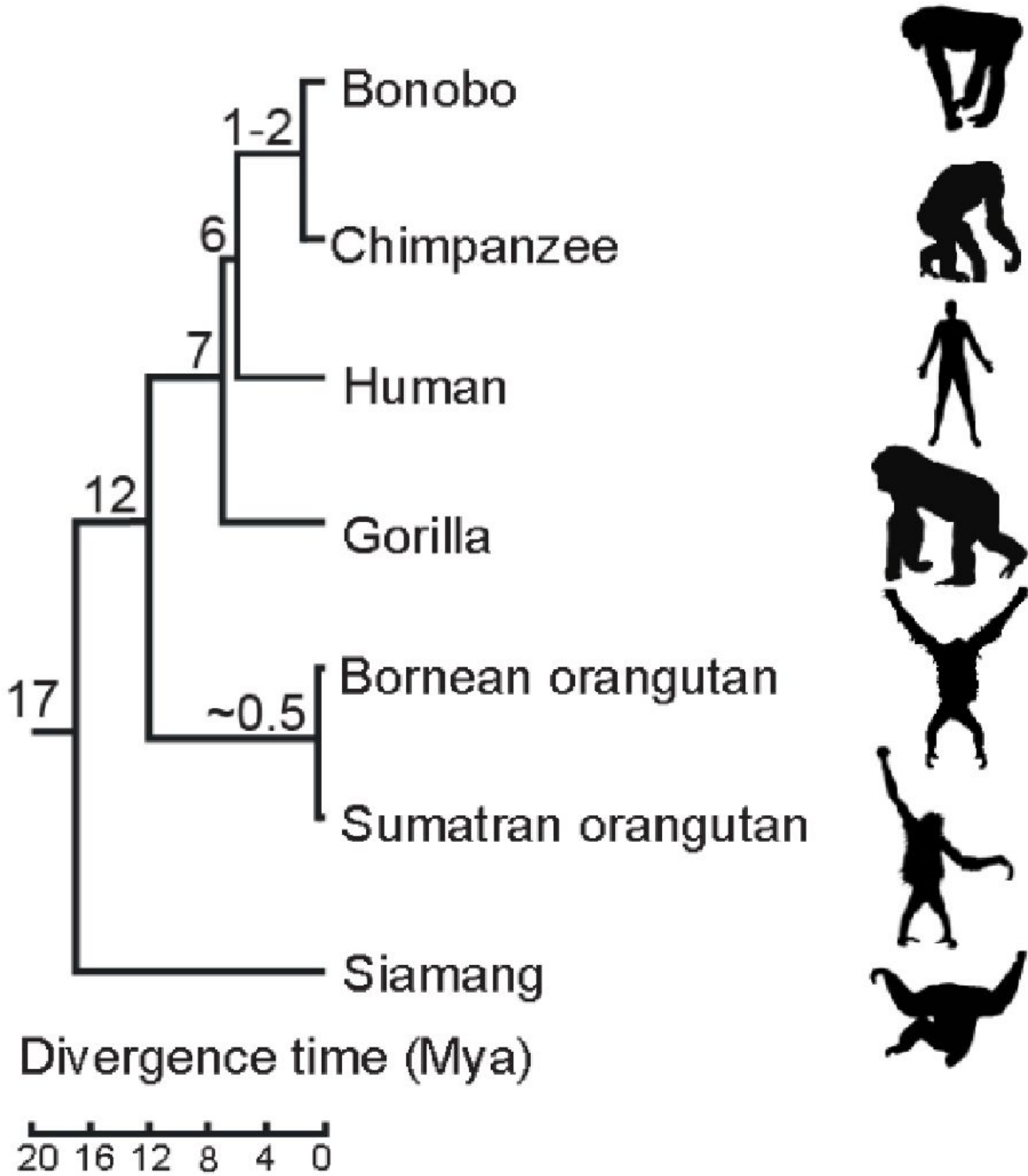
Sergey Koren



Adam Phillippy

Gerton, Phillippy, Garrison, in prep

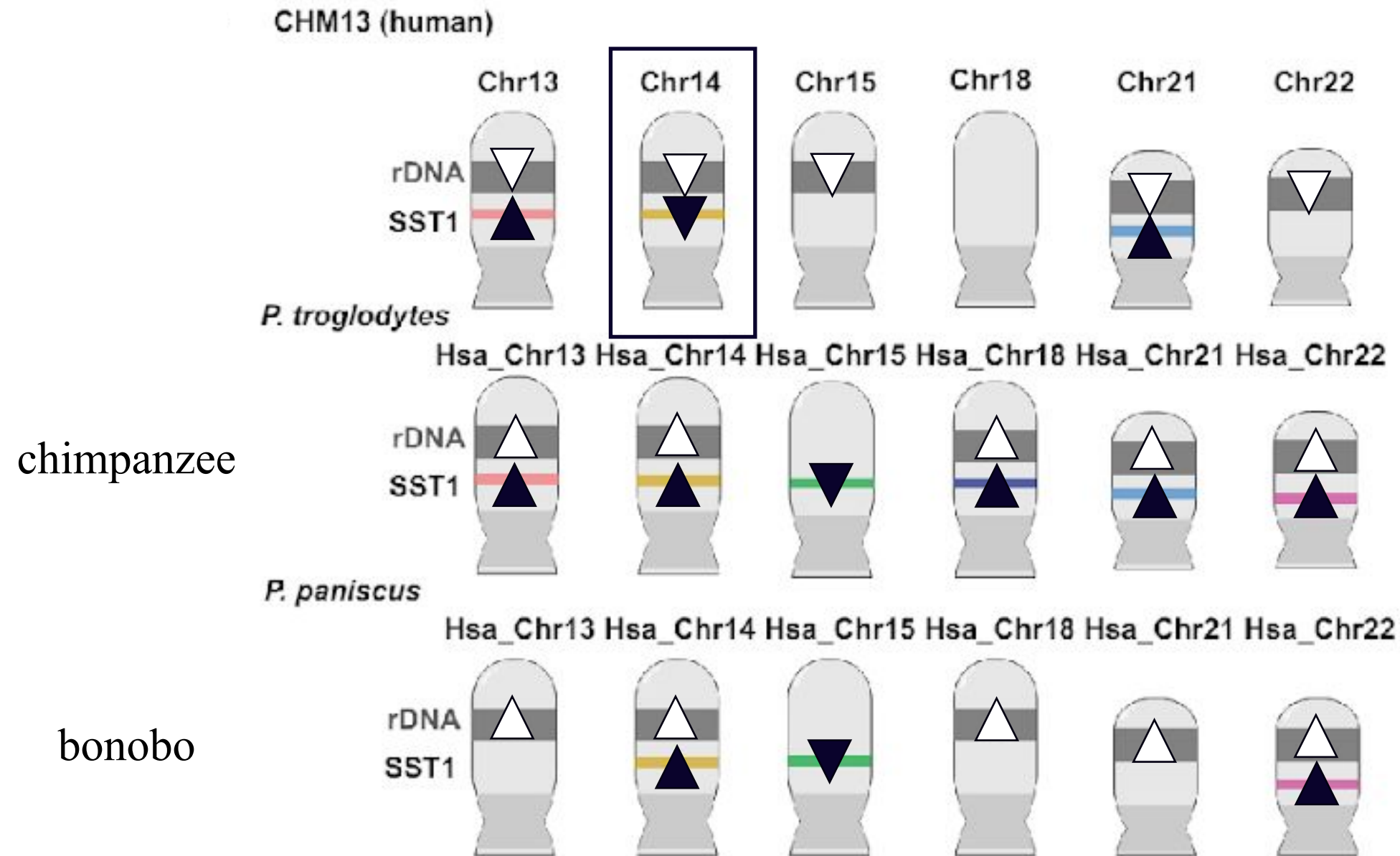
New primate assemblies enable evolutionary insights



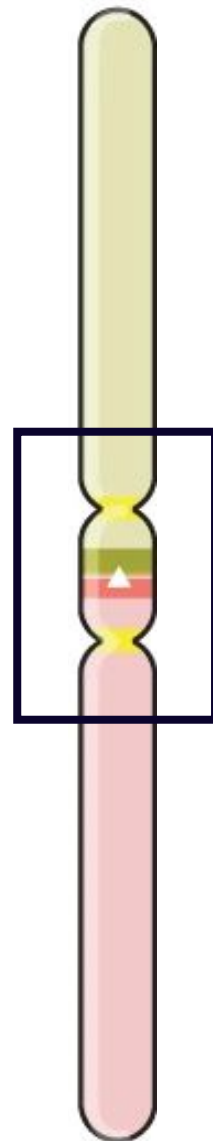
Eichler et al, 2024, Primate autosome assemblies, submitted



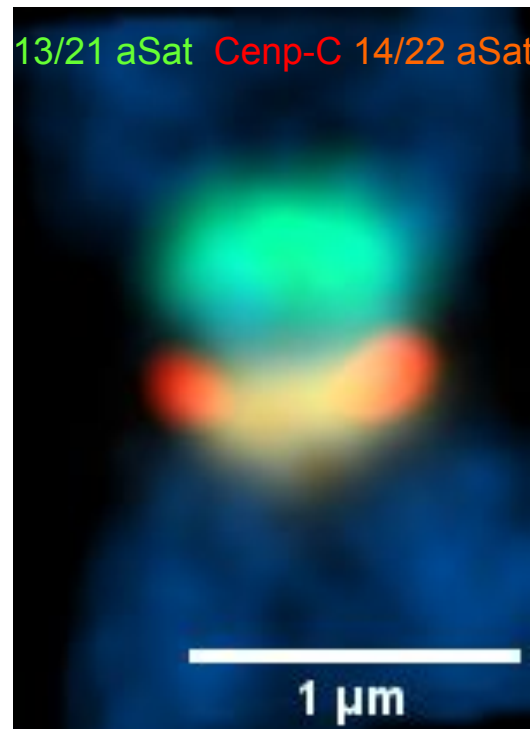
Inversion of SST1 + rDNA array-unique to human genome!



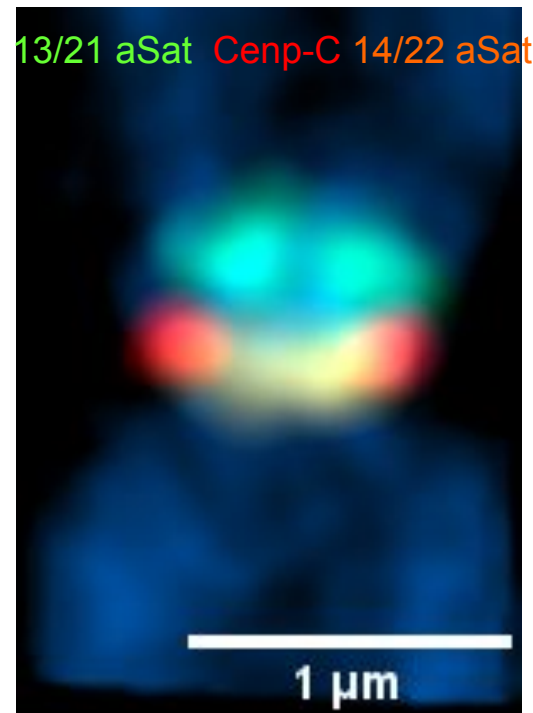
ROBs-epigenetic alterations at centromeres enable stable chromosome transmission



t(13;14)

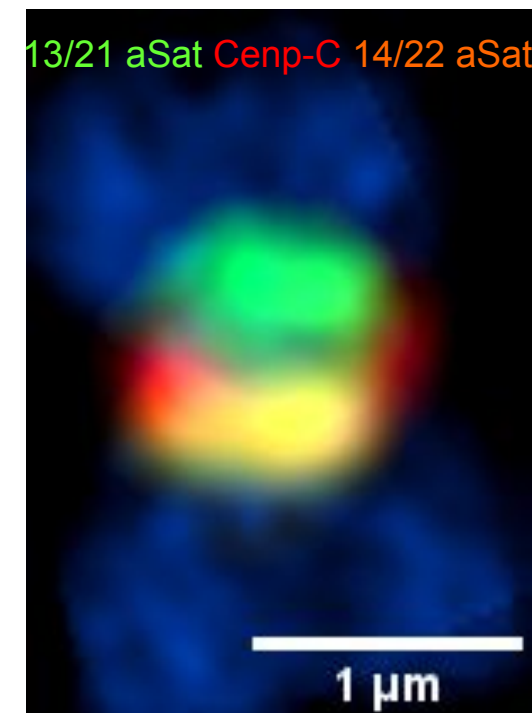


Averaged image 11 ROB chromosomes, GM08490

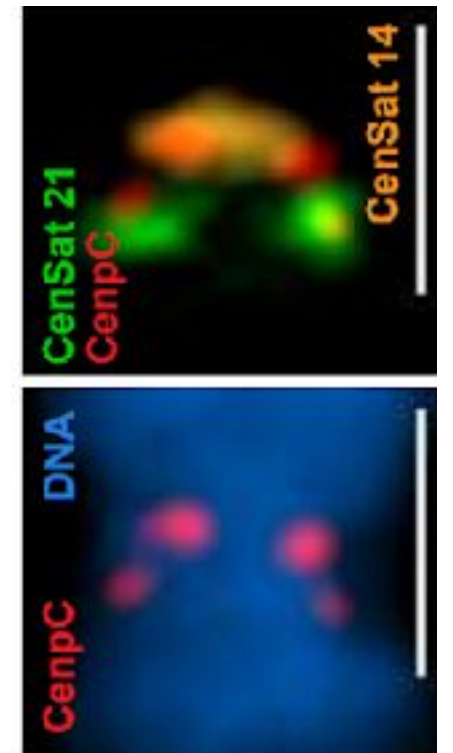


Averaged image 11 ROB chromosomes, GM03786

t(14;21)



Averaged image 10 ROB chromosomes, GM03417

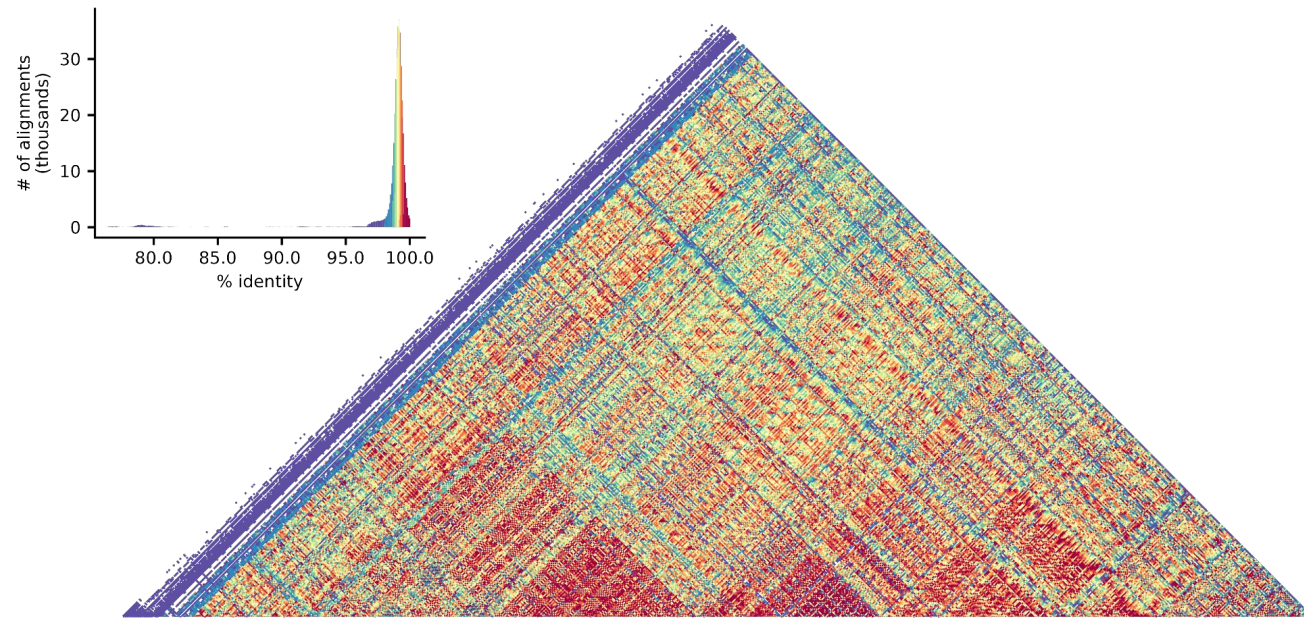


Cen14 wins

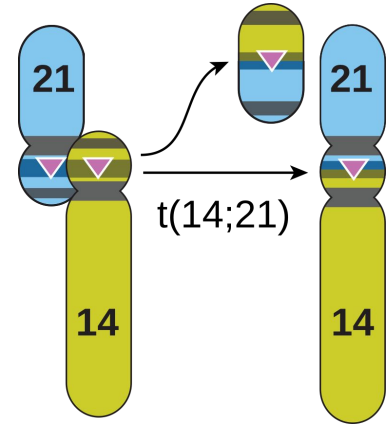
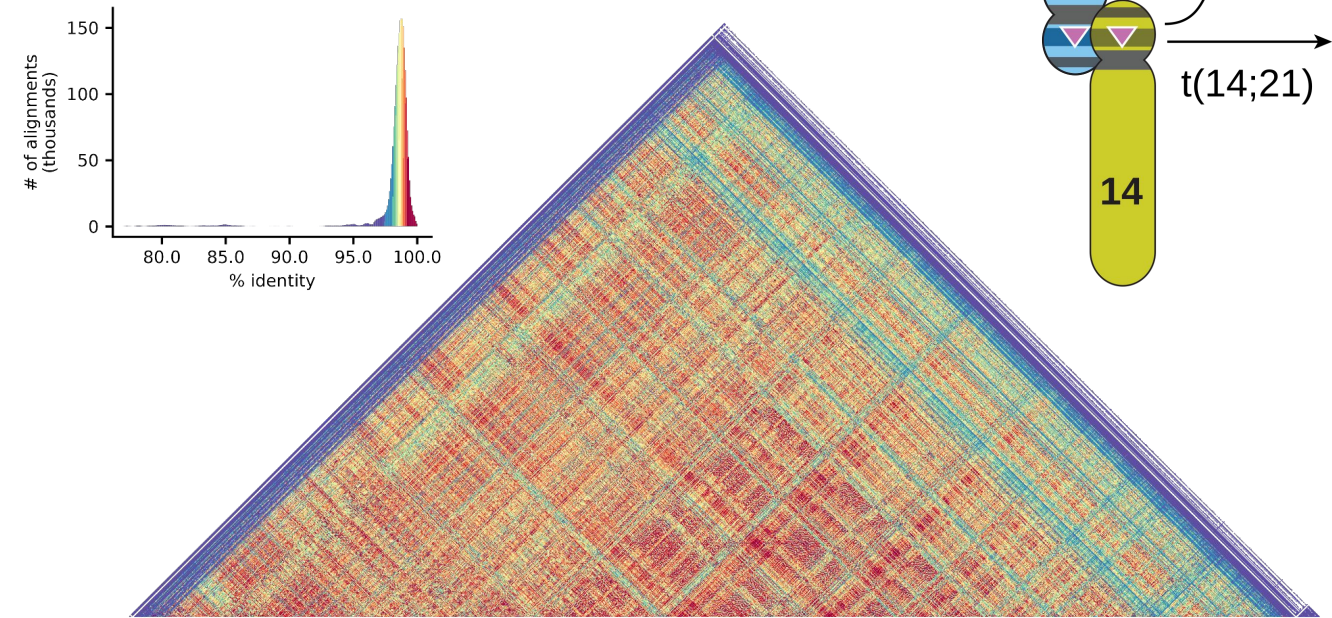
Sullivan et al., 1994

Both cen14 and cen21 may remain active in t(14;21)

GM03417#chr21#haplotype1-0000006

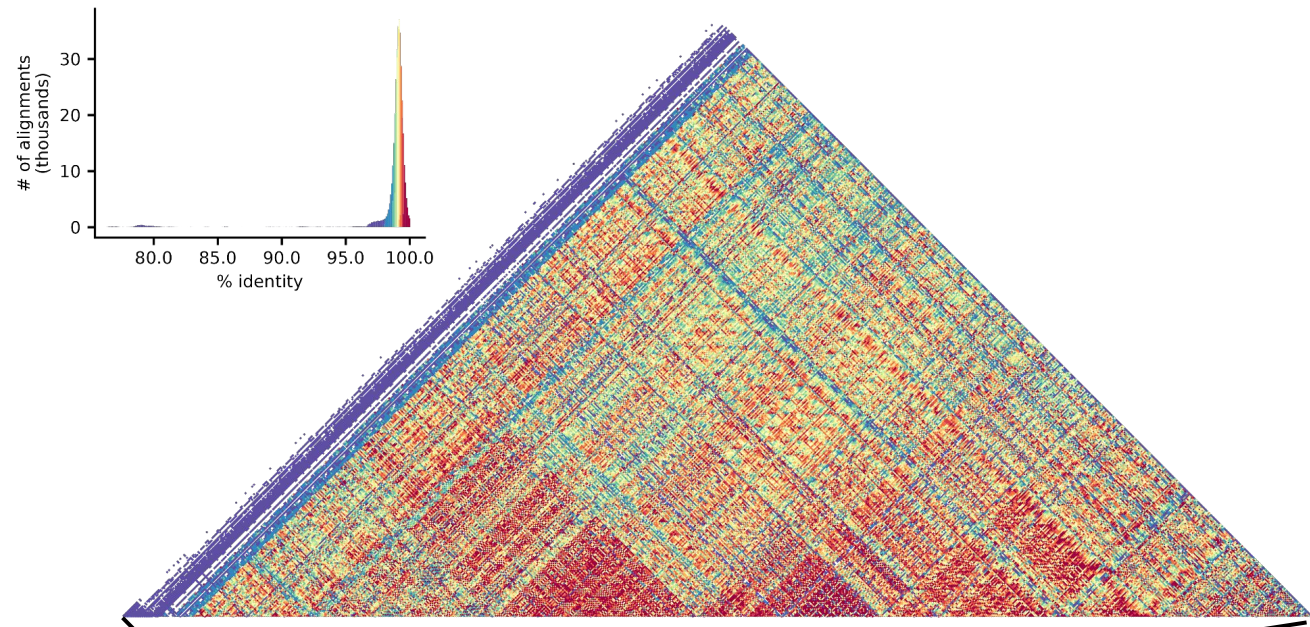


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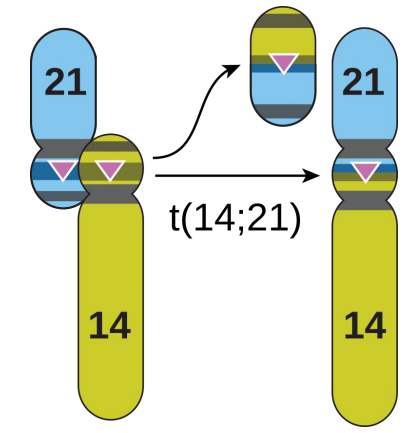
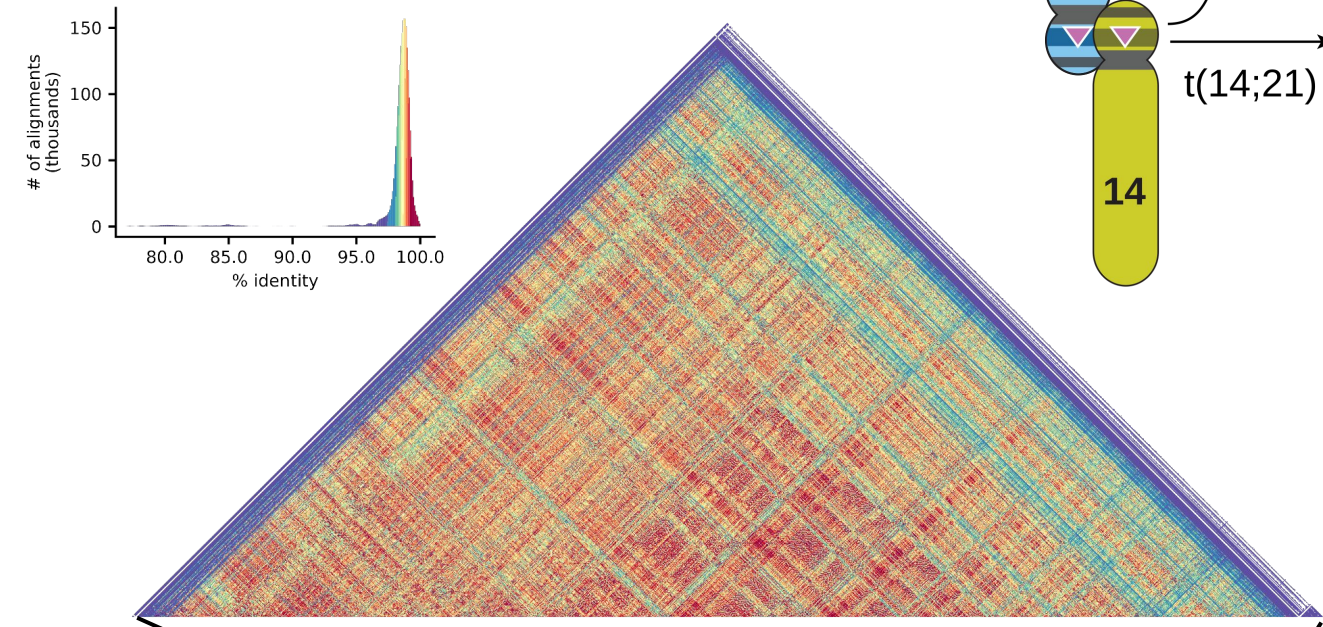


Both cen14 and cen21 may remain active in t(14;21)

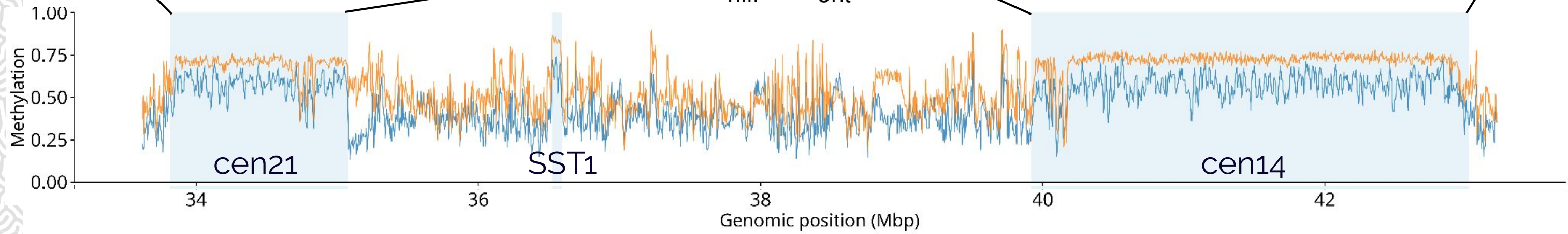
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GM03417#chr14#haplotype1-0000006

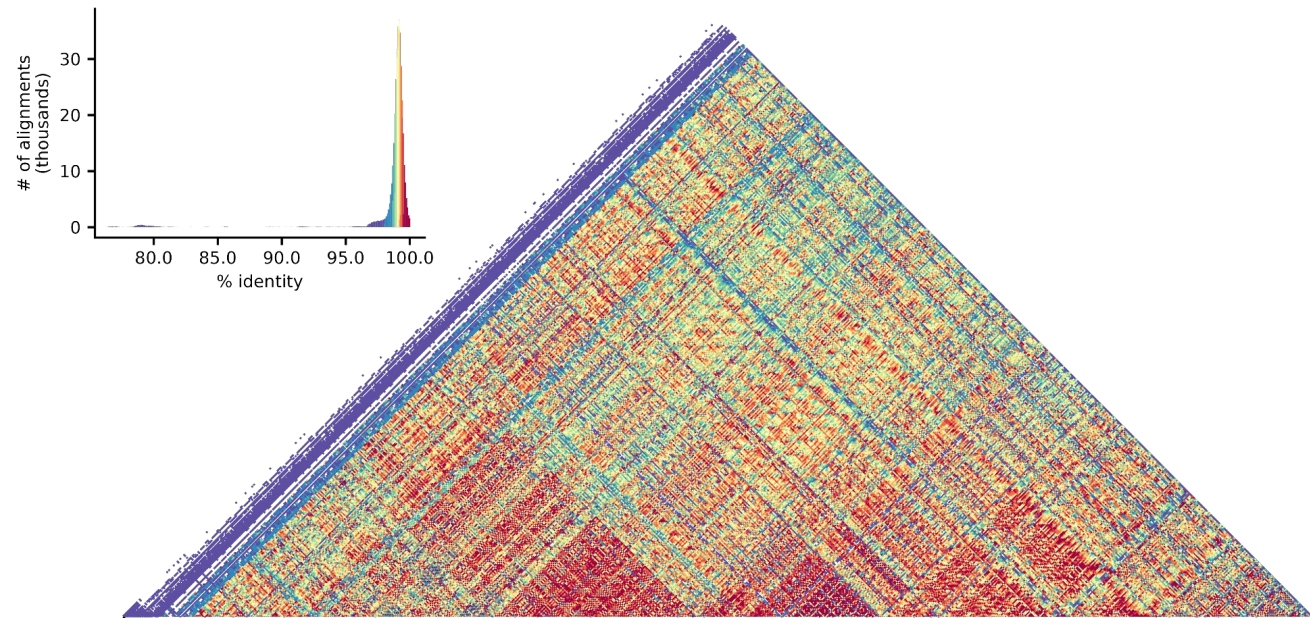


— hifi — ont

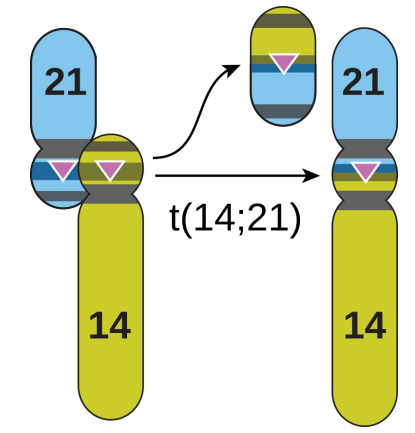
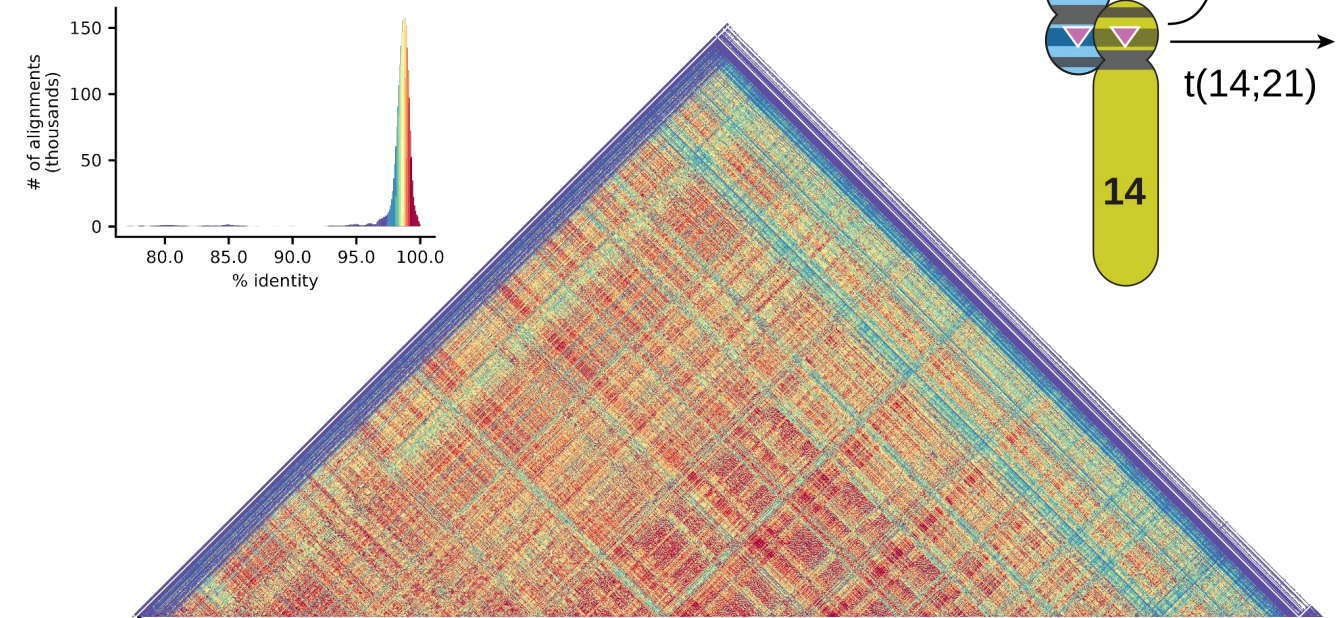


Both cen14 and cen21 may remain active in t(14;21)

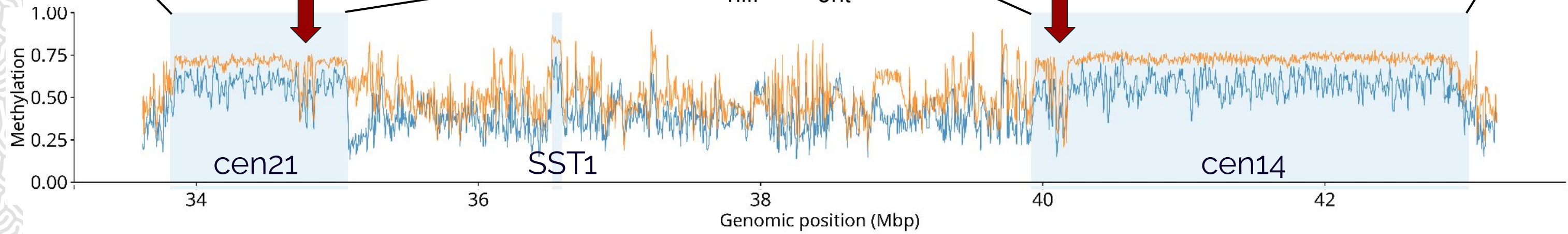
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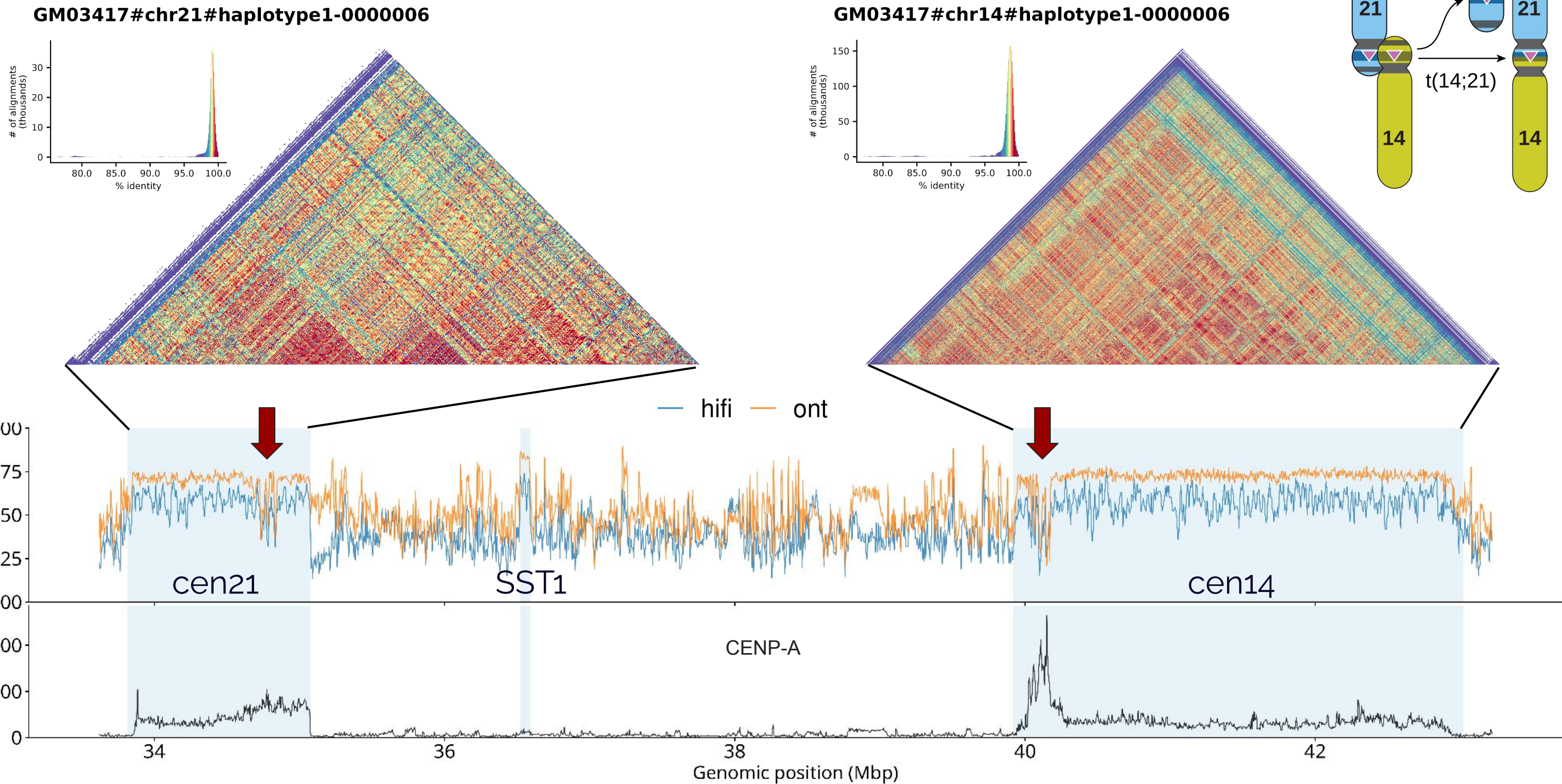
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— hifi — ont

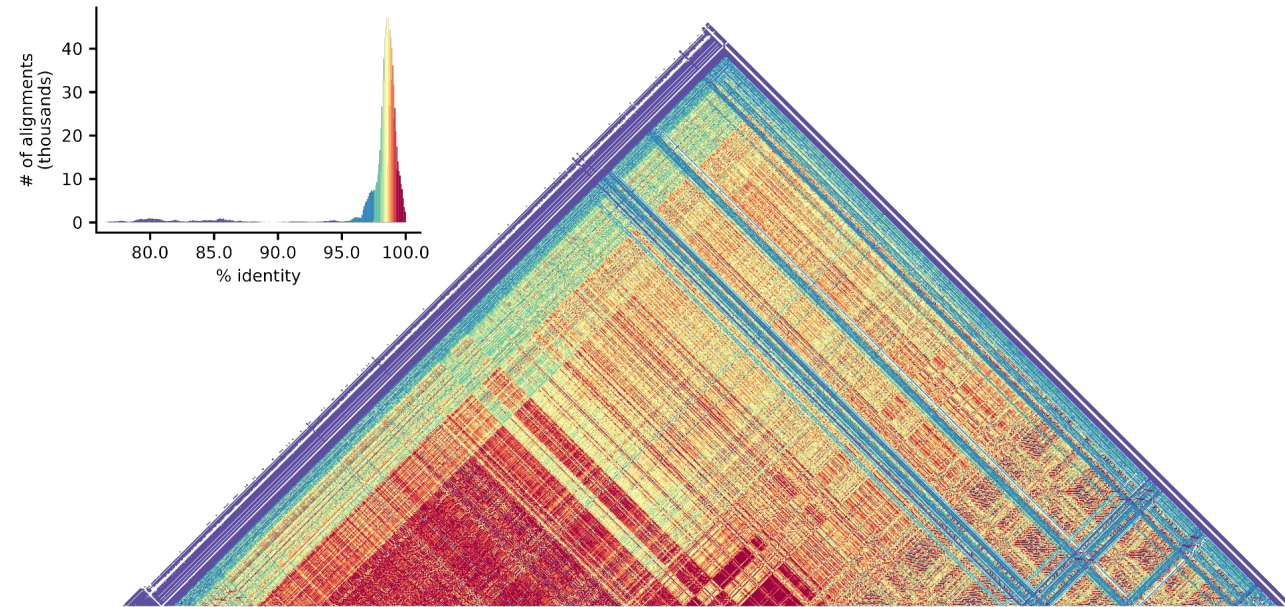


Both cen14 and cen21 may remain active in t(14;21)

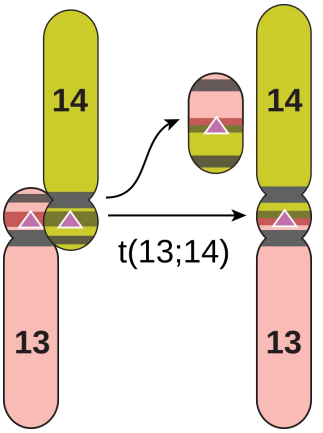
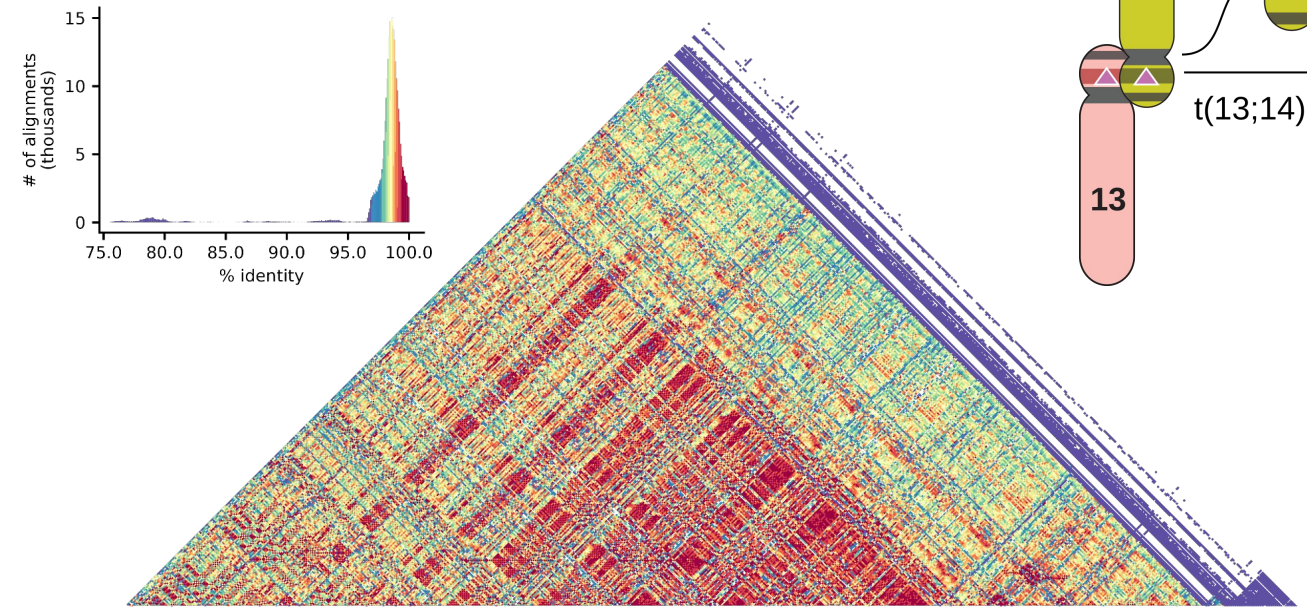


Cen14 is active, cen13 is inactive in t(13;14)

GM03786#chr14#haplotype1-0000026

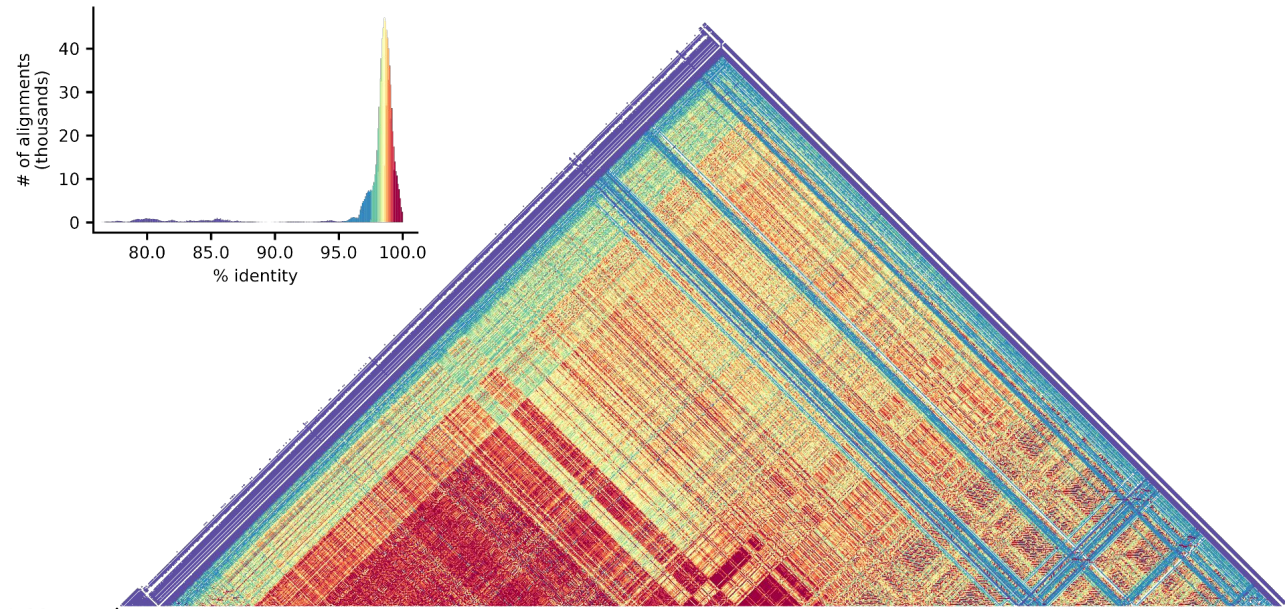


GM03786#chr13#haplotype1-0000026

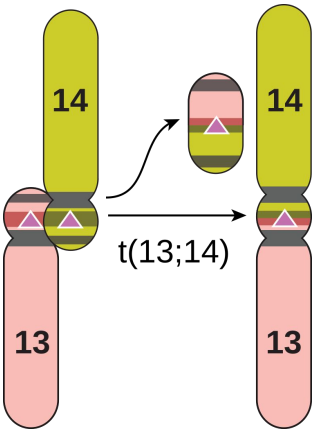
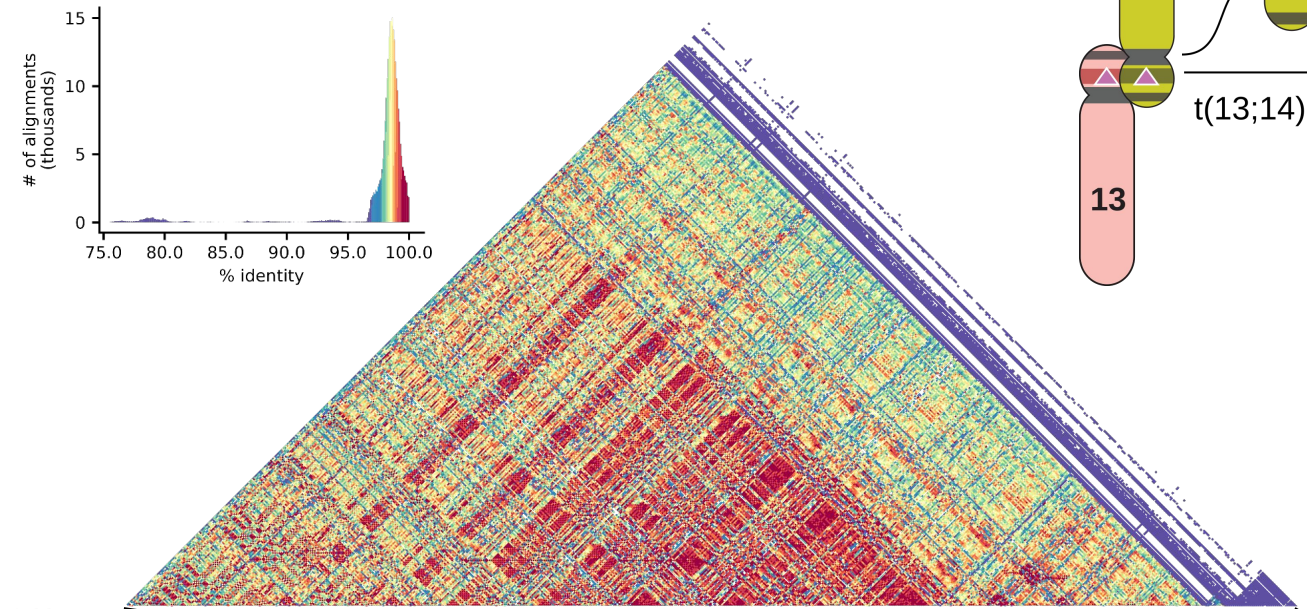


Cen14 is active, cen13 is inactive in t(13;14)

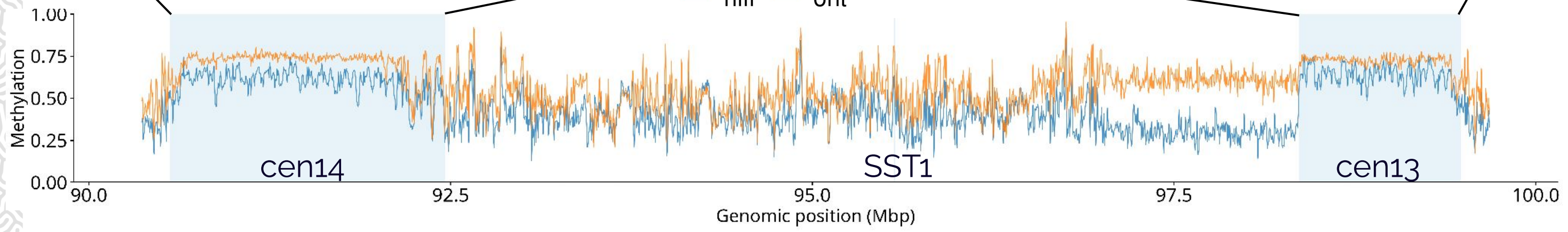
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GM03786#chr13#haplotype1-0000026

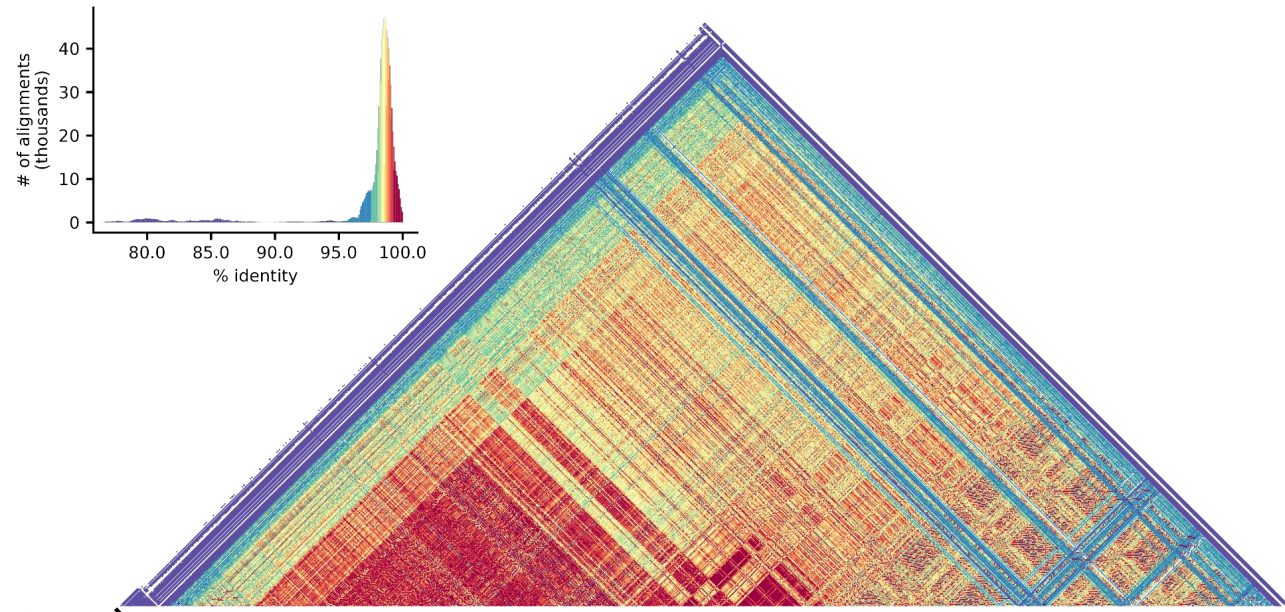


— hifi — ont

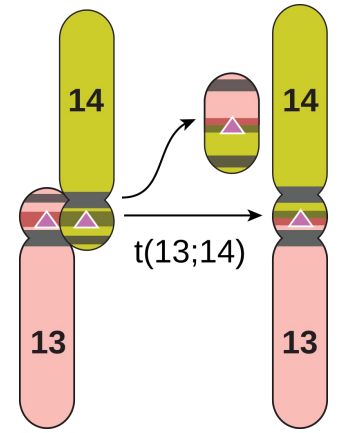
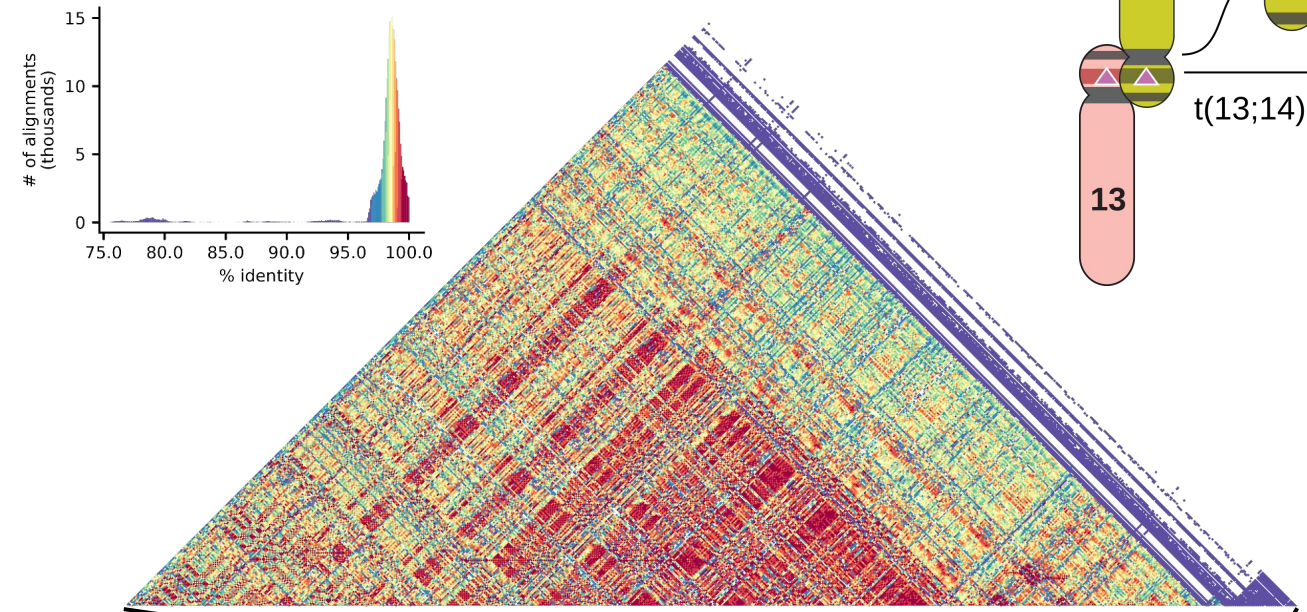


Cen14 is active, cen13 is inactive in t(13;14)

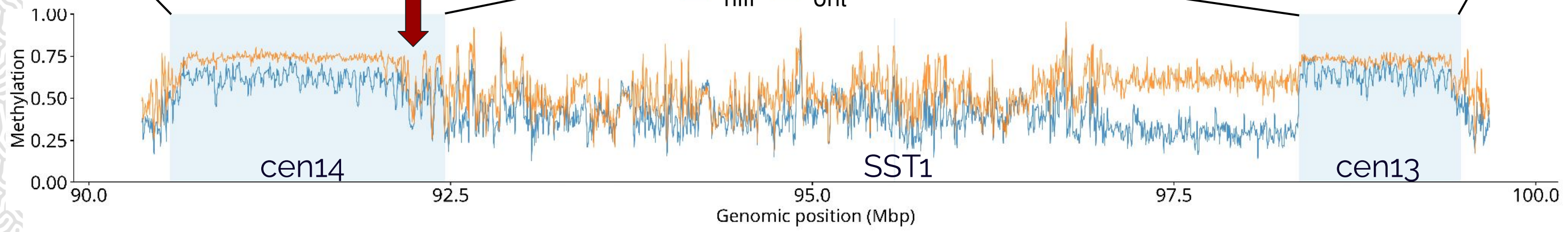
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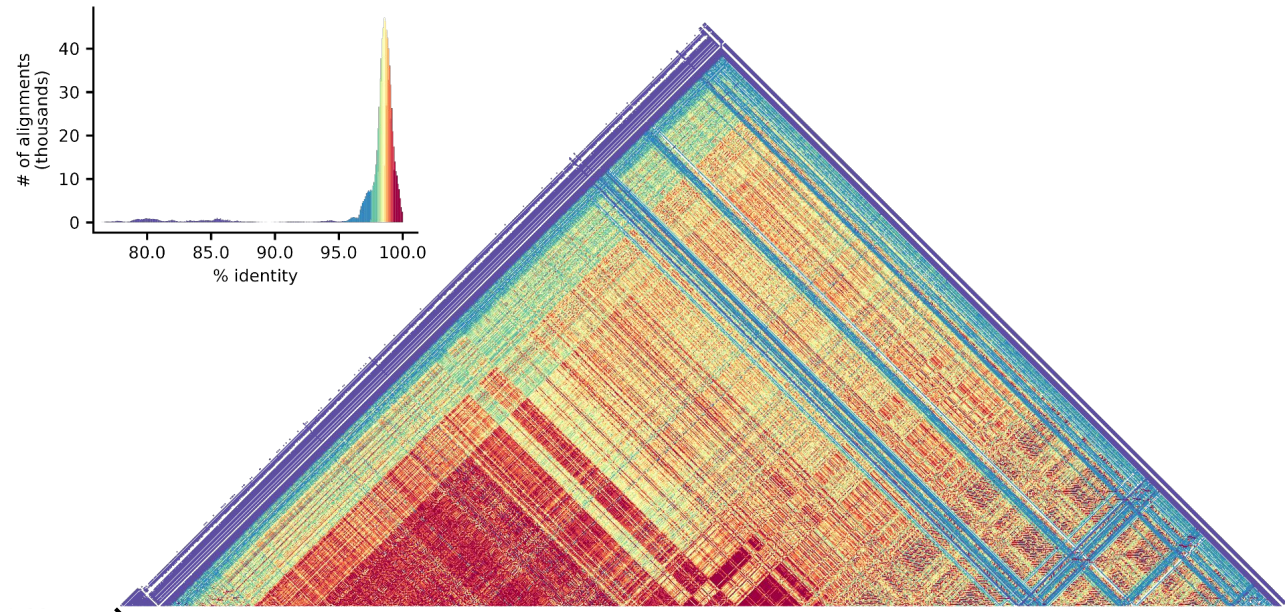


— hifi — ont

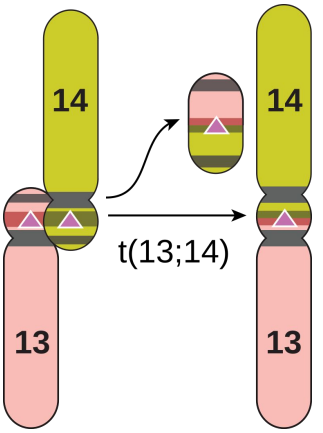
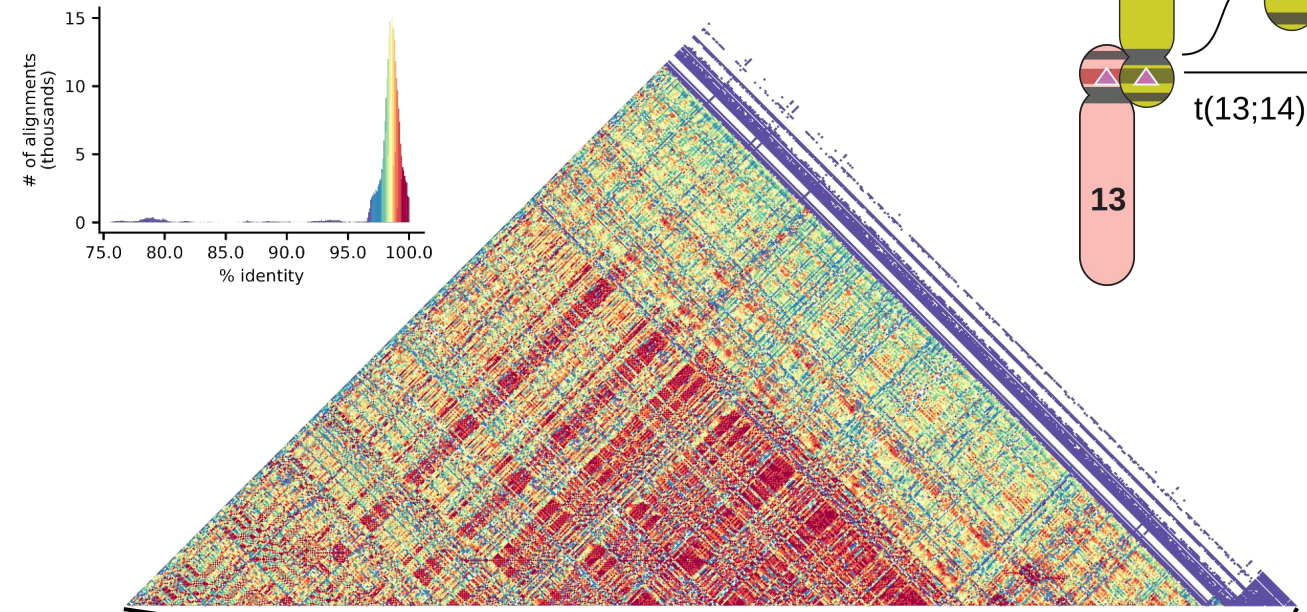


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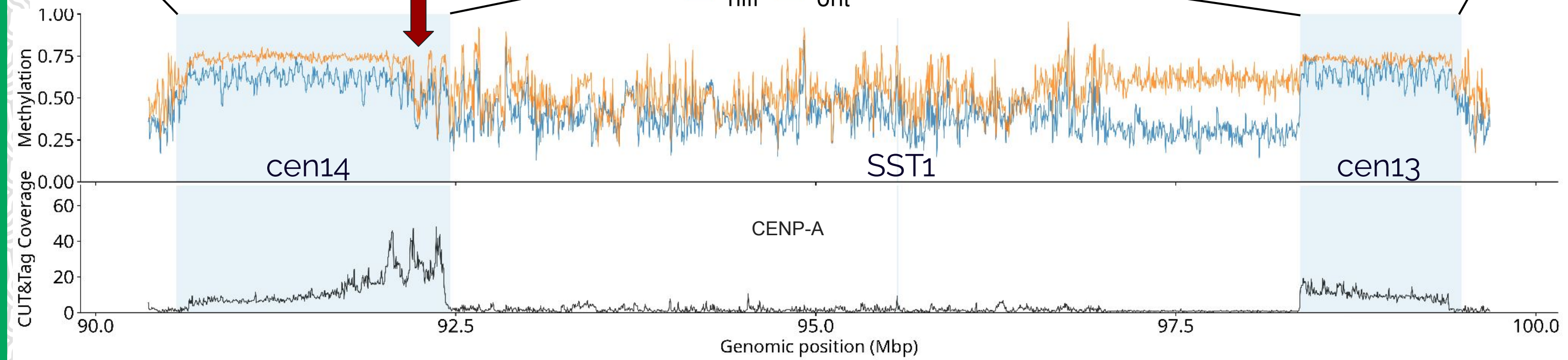
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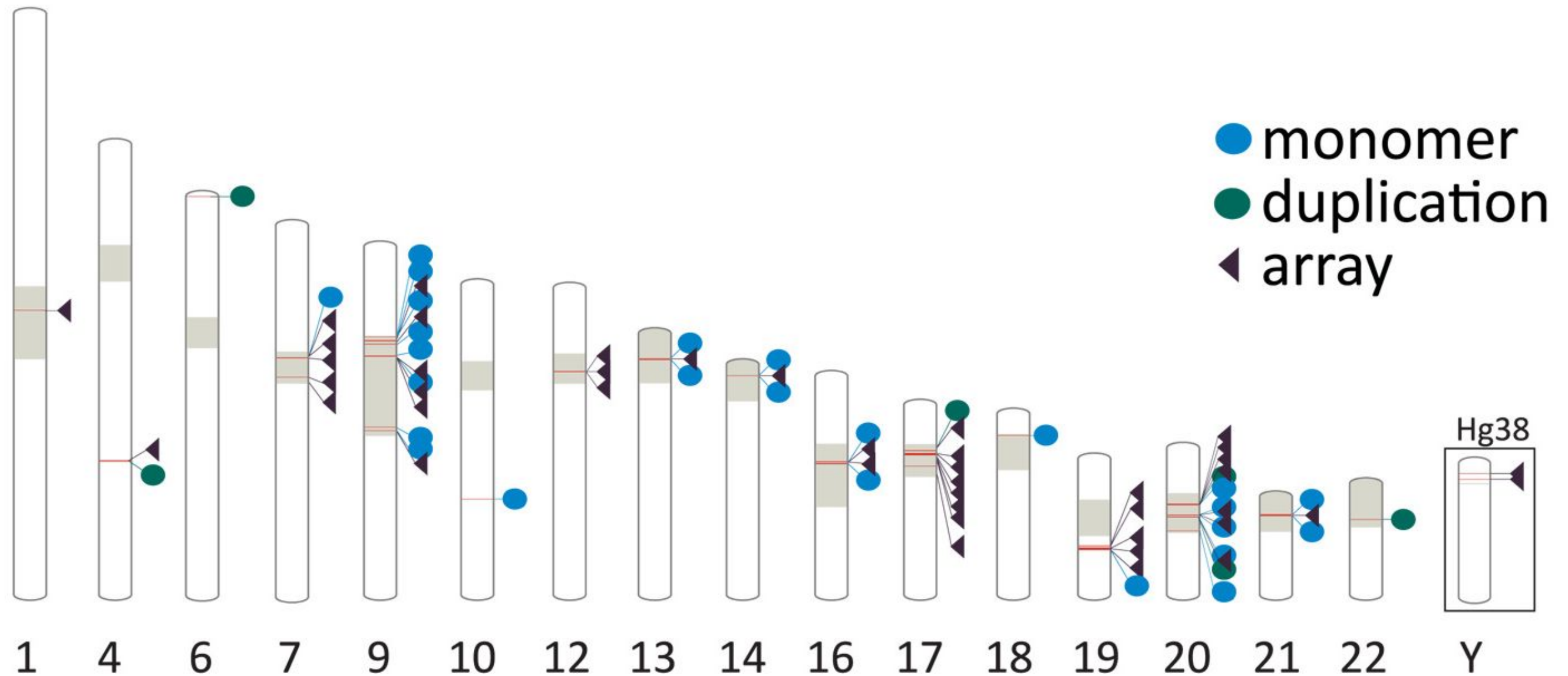
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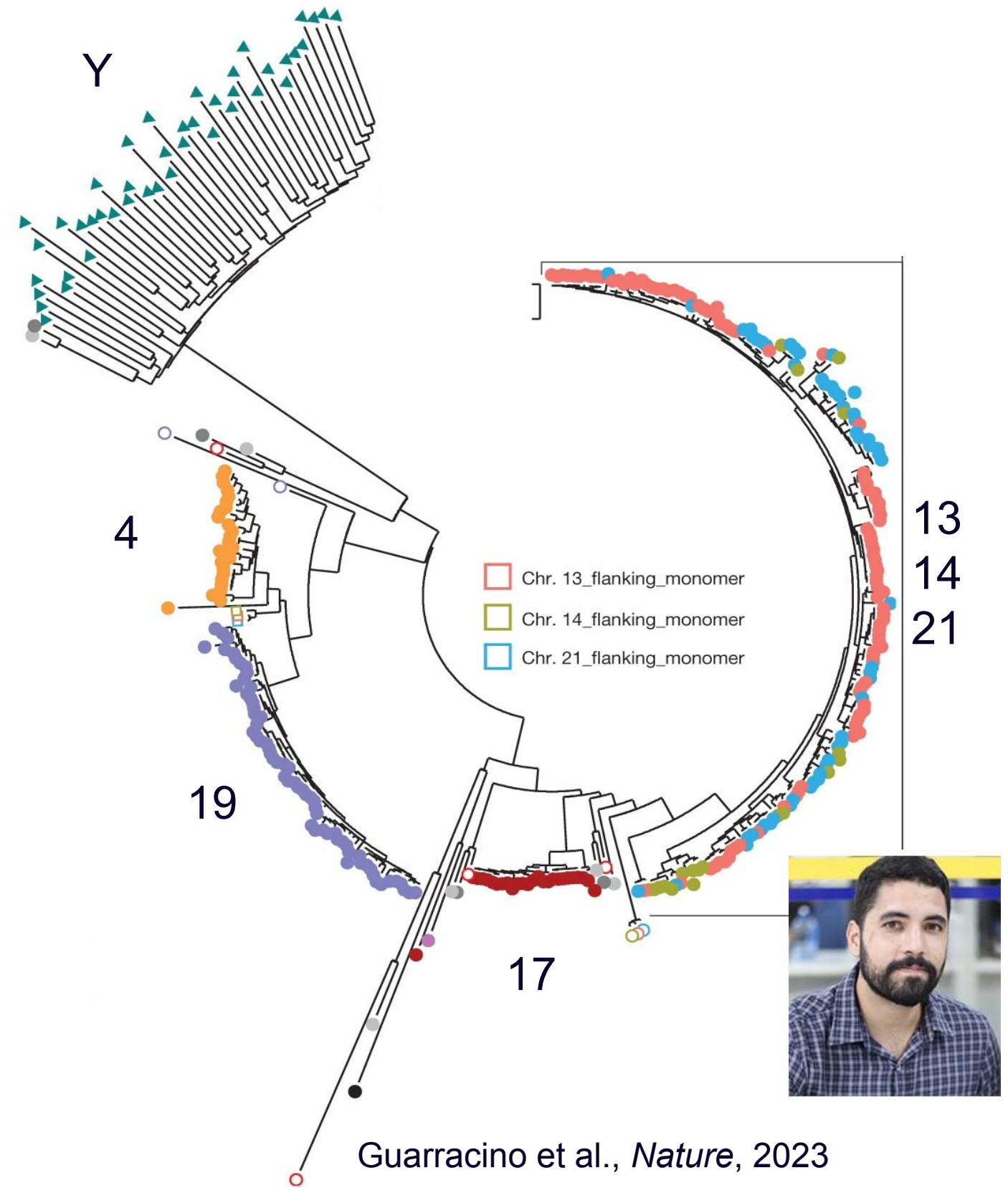
— hifi — ont



SST1-a key regulator of structural variation

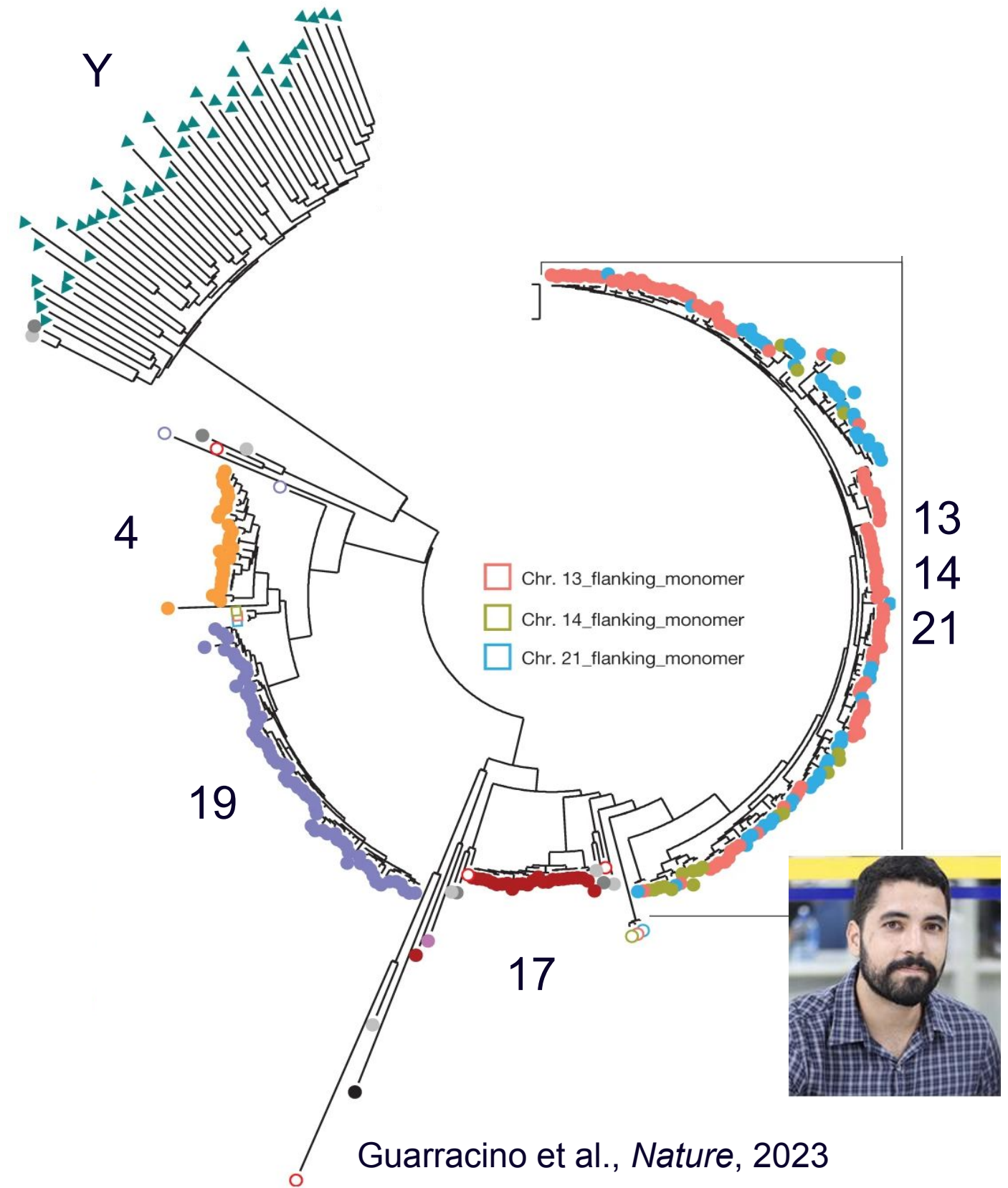
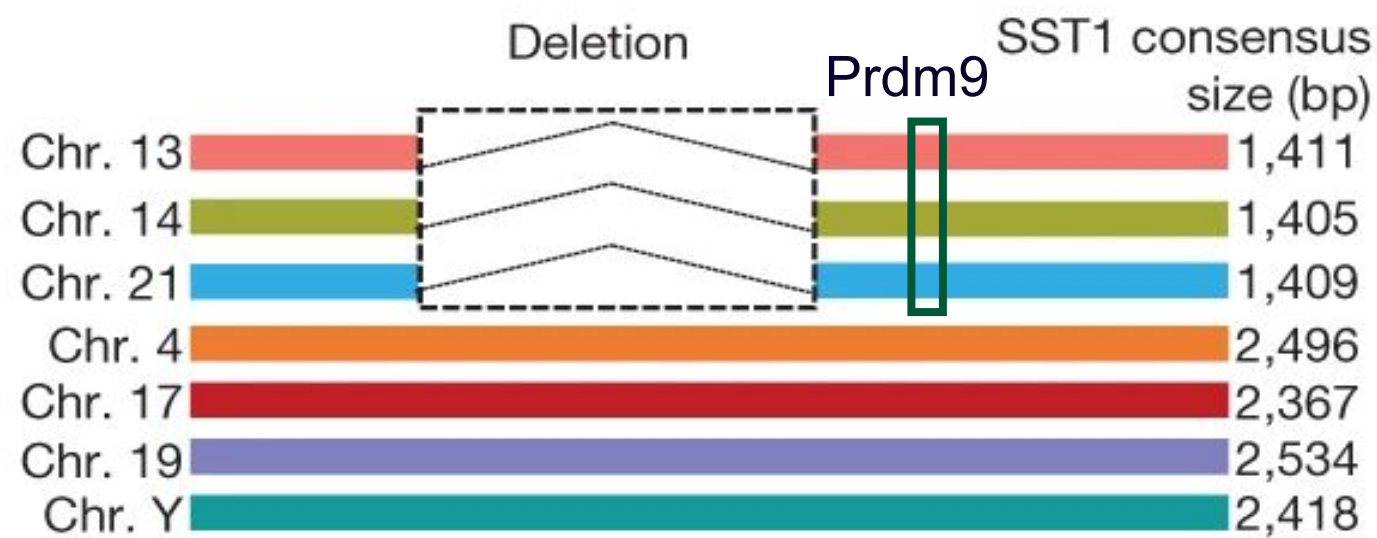


Phylogenetic analysis indicates frequent recombination between SST1 repeats on acrocentric chromosomes

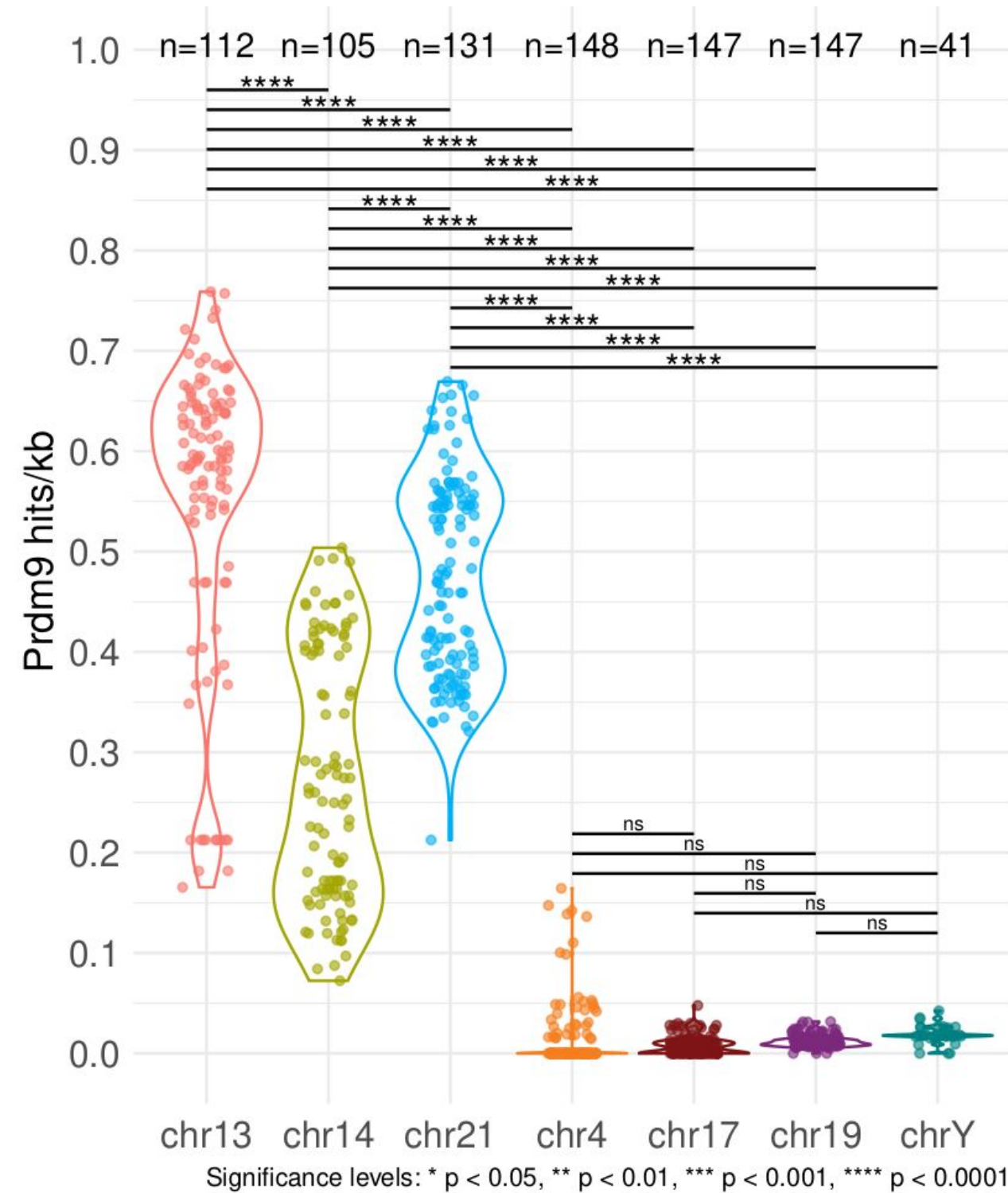


Guarracino et al., *Nature*, 2023

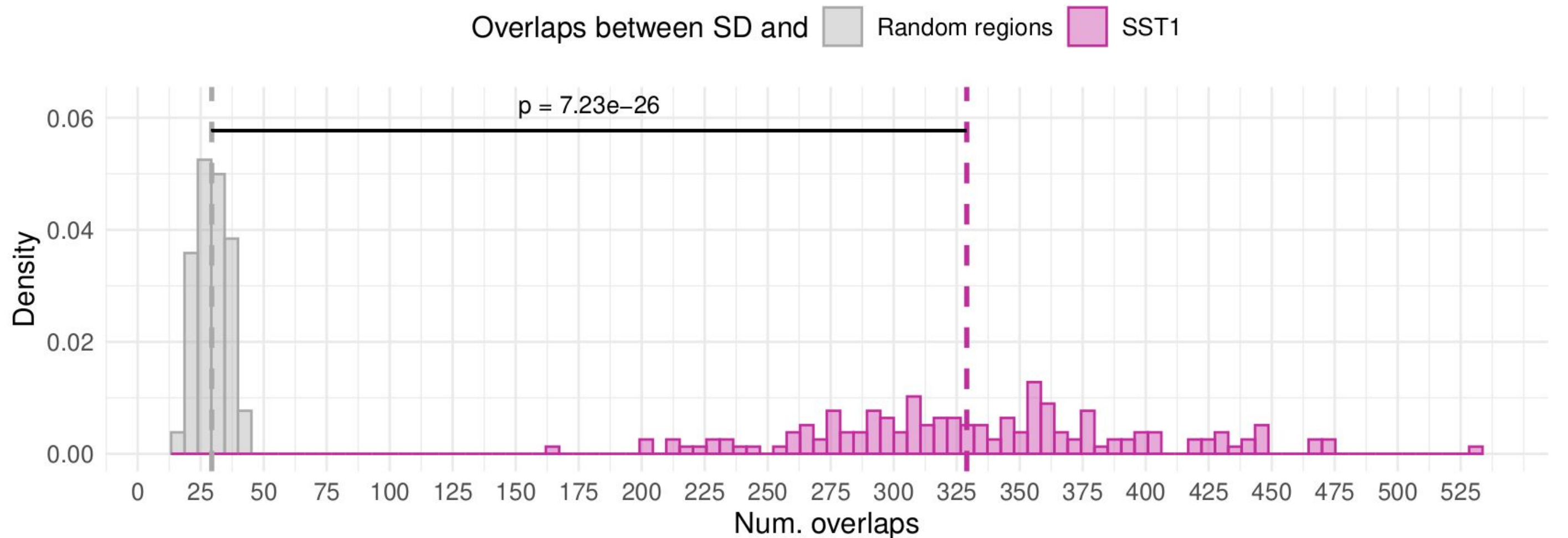
Phylogenetic analysis indicates frequent recombination between SST1 repeats on acrocentric chromosomes



Density of Prdm9 sites in SST1 in the pangenome



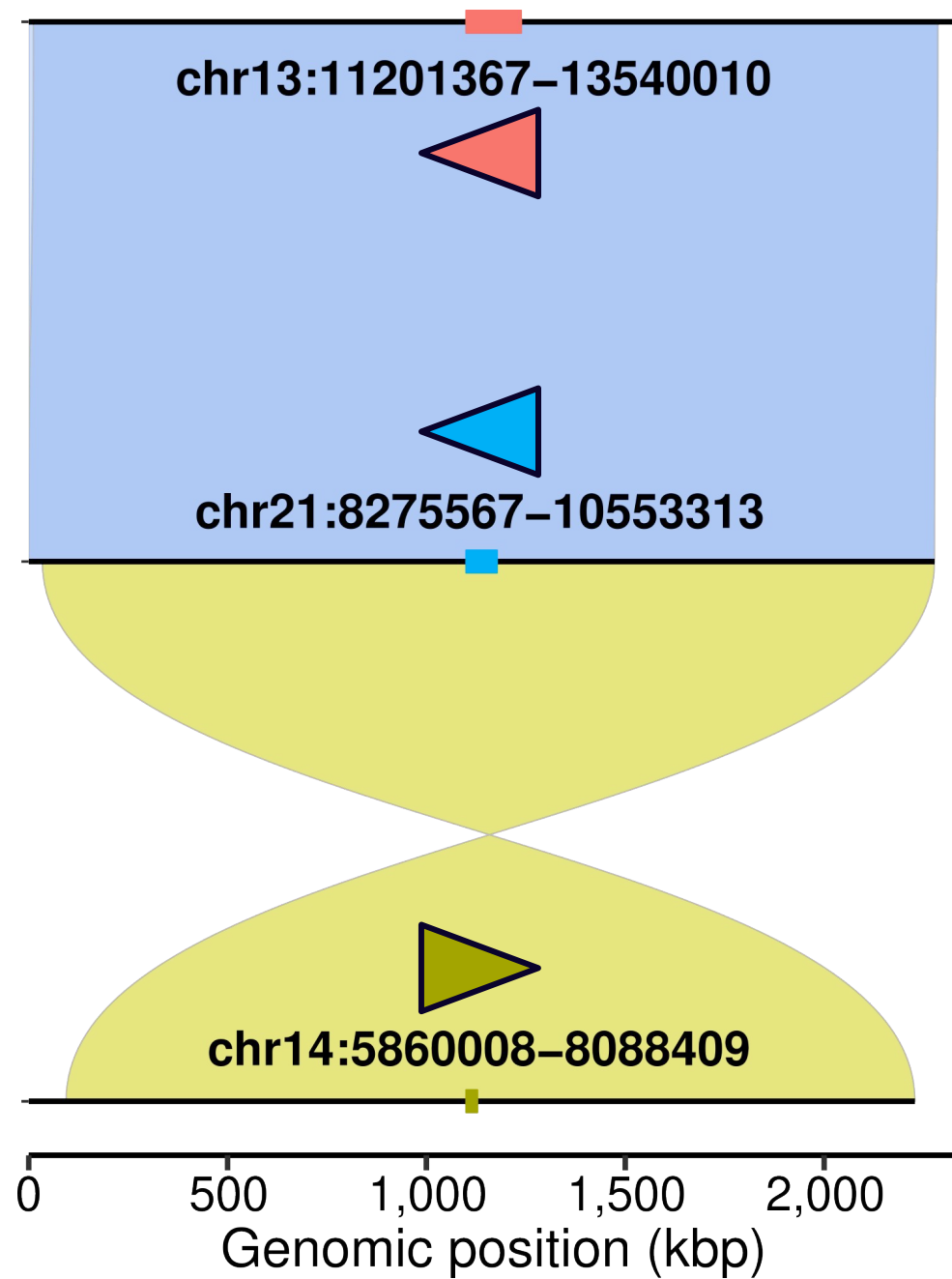
Association between SST1 and segdups



Wilcoxon signed-rank test, paired

PHR polymorphisms

CHM13



Annotation

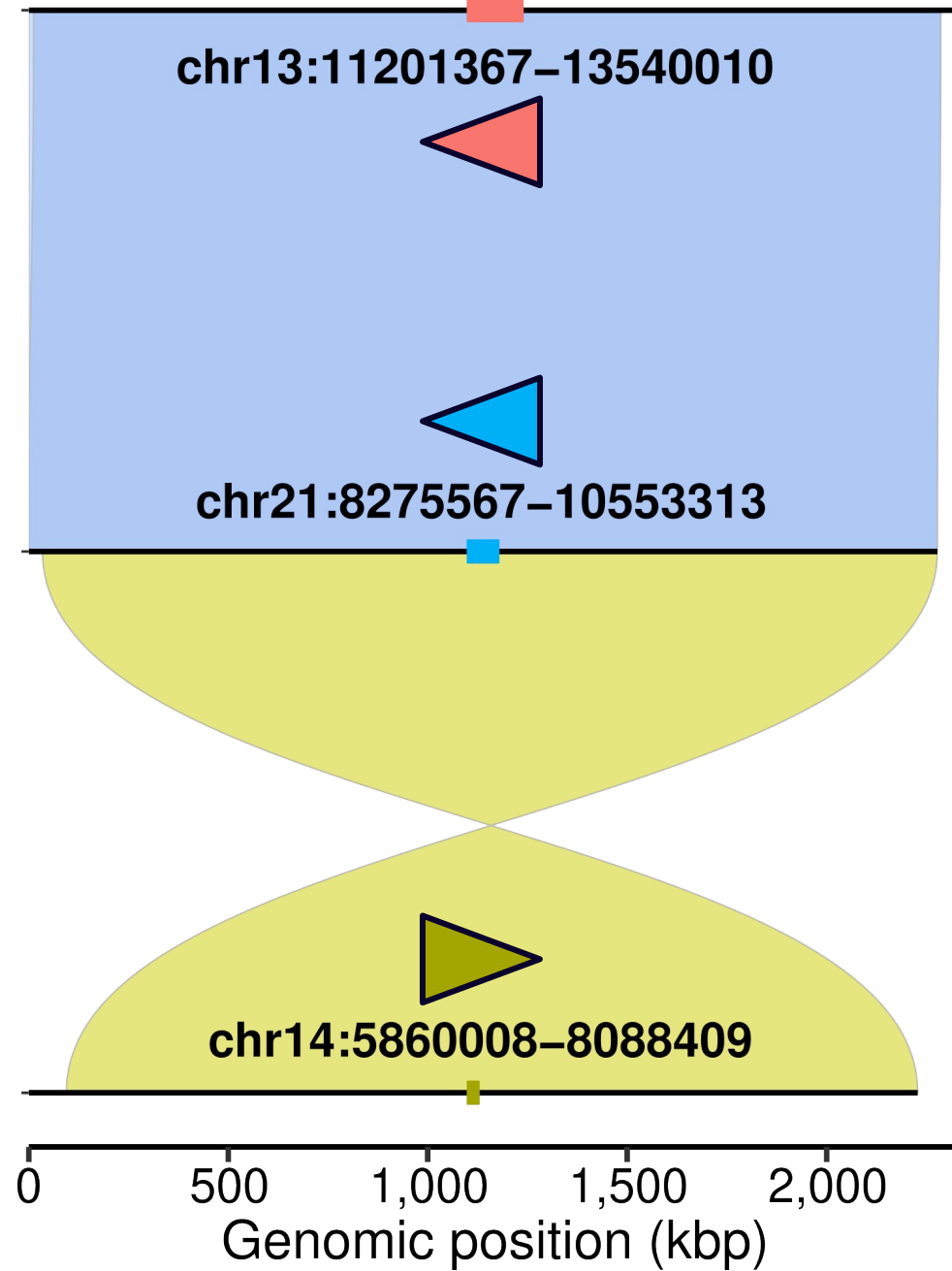
- SST1_chr13
- SST1_chr14
- SST1_chr21

Alignment
direction

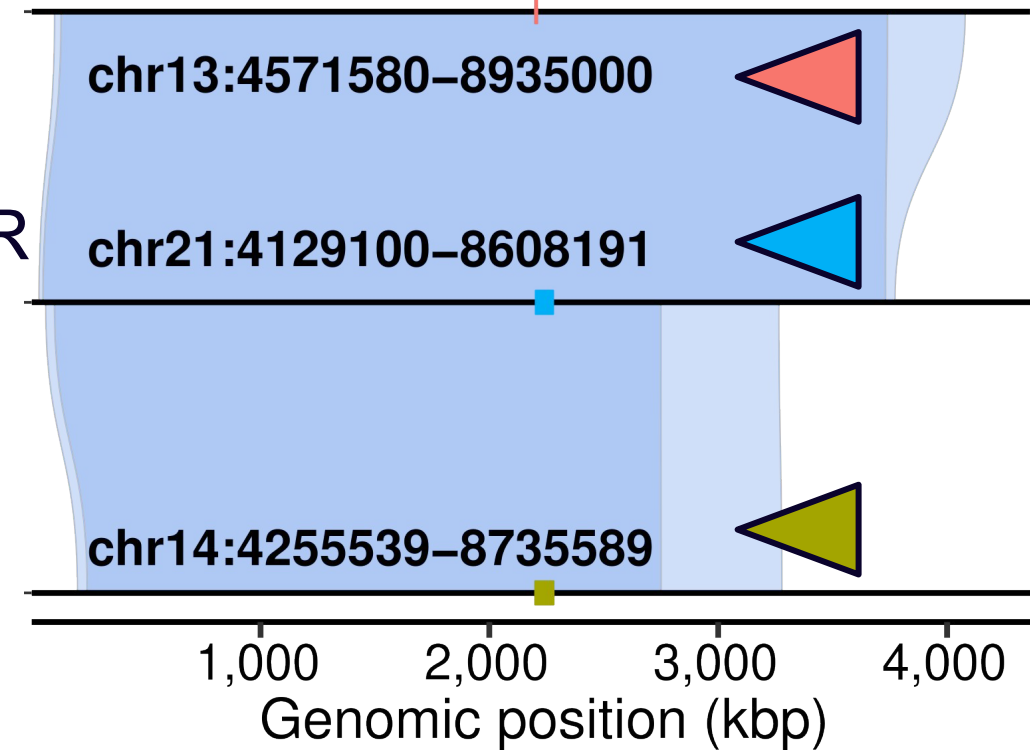
-
- +

PHR polymorphisms

CHM13



HG0544#M



Reversed PHR
(chr13 ?%
chr14 ~1%)

Annotation

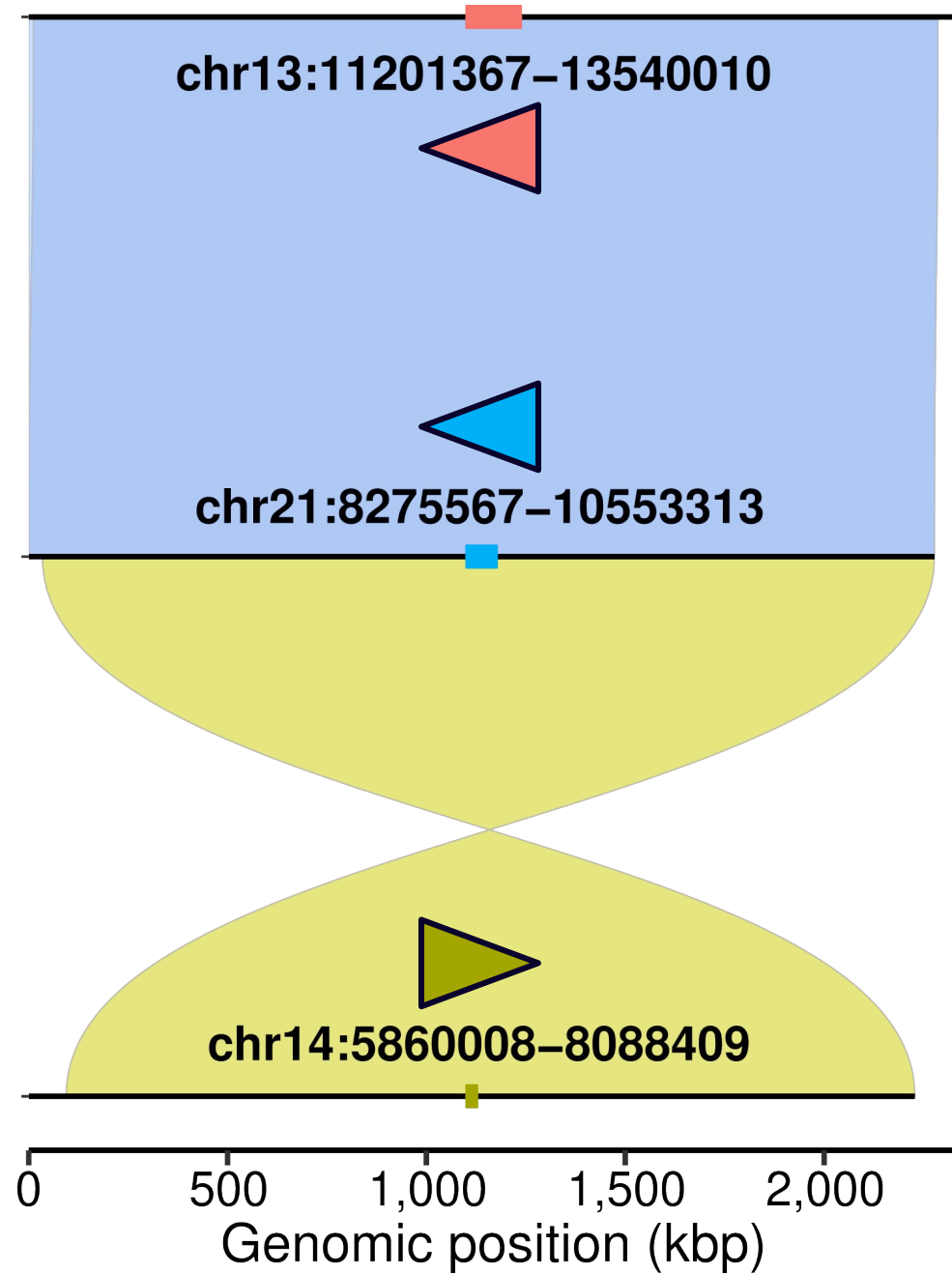
- SST1_chr13
- SST1_chr14
- SST1_chr21

Alignment
direction

-
- +

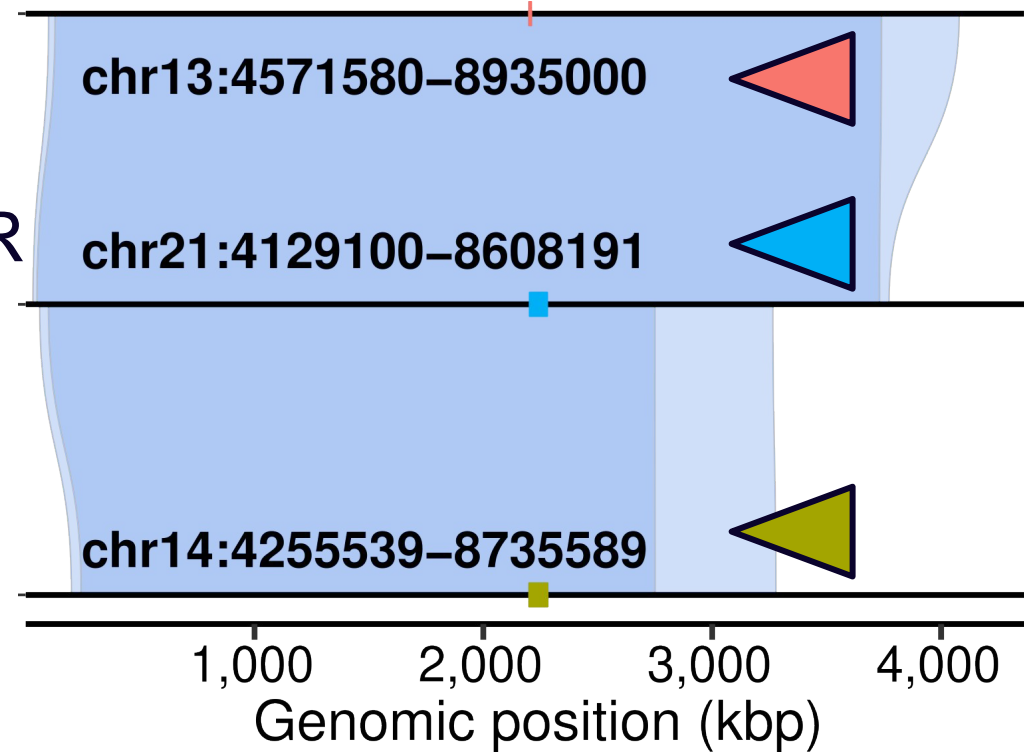
PHR polymorphisms

CHM13

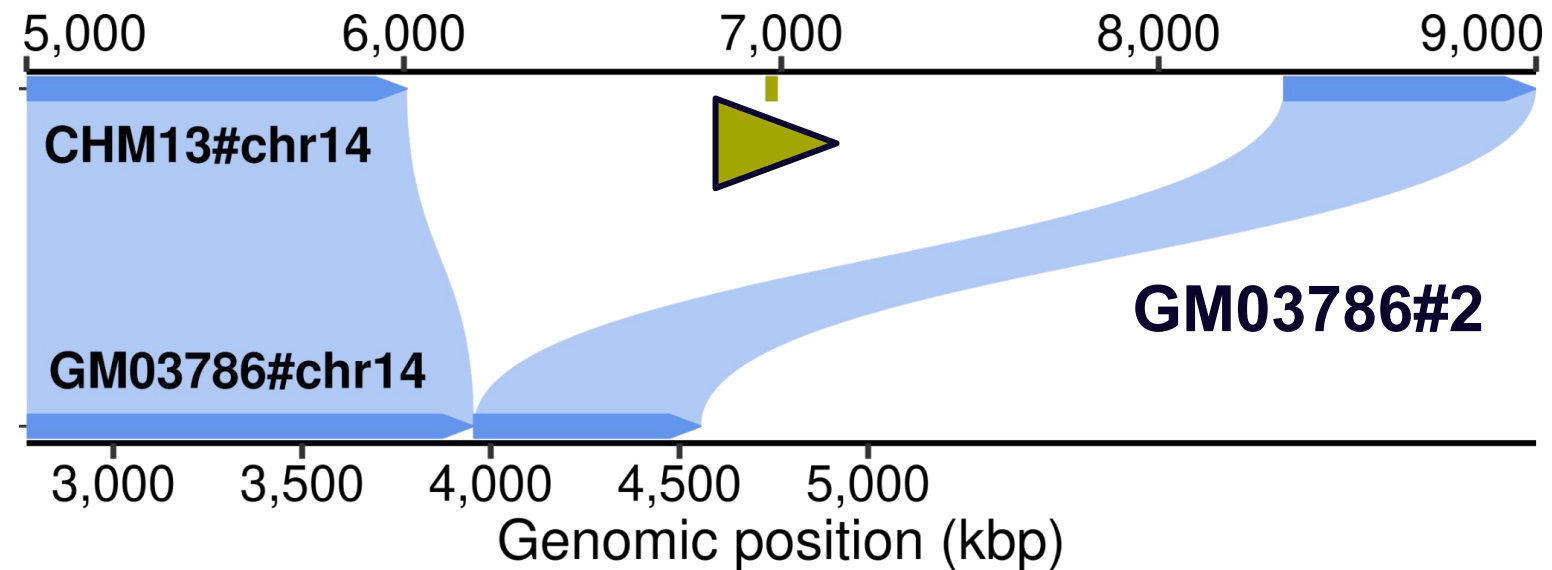


Reversed PHR
(chr13 ?%
chr14 ~1%)

HG0544#M



Deleted PHR
(chr13 <1%
chr14 ~25%)



Annotation

- SST1_chr13
- SST1_chr14
- SST1_chr21

Alignment direction

- -
- +

Summary

- The formation of Robertsonian chromosomes depends on homology, proximity, and recombination initiation
- Robertsonian chromosomes can propagate as functional monocentrics or dicentrics
- The macrosatellite SST1 may have a broad role in genome variation and chromosome evolution



Gerton team



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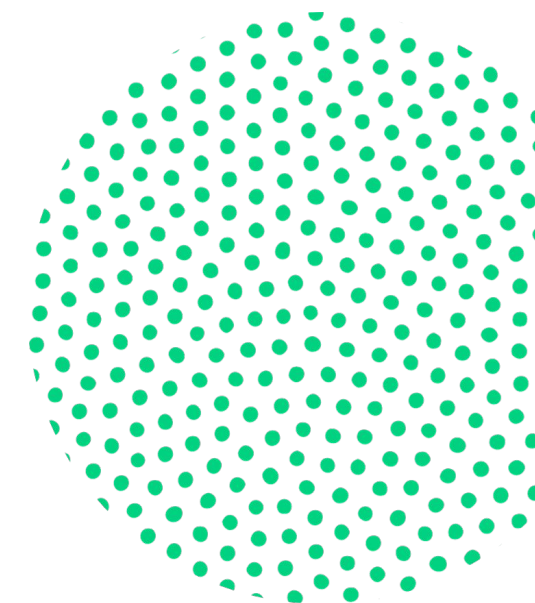
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Andrea Guaracino (UTHSC)





Garrison team



Erik Garrison (UTHSC) Andrea Guaracino (UTHSC)

Gerton team



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Phillippy team



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Adam Phillippy (NHGRI)

