Lessons from the amylase locus

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Seymour Marine Discovery Center, Santa Cruz, USA
2024/09/05

Panteam










- Human Technopole, Italy
- UTHSC, Tennessee
- UC Berkeley, California
- GeneDX and others, California

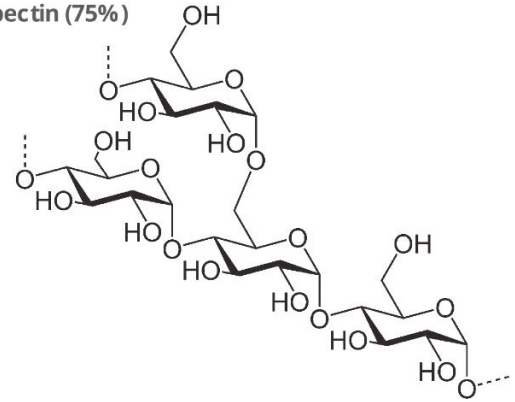
Outline

- Introduction
- Method
- Result

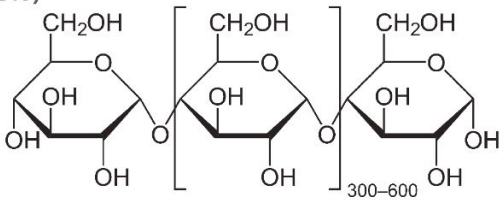
Amylase breaks down starches to sugars

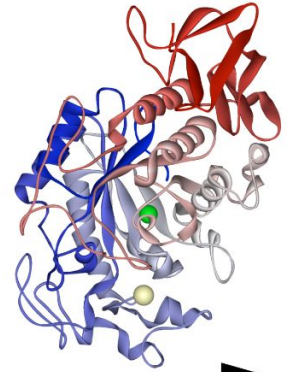
Starch

amylopectin (75%)



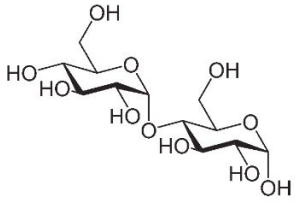
amylose (25%)



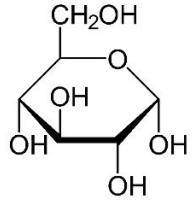


human salivary
α amylase

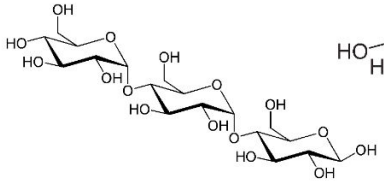
Sugar



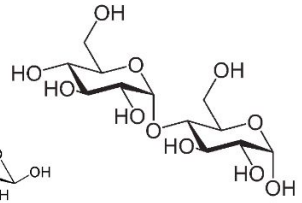
Maltose



Glucose



Maltotriose



Maltose

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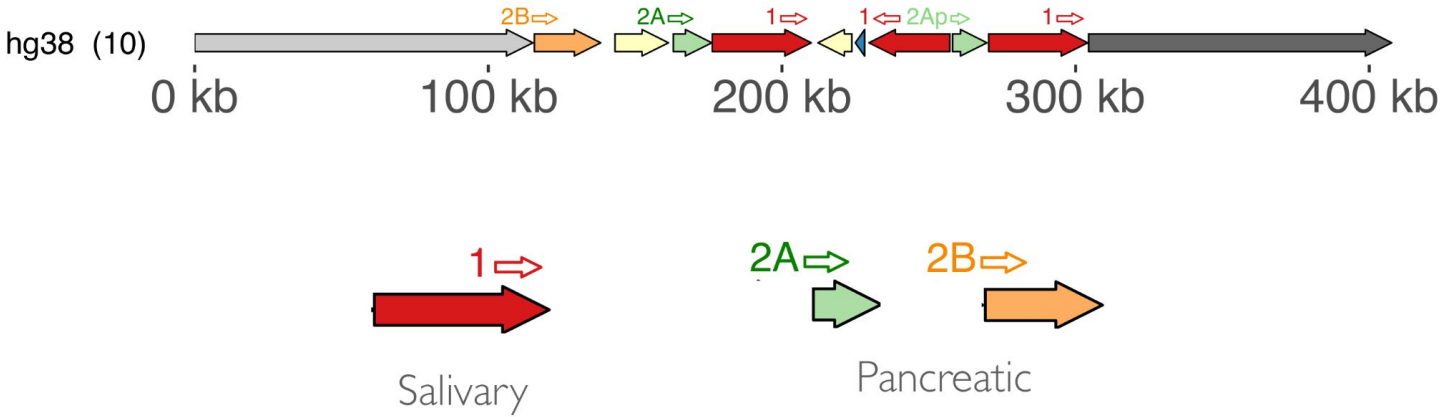
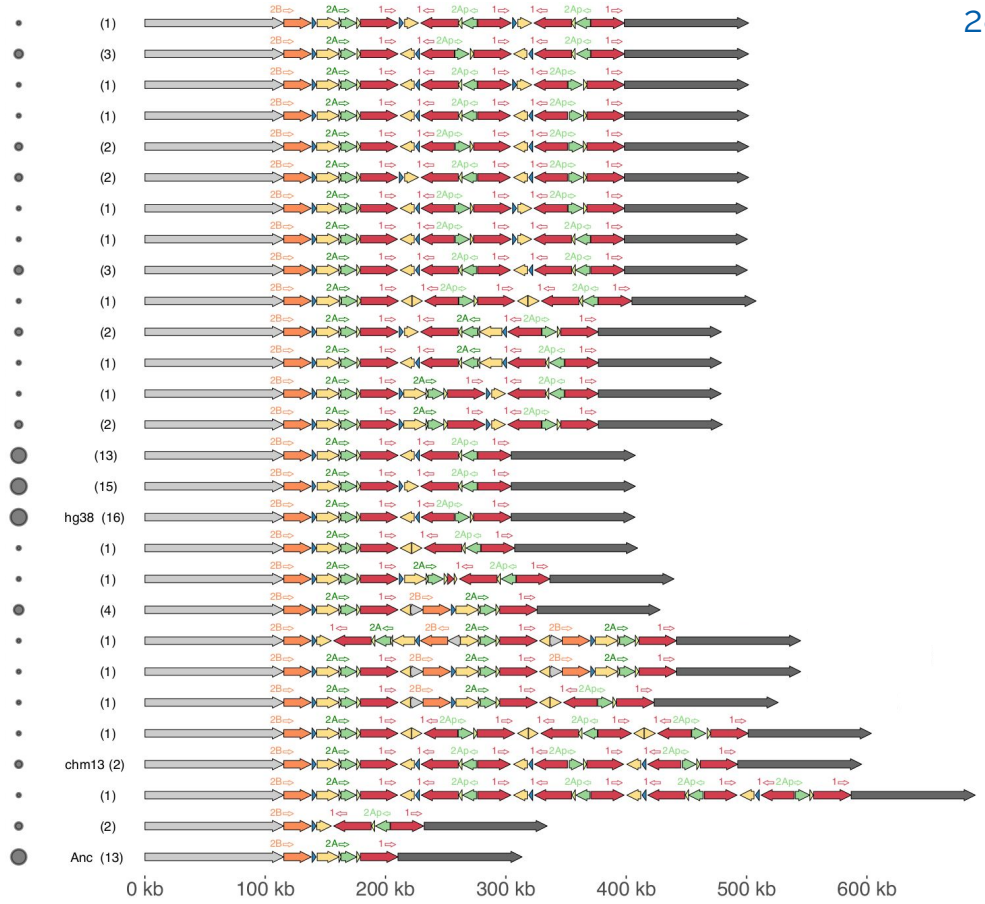
Amylase is a multi-copy gene family

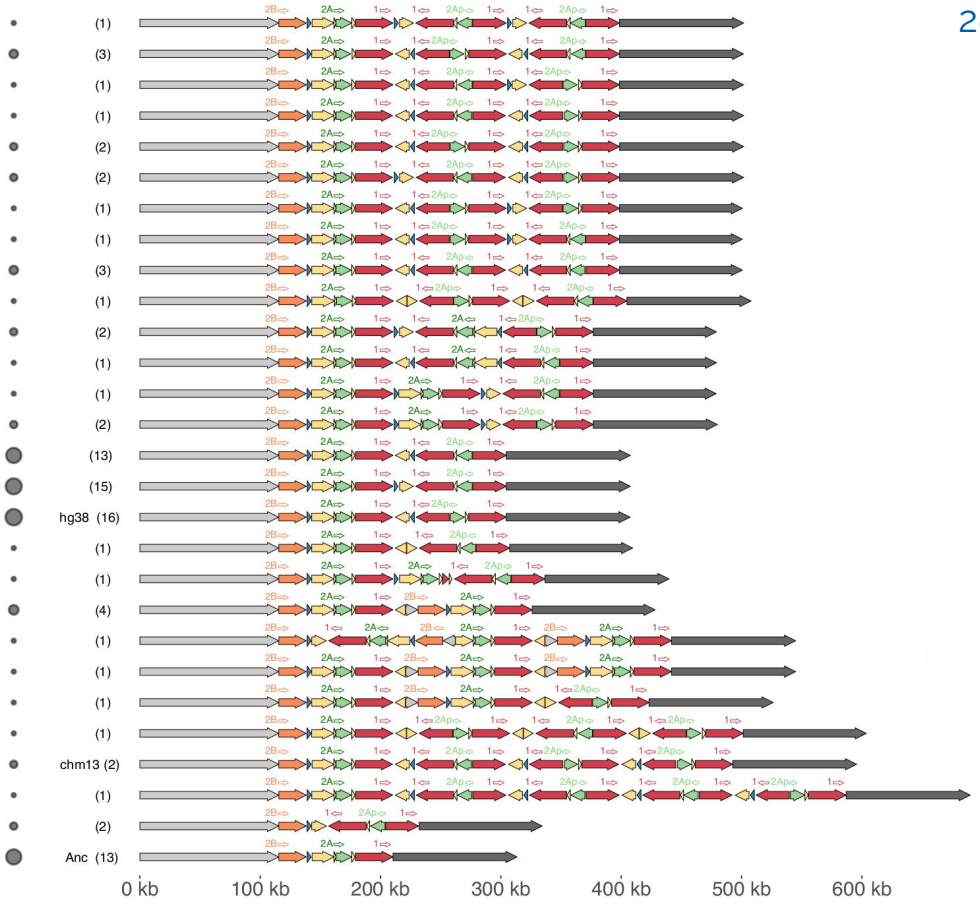


Human amylase copy number diversity

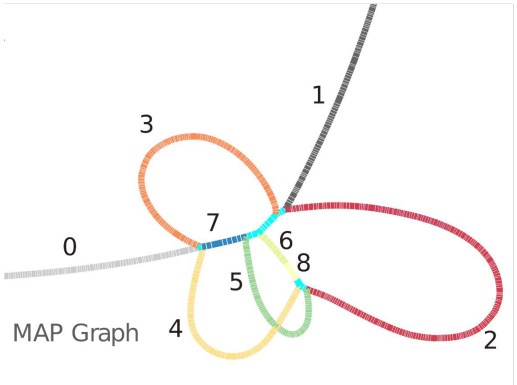


28 amylase structural haplotypes

Human amylase copy number diversity



28 amylase structural haplotypes



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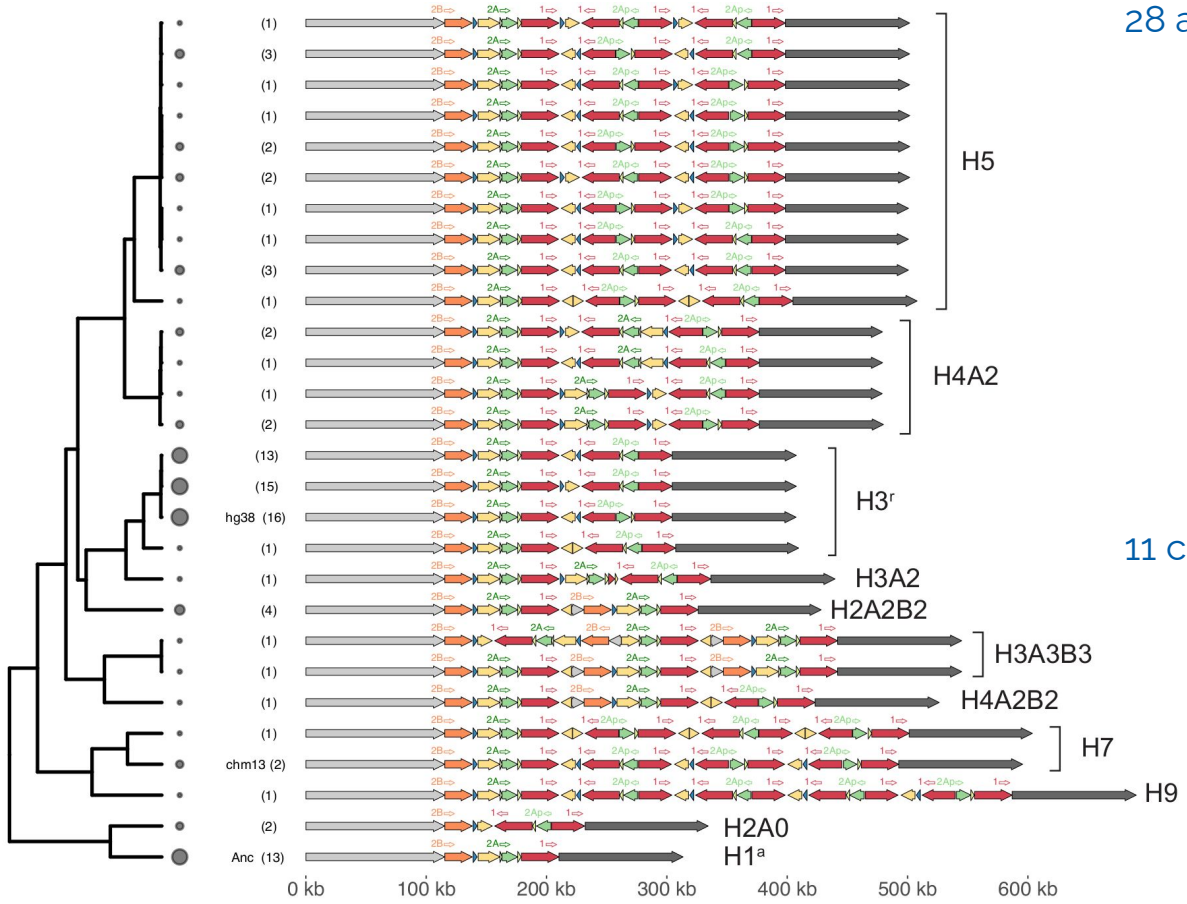

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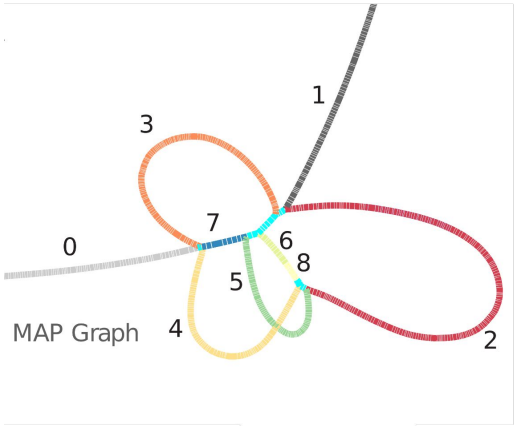
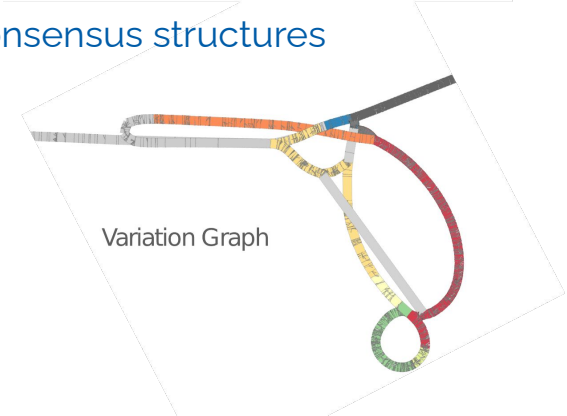
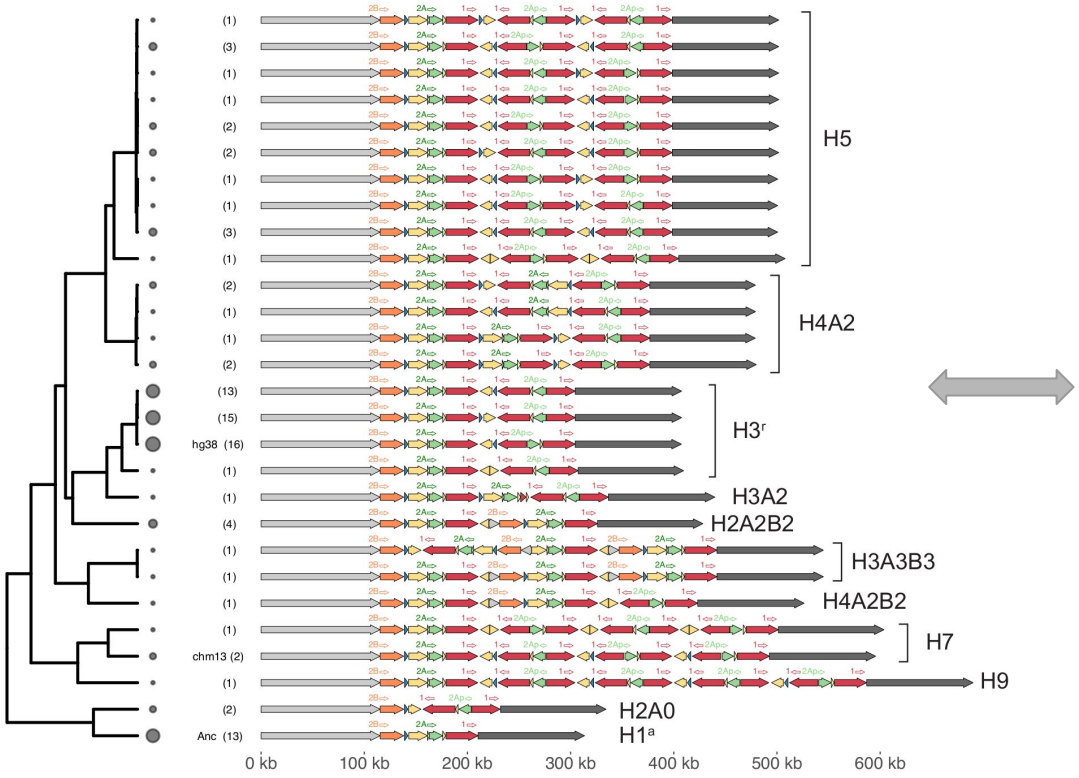
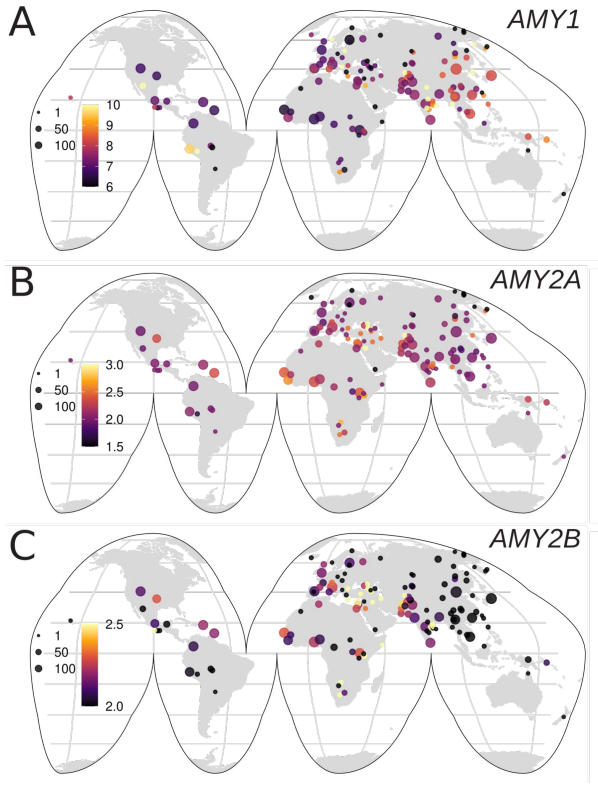


11 consensus structures



We want more





94 long read haplotypes

~5600 short read haplotypes

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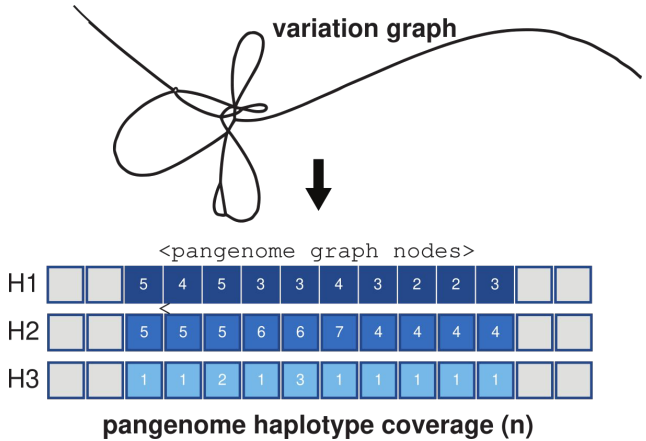
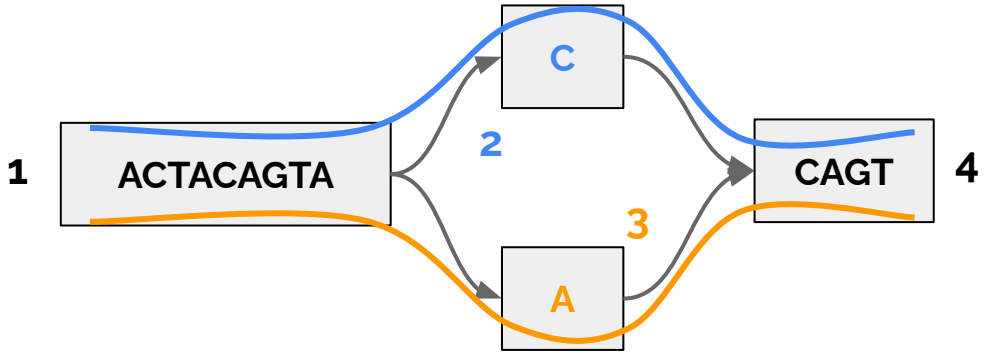


Node coverage matrix

Genome 1: **ACTACAGTACCAGT**

Genome 2: **ACTACAGTAACAGT**



ACTACAGTA	C	A	CAGT
1	2	3	4

Node coverage matrix

Genome 1: **ACTACAGTACCAGT**

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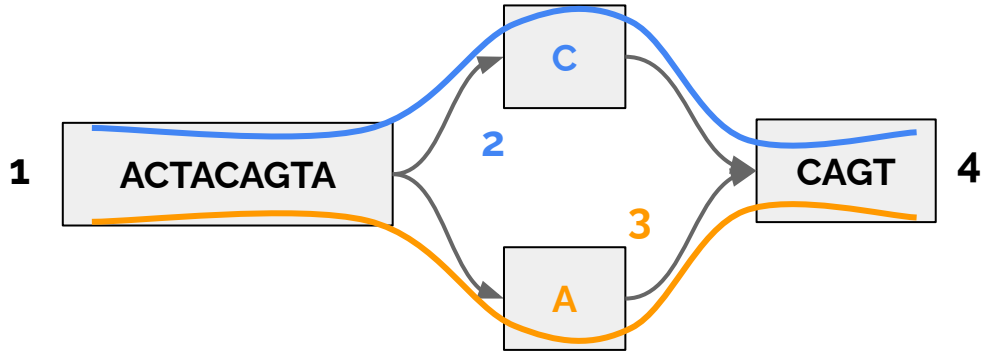

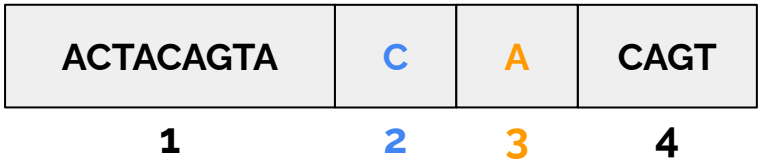

Path coverage matrix

	1	2	3	4
Genome 1	1	1	0	1
Genome 2	1	0	1	1

Node coverage matrix

Genome 1: **ACTACAGTACCAGT**

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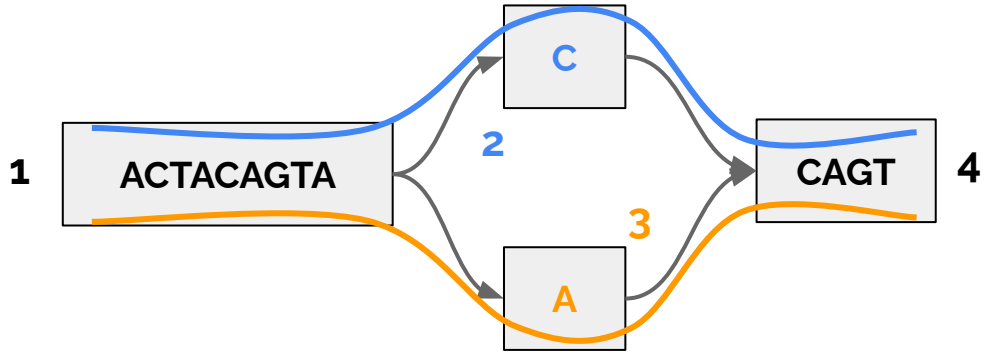

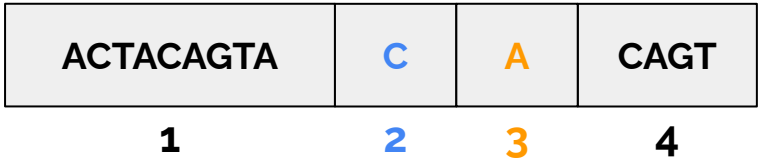

Path coverage matrix

	1	2	3	4
Genome 1	1	1	0	1
Genome 2	1	0	1	1

Sample coverage matrix

	1	2	3	4
Sample 1	29	31	1	27
Sample 2	28	0	30	28

Graph-based genotyping with COSIGT

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https://github.com/davidebolo1993/cosigt

COSIGT

COSINE SIMILARITY-BASED GENOTYPER

Graph-based genotyping with COSIGT

build ROI-specific graph

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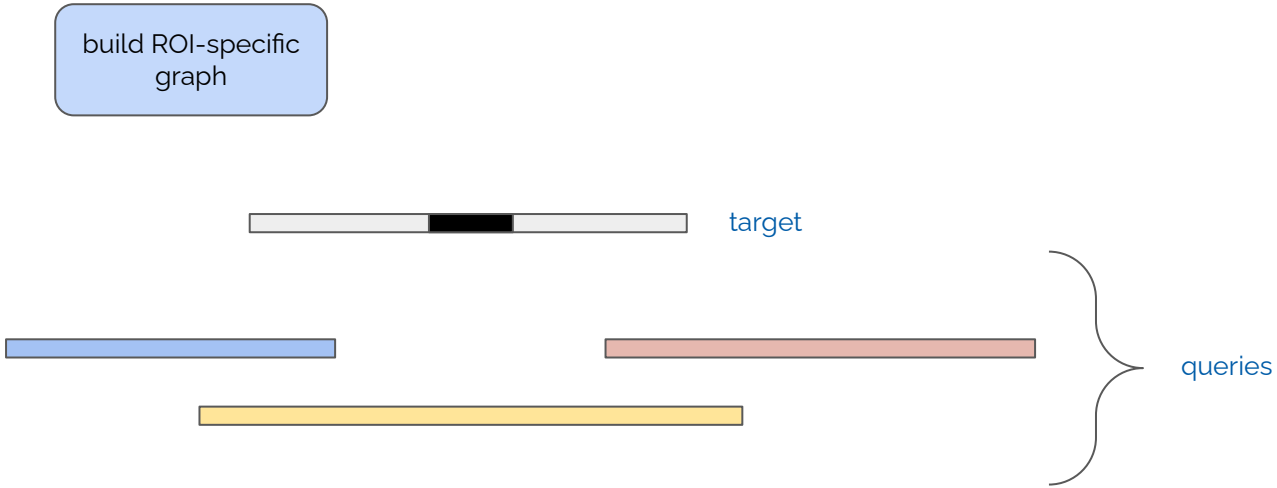

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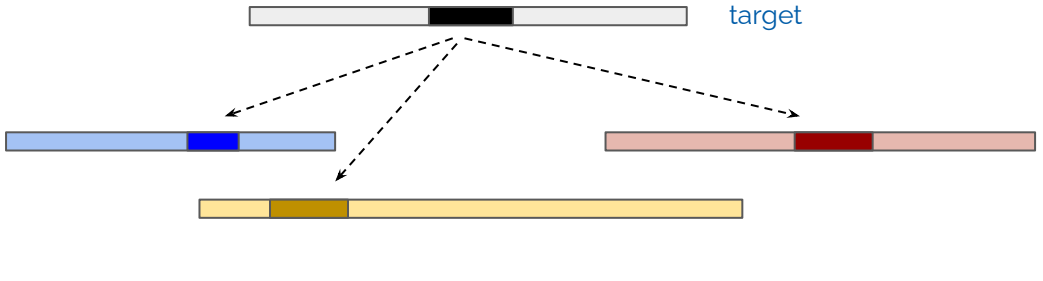

IMPG

impg

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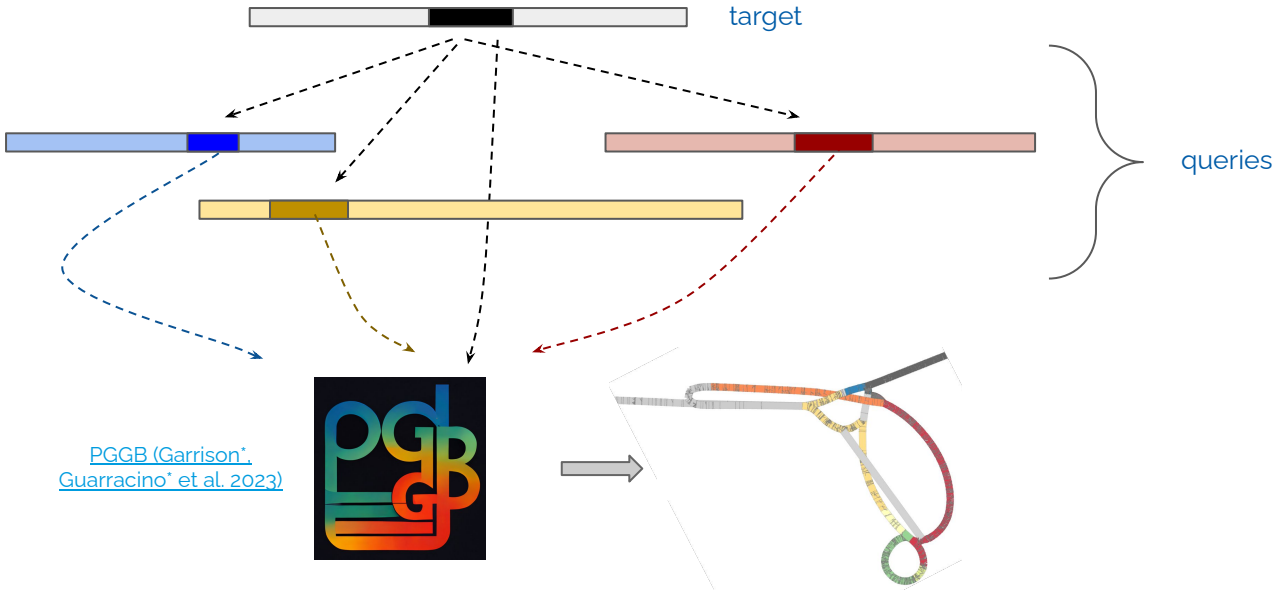

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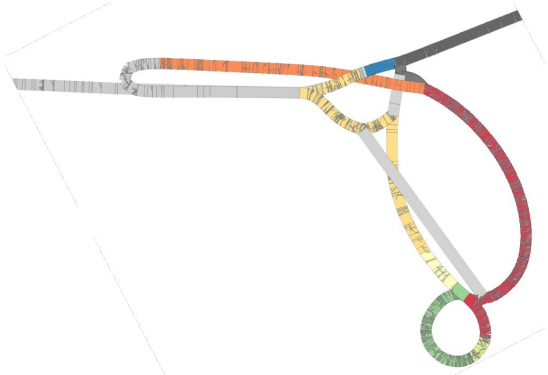
build ROI-specific graph → compute path coverage matrix



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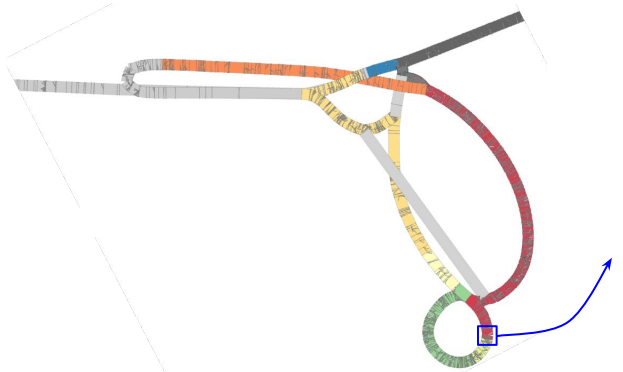
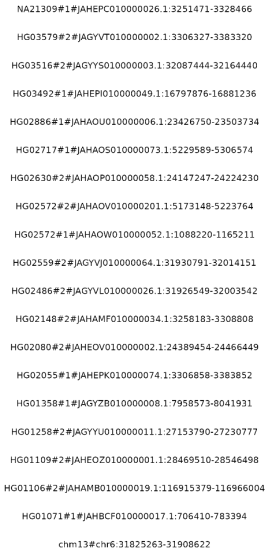
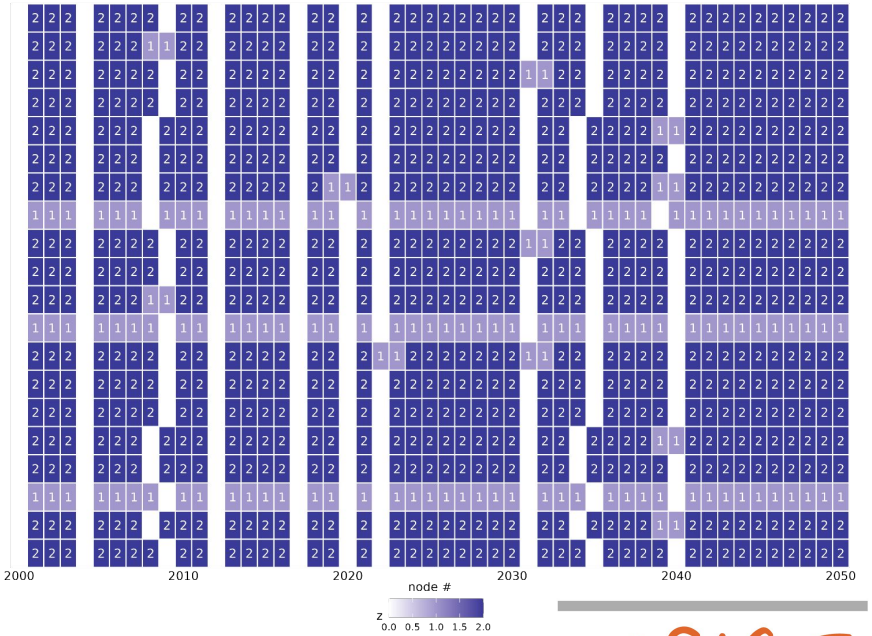


ODGI (Guarracino, Heumos et al., 2022)





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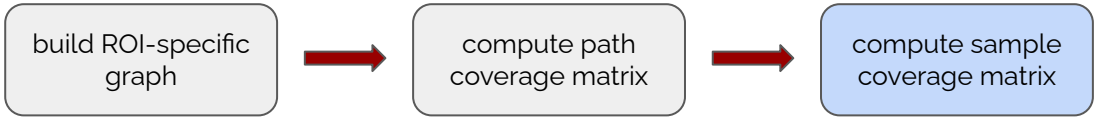

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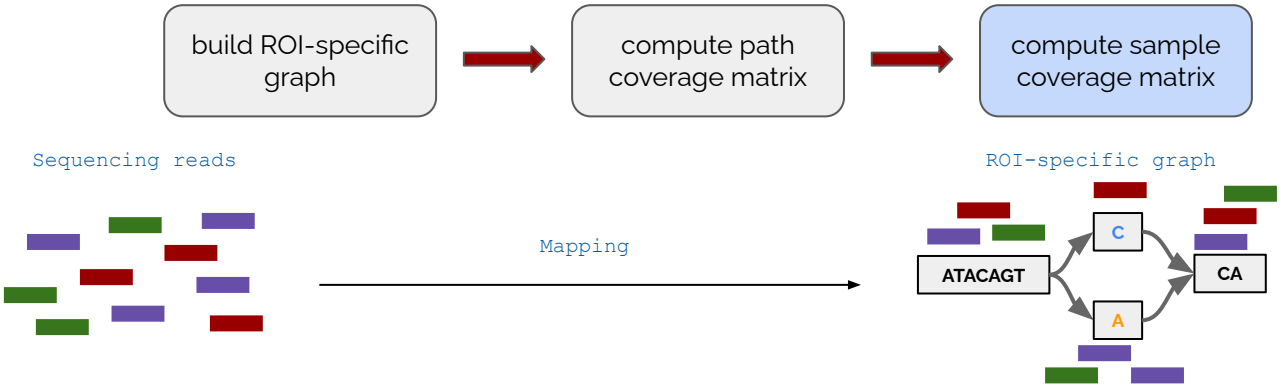

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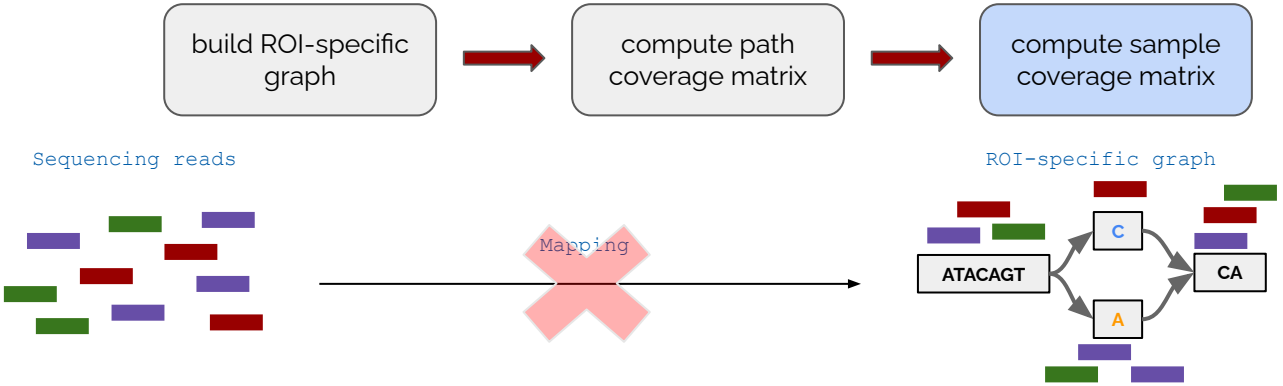

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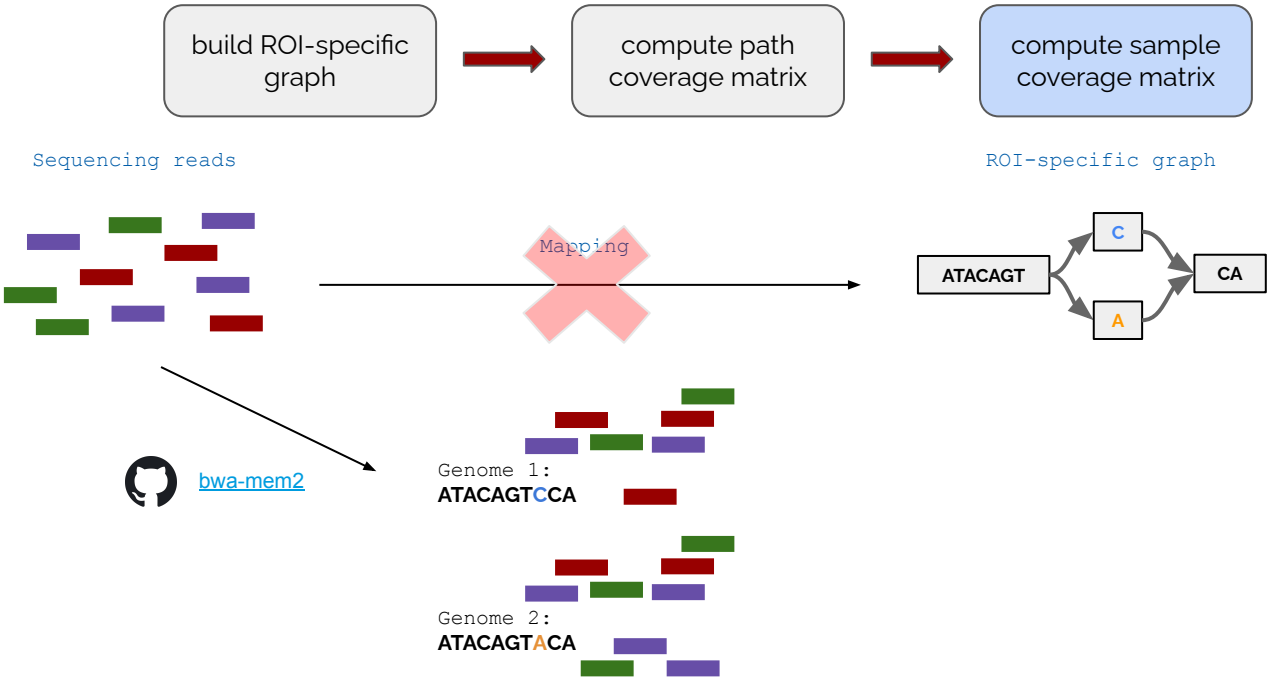

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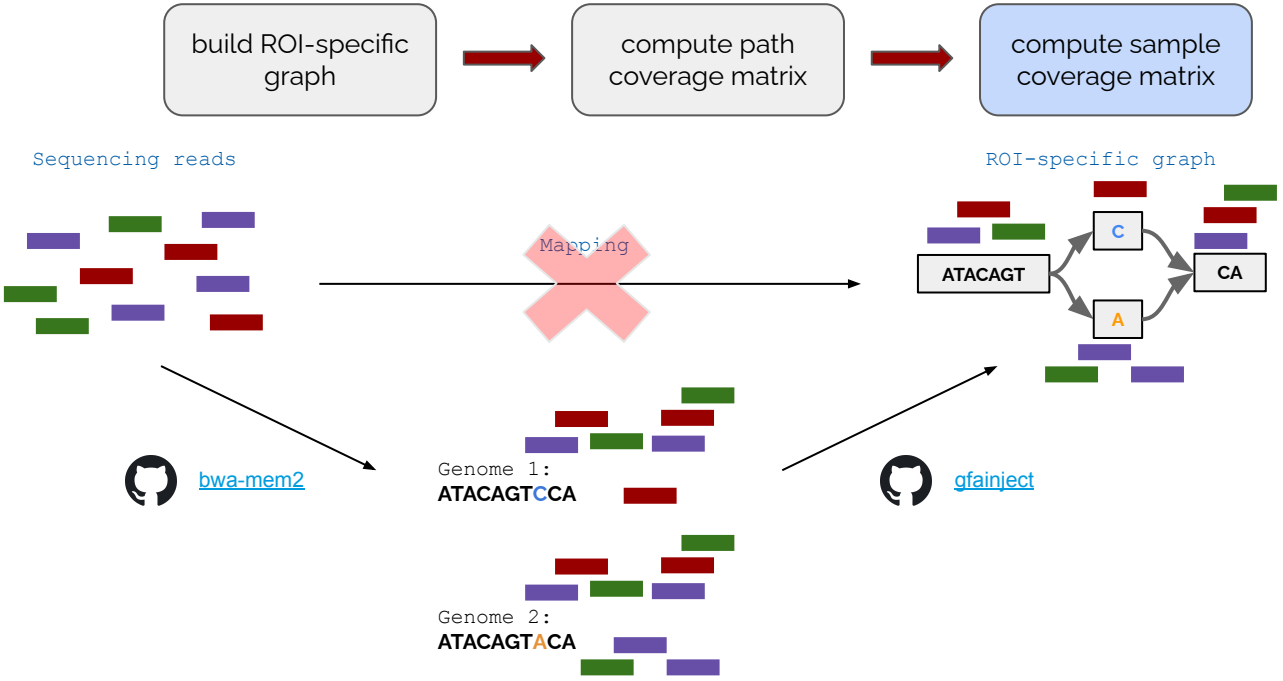

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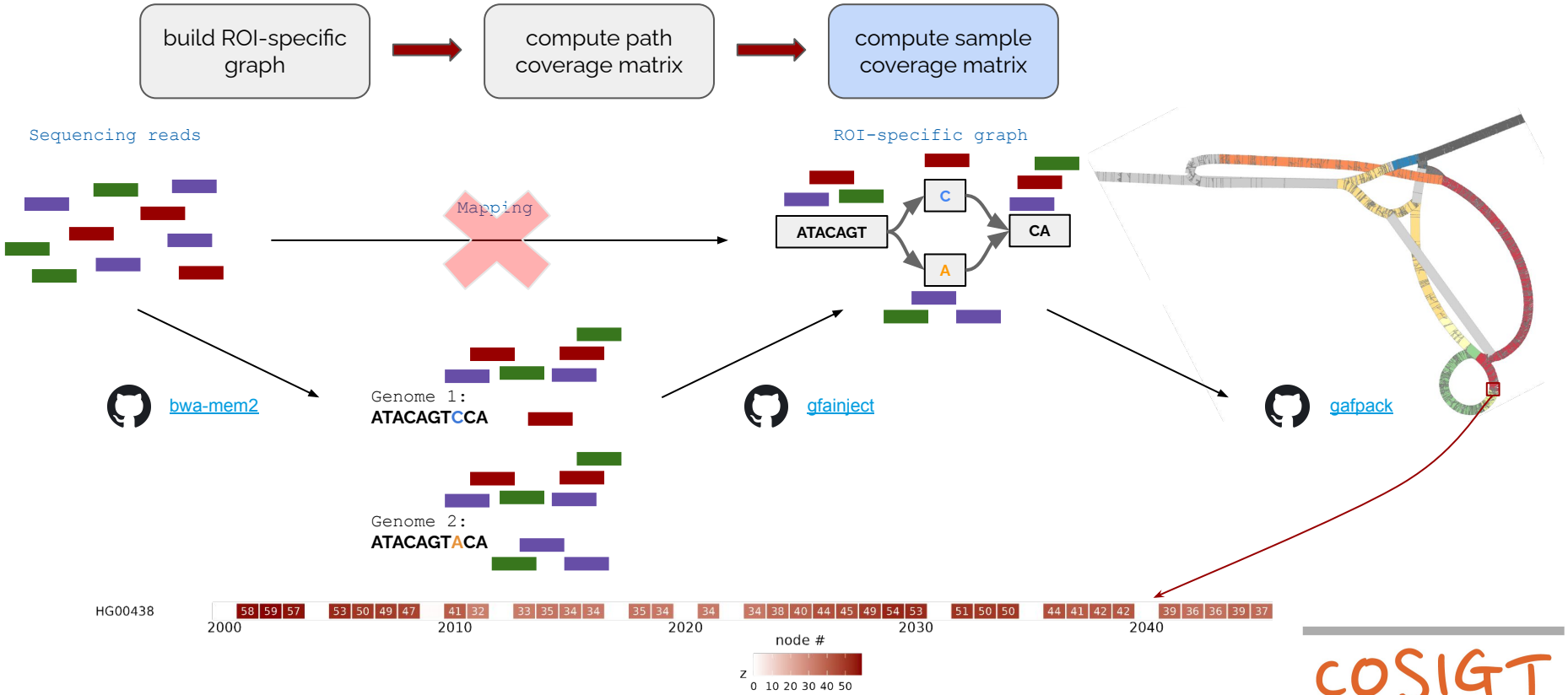

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haplotype deconvolution: find the combination of *N* path coverage vectors best representing the trend observed in the sample coverage vector

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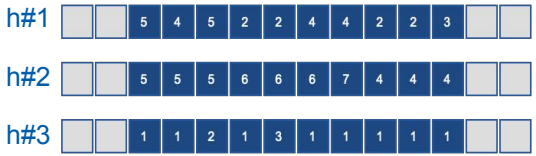
path coverage matrix



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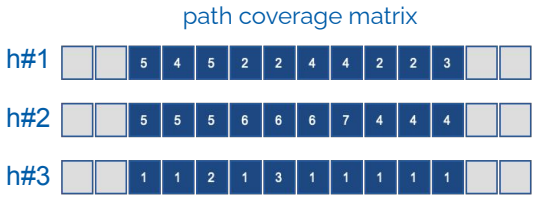

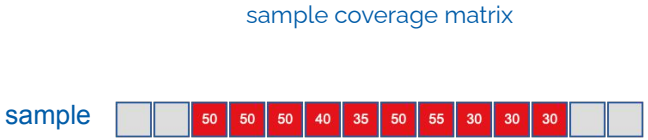

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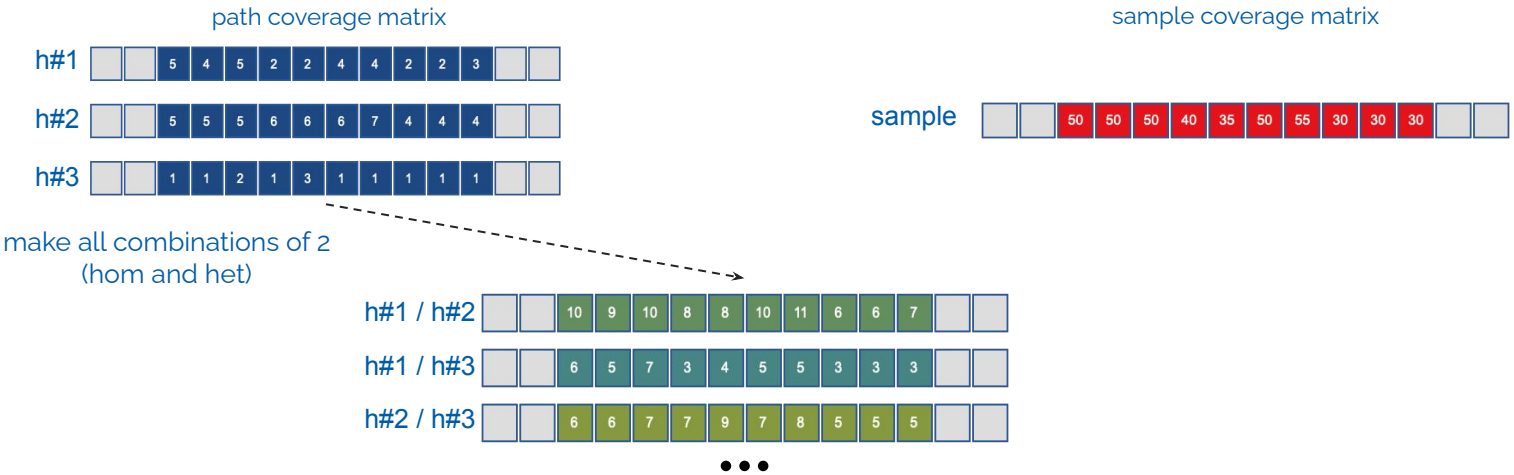

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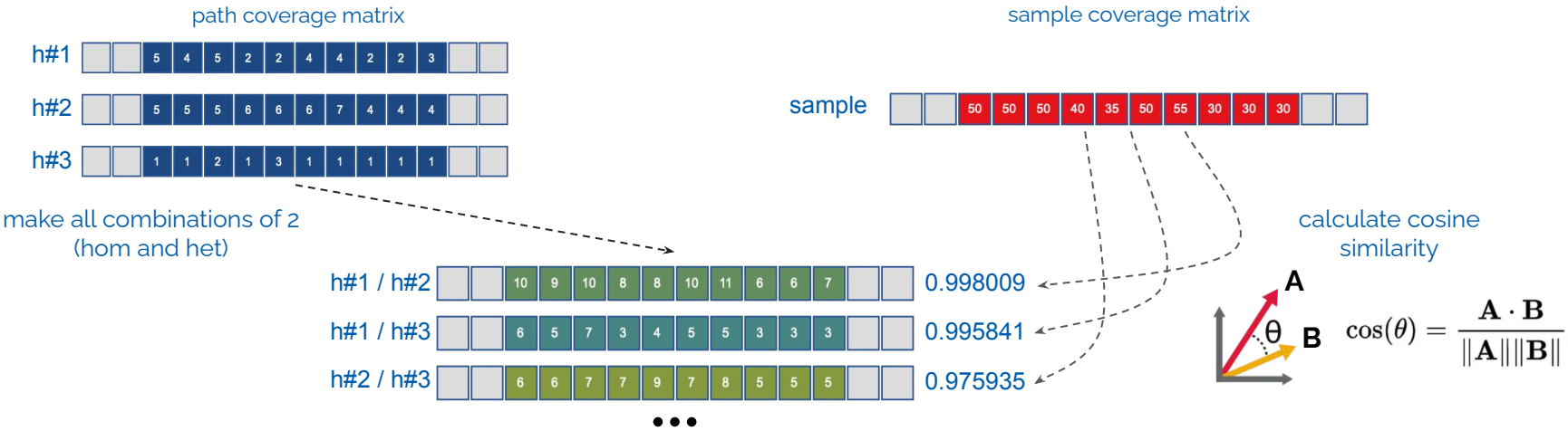

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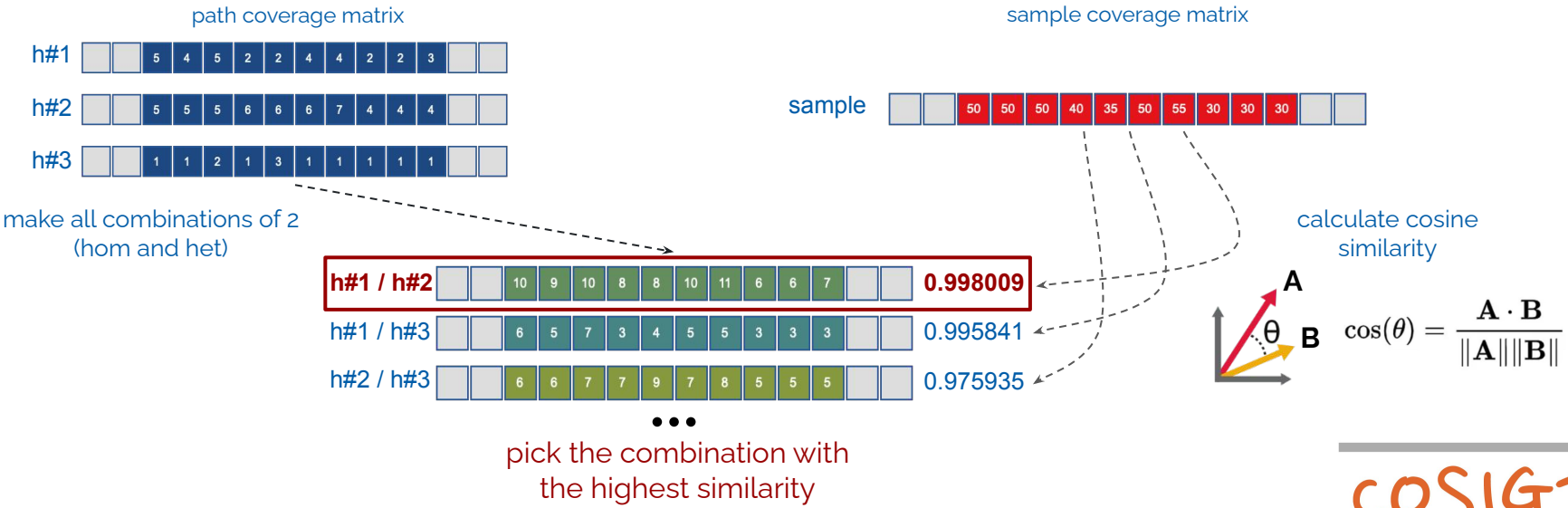

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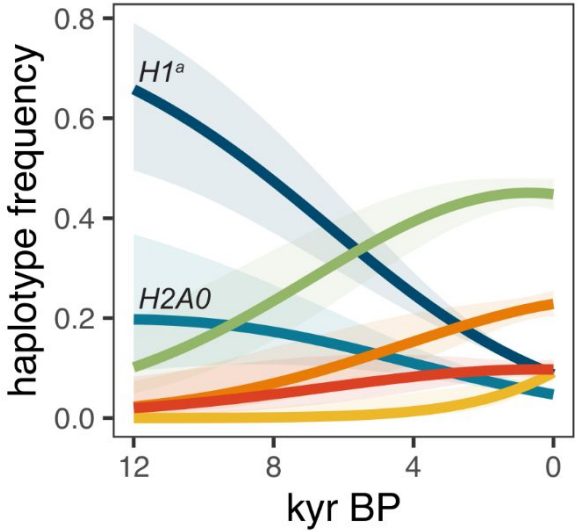
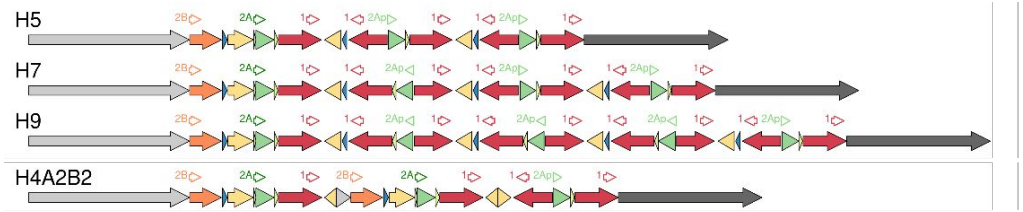
- Method
- Result

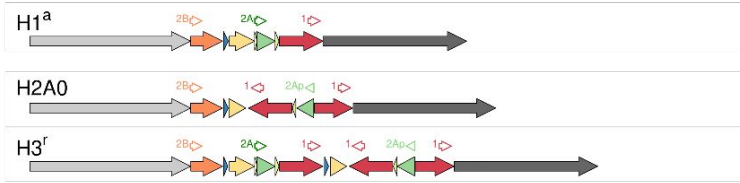


Allele frequencies of complex structural haplotypes

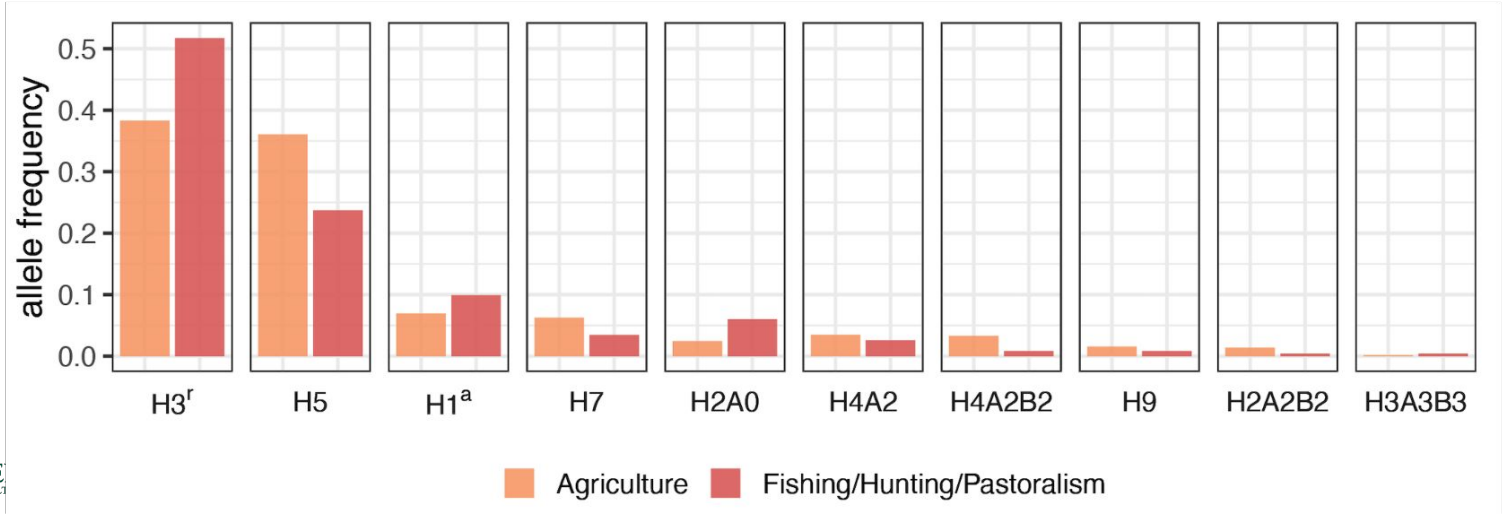
Pangenome-based haplotype deconvolution for ~5600 short read haplotypes



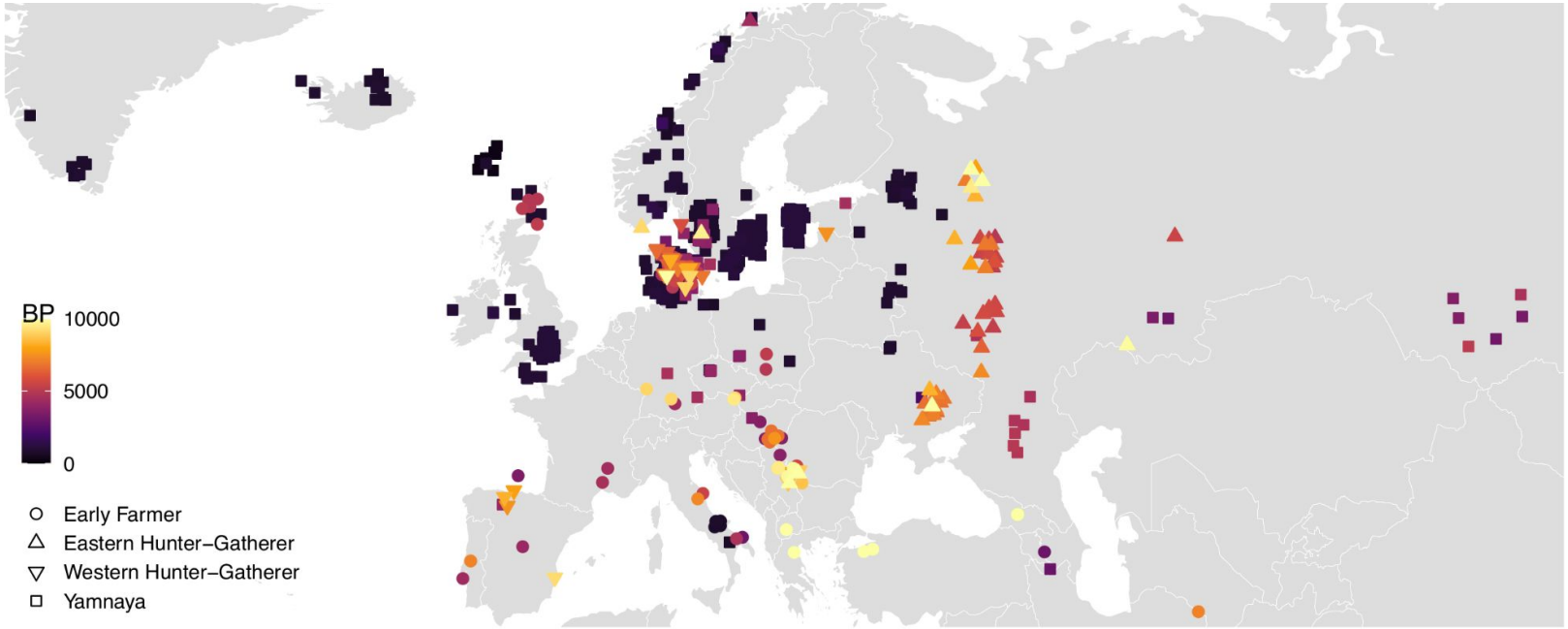
Agriculture enriched (LONG!)



Fishing/Hunting/Pastoralism Enriched (SHORT!)

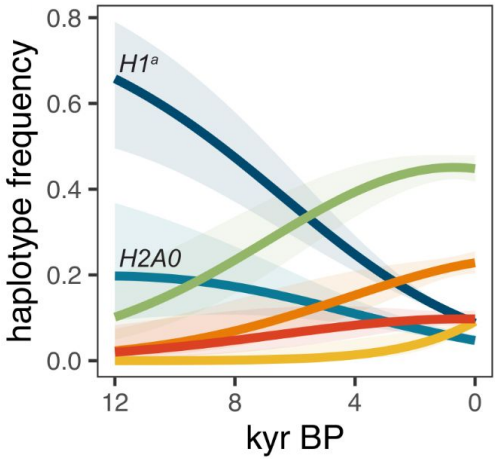


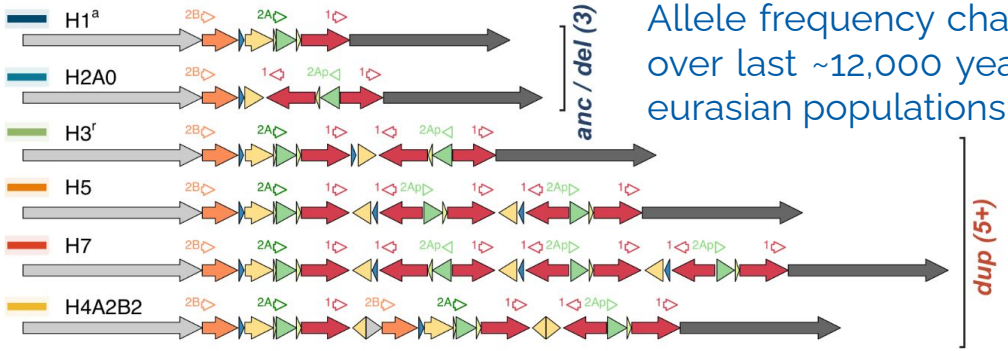
Recent evolution from 533 ancient European genomes



Data from Allentoft et al. 2024, Nature

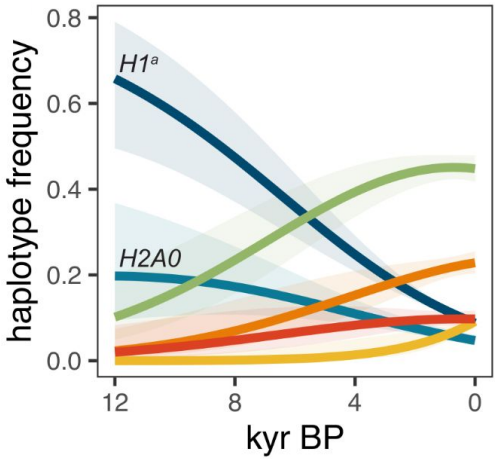
Evidence for selection of high-copy amylase haplotypes

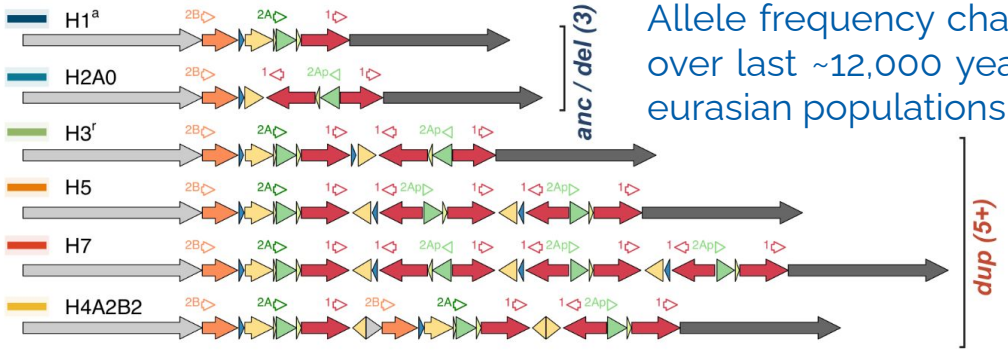




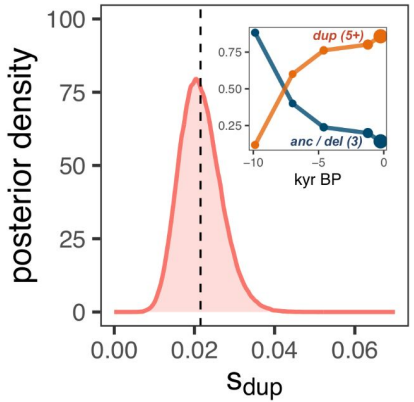
Allele frequency changes over last ~12,000 years in eurasian populations.

Evidence for selection of high-copy amylase haplotypes





Allele frequency changes over last ~12,000 years in eurasian populations.



Selection coefficient of 0.02 is equivalent to selection at lactase (Mathieson, 2020).

Panpublication

Article

Recurrent evolution and selection shape structural diversity at the amylase locus

https://doi.org/10.1038/s41586-024-07911-1

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Davide Bolognini[1,10], Alma Halgren[2,10], Runyang Nicolas Lou[2,10], Alessandro Raveane[1,10], Joana L. Rocha[2,10], Andrea Guarracino[3], Nicole Soranzo[1,4,5,6,7], Chen-Shan Chin[8], Erik Garrison[3] ✉ & Peter H. Sudmant[2,9] ✉

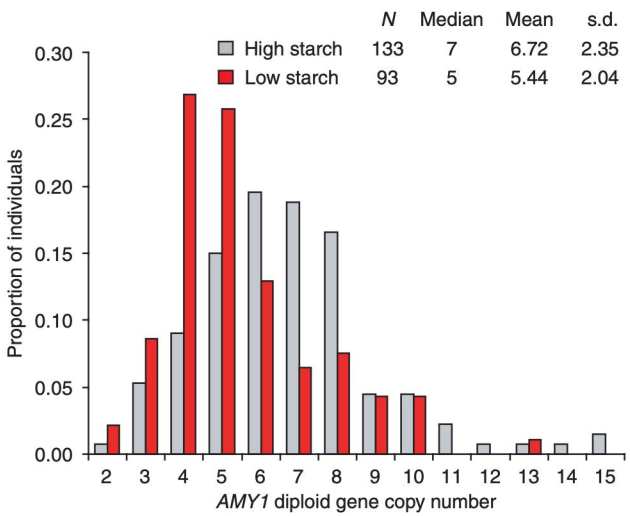
Integrative Biology

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER.

HUMAN TECHNOPOLE

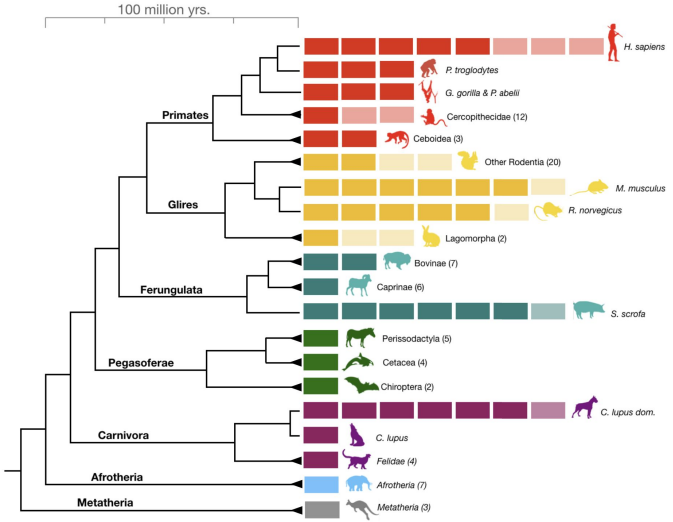
THE VALLEE FOUNDATION

Diet correlates with amylase copy number



Across humans

Perry et al., 2007

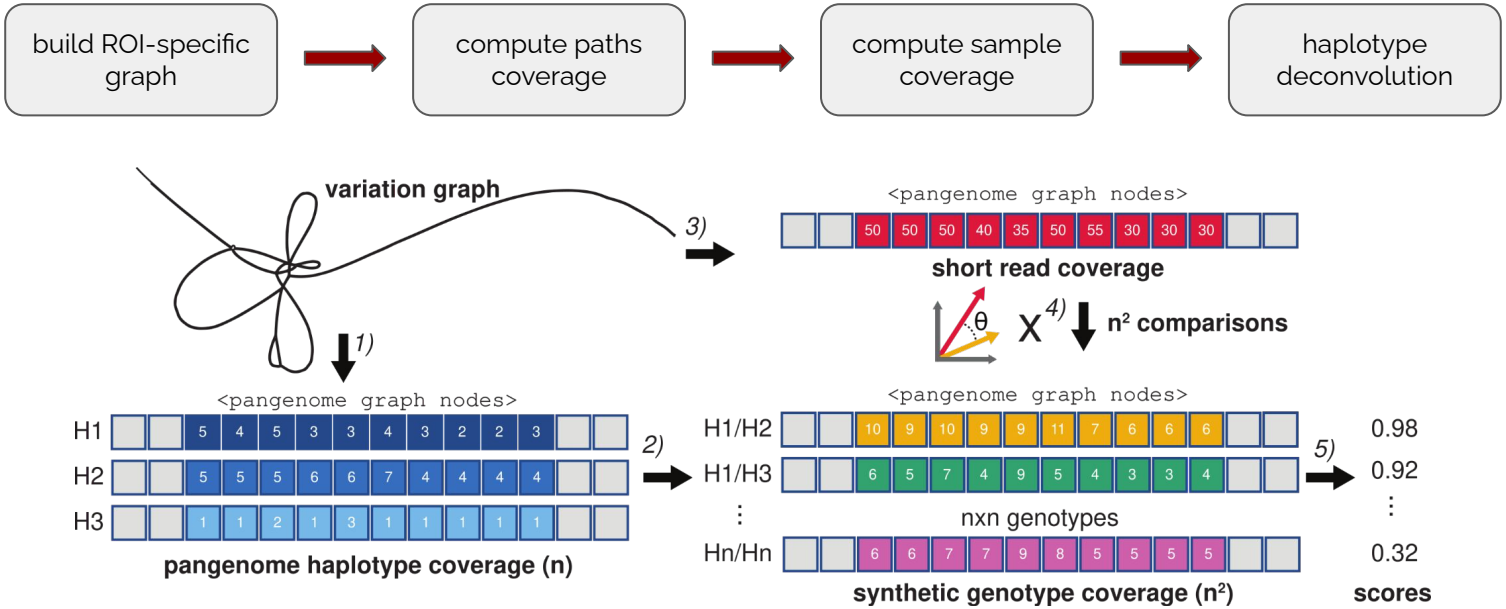


Across mammals

Pajic et al., 2019

No evidence of recent selection

Graph-based genotyping with COSIGT works!



- 100% accurate when mapping individuals with both long reads and short reads (n=35)
- ~95% accurate by mendelian inheritance patterns (561 short read trios)
- 95-99% accurate by copy number prediction compared to read depth (n=3102)

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https://github.com/davidebolo1993/cosigt

COSIGT
COSINE SIMILARITY-BASED GENOTYPER

Allele frequencies of complex structural haplotypes

Pangenome-based haplotype deconvolution for ~8000 short read haplotypes