MultiSuSiE improves multi-ancestry fine-mapping in All of Us whole-genome sequencing data

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Outline

1. Background
2. Method and Simulations
3. Results on Real Traits
4. Conclusions and Future Directions

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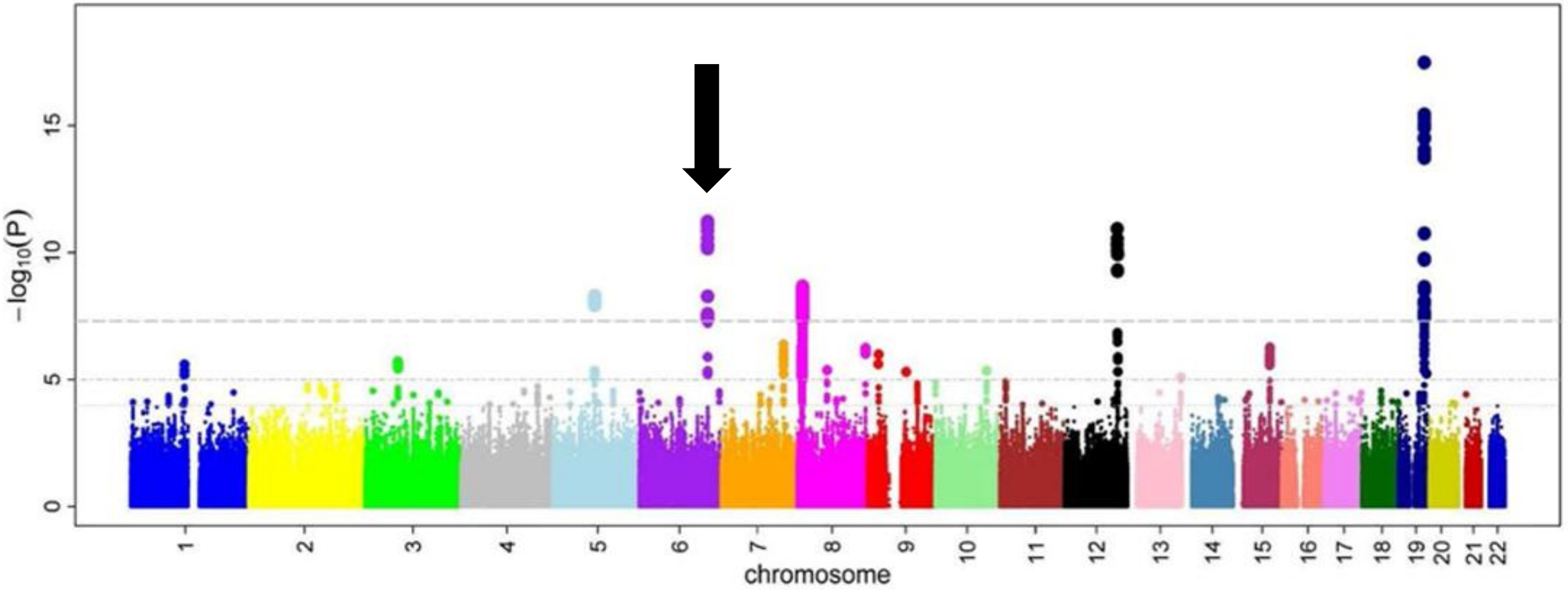
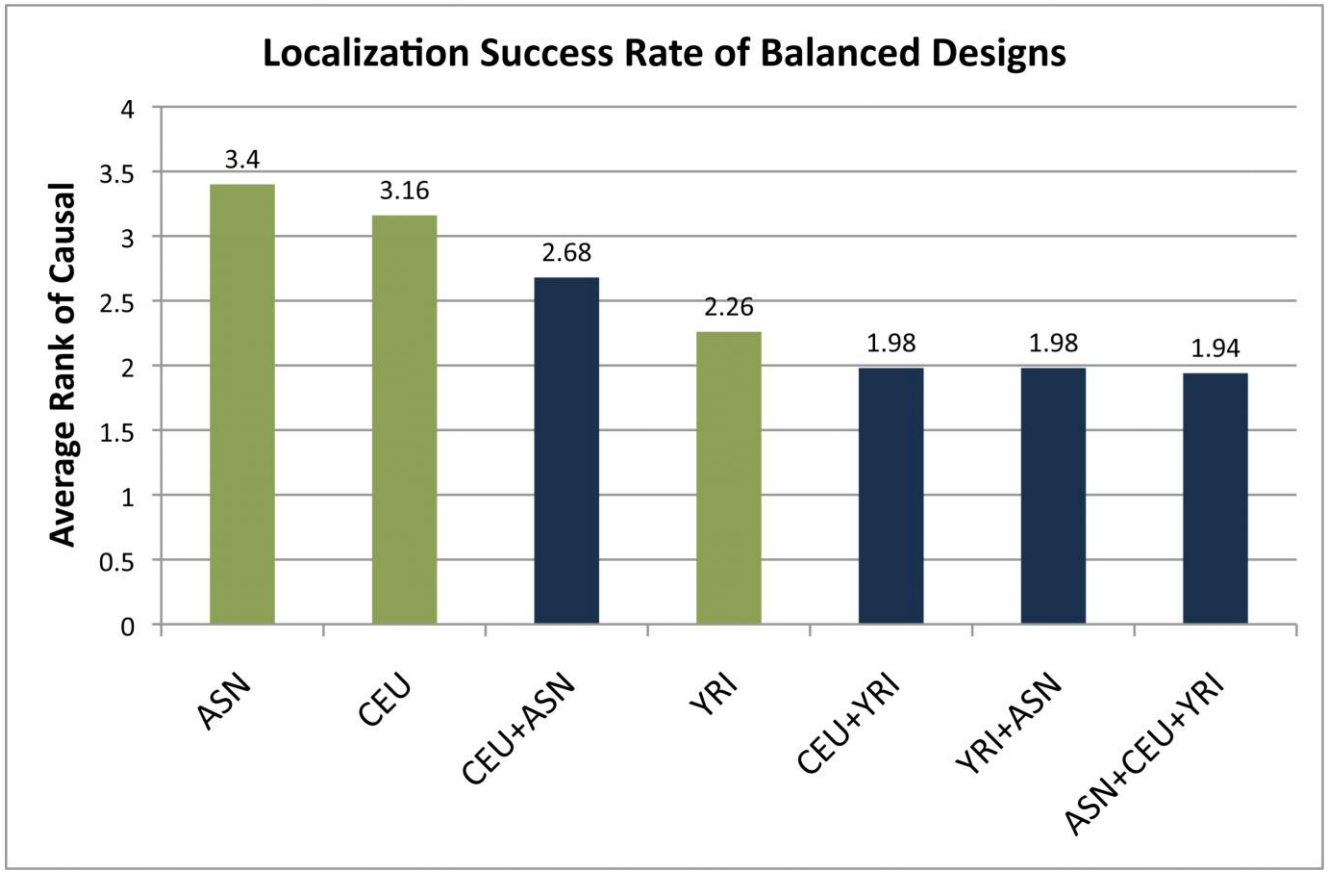
Fine-mapping methods identify causal mutations at GWAS loci



Manhattan plot from Ikram et al. 2010 PLoS Genet

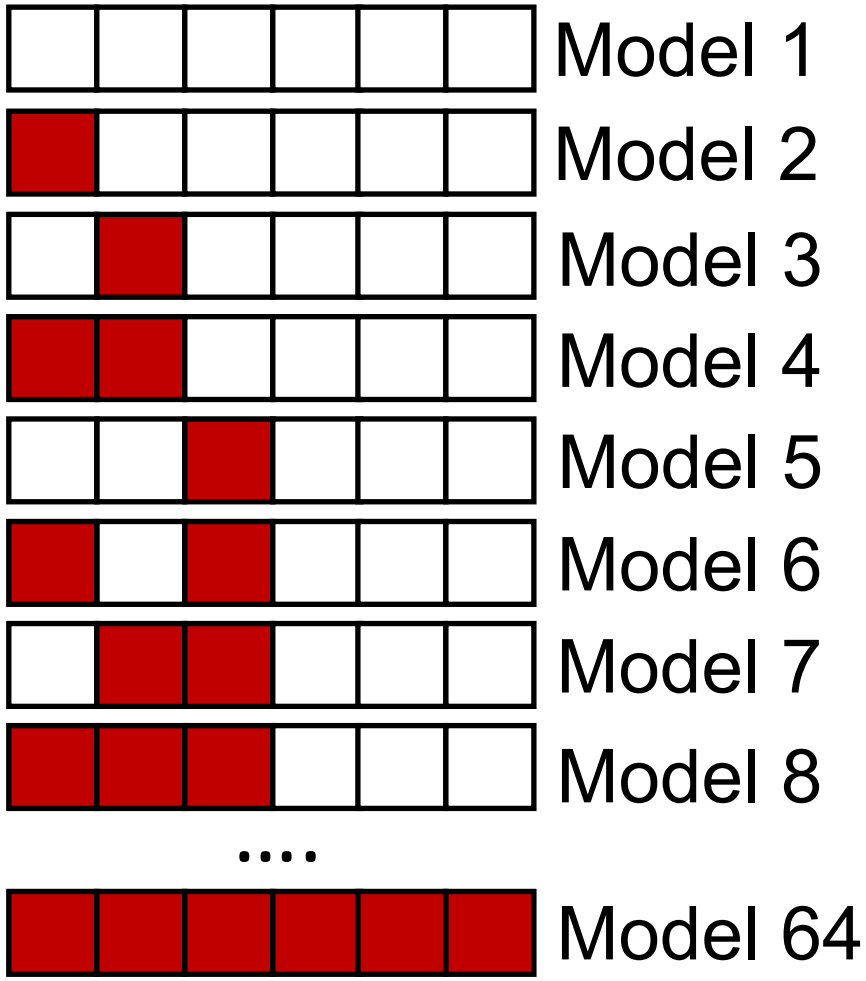
Integrating data from multiple ancestries improves fine-mapping

- Fine-mapping is hard because of linkage disequilibrium (LD)
- Integrating data from multiple population improves ability to detect causal SNPs



Zaitlen et al. 2010 Am. J. Hum. Genet.

Published multi-ancestry methods fail at multiple causal variant fine-mapping

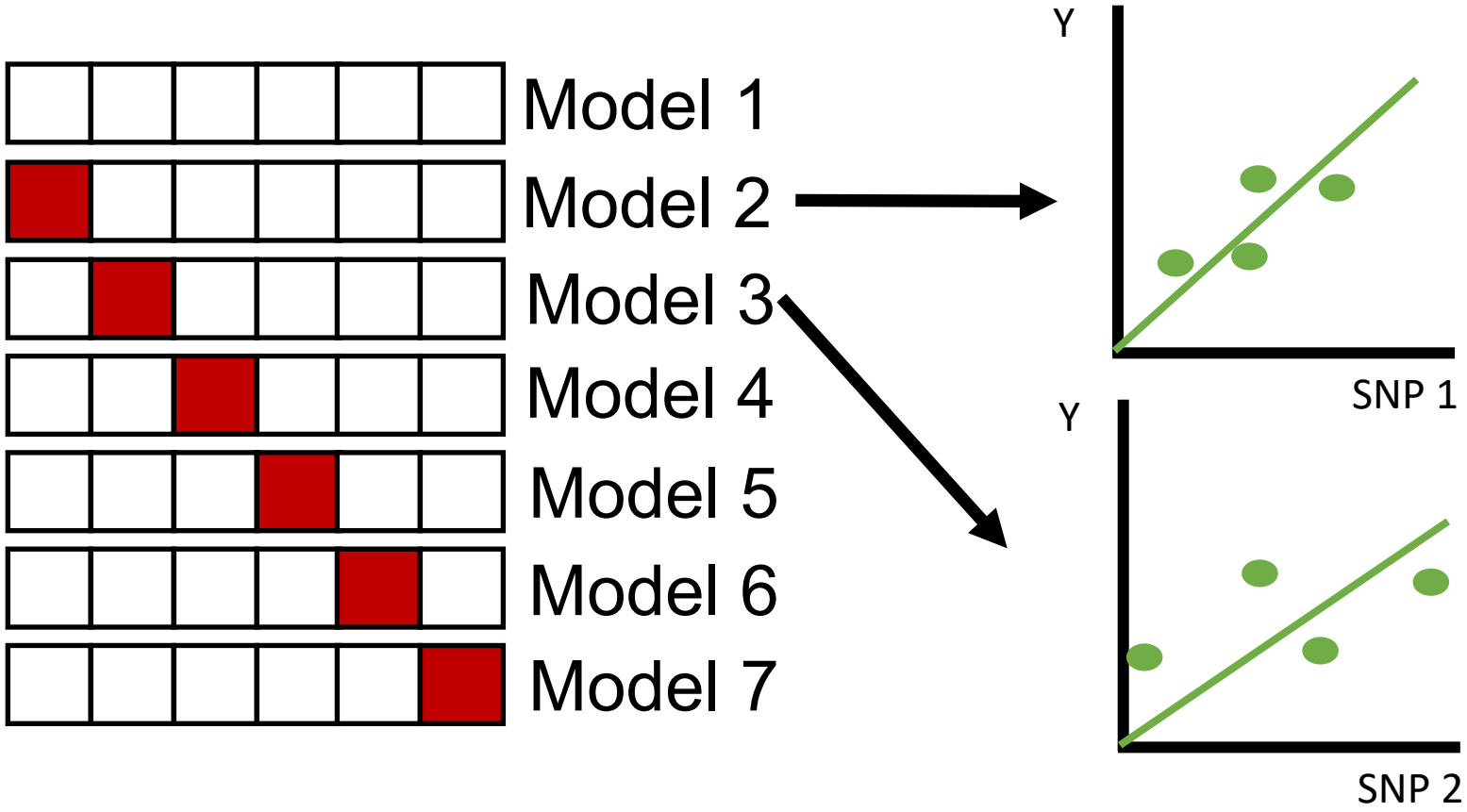


- Exhaustively evaluating all possible configurations of causal variants is very expensive for large numbers of SNPs, $O(2^P)$ models must be evaluated
- Published multi-ancestry methods use non-exhaustive search algorithms that often fail

Null SNP

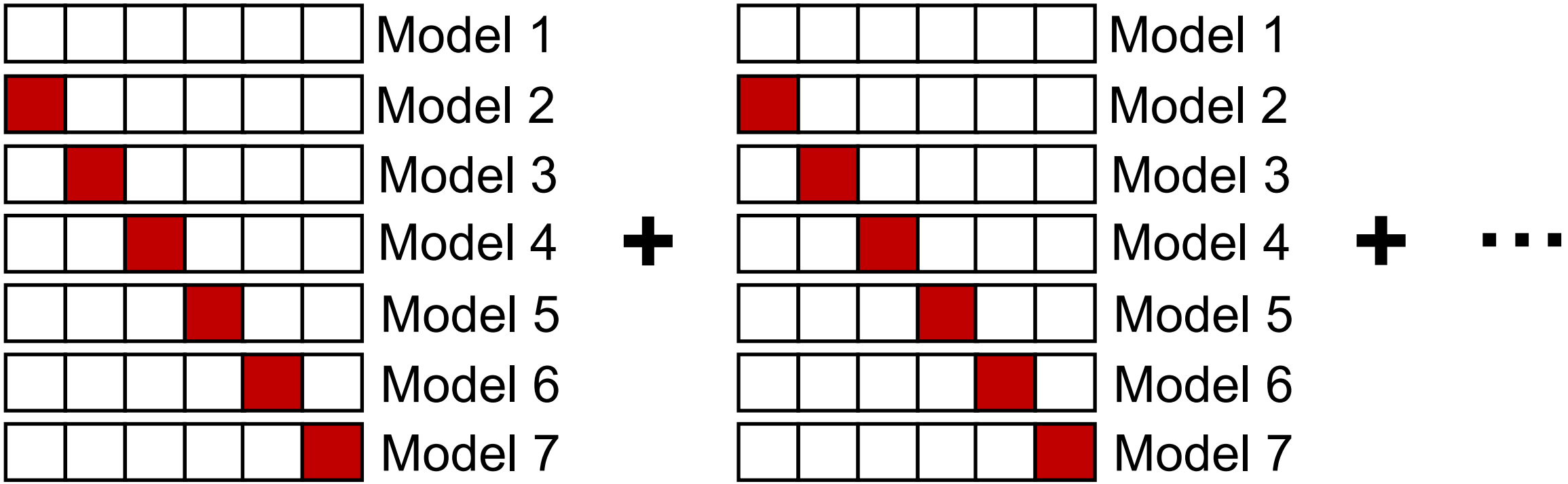
Causal SNP

SuSiE provides an elegant approach for efficient multiple-causal variant fine-mapping



Wang et al. 2020 J R Stat Soc Series B Stat Methodol

SuSiE provides an elegant approach for efficient multiple-causal variant fine-mapping



Null SNP Causal SNP

Wang et al. 2020 J R Stat Soc Series B Stat Methodol

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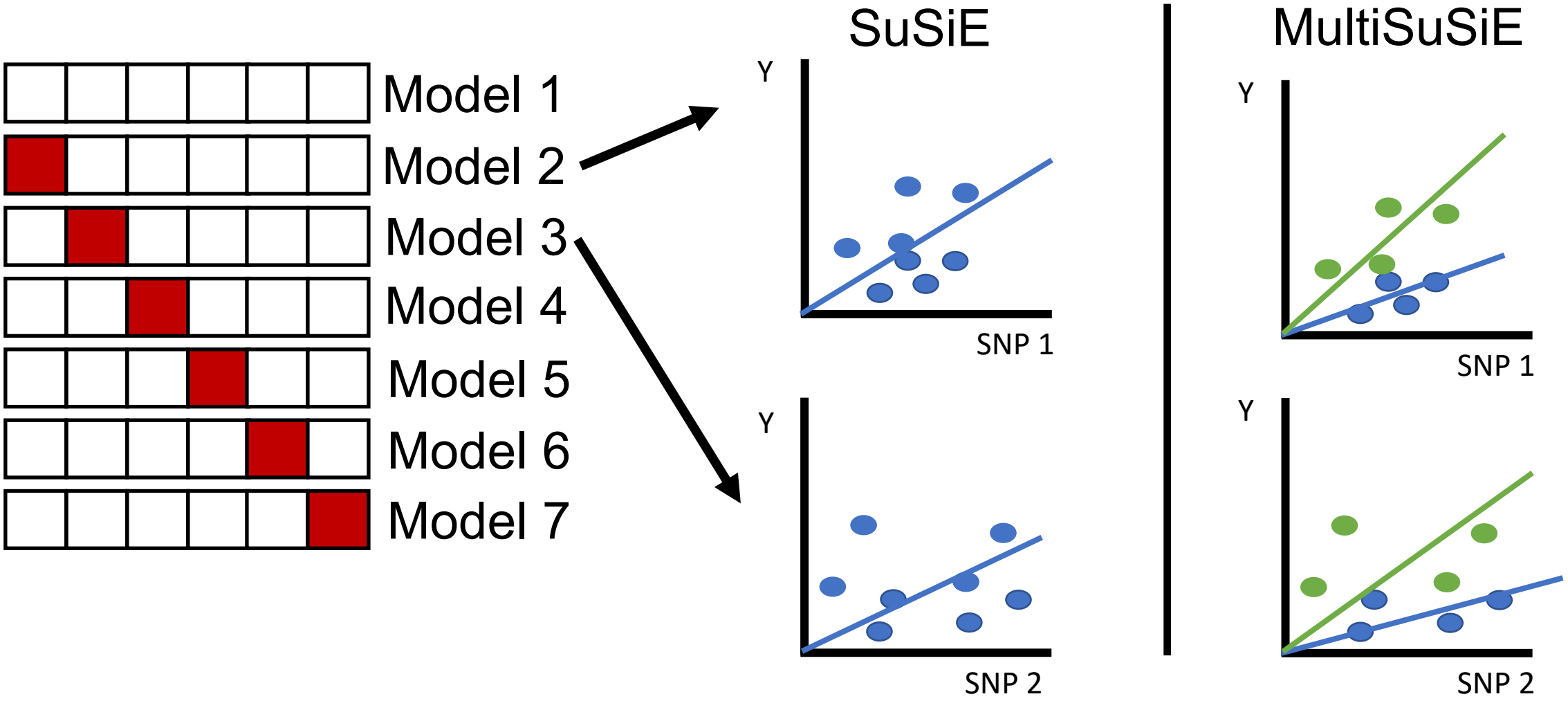
MultiSuSiE extends SuSiE to allow for population-specific effect sizes



MultiSuSiE extends SuSiE to allow for population-specific effect sizes

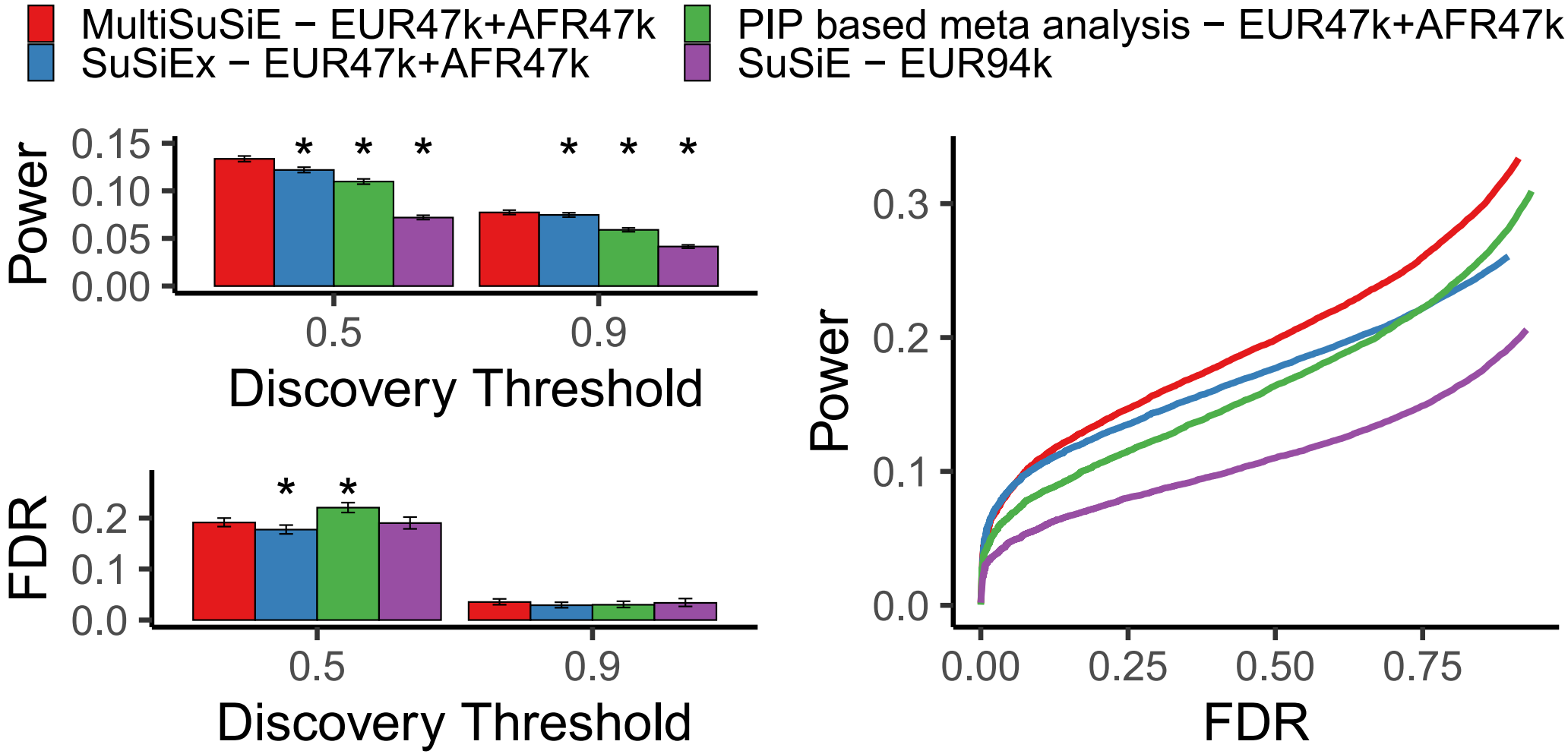
$$Y_k = \sum_{l=1}^{L} X_k \beta_{k,l} \gamma_l + \epsilon_k$$

$$\begin{bmatrix} \beta_{l,1} \\ \beta_{l,2} \end{bmatrix} \sim \mathrm{MVN}_2 \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} v_{l,1}^2 & v_{l,1} v_{l,2} \rho \\ v_{l,1} v_{l,2} \rho & v_{l,2}^2 \end{bmatrix} \right)$$

$$\gamma_l \sim \mathrm{Categorical}_P(\pi)$$

- *k* indexes populations
- *l* indexes causal effects

MultiSuSiE outperforms alternative published methods in simulations



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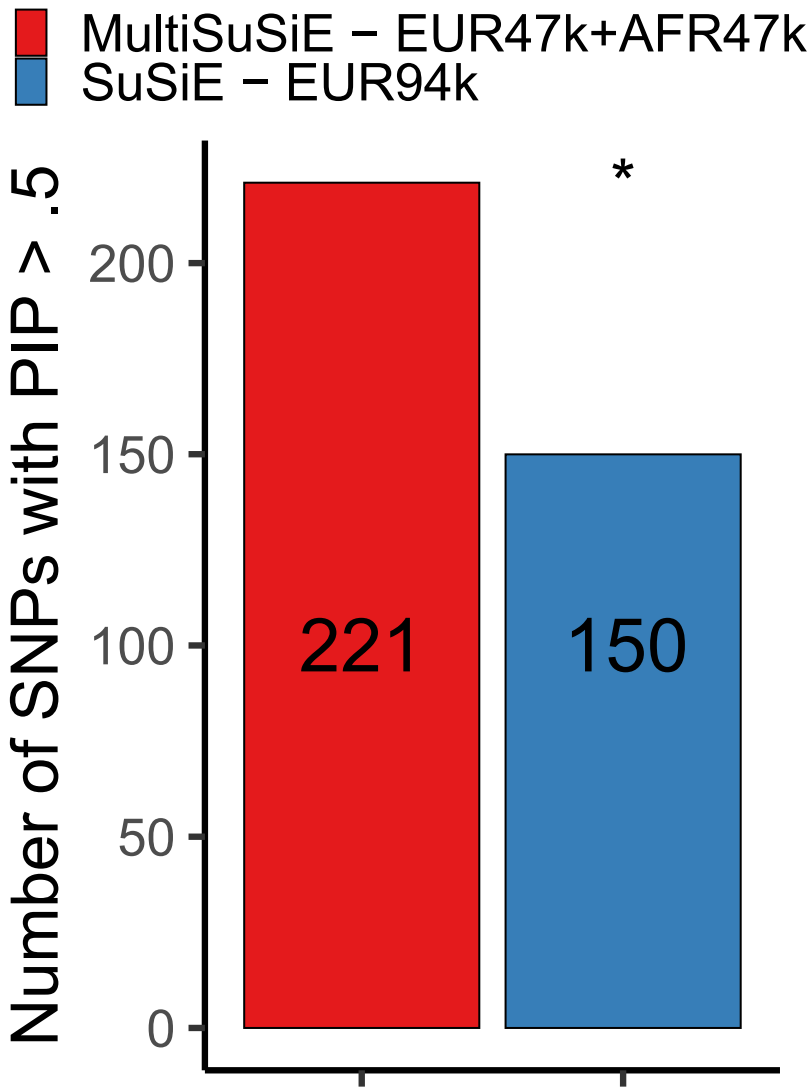
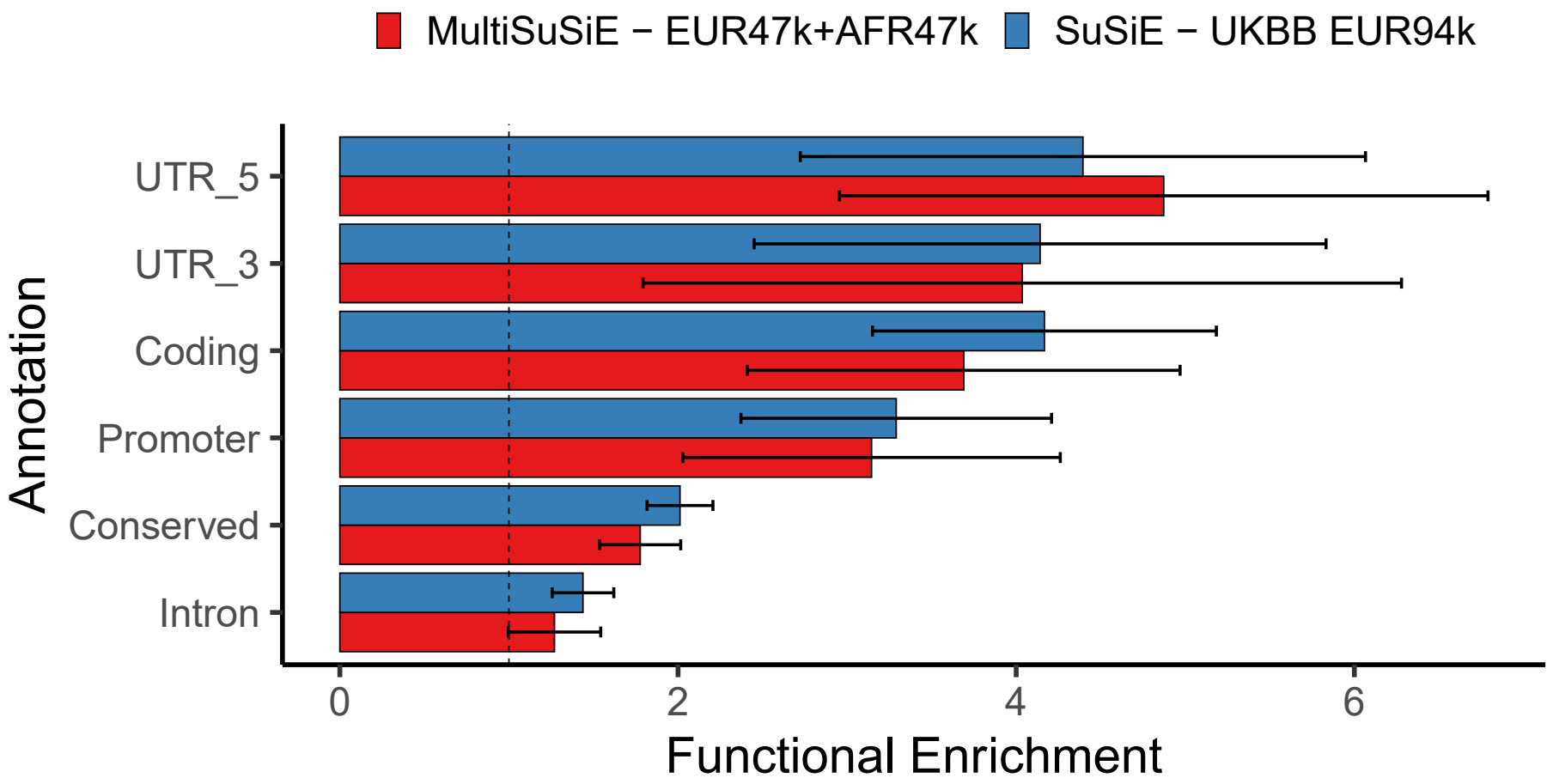
Multi-ancestry fine-mapping using MultiSuSiE outperforms single ancestry fine-mapping at matched sample sizes

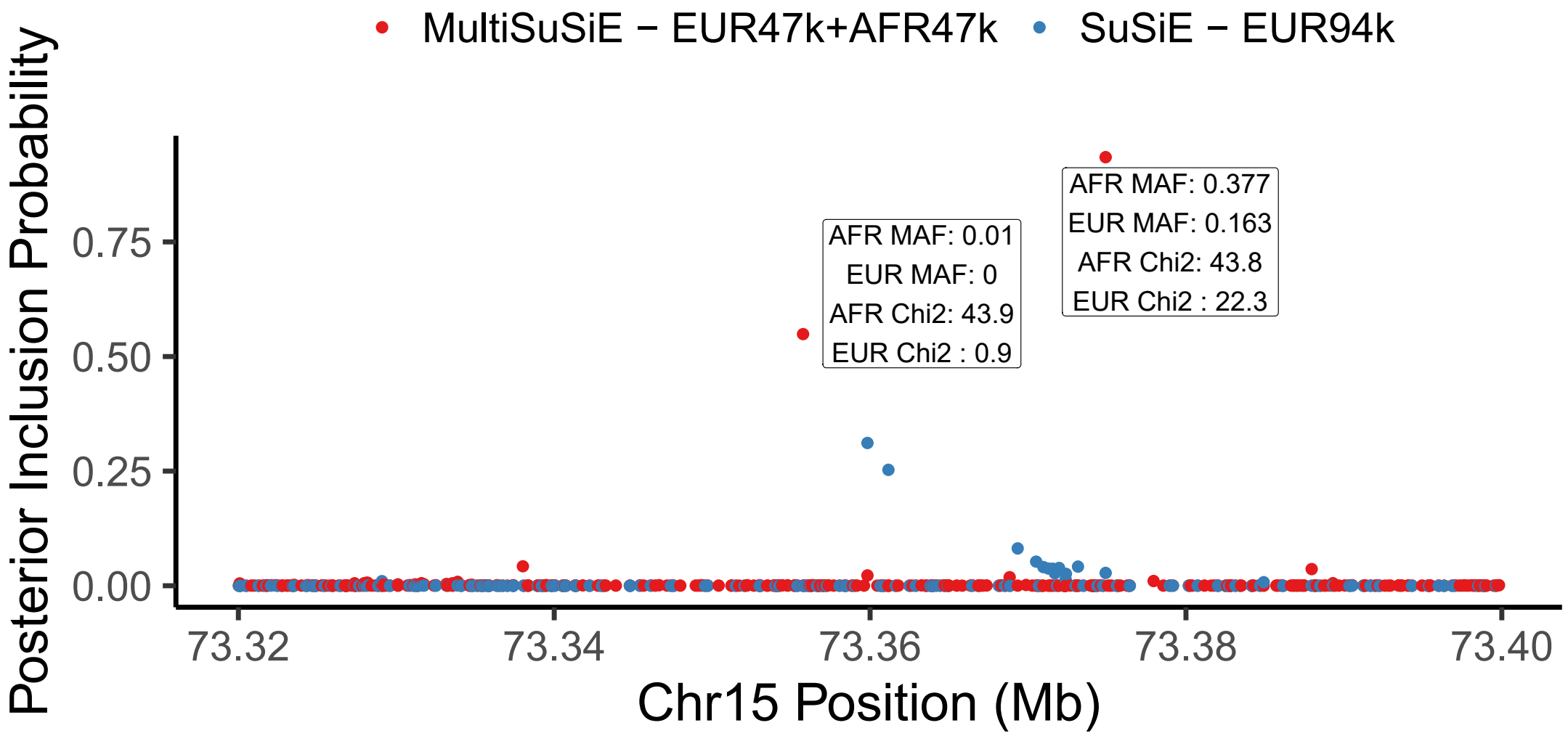
- We fine-mapped 5 anthropomorphic traits using All of Us whole-genome sequencing data
- MultiSuSiE uses 47,000 European-ancestry samples and 47,000 African-ancestry samples
- SuSiE uses 94,000 European-ancestry samples



Causal SNPs identified by MultiSuSiE have similar functional enrichment to those of SuSiE



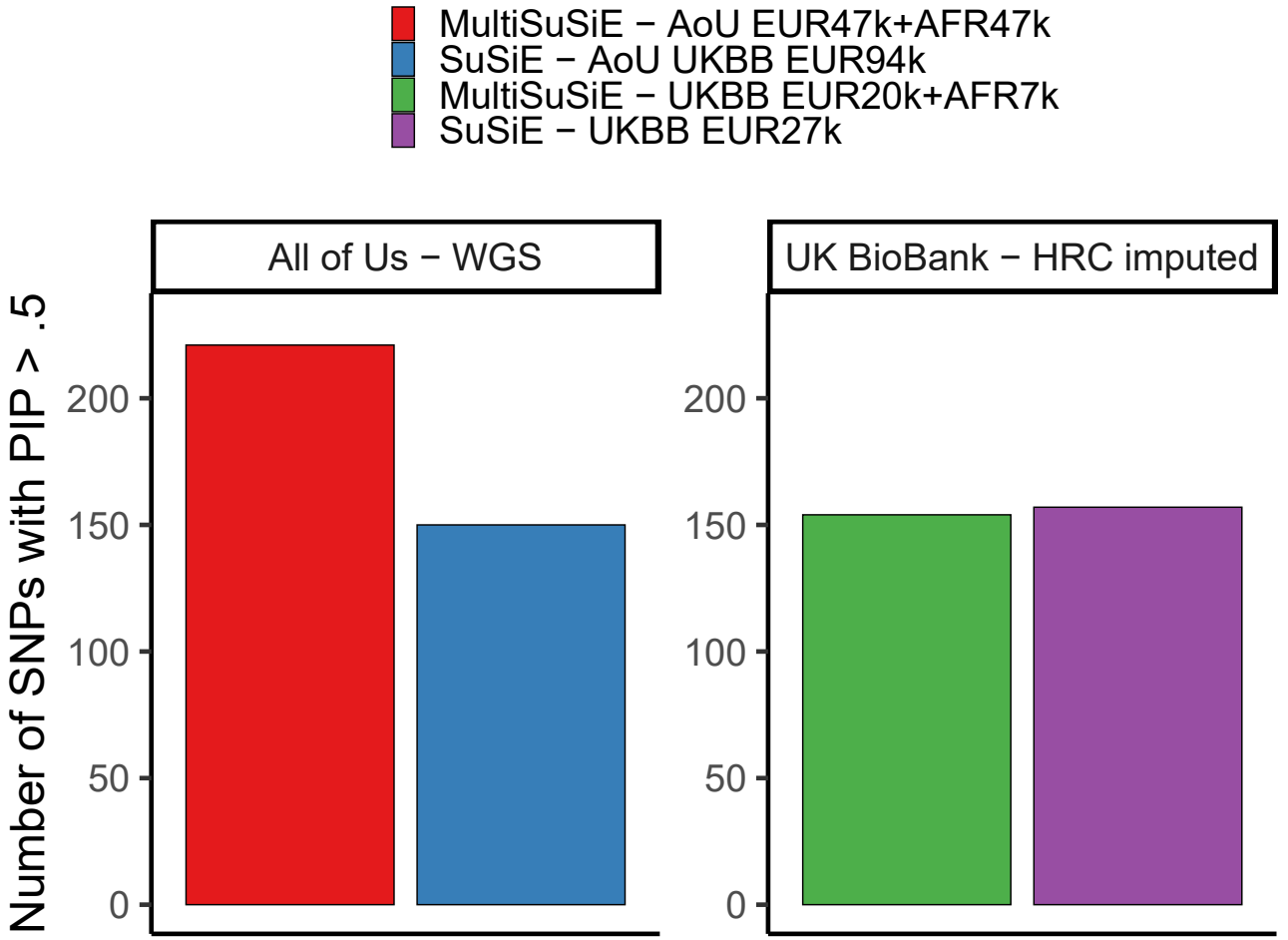
At the HCN4 locus, MultiSuSiE identifies two likely causal variants



Multi-ancestry fine-mapping does outperform single-ancestry using UKBioBank HRC imputed data

We fine-mapped:

- 5 anthropomorphic traits using All of Us whole-genome sequencing data
- 8 highly heritable traits using UKBioBank data



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Conclusions and Future Directions

Conclusions:

- MultiSuSiE enables powerful multi-ancestry fine-mapping
- Multi-ancestry fine-mapping using whole-genome-sequencing data outperforms single-ancestry fine-mapping in simulations and in applications to real traits

Future Directions:

- Include EHR-derived traits with substantial missingness
- Develop recommendations for fine-mapping of binary traits