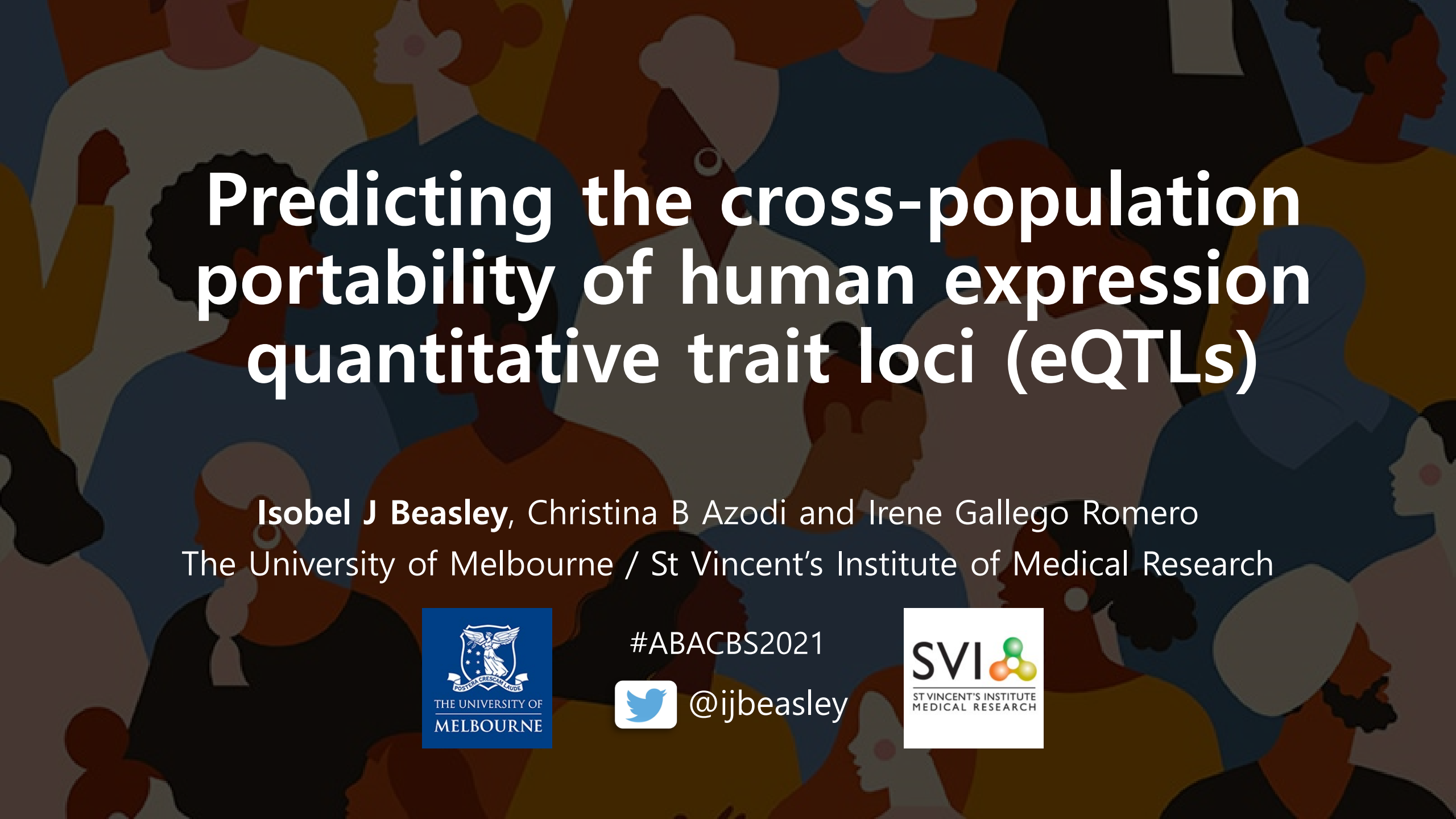
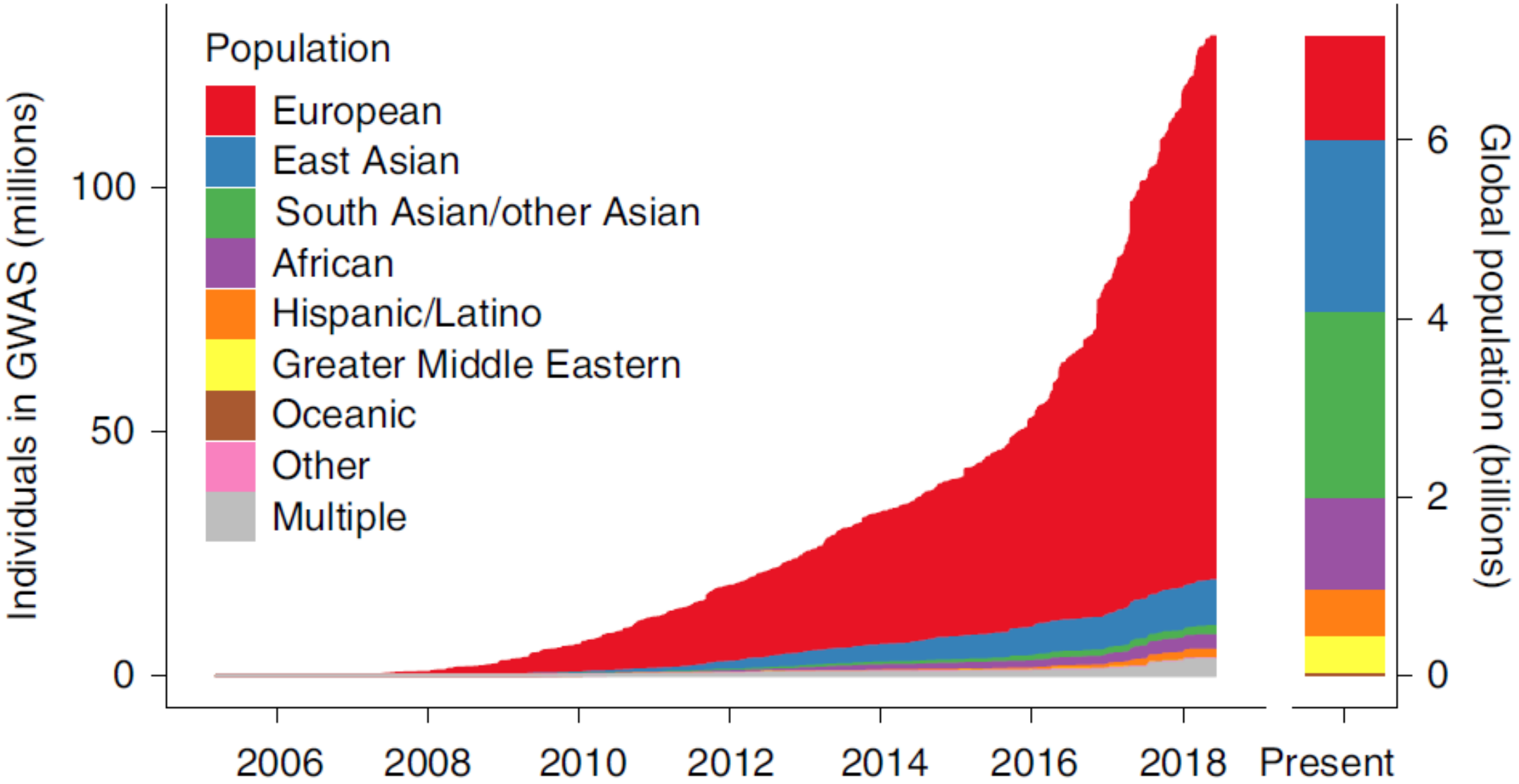


Predicting the cross-population portability of human expression quantitative trait loci (eQTLs)

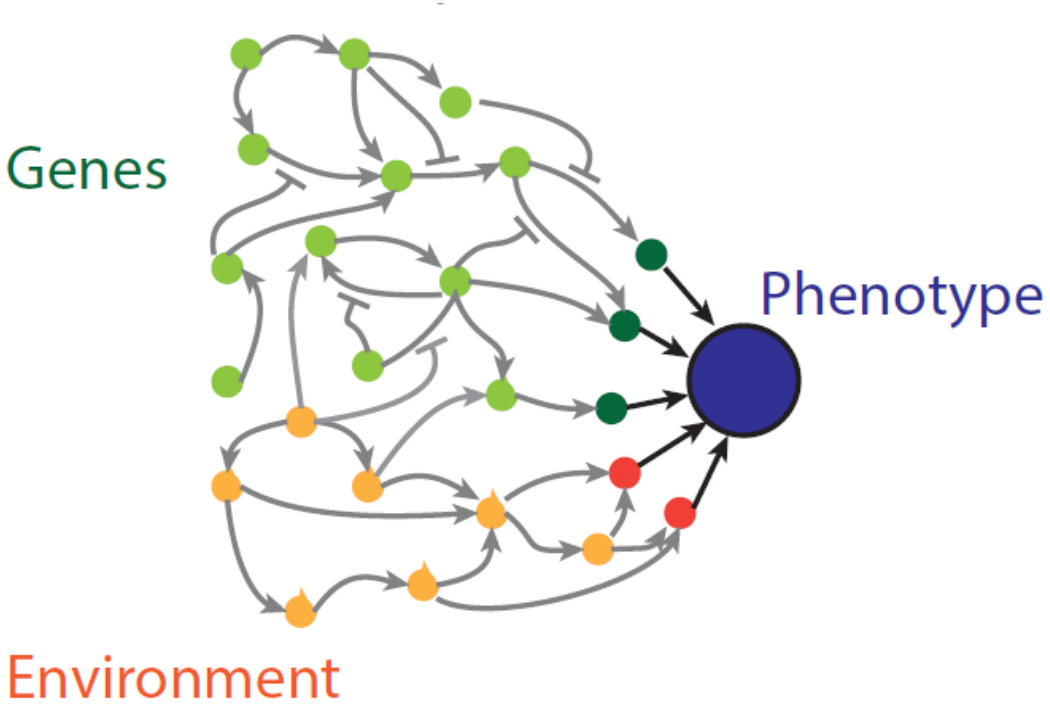
Isobel J Beasley, Christina B Azodi and Irene Gallego Romero
The University of Melbourne / St Vincent's Institute of Medical Research

#ABACBS2021

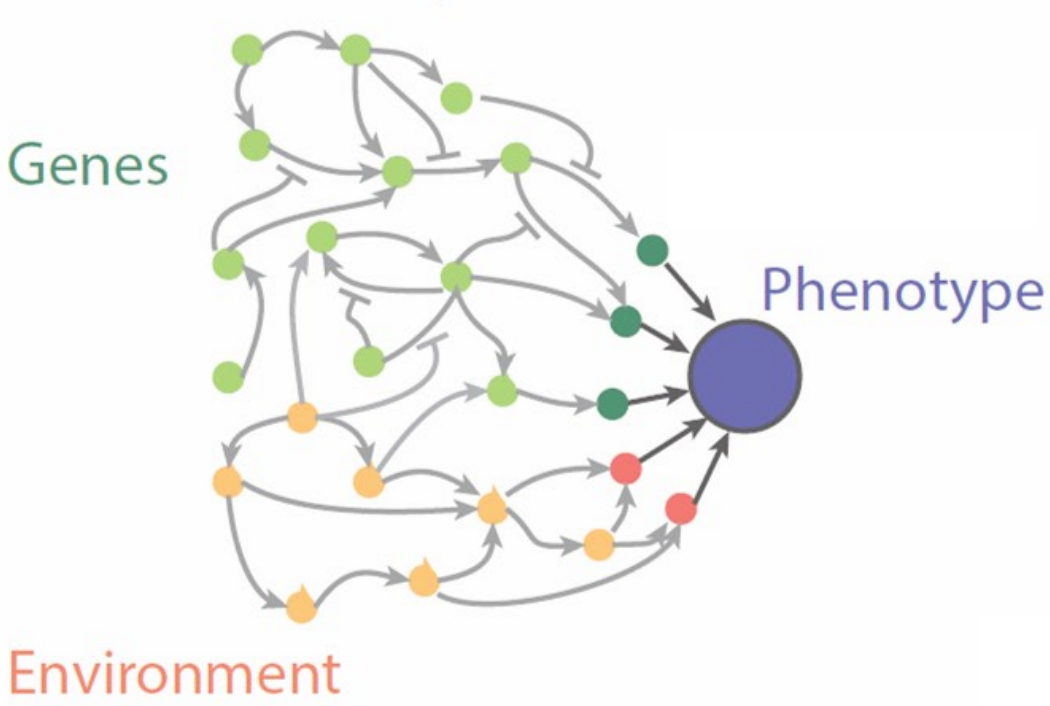
@ijbeasley

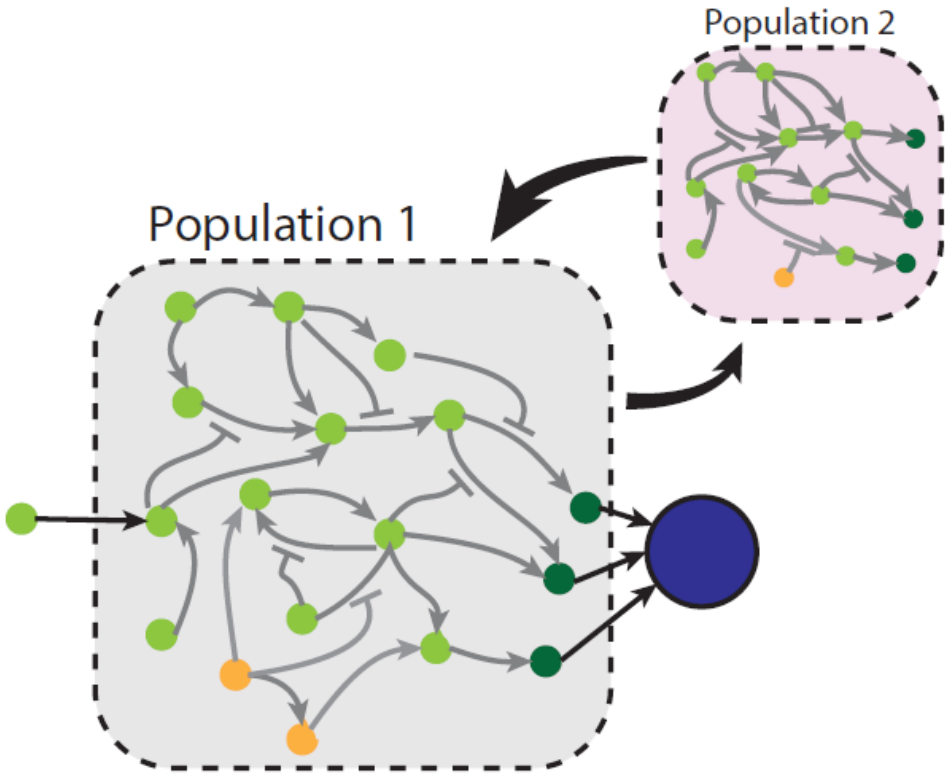


Martin et al., 2019, *Nature Genetics*



Iain Mathieson., 2021, *AJHG*

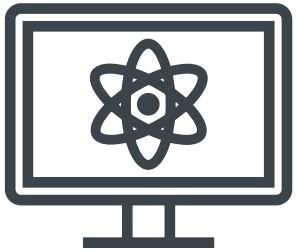




Iain Mathieson., 2021, *AJHG*

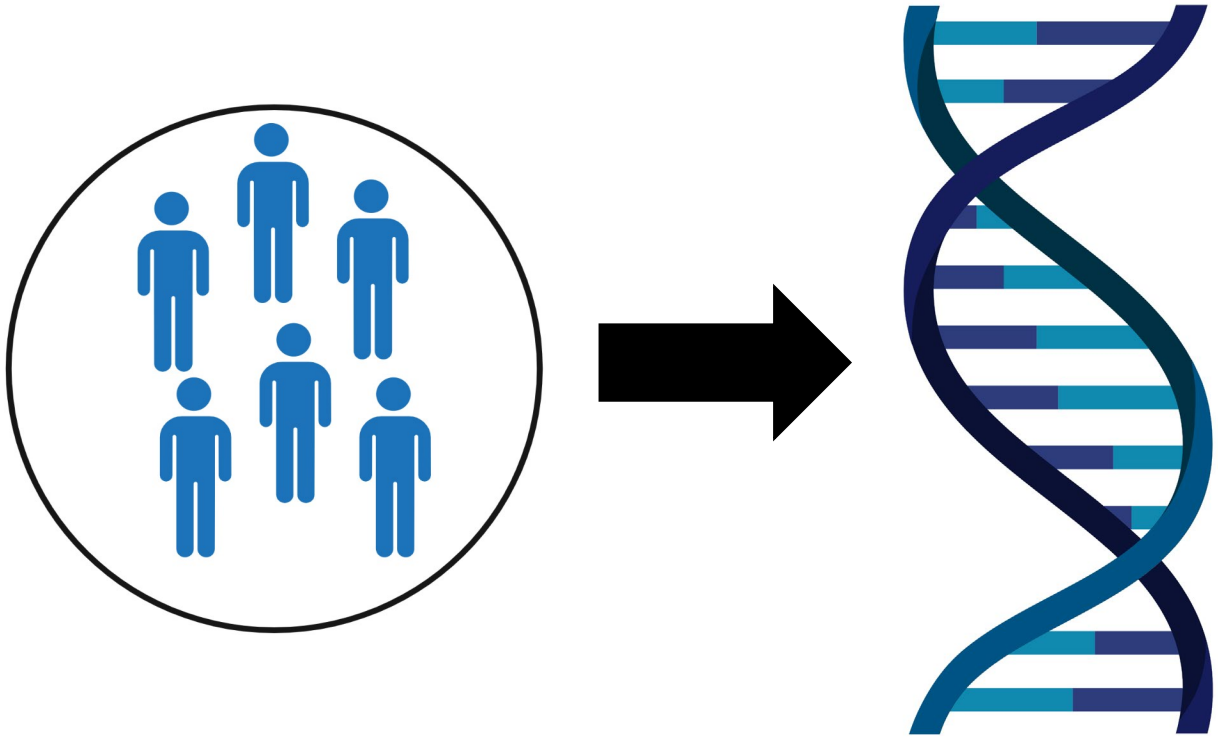
Outline

1. eQTLs



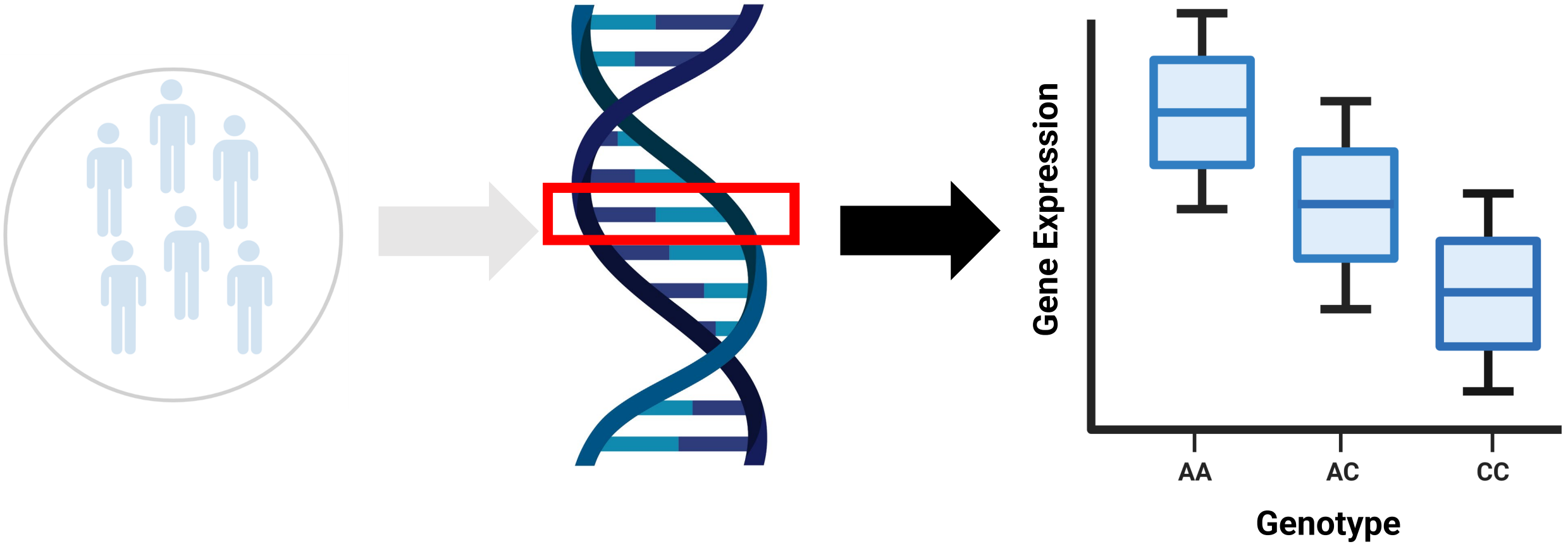
2. Building machine learning models

3. Findings (expected and puzzling)



Created with BioRender.com

eQTLs (expression Quantitative Trait Loci)



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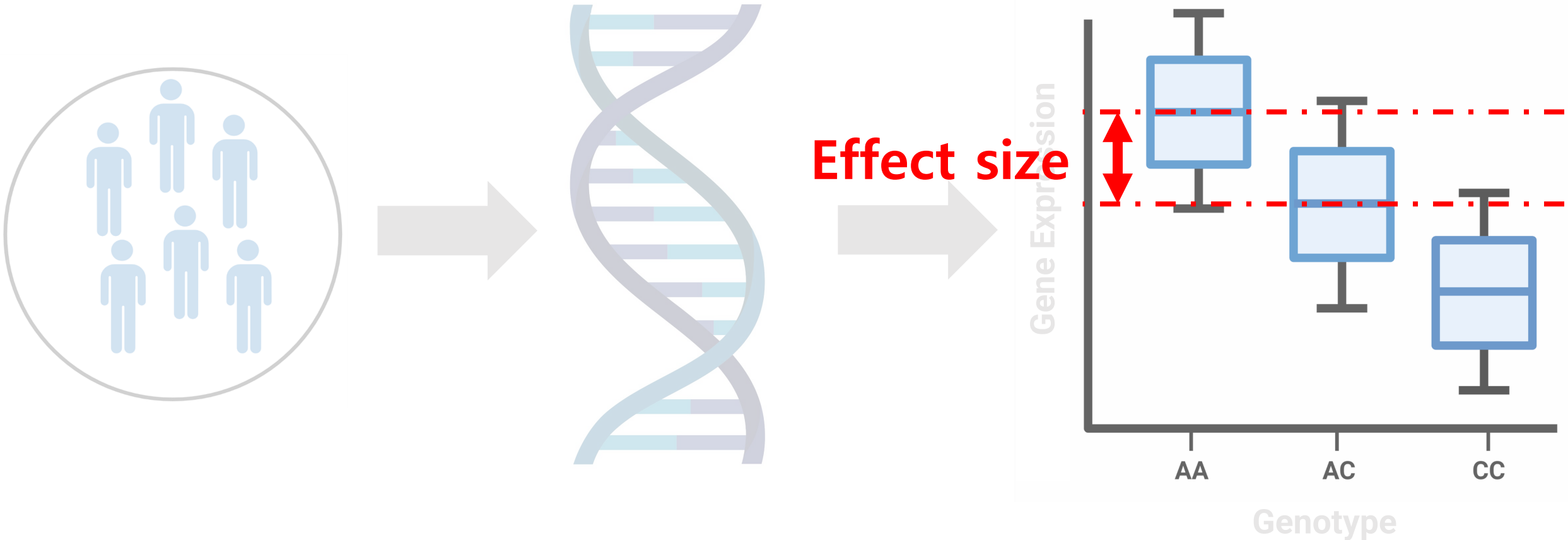

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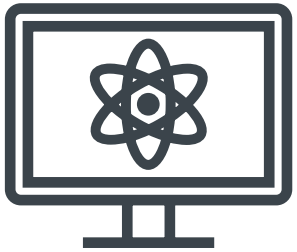
Outline

1. eQTLs



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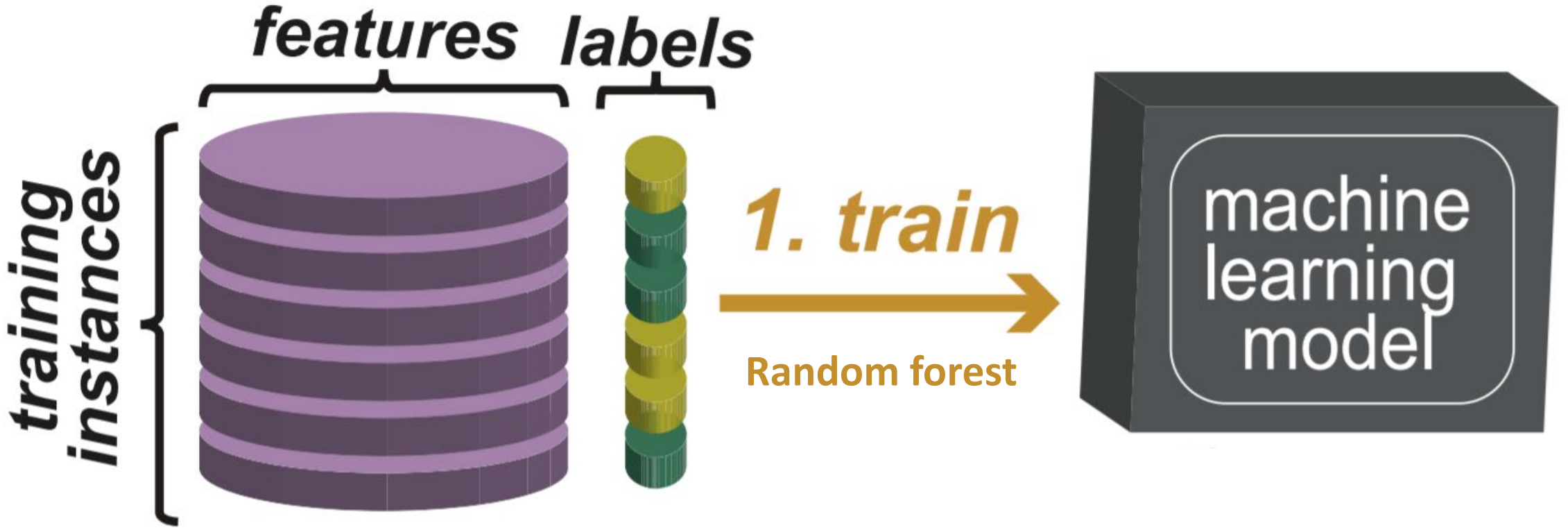


Azodi, Tang and Shiu, 2020, *Trends in Genetics*

The training data

European (n = 471, Lepik et al. 2017)

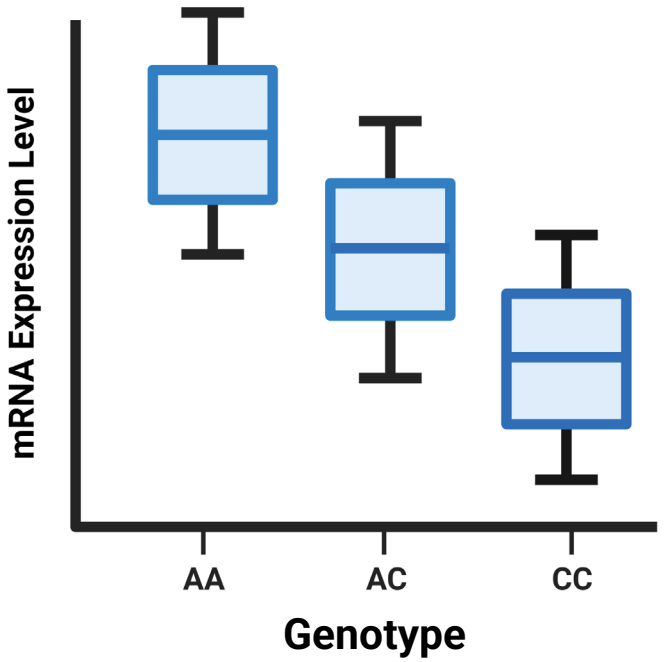
European (n = 379, GTEx. 2020)

European (n = 195, TwinsUK 2015)

Indonesian (n = 115, Natri et al. 2020)

eQTLs

eQTLs



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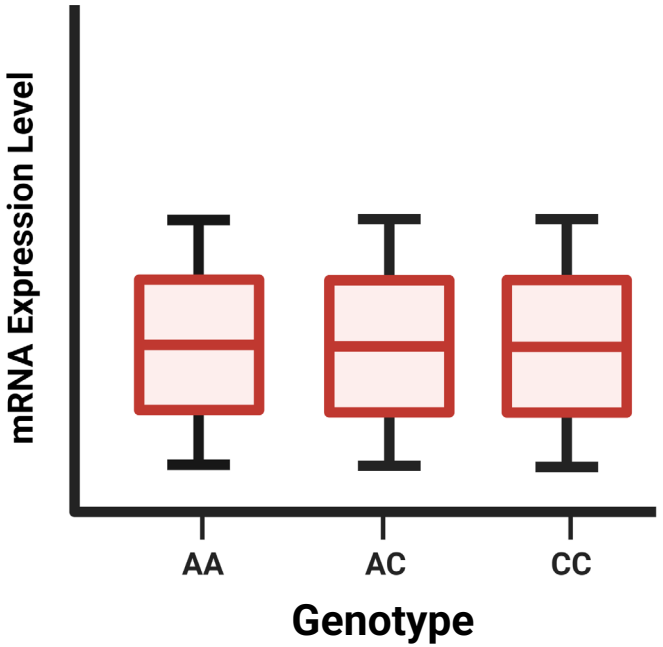

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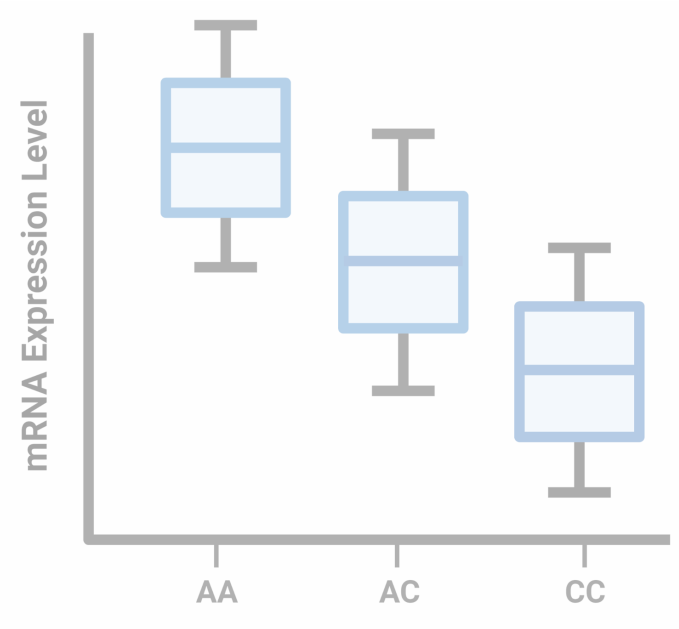
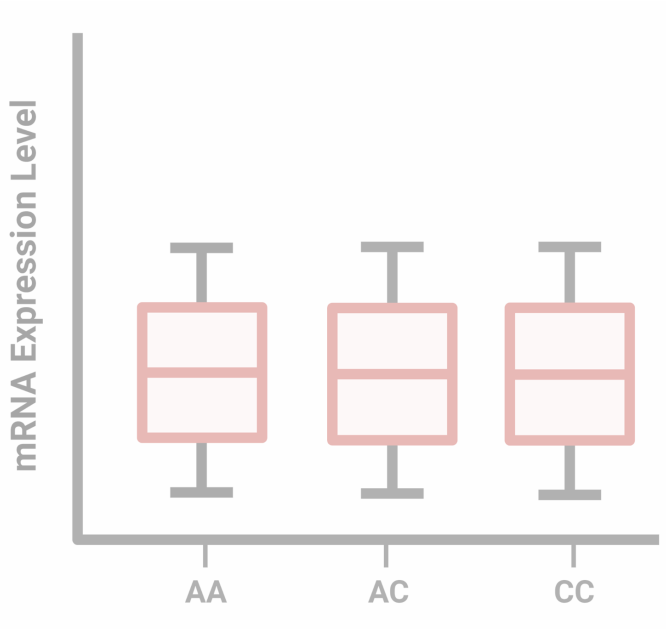
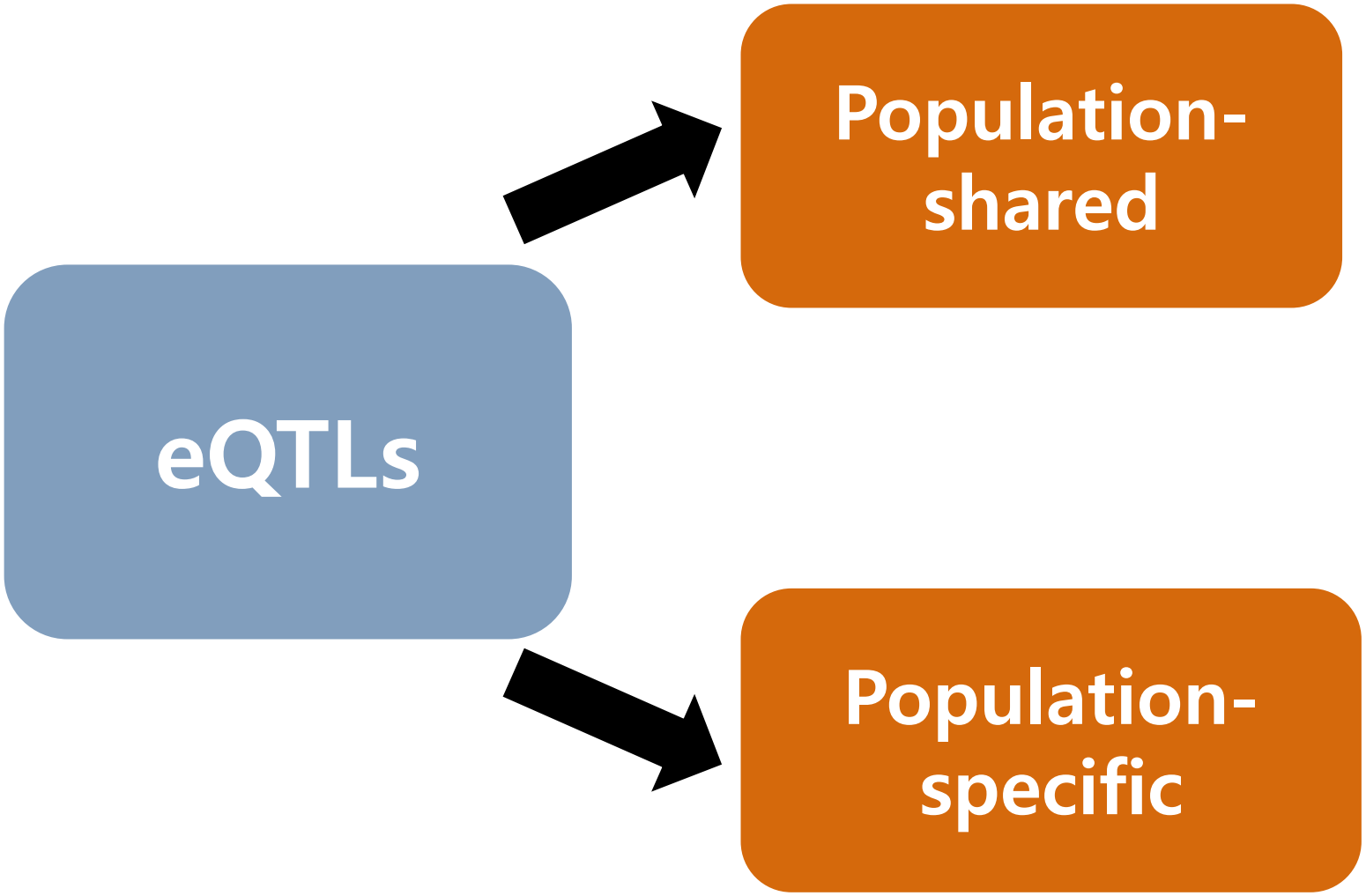
Created with BioRender.com

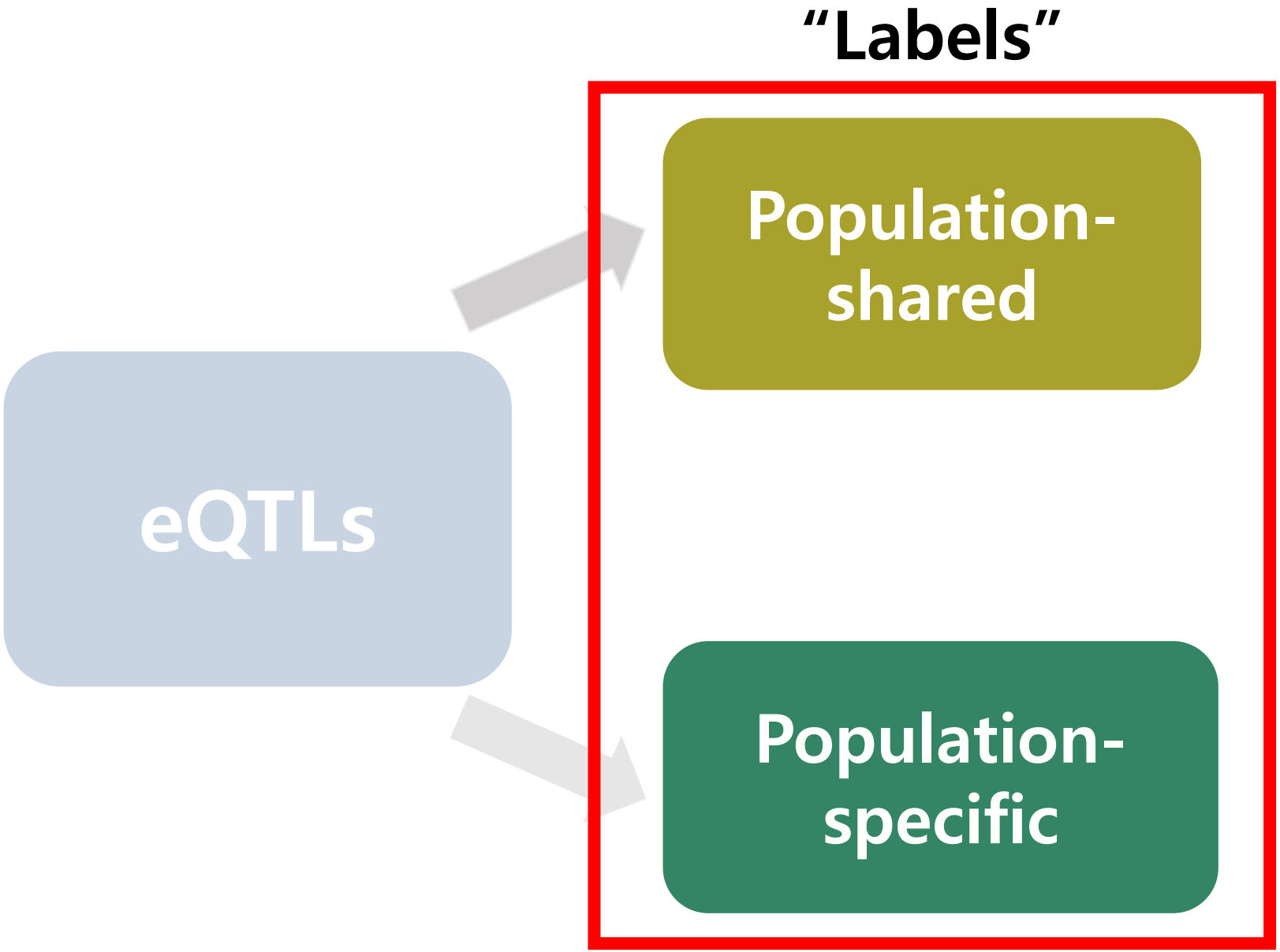
eQTLs

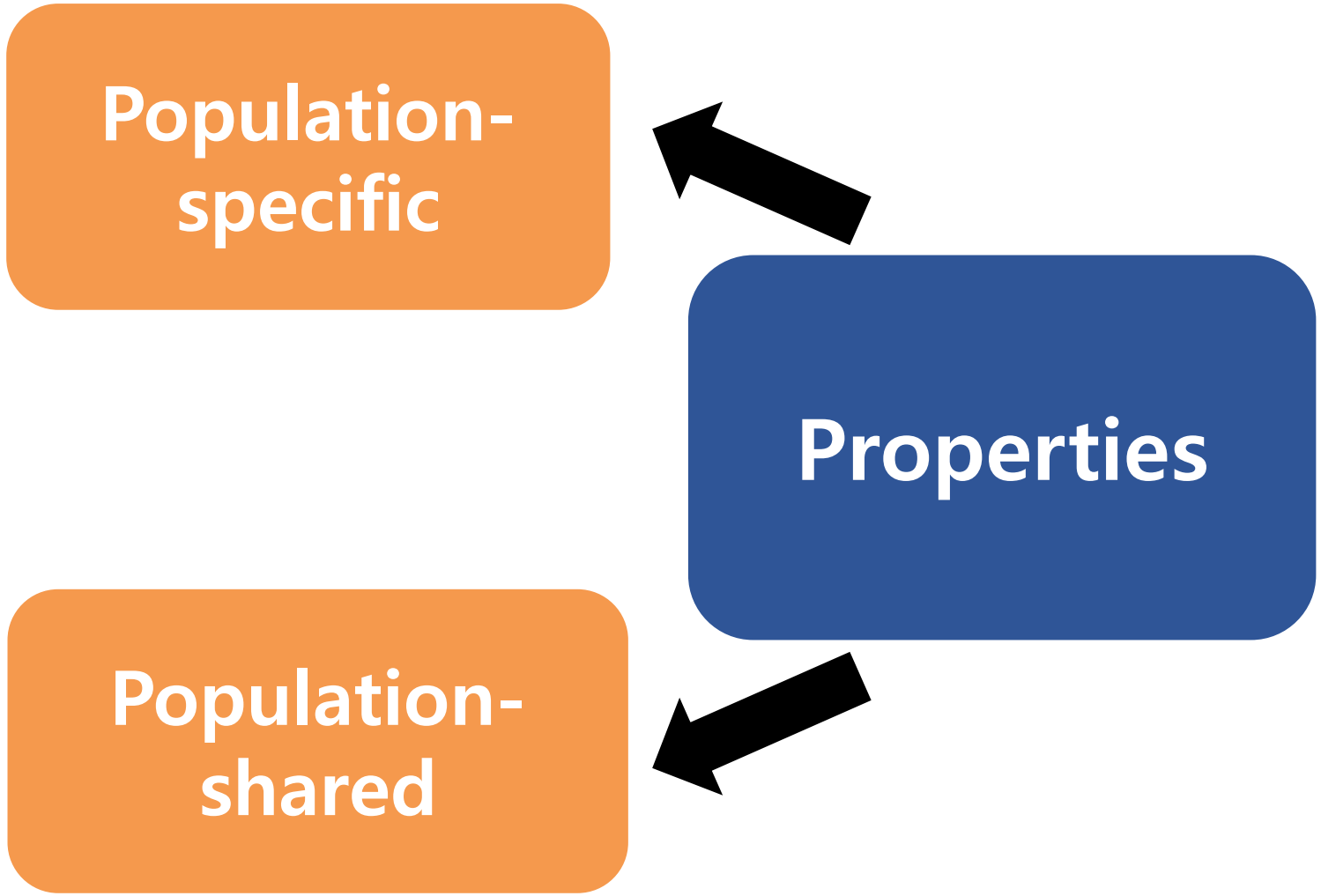


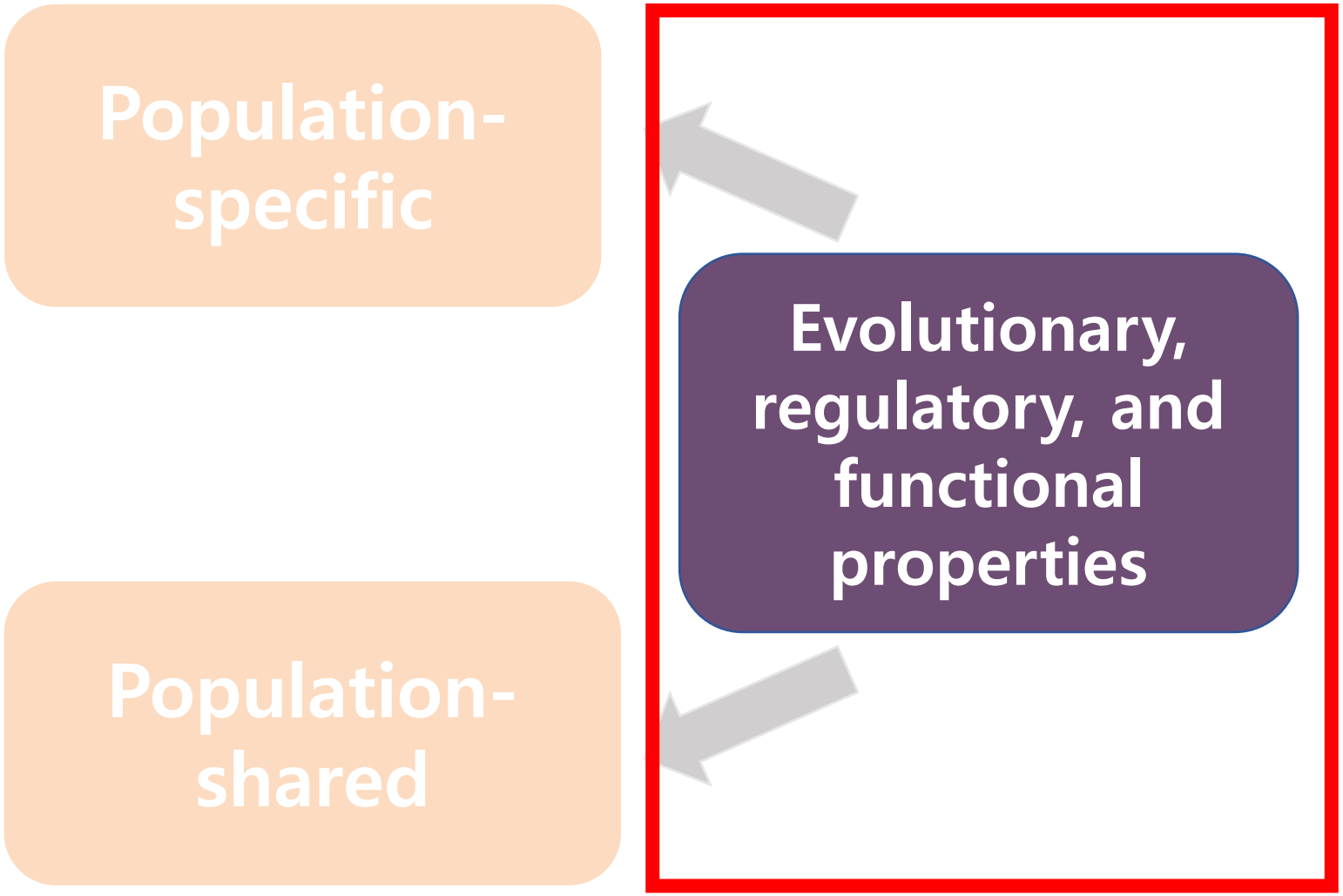


Population-specific

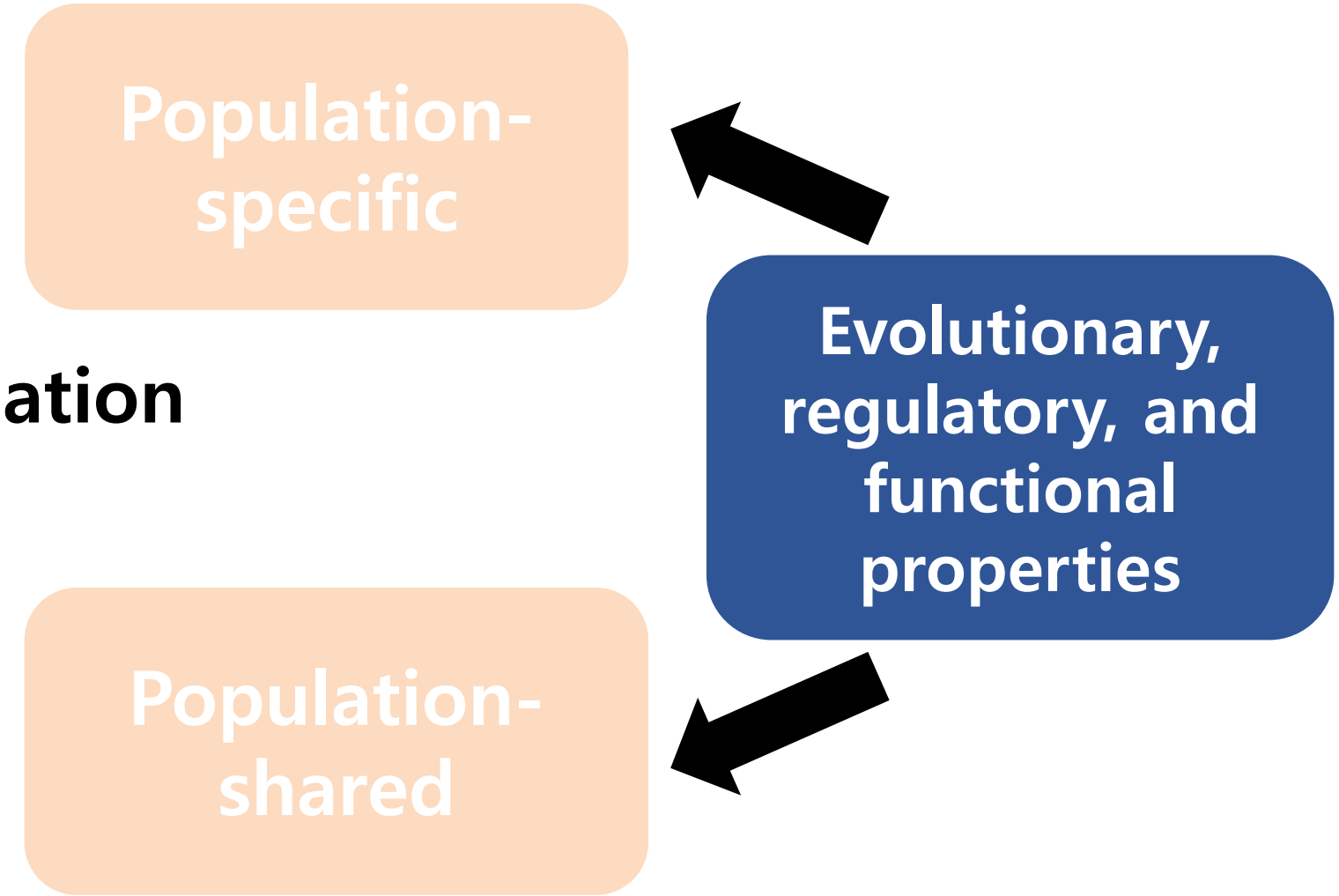

eQTLs
Population-shared
Population-specific


"Labels"
eQTLs
Population-shared
Population-specific


Population-specific
Properties
Population-shared


Population-specific
Population-shared
Evolutionary, regulatory, and functional properties
"Features"

- eQTL effect size
- Allele frequency
- Gene and SNP Conservation
- Gene Expression
- SNP Genomic location
- % Nucleotide
- Gene Ontology



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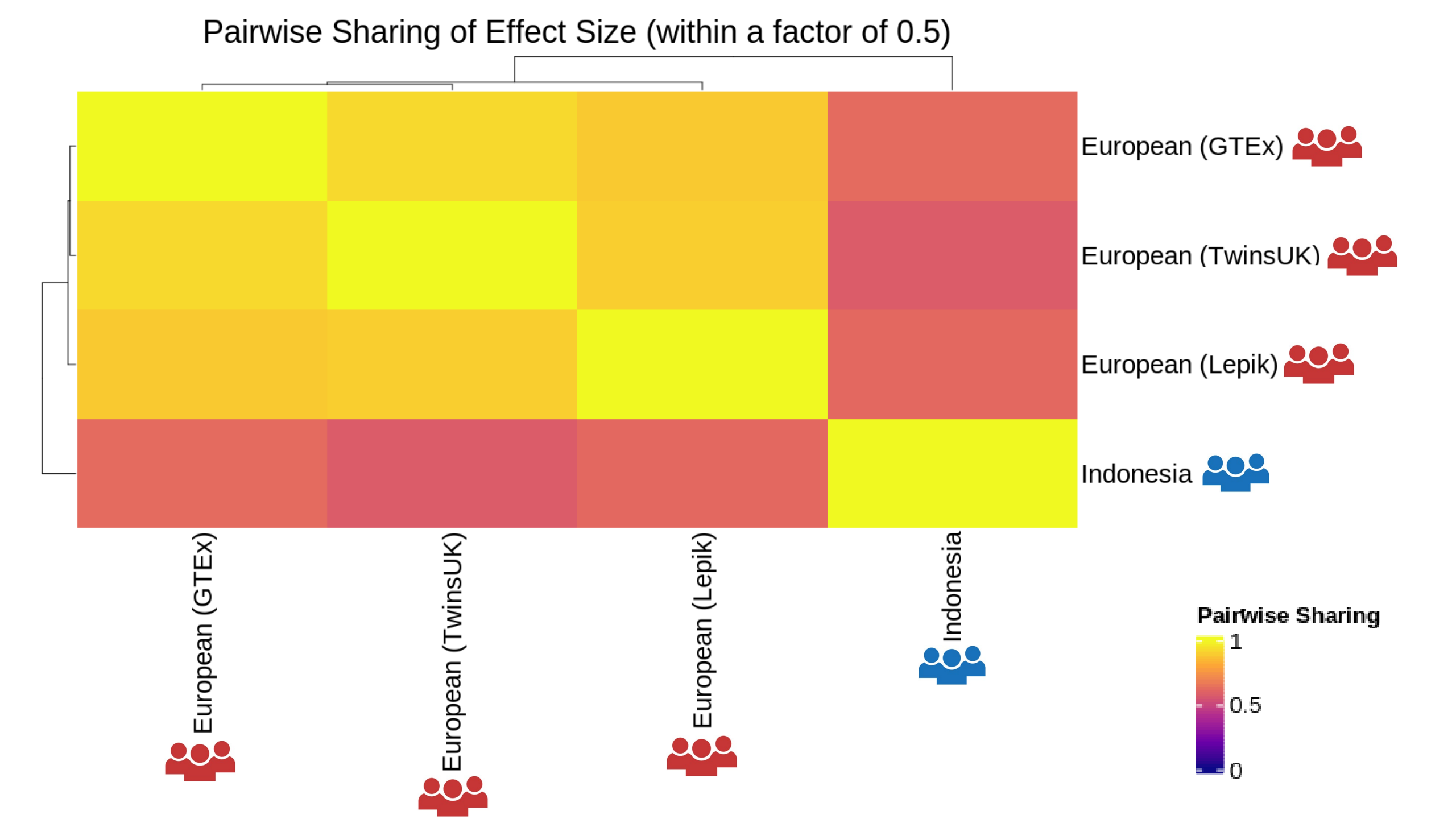
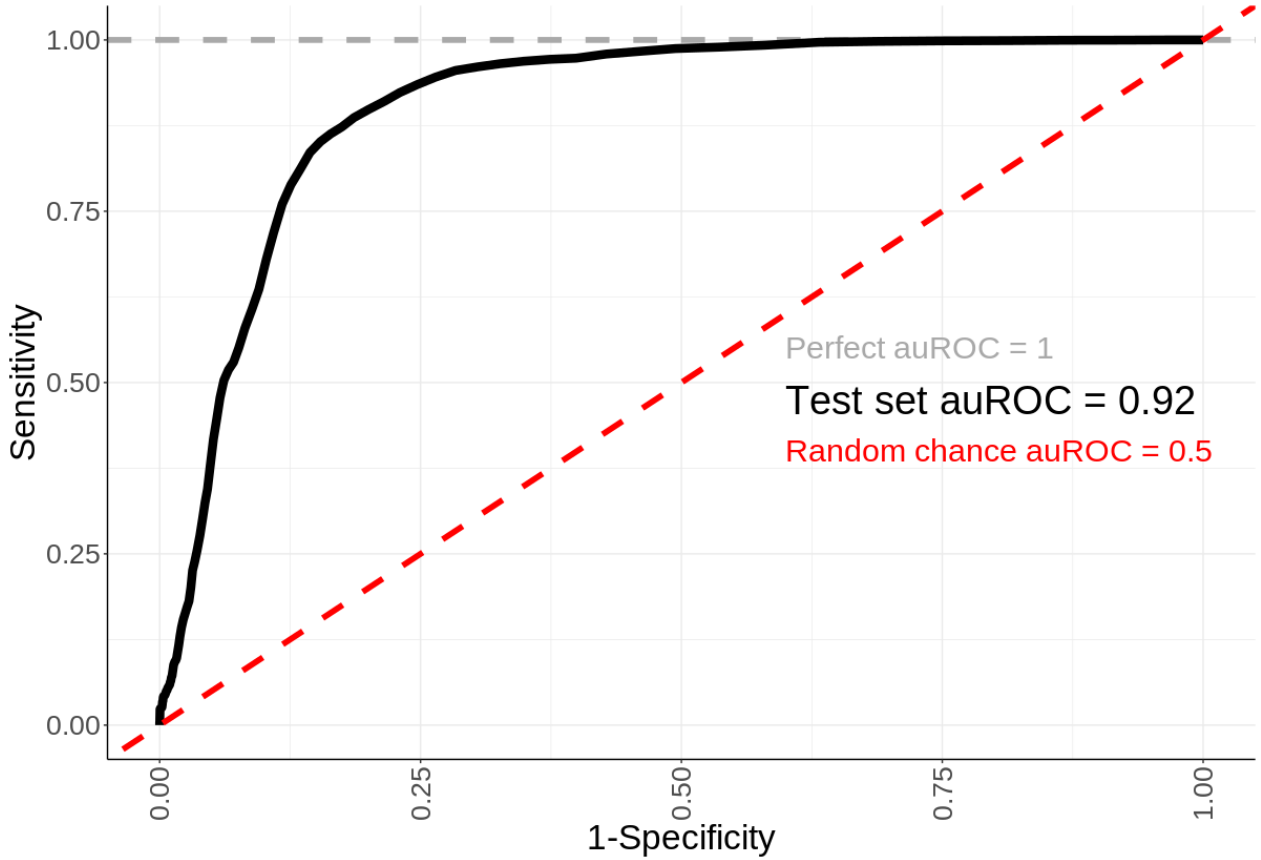
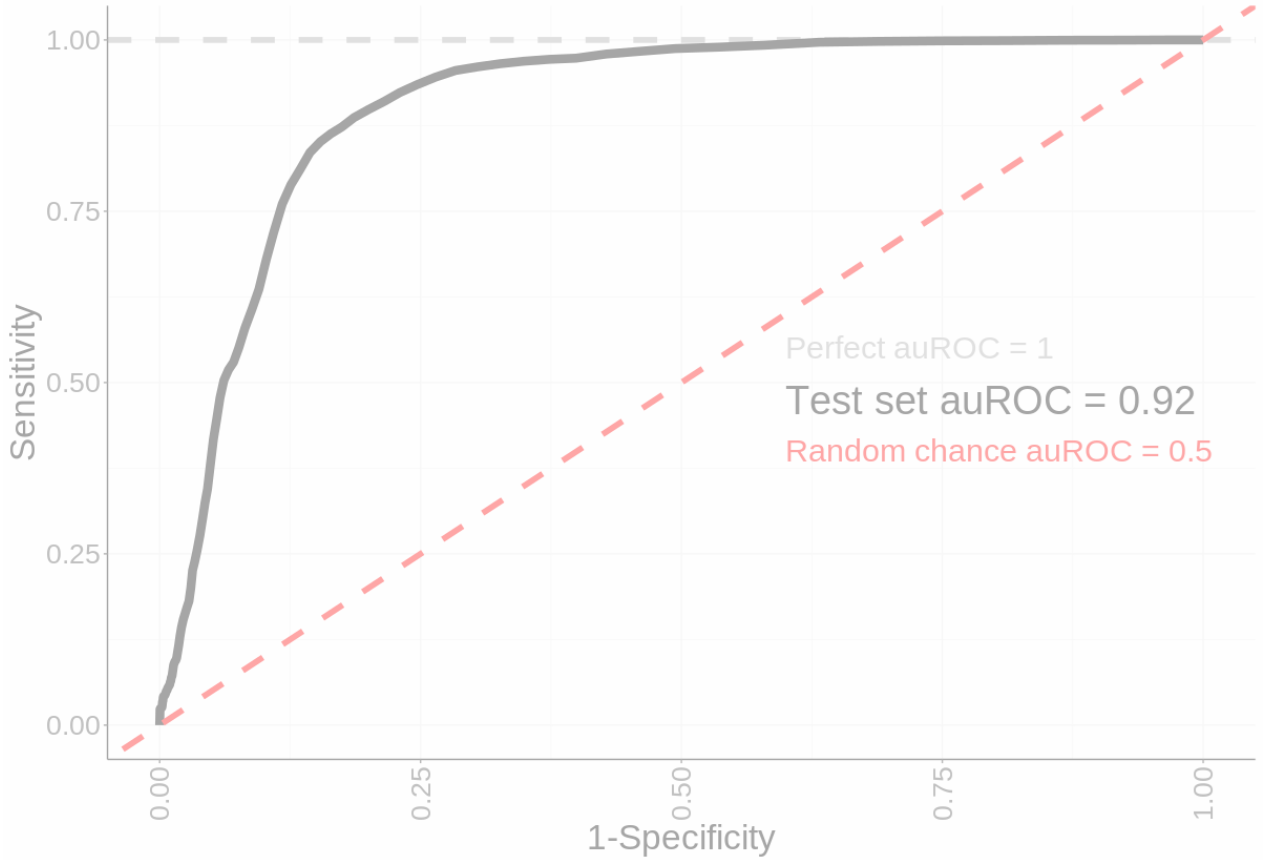

Pairwise Sharing of Effect Size (within a factor of 0.5)
European (GTEx)
European (TwinsUK)
European (Lepik)
Indonesia
European (GTEx)
European (TwinsUK)
European (Lepik)
Indonesia
Pairwise Sharing
1
0.5
0

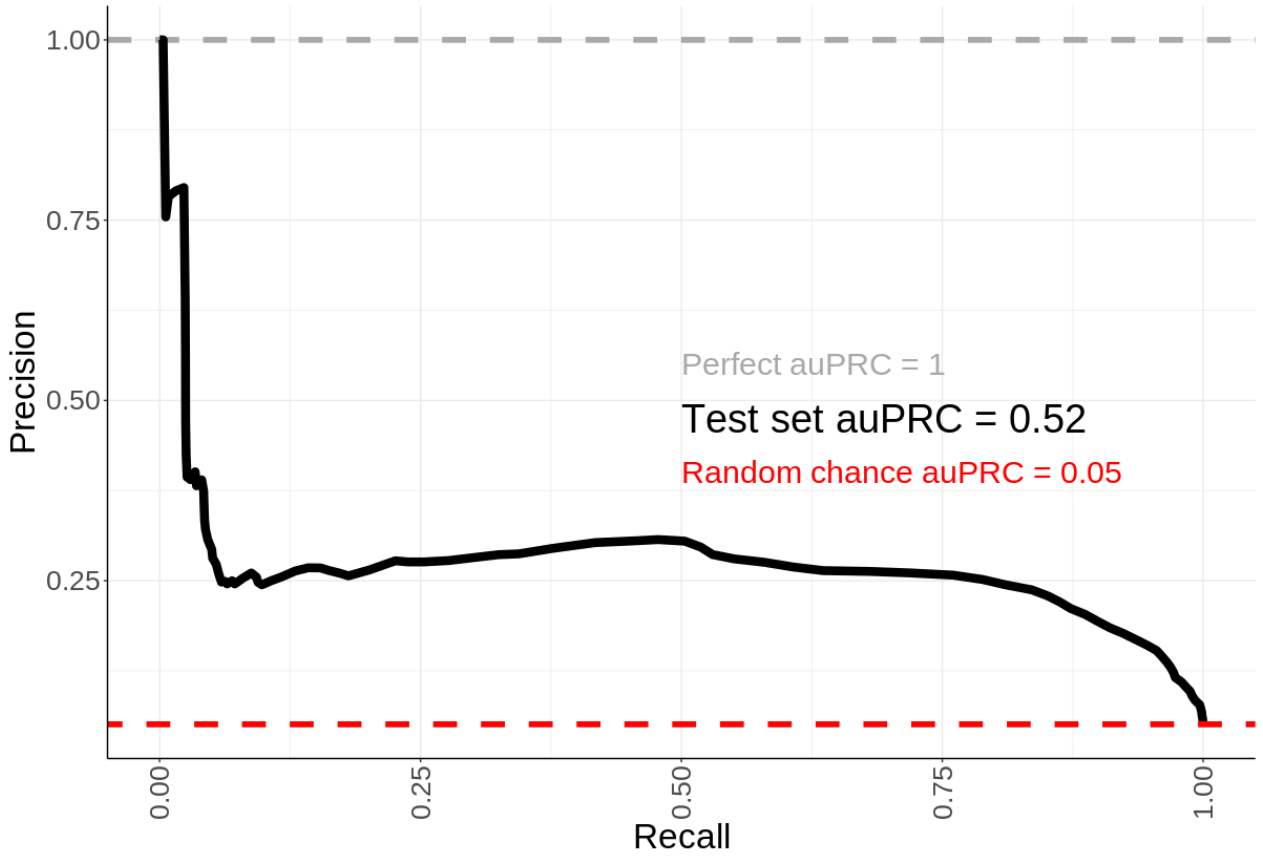
Prediction Performance



Test set: Chromosomes 8,16

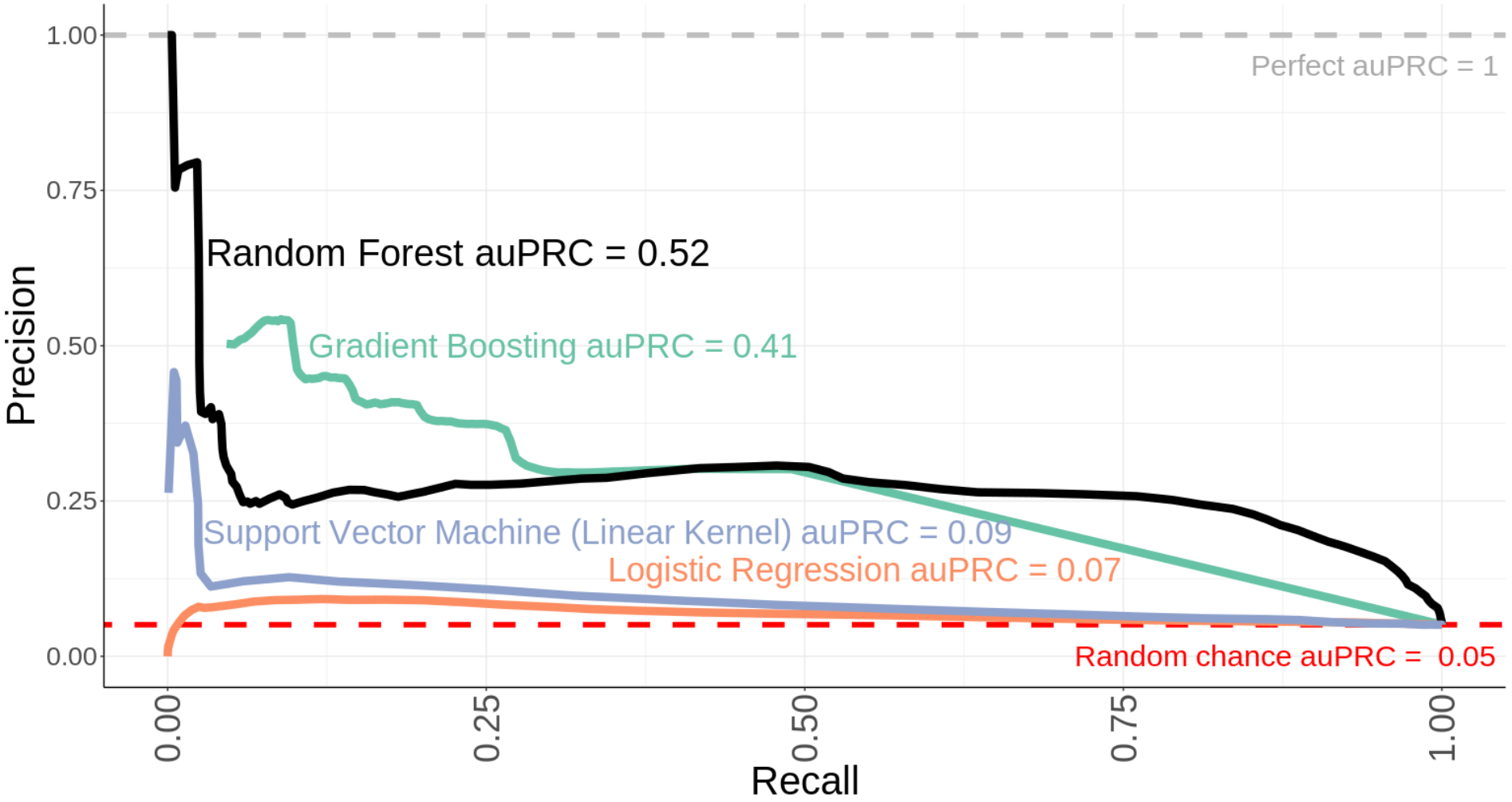
Prediction Performance



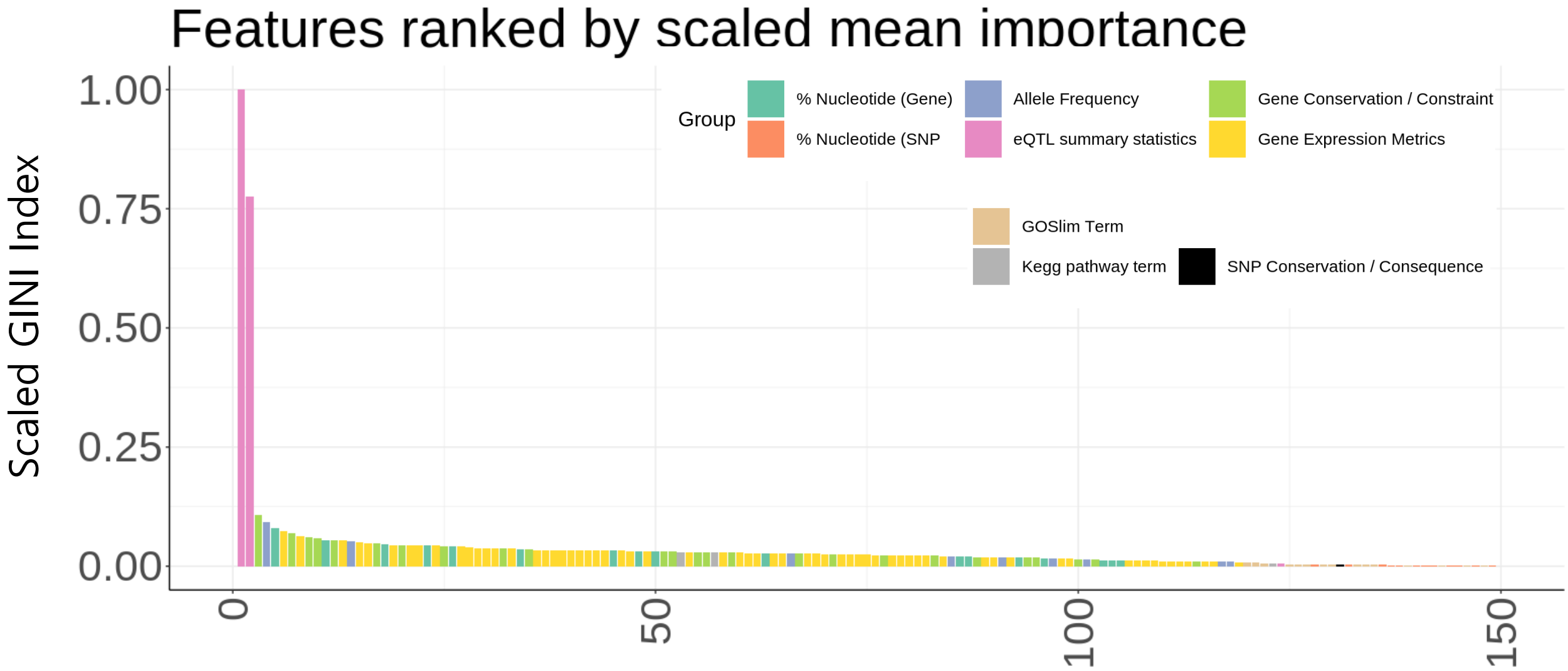


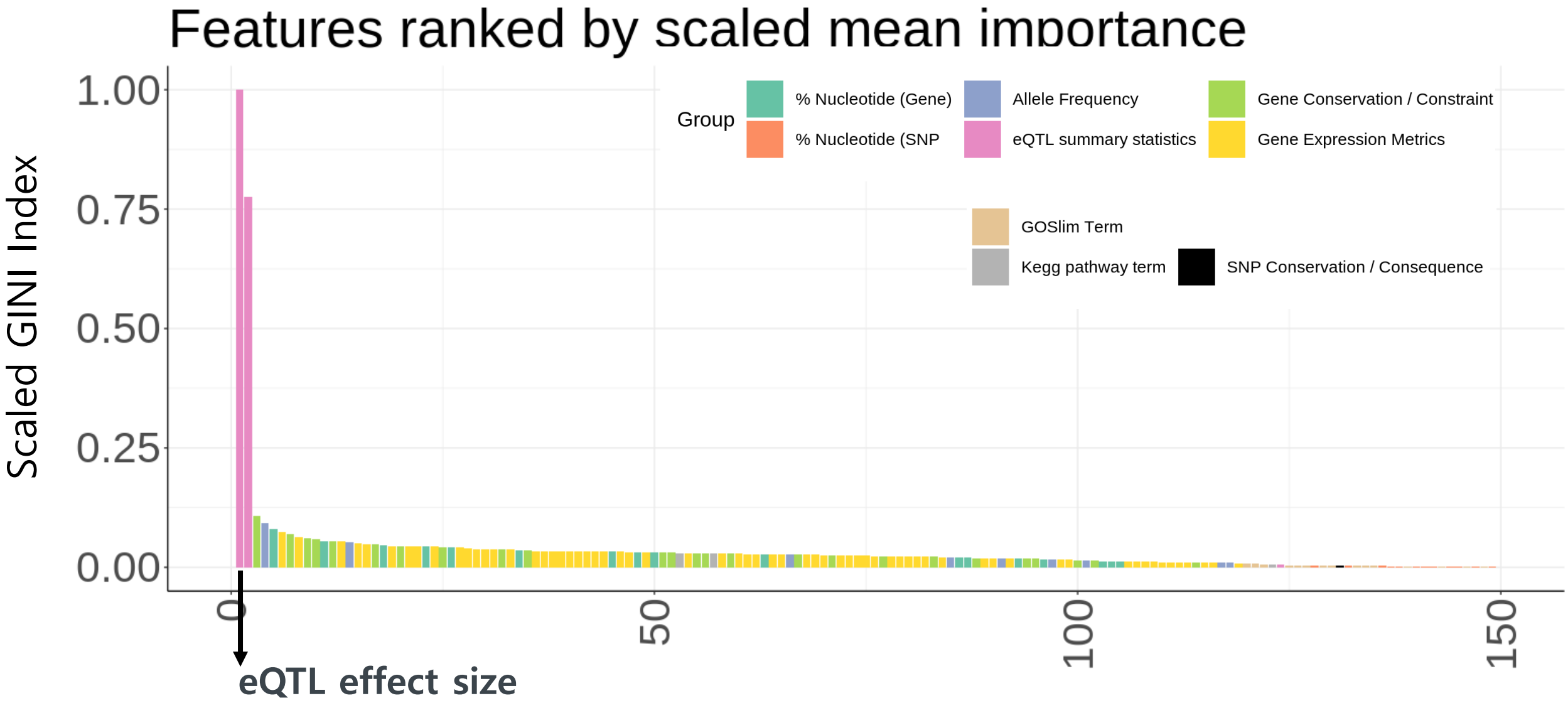
Test set: Chromosomes 8,16

Prediction Performance across Algorithms



Test set: Chromosomes 8,16


Features ranked by scaled mean importance
Scaled GINI Index
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Group
% Nucleotide (Gene)
% Nucleotide (SNP
Allele Frequency
eQTL summary statistics
Gene Conservation / Constraint
Gene Expression Metrics
GOSlim Term
Kegg pathway term
SNP Conservation / Consequence


Features ranked by scaled mean importance
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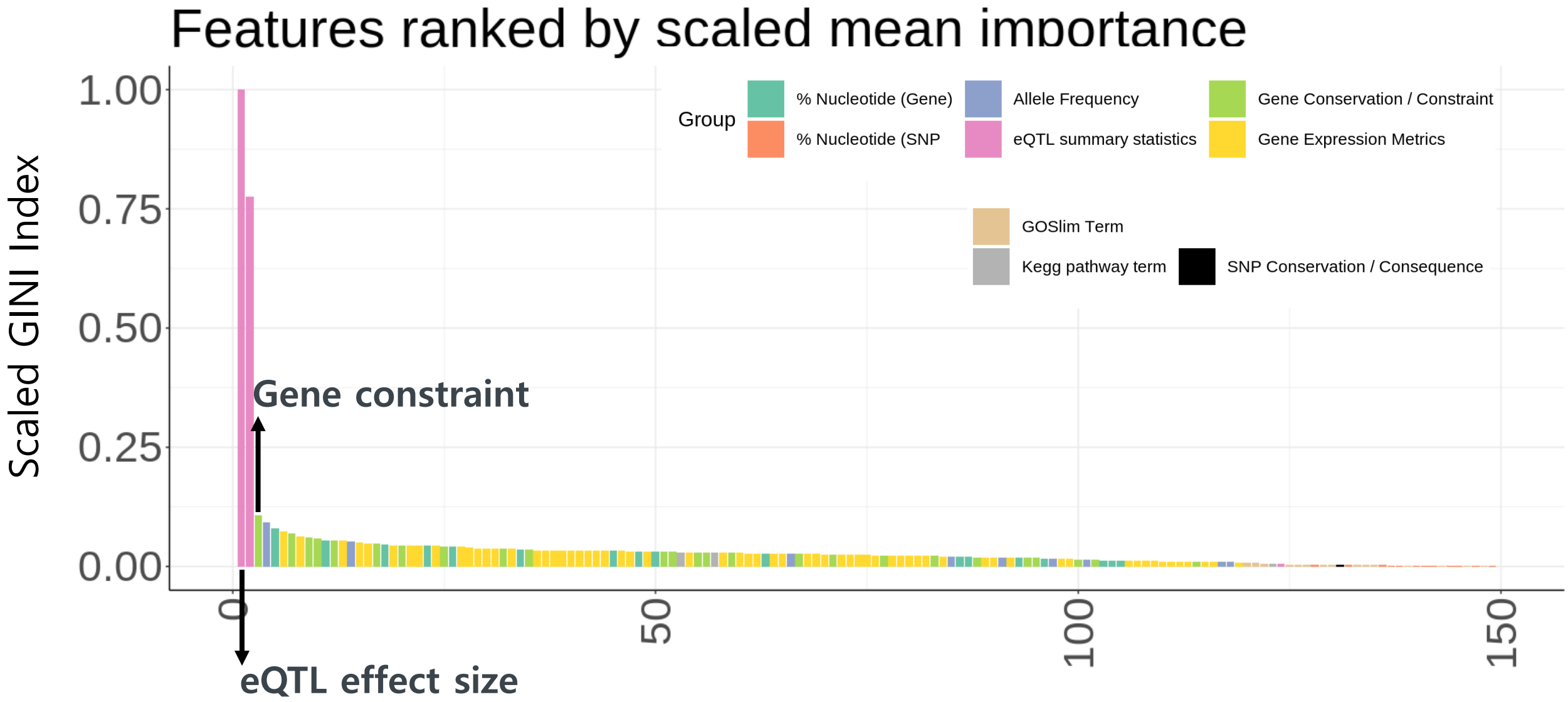
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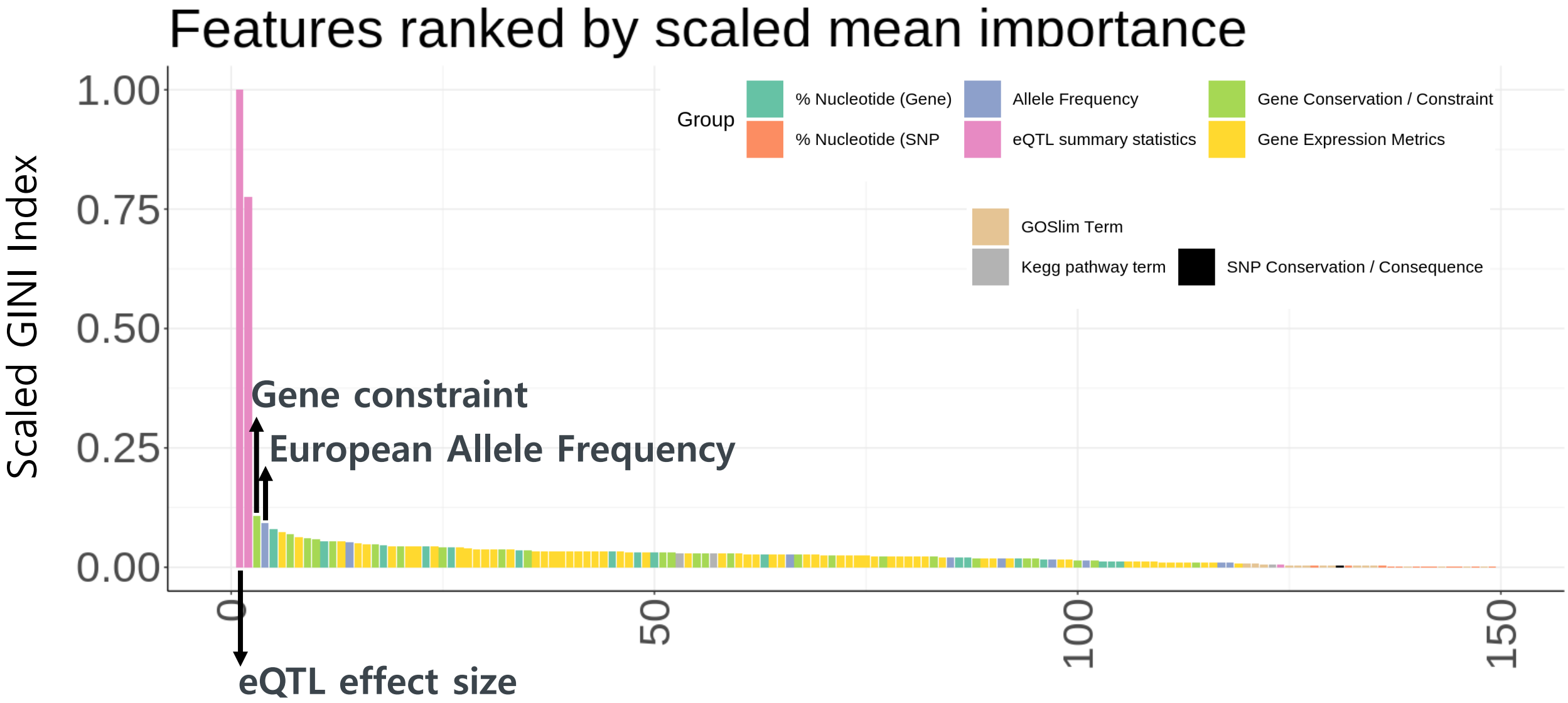
Gene constraint
eQTL effect size


Features ranked by scaled mean importance
Scaled GINI Index
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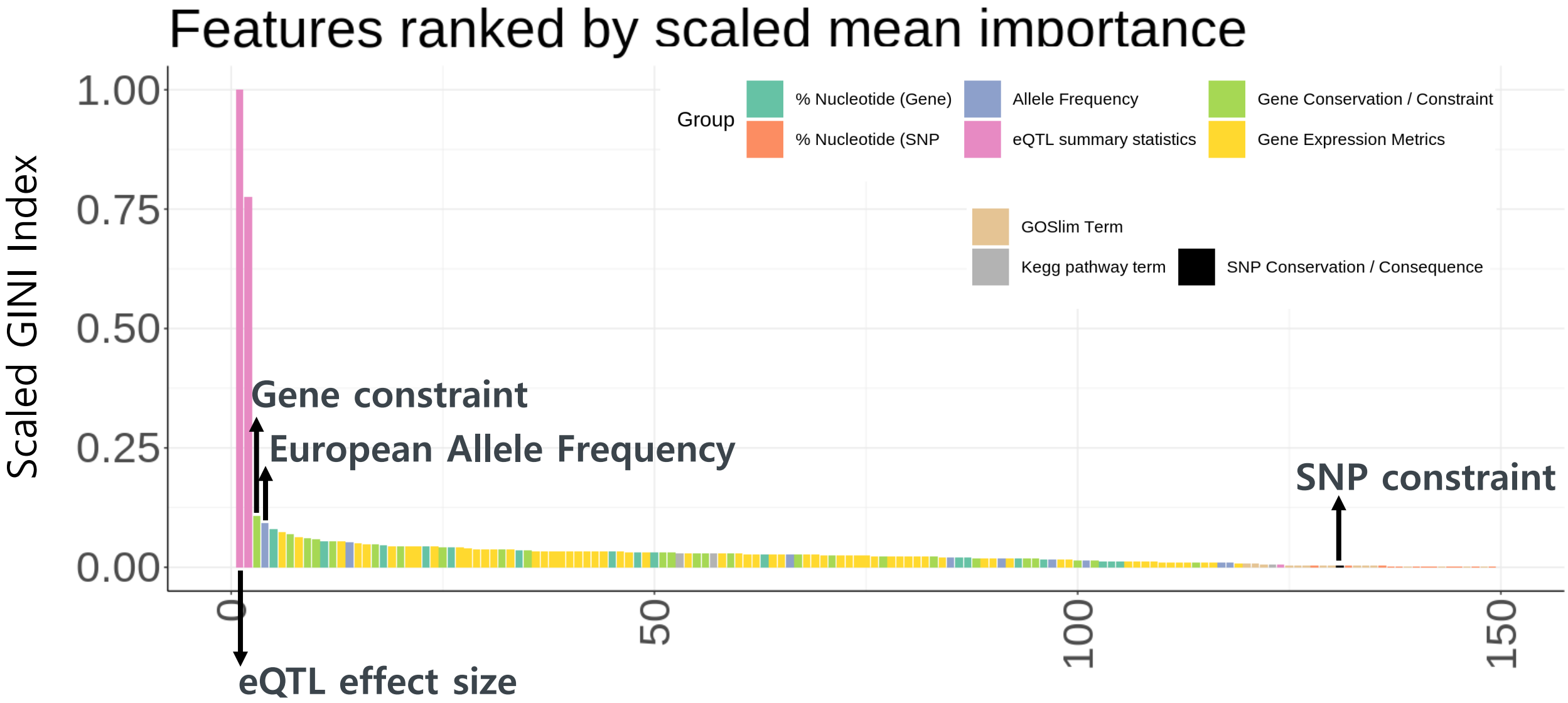
eQTL summary statistics
Gene Conservation / Constraint
Gene Expression Metrics
GOSlim Term
Kegg pathway term
SNP Conservation / Consequence
Gene constraint
European Allele Frequency
eQTL effect size


Features ranked by scaled mean importance
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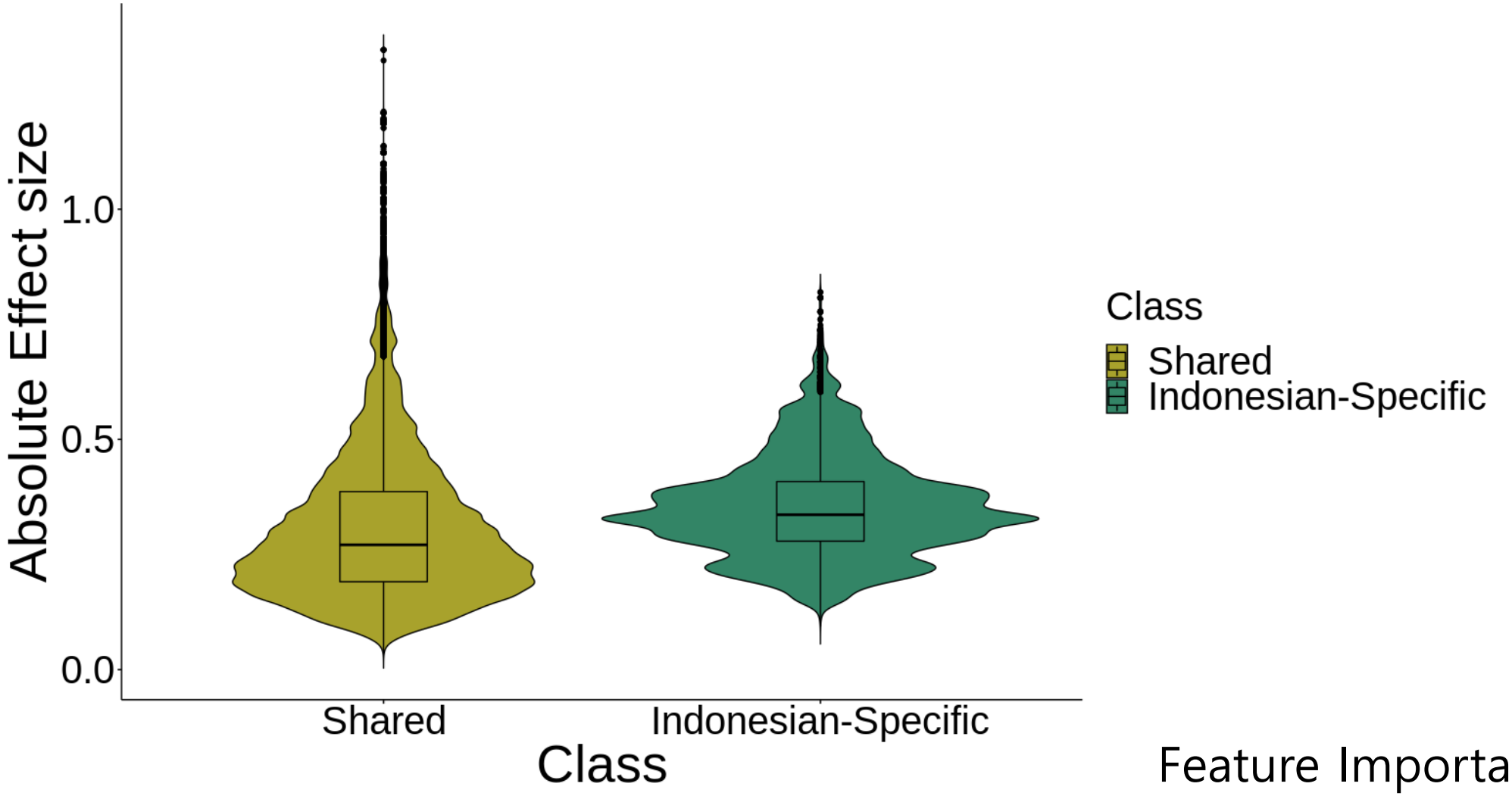
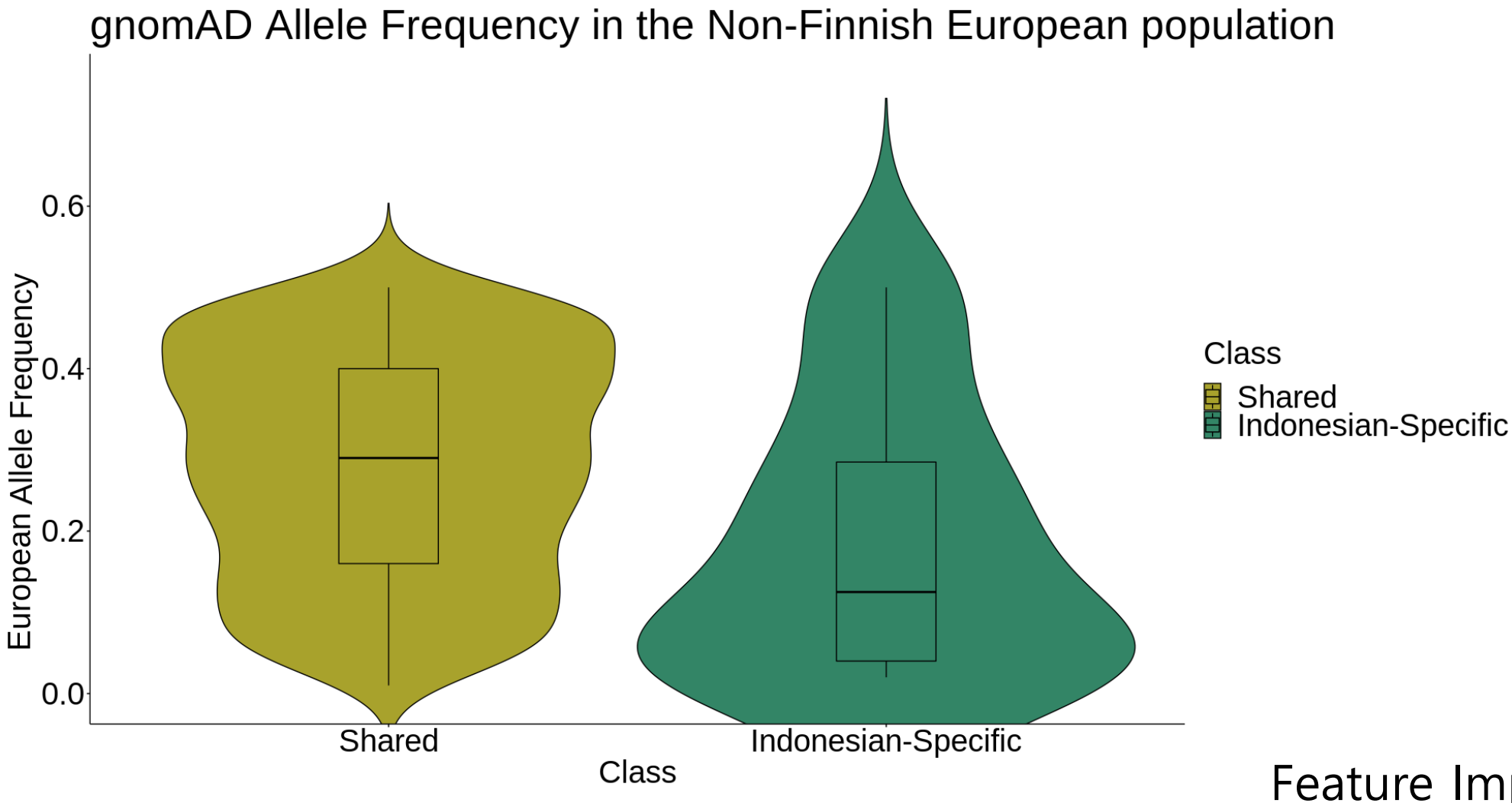
GOSlim Term
Kegg pathway term
SNP Conservation / Consequence
Gene constraint
European Allele Frequency
SNP constraint
eQTL effect size

Population-specific eQTLs have higher effect sizes in their discovery population



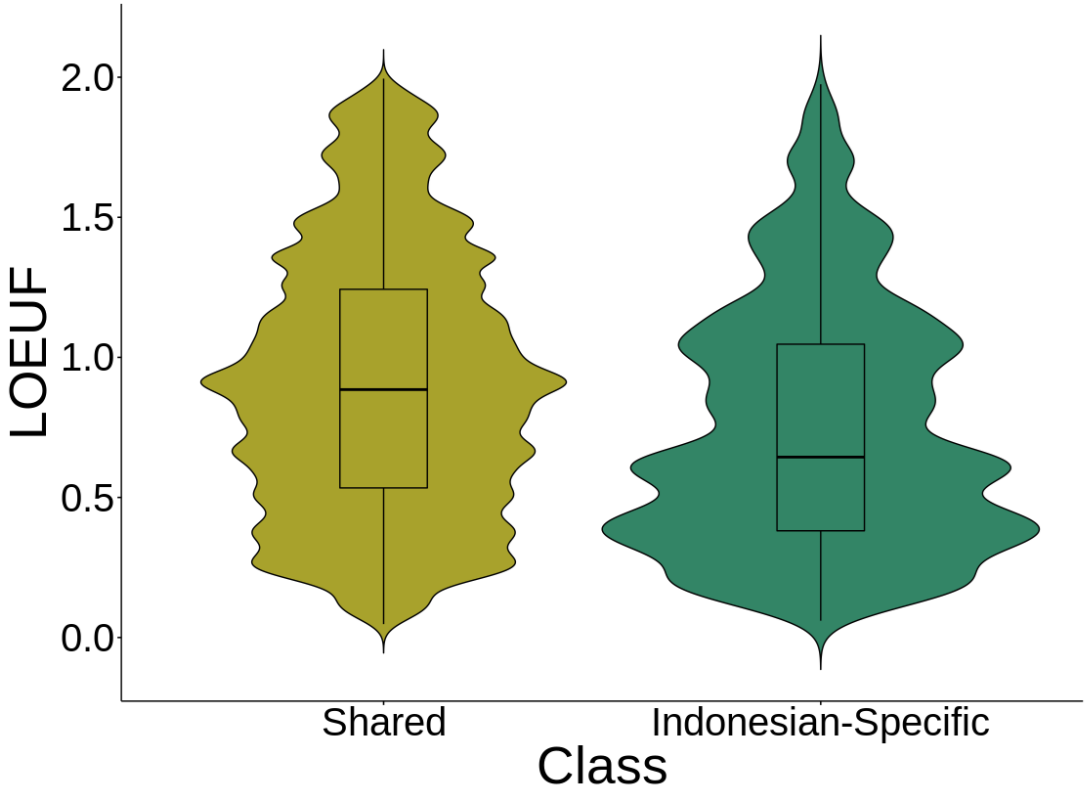
Feature Importance rank: 1

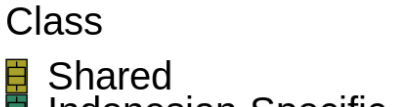
Population-specific eQTLs have different allele frequencies across populations

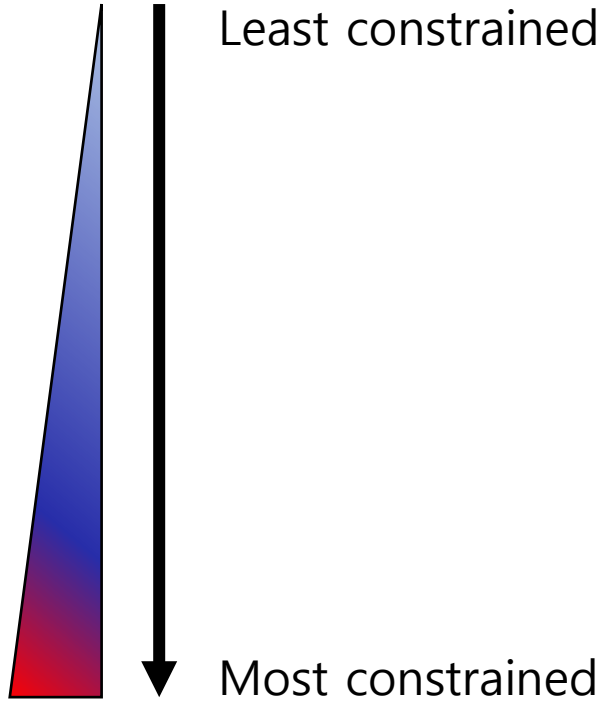


Feature Importance rank: 4

Population-specific eGenes are more highly conserved



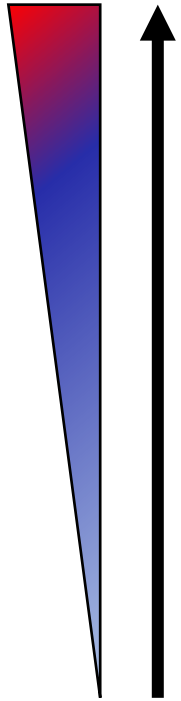




LOEUF = Upper bound of the confidence interval observed over expected number of loss of function variants

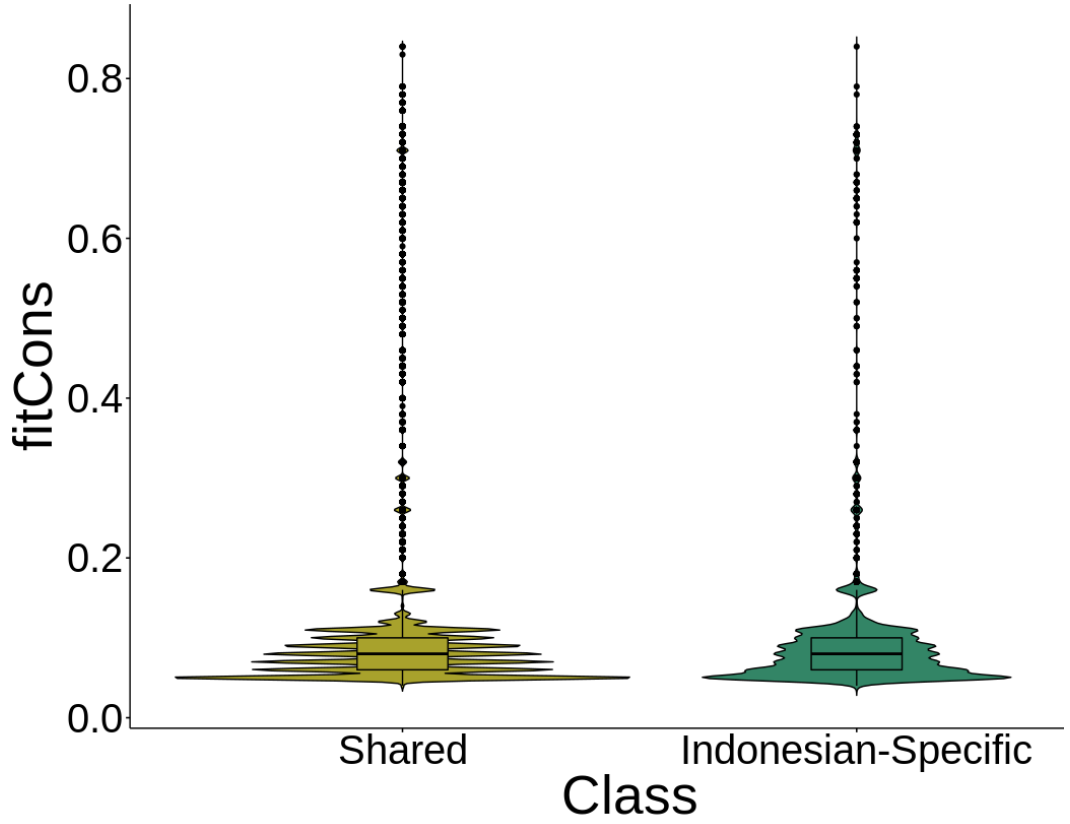
Gene Conservation Feature Importance rank: 3

Population-specific eGenes are more highly conserved … but not eSNPs

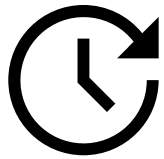


Highest probability of impacting fitness

Lowest probability of impacting fitness



SNP Conservation Feature Importance rank: 131

… toward the future 

Conclusions

- Machine learning models could improve the transferability of eQTLs from Europeans to underrepresented populations

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- Machine learning models could improve the transferability of eQTLs from Europeans to underrepresented populations
- Some properties are different between shared and specific eQTLs
- Eurocentric biases prevent equitable research translation

Thank you!

Irene Gallego Romero[1,2]

Christina B Azodi[1,3]

Gallego Romero + Bioinformatics and Cellular Genomics Groups

1. Melbourne Integrative Genomics

2. School of BioSciences

3. Bioinformatics and Cellular Genomics

More questions or eQTL datasets? @ijbeasley