Next-generation sequencing studies in founder populations

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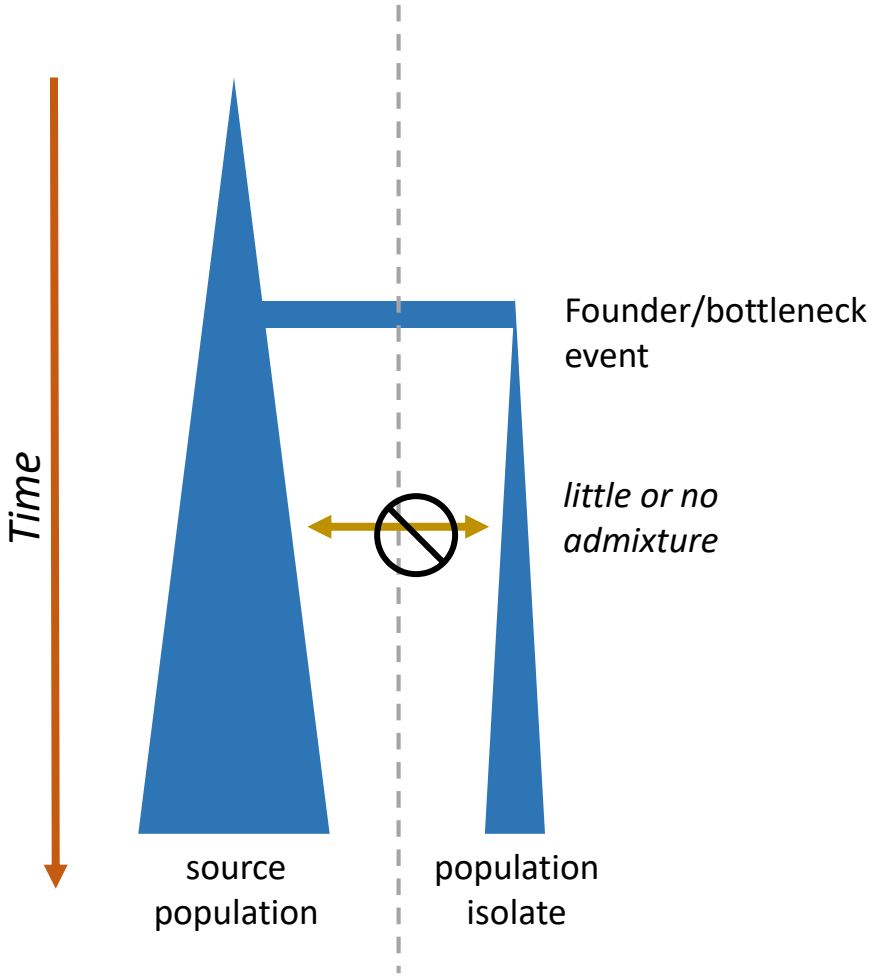
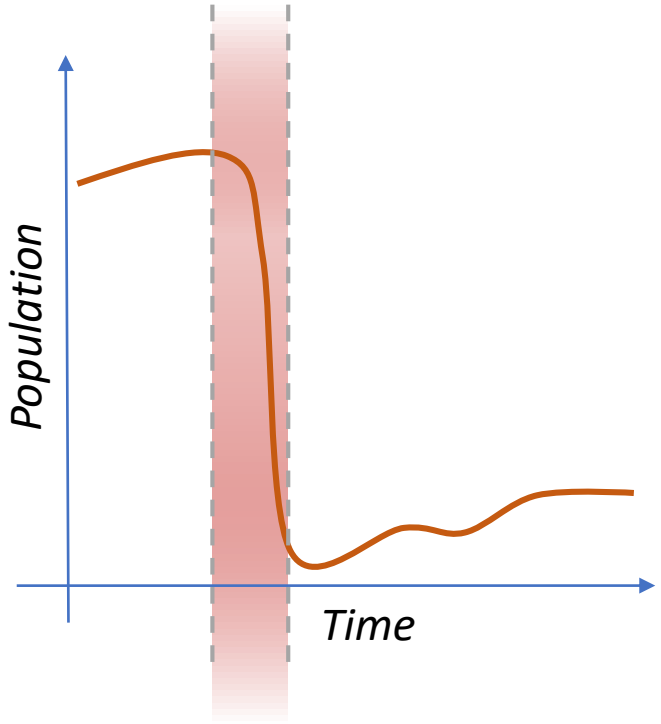
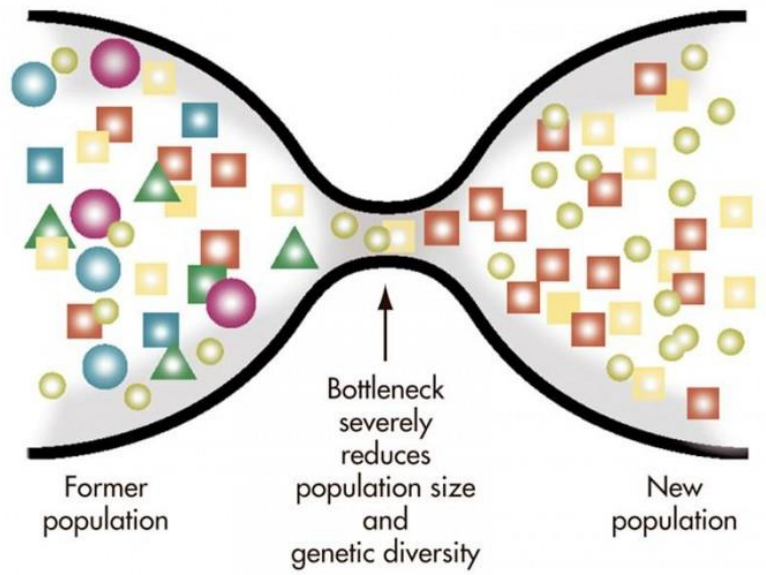
Wellcome Sanger Institute, Cambridge, UK

presented at the "New Statistical Methods for Family-Based Sequencing Studies" workshop in Banff, August 2018

Population isolates





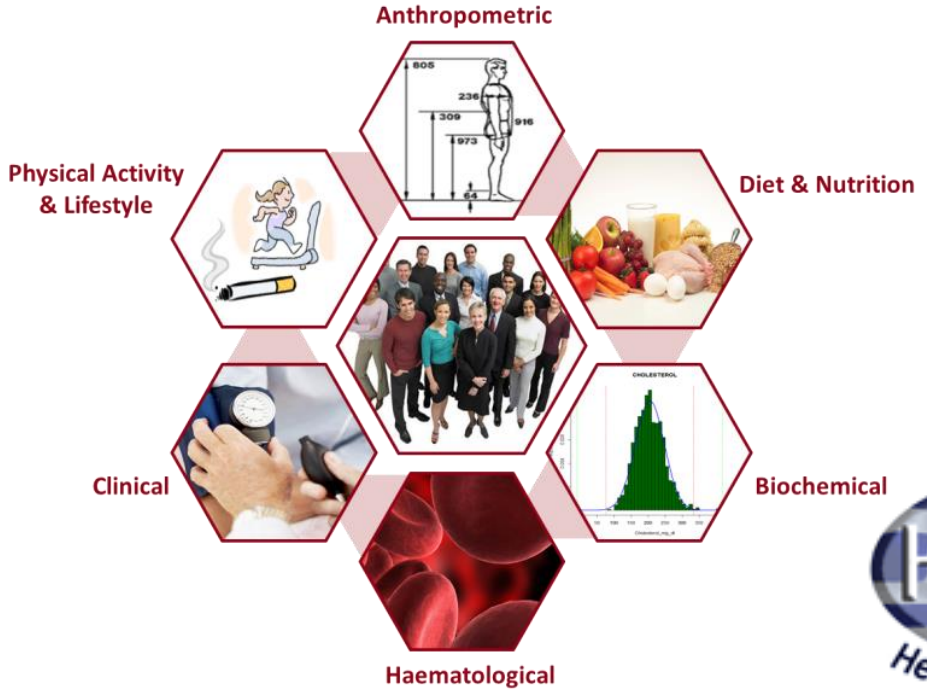


HELIC: Hellenic isolated cohorts

HELIC-MANOLIS (Minoan Isolates)

- Mylopotamos villages, Crete, Greece
- Geographically isolated
- Ancient Dorian dialect
- N~4,500 of which 1,800 collected

- Deeply phenotyped
- High fat content diet
- High rates of longevity
- Low rates of metabolic disease complications
- Ability to recontact individuals



HELIC
Hellenic Isolated Cohorts

www.helic.org

MANOLIS

n=1265

Omni Express

n=1265

Exome Chip

n=211

Core Exome

n=990

1X WGS

n=249

4X WGS

n=1482

22X WGS

n=5

WES

HELIC datasets

Single-point association

GWAS, very-low-depth WGS

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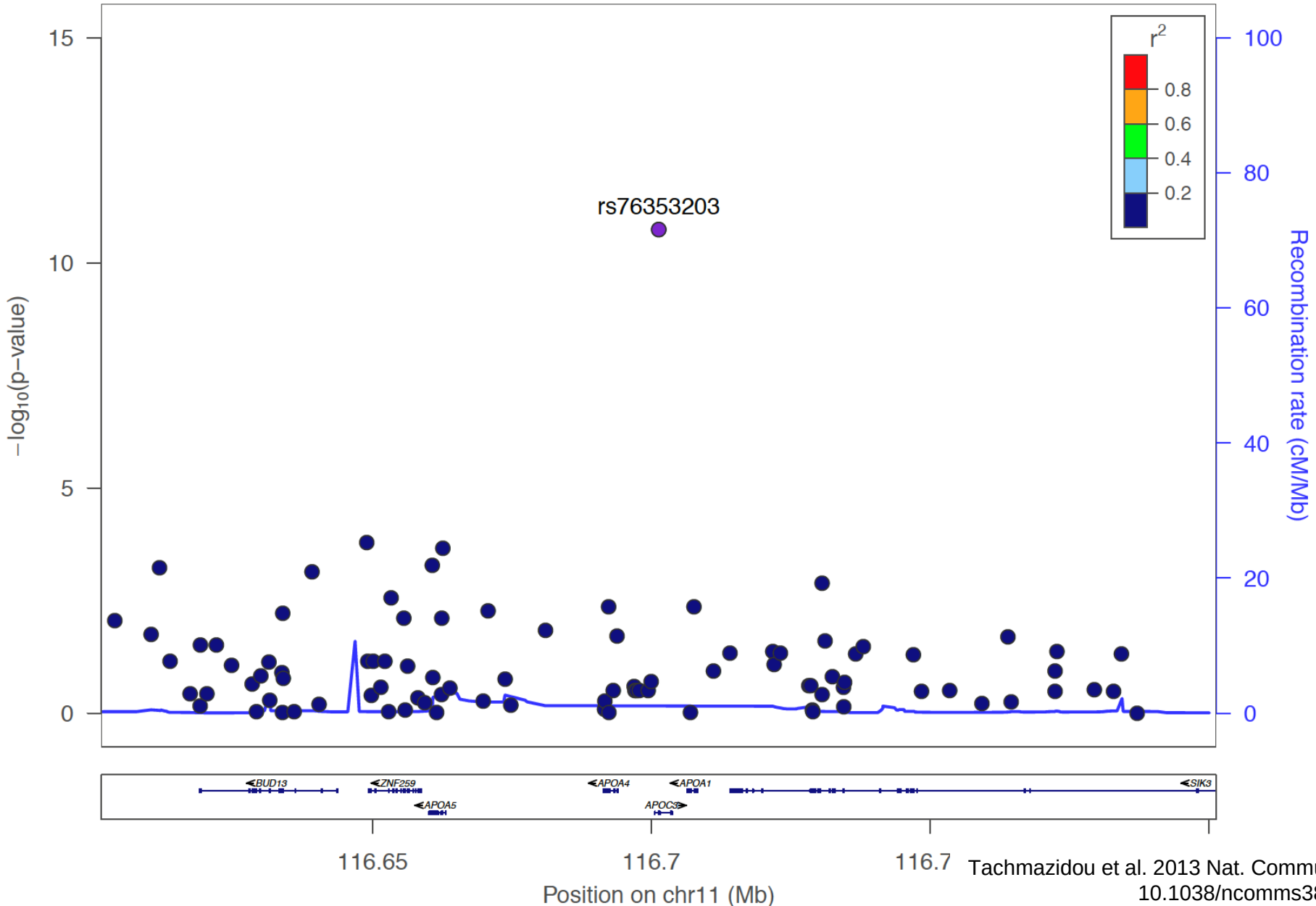
Cardioprotective R19X variant in *APOC3*
ExomeChip data



Tachmazidou et al. 2013 Nat. Commun.
10.1038/ncomms3872

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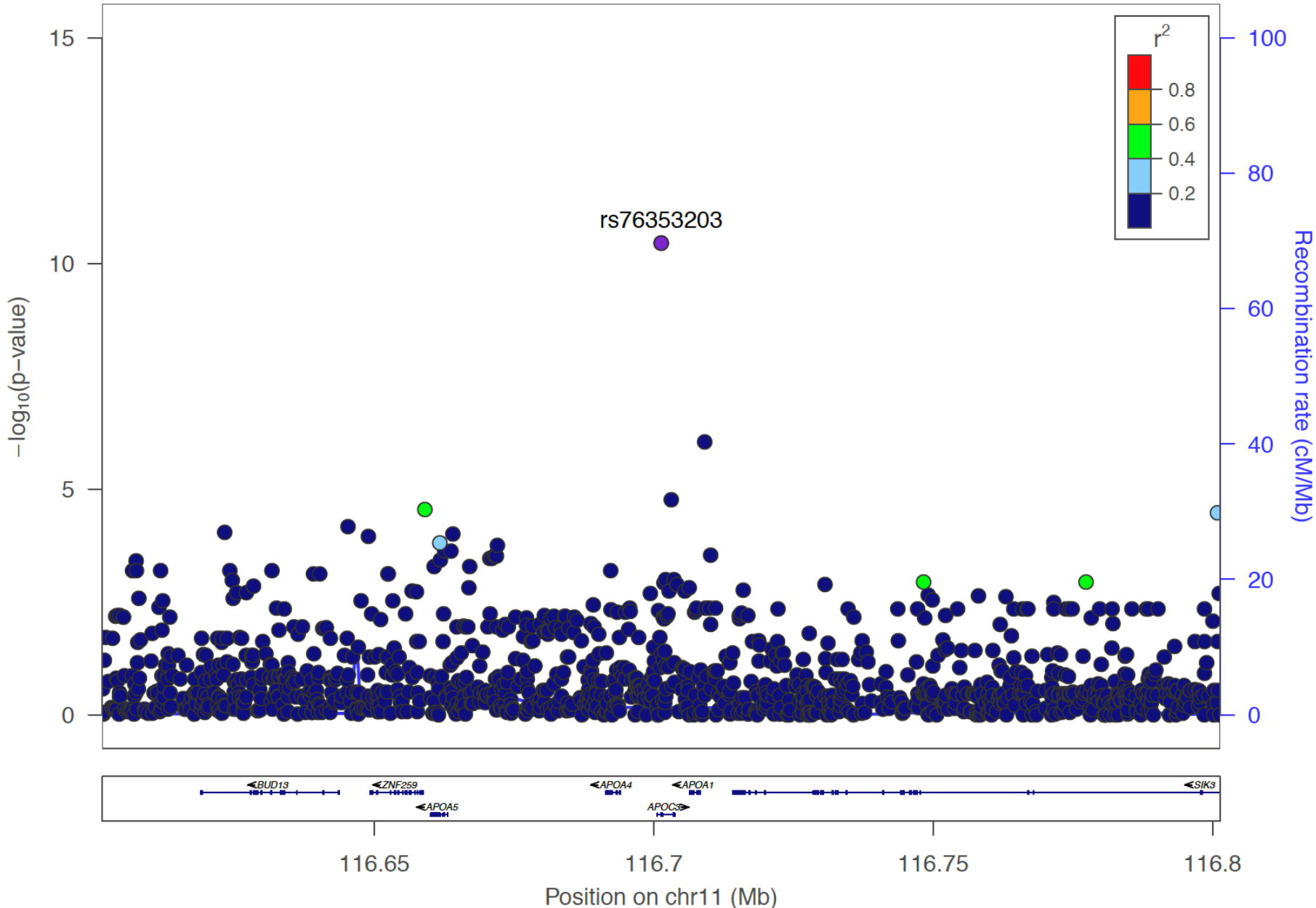
Cardioprotective R19X variant in *APOC3*
Imputed OmniExpress/ExomeChip data



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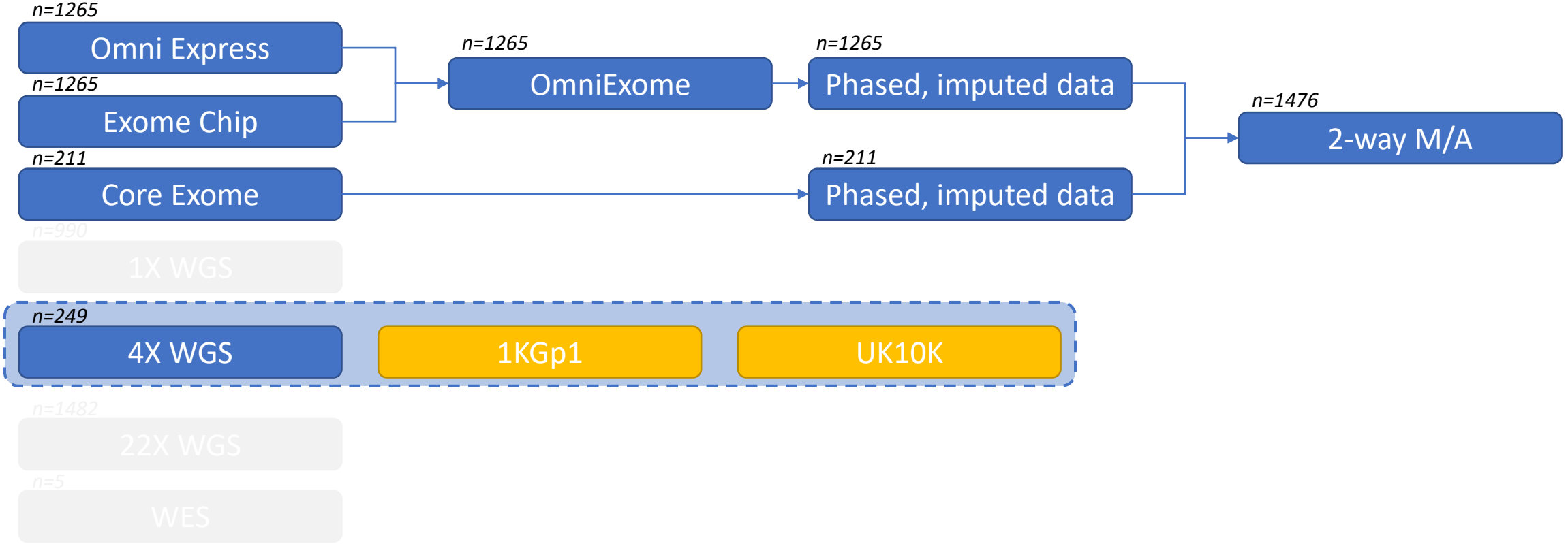

Method:

- GEMMA (with empirical relatedness matrix)
- METACARPA: meta-analysis accounting for sample relatedness

Lorraine Southam

Southam, Gilly et al. Nat Comms. doi: 10.1038/ncomms15606

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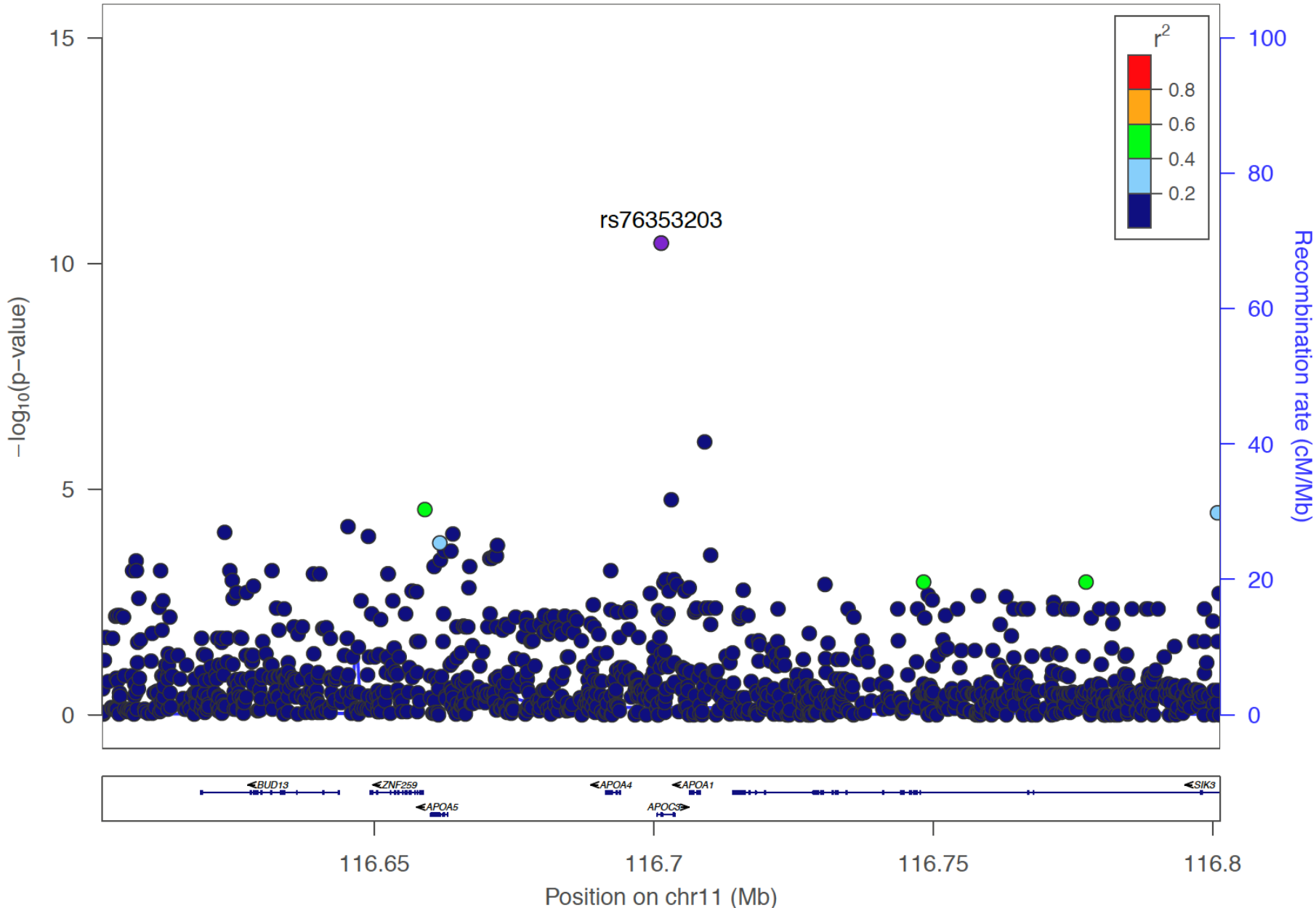

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Cardioprotective R19X variant in *APOC3*
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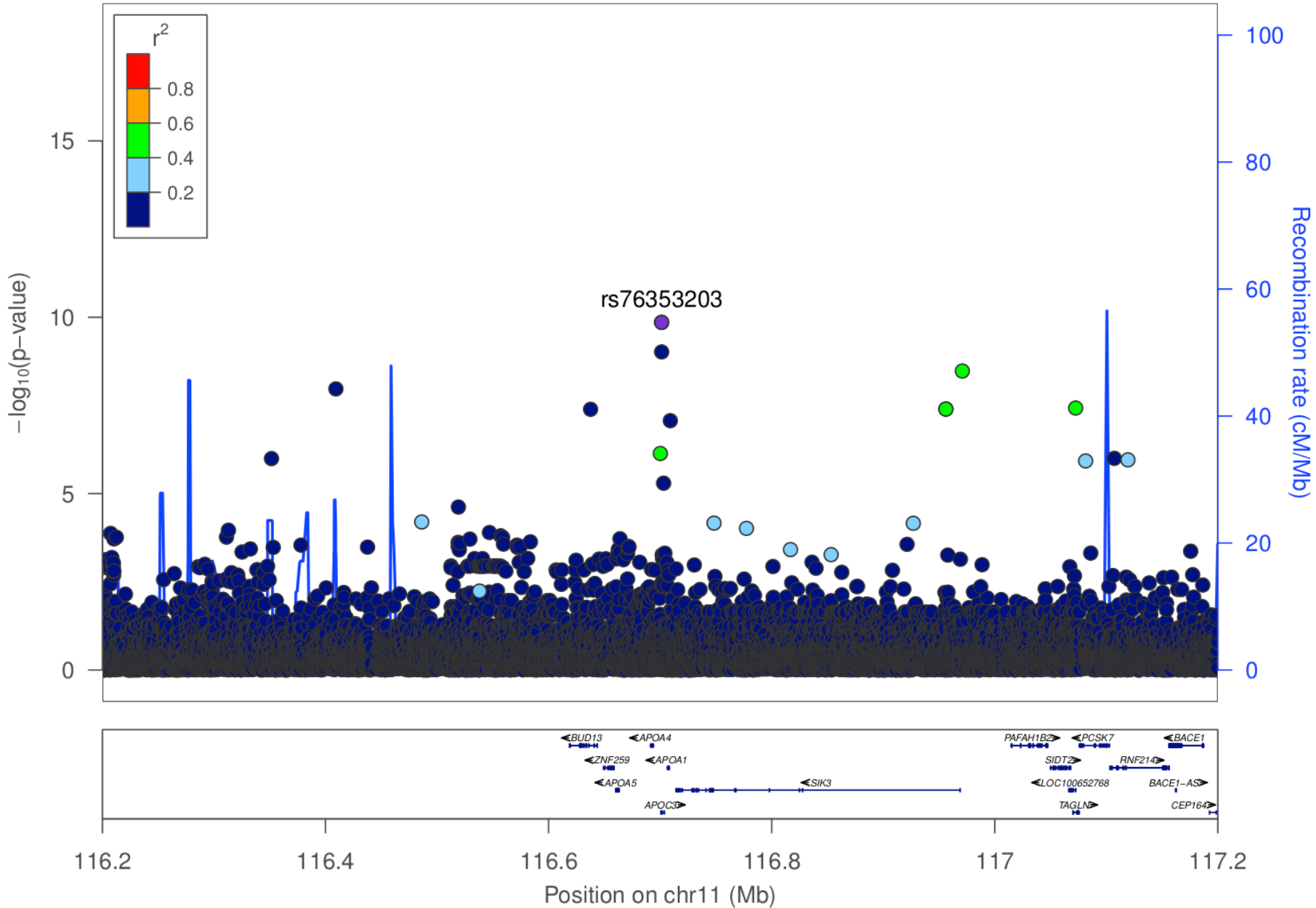

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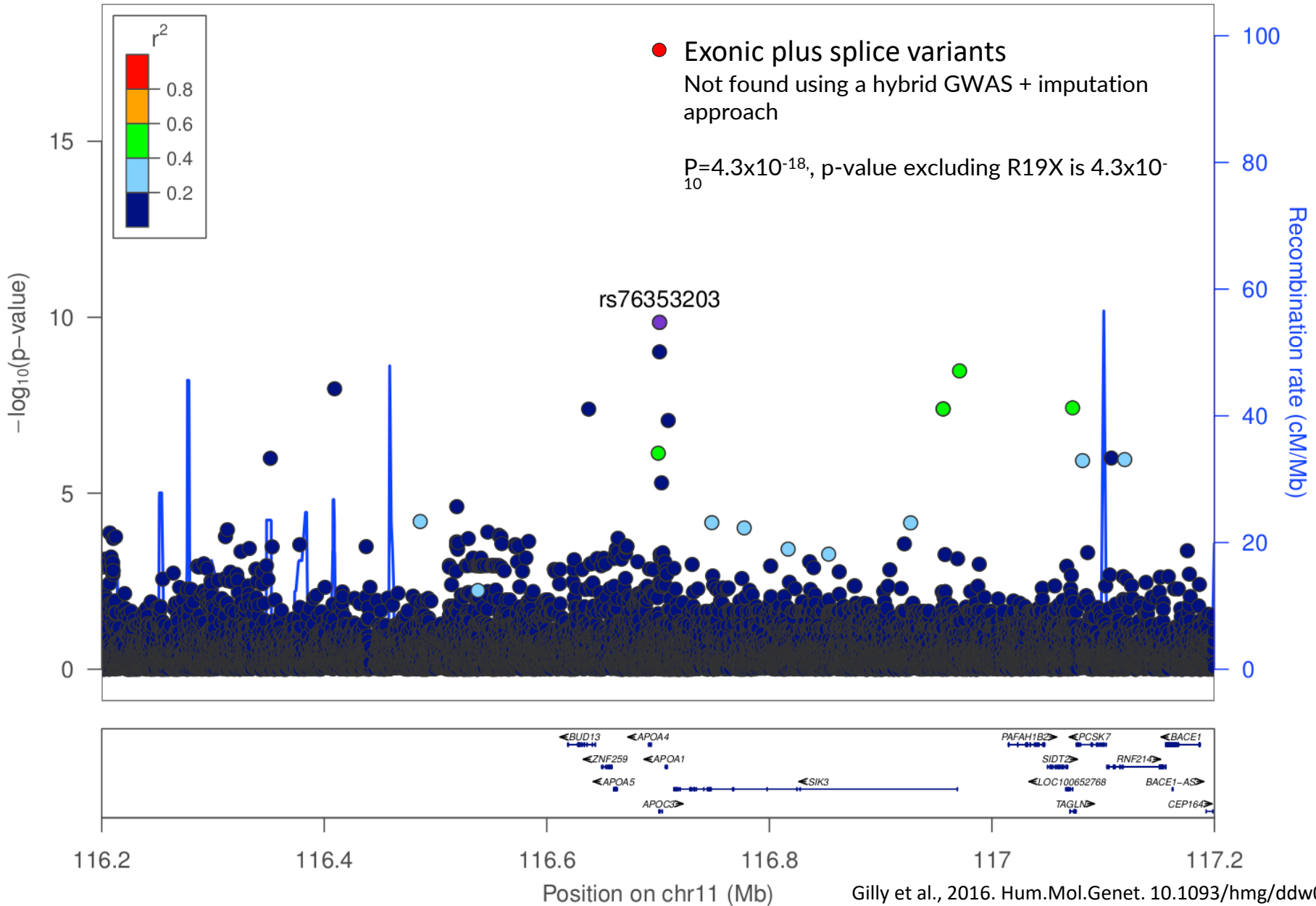
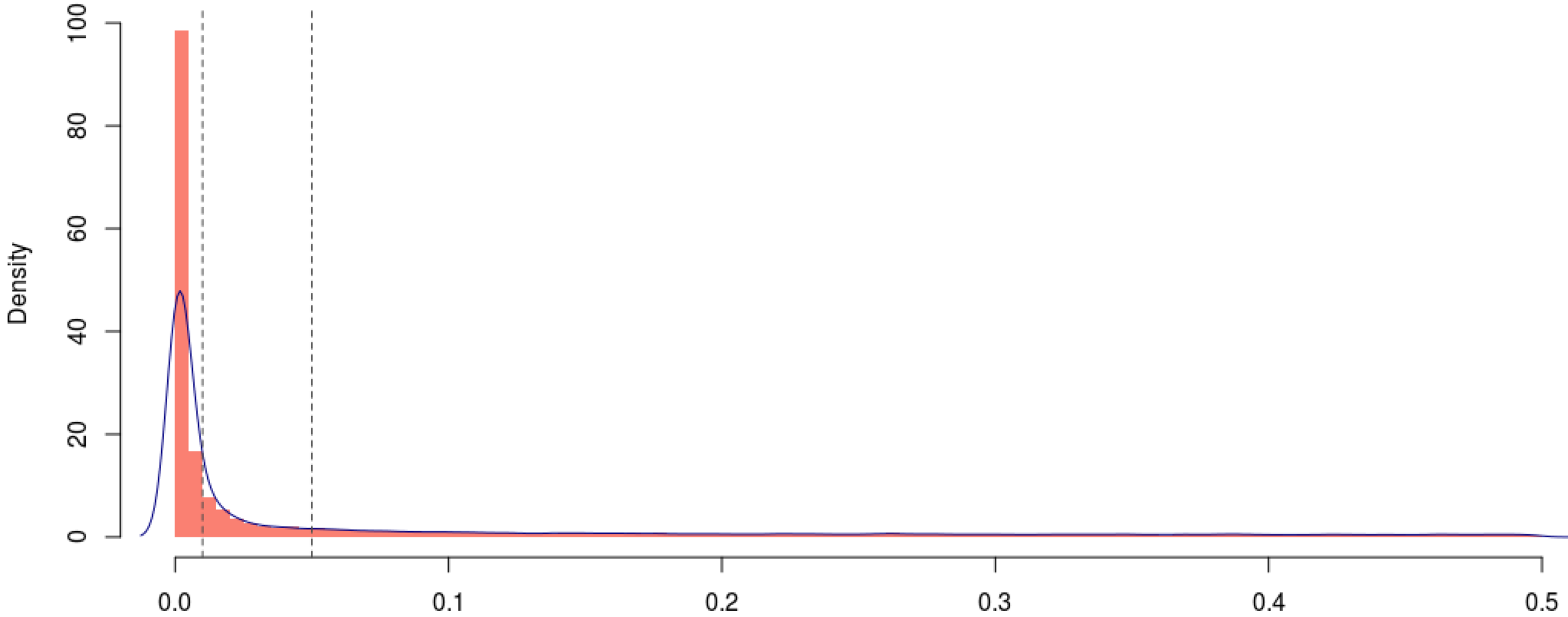


Gilly et al., 2016. Hum.Mol.Genet. 10.1093/hmg/ddw088

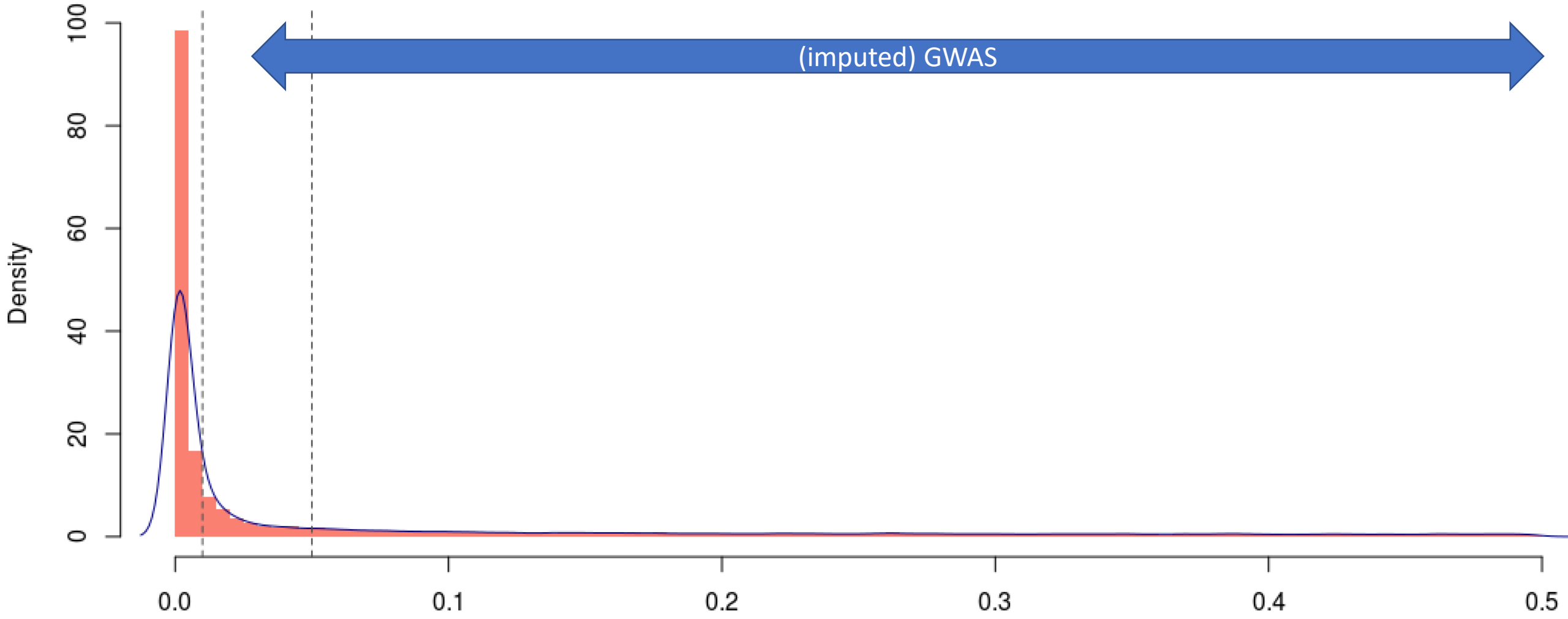
Rare variant aggregation tests

High-depth sequencing (18-22x WGS)

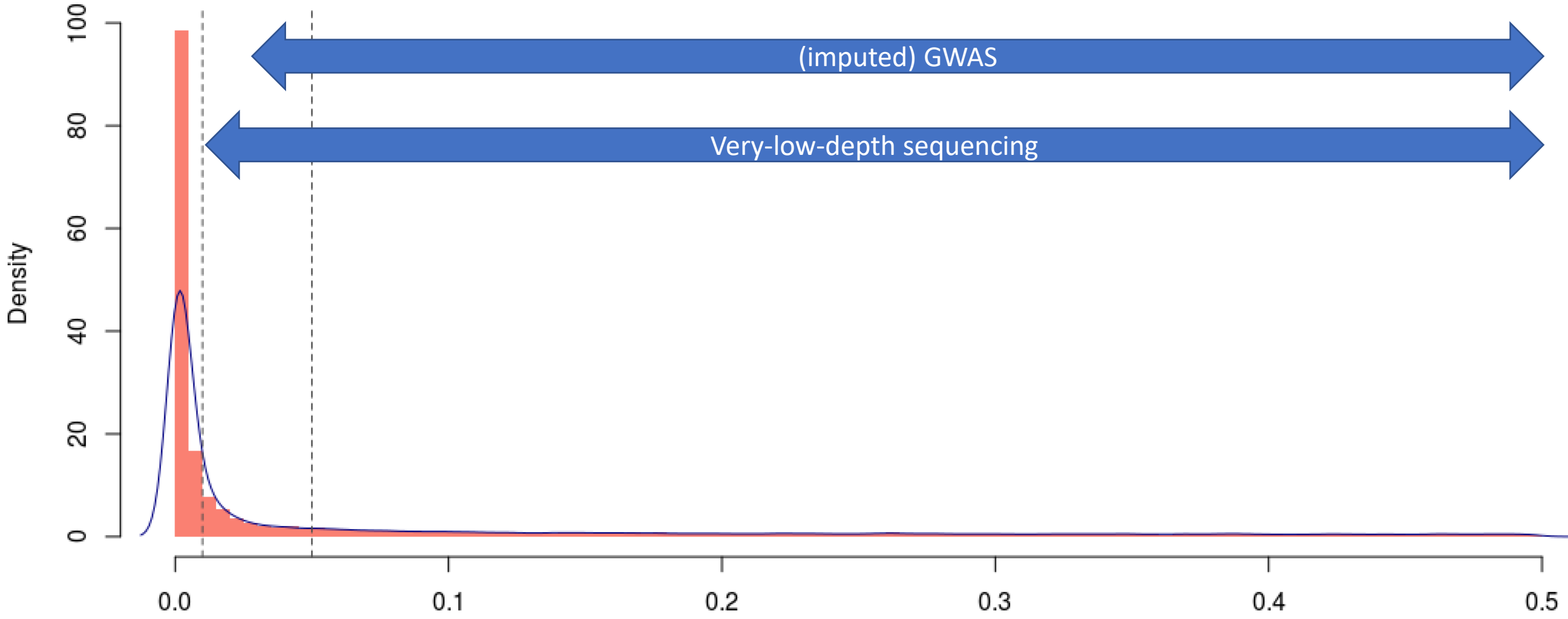
Allele frequencies



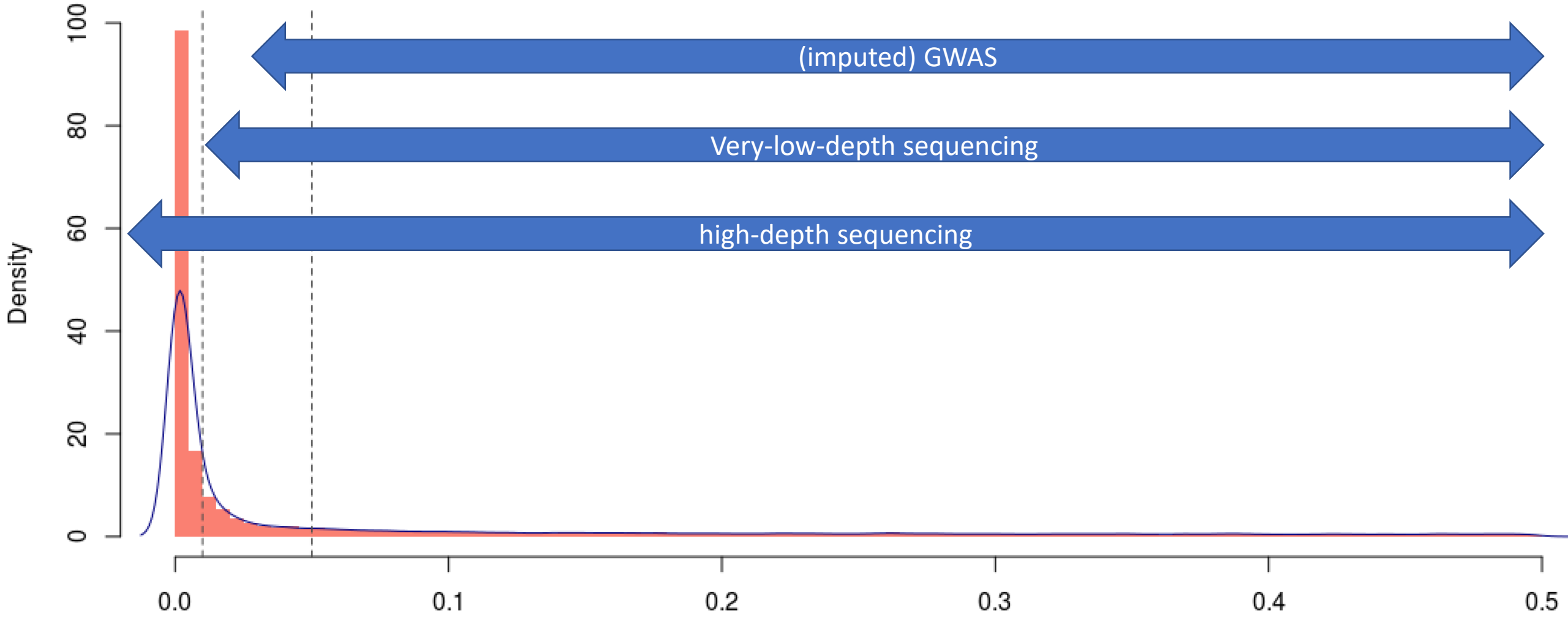
Allele frequencies



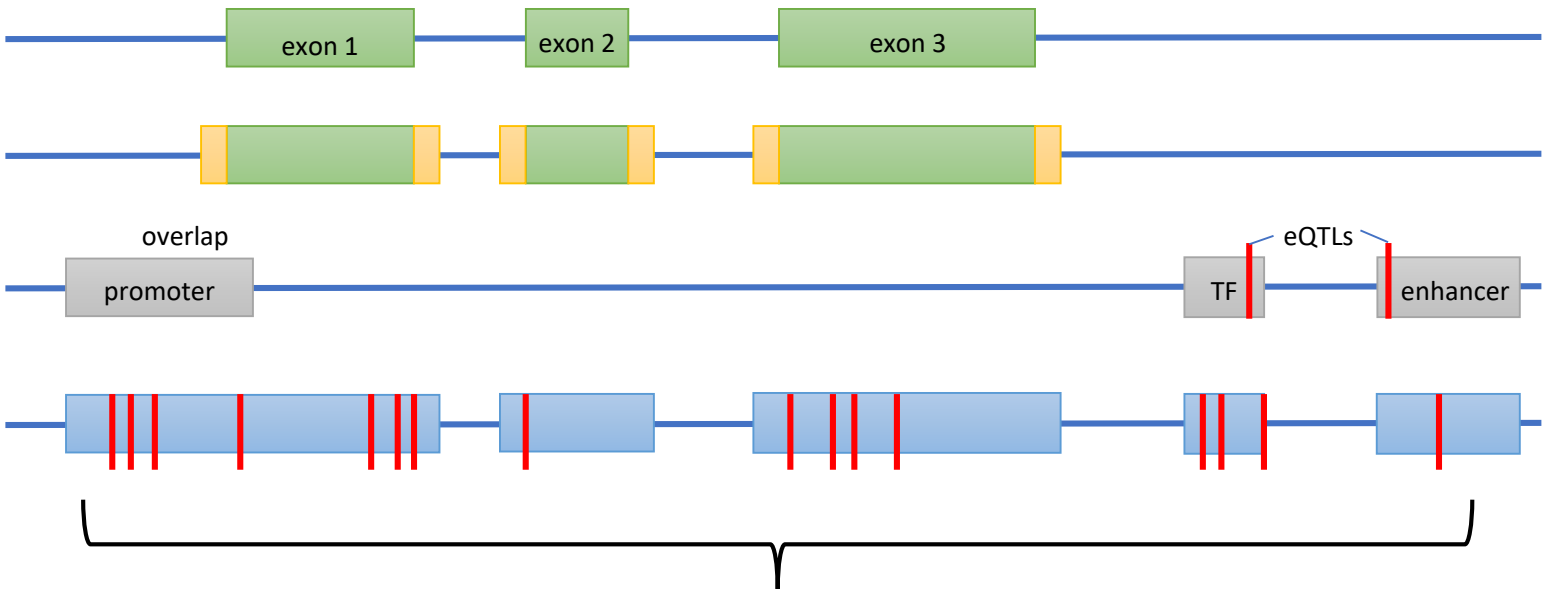
Allele frequencies



Allele frequencies



Selecting variants for burden testing:



Selecting GENCODE features eg. exons

Extending GENCODE features

Selecting associated reg. features

Select overlapping variants

Pooling variants and apply further filters:

- Upper MAF threshold: 5%
- Upper missingness threshold: 1% (remaining missingness is imputed)
- Optional selection of variants based on predicted consequence

If variants are included, which scoring method should we use?

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Method:

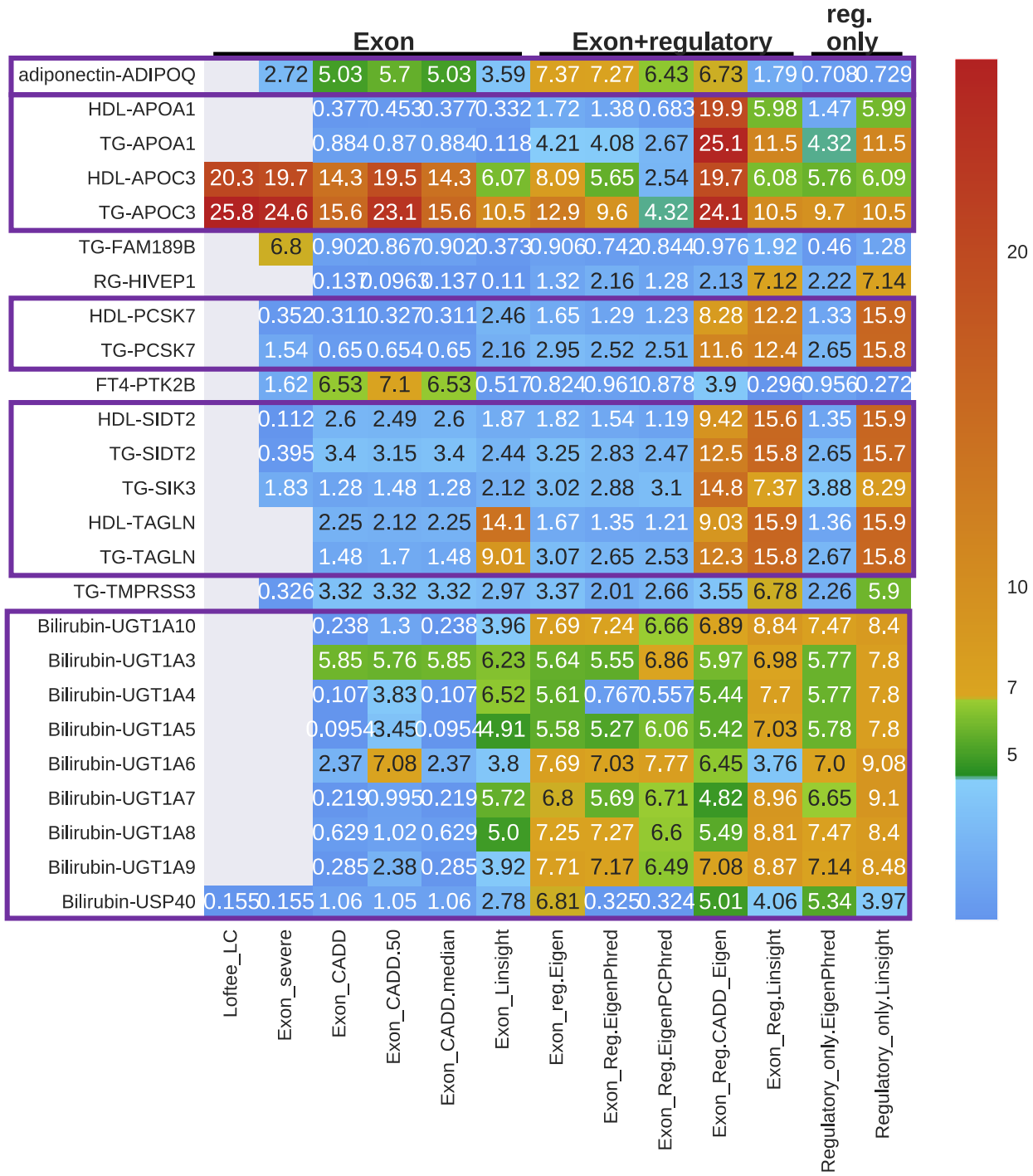
- MONSTER (SKAT-O-type unified test, with empirical relatedness matrix)
- Also accepts family information

Phenotypes:

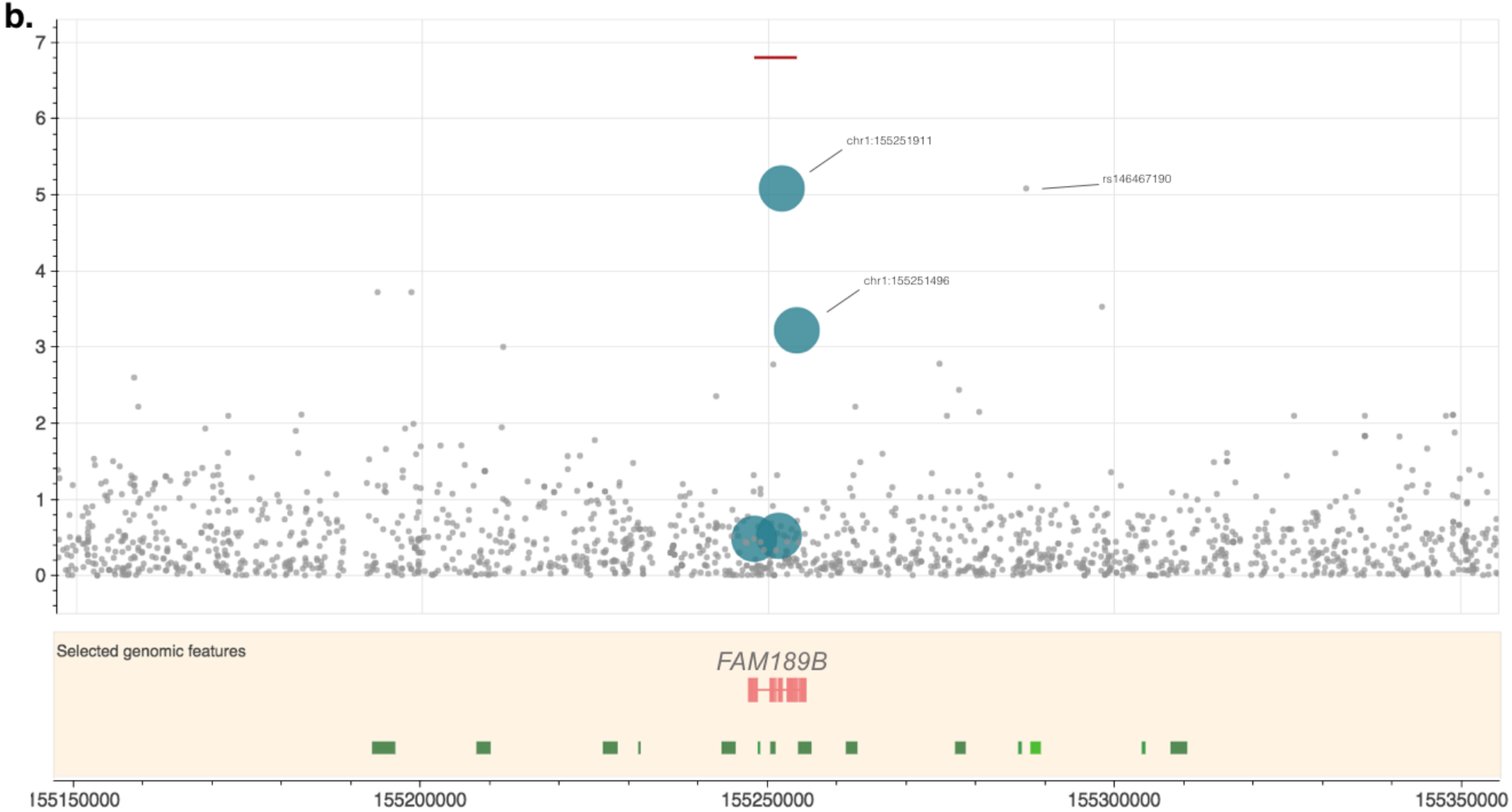
- 59 quantitative traits

Results:

- 14 conditions
- At least 1 run is SW significant ($p<1.3x10^{-7}$)
  - 39 trait/gene pairs
  - 24 unique genes



A burden driven by isolate-specific rare variants



Gilly, Suveges, Kuchenbaecker et al. doi: 10.1101/283481

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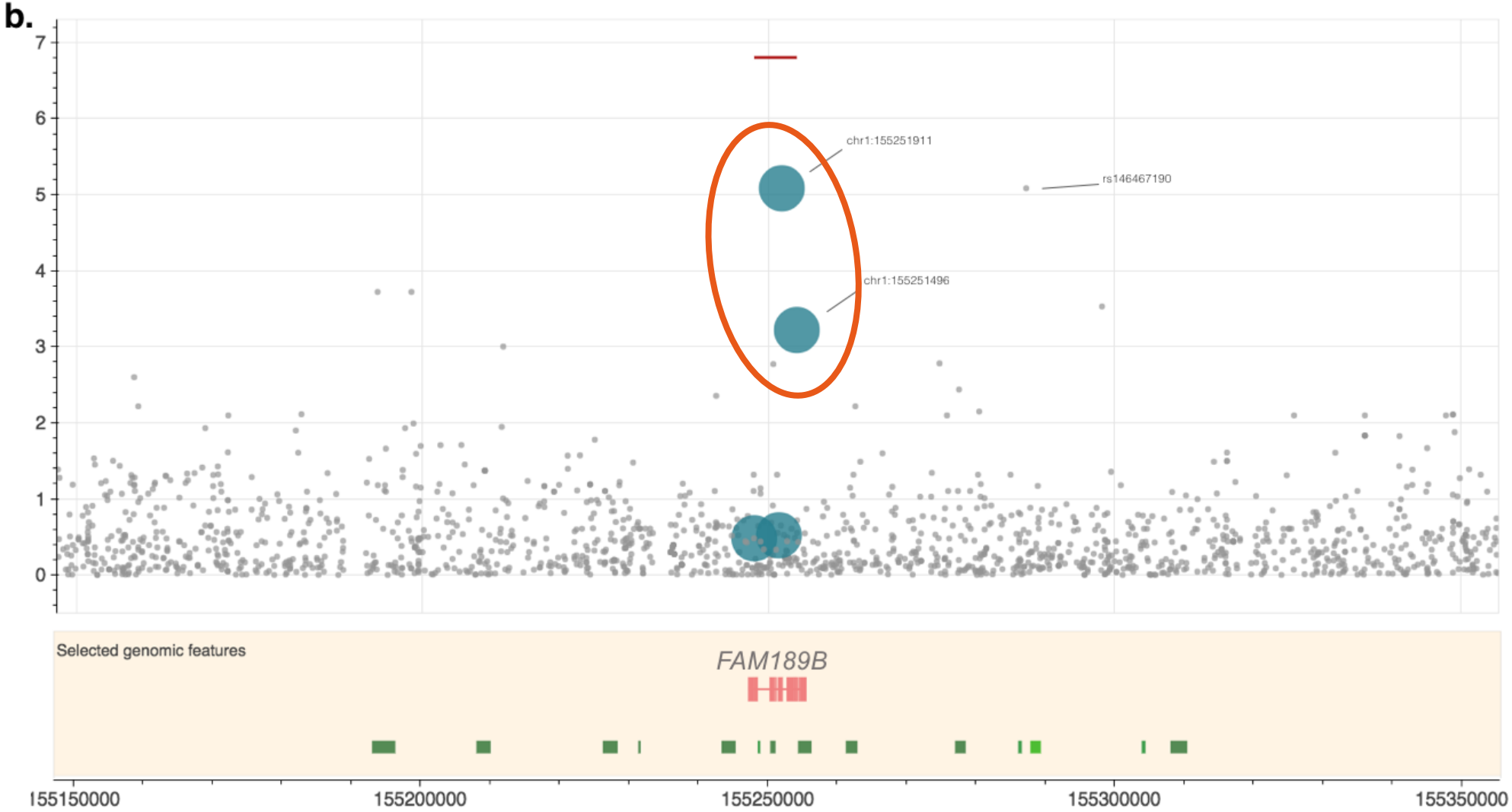

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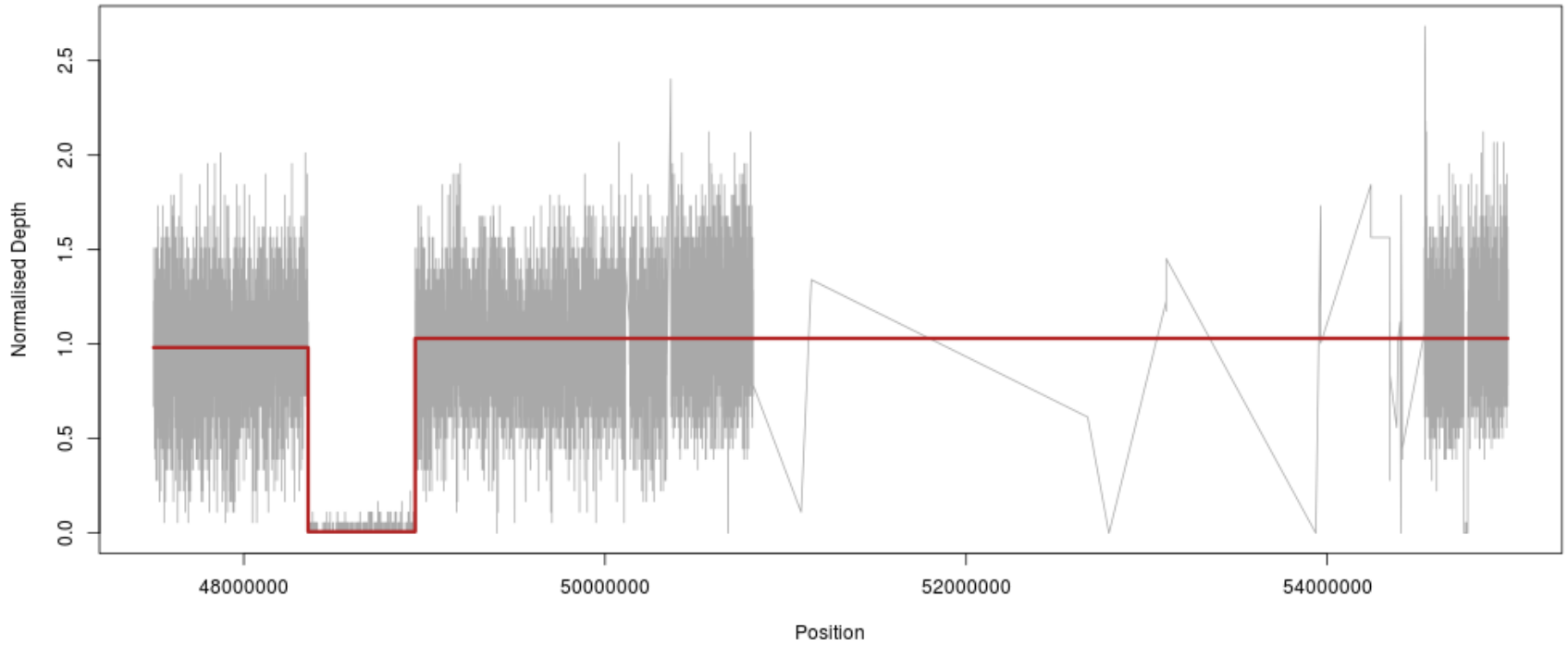
Large CNV calling from high-depth WGS variant calls

UN-CNVC (github.com/agilly/un-cnvc)

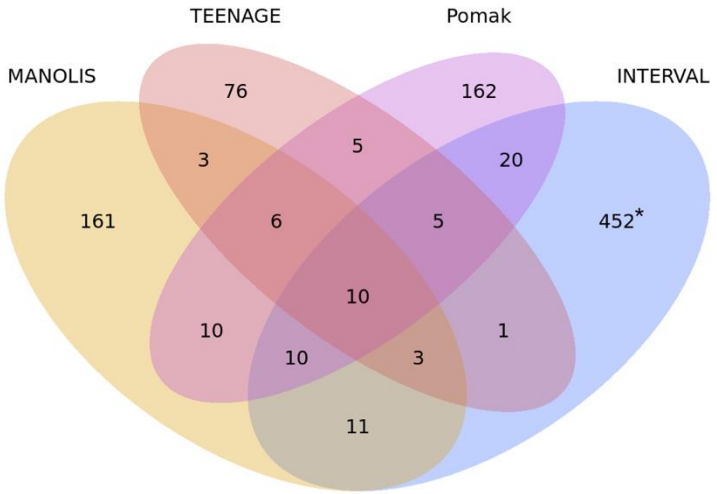
Large CNV calling based on WGS variant calls

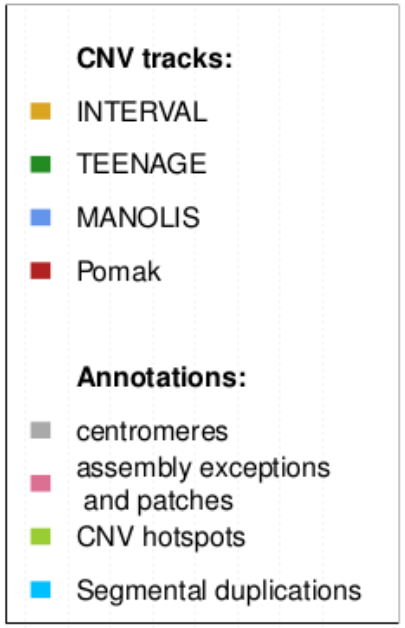
- UN-CNVc (written in R)
- Uses piecewise constant regression (regression trees) to smooth out noise and find “segments” of “constant” depth
- Uses only marker-level data

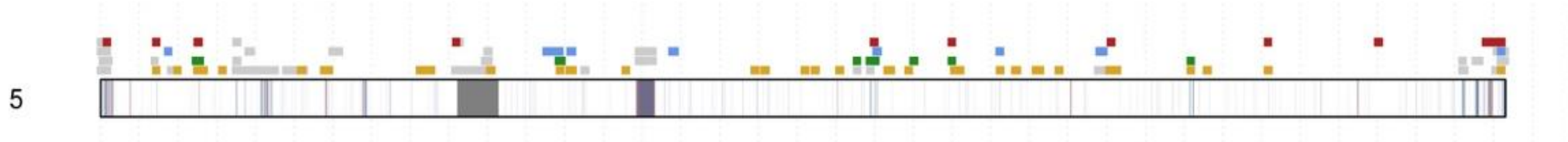


Large CNV calling based on WGS variant calls

- The proportion of CNVs private to the isolates is similar to that in a cosmopolitan cohort
- 37% of shared CNVs had significant frequency differences between cohorts, mostly between isolates and cosmopolitan populations

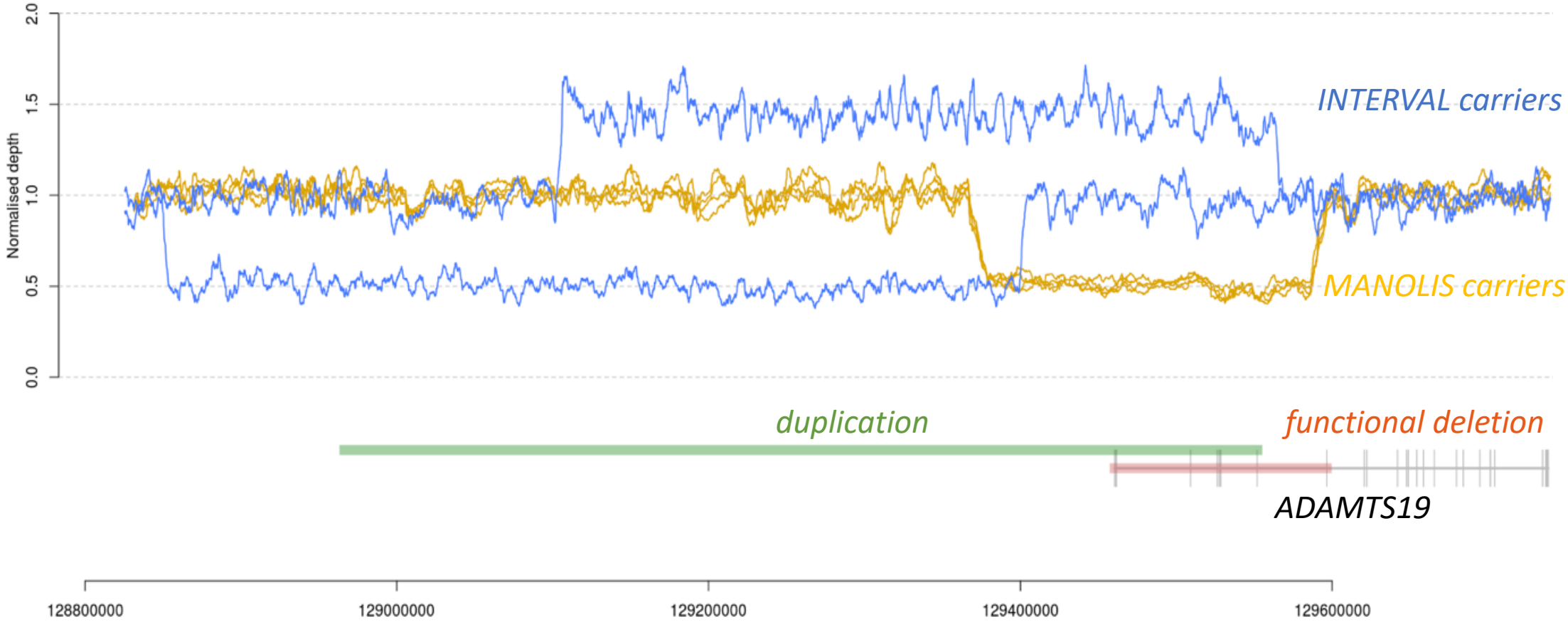






Population-specific structure in the *ADAMTS19 region*

- found by F. Wünemann's lab at the Cardiovascular unit at CHU Sainte Justine Research Center, Montreal
- four individuals from two consanguineous families with a rare form of cardiac valve disease
- also present in one AMR (Latino) sample in ExAc

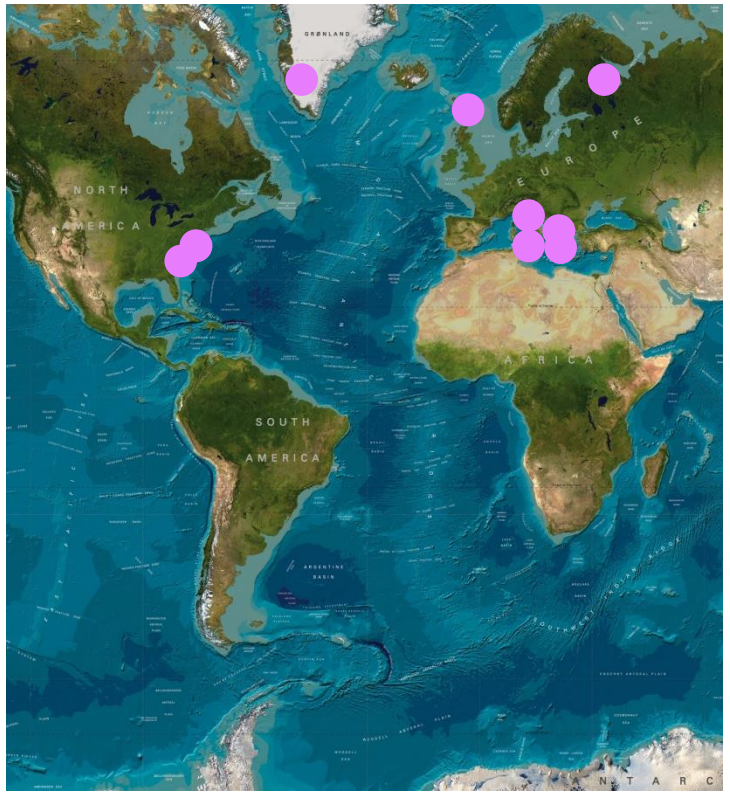


Network of isolated population cohorts

Sequencing Isolates Consortium

Over 15 well-phenotyped cohorts, including founder populations in:

- Greece (Pomak and Mylopotamos villages),
- Finland (general Finnish population cohorts and Northern Finland sub-isolates),
- Italy (Carlantino, Val Borbera and Friuli Venezia Giulia villages, Sardinia),
- UK (Orkney islands),
- USA (Amish, Ashkenazi Jewish),
- Greenland

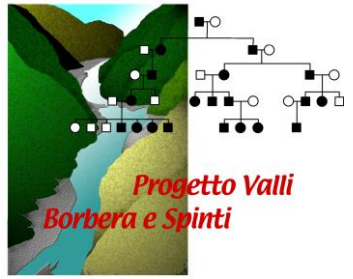


Emerging international WGS isolates consortium currently amassing in excess of 30,000 samples

University of Maryland School of Medicine

Uppsala Universitet

RGB Istituto di Ricerca Genetica e Biomedica



National Institute for Health and Welfare

Thank you!

wtsi-team144

Sample collection

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Phenotype database

Britt Kilian, Nigel W. Rayner

Dániel Süveges

Grace Png