Insights from complex trait fine-mapping across diverse biobanks

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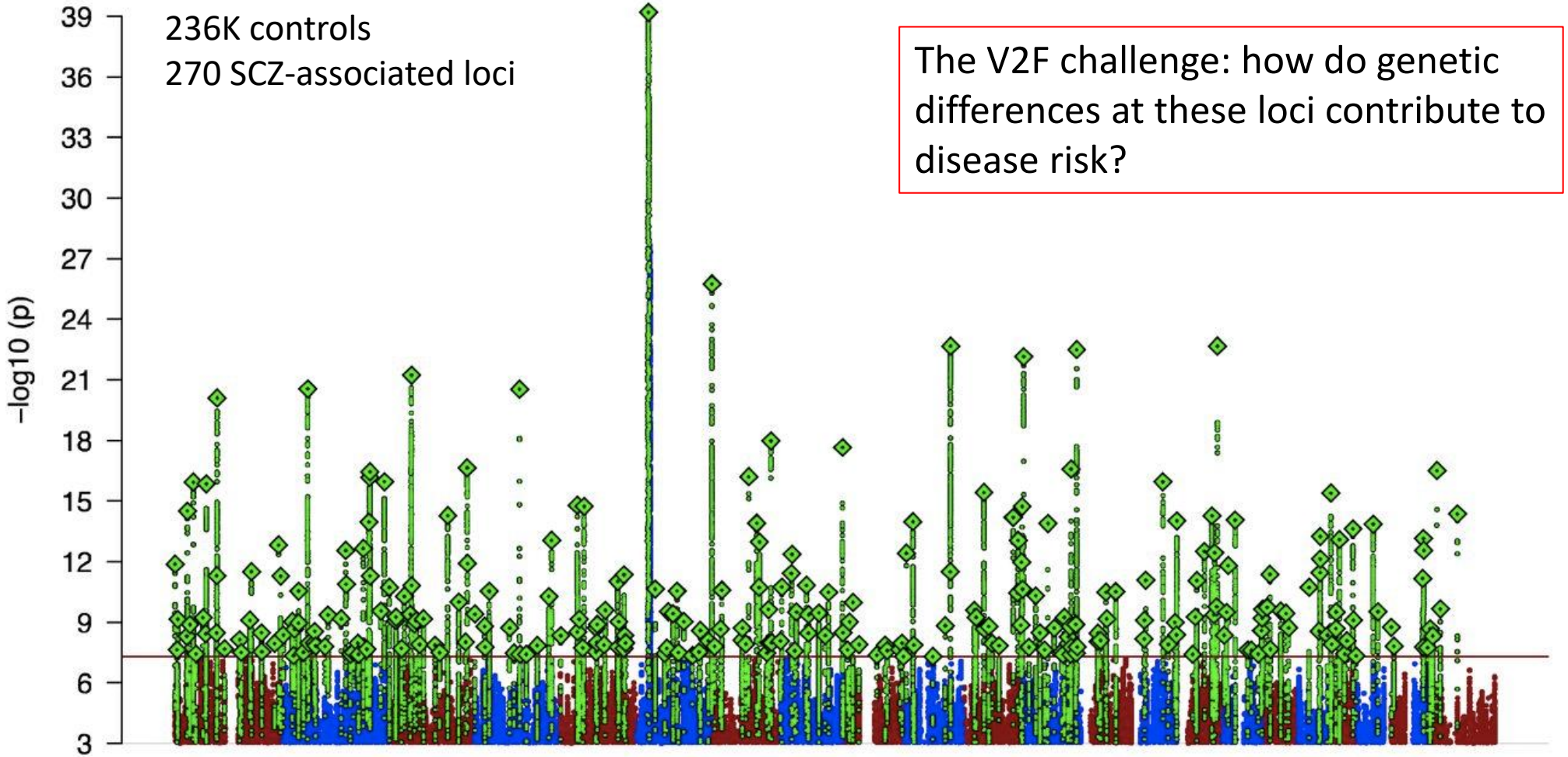
270 SCZ-associated loci

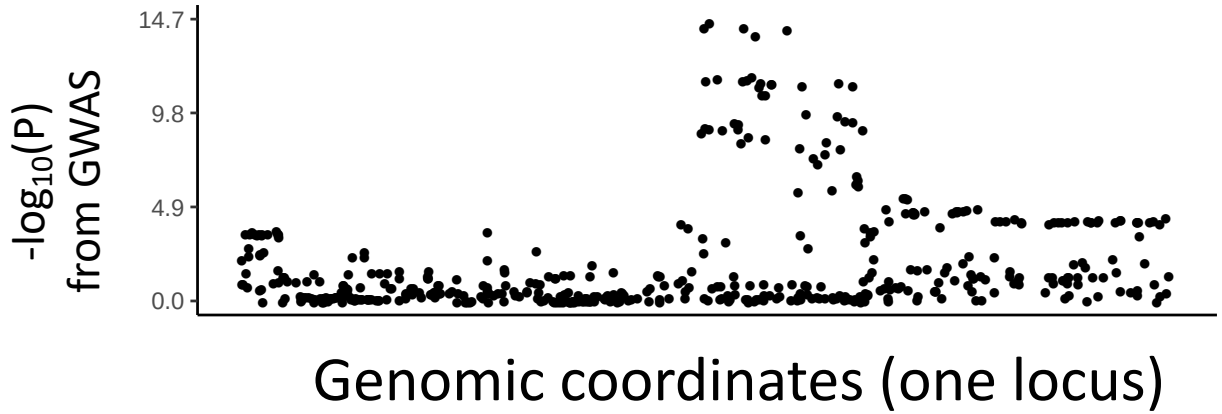
69K cases
236K controls
270 SCZ-associated loci



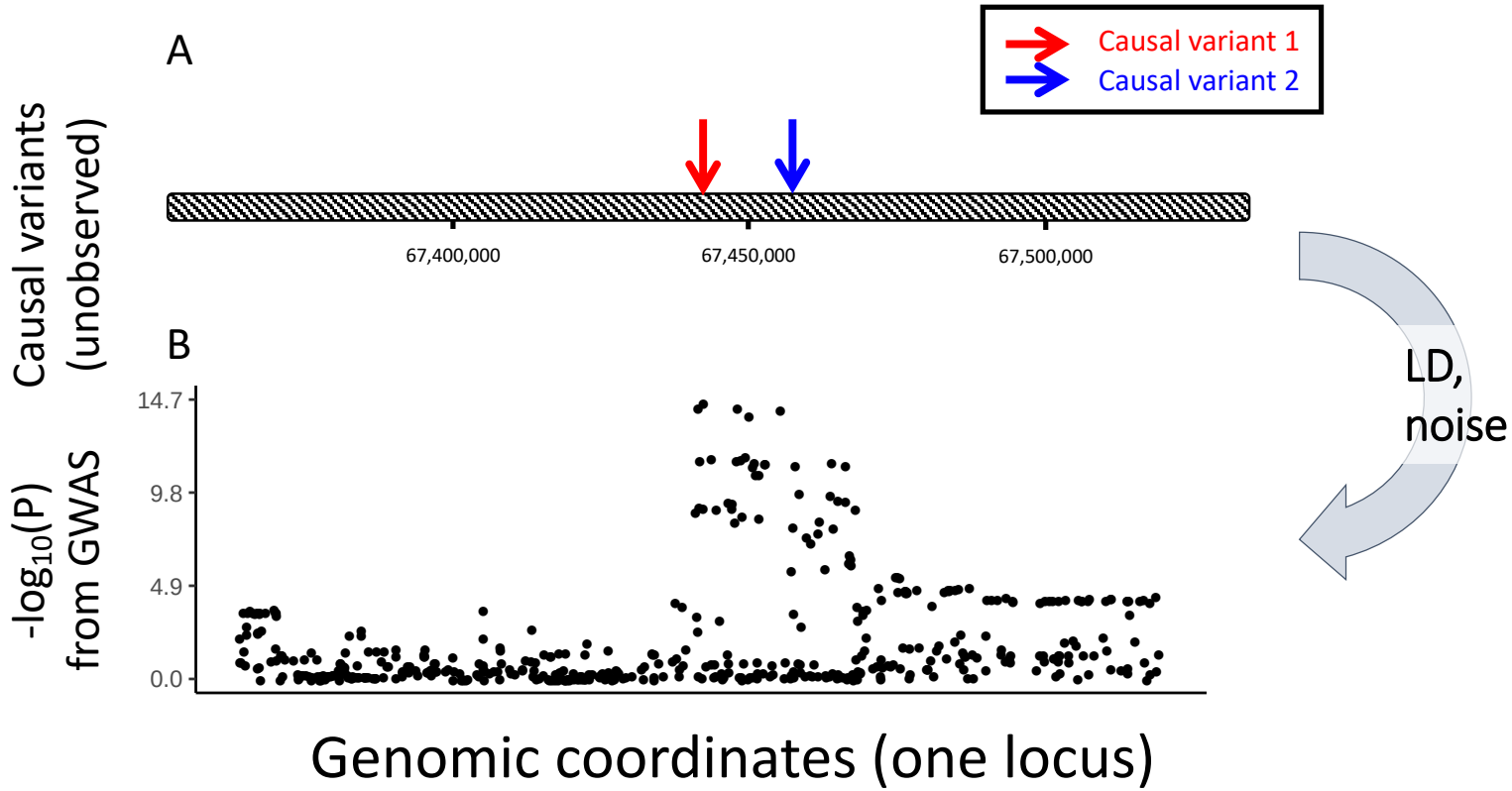
The V2F challenge: how do genetic differences at these loci contribute to disease risk?

Schizophrenia Working Group of the PGC, 2020 *medRxiv*

Fine-mapping: what are the causal SNPs?



Fine-mapping: what are the causal SNPs?



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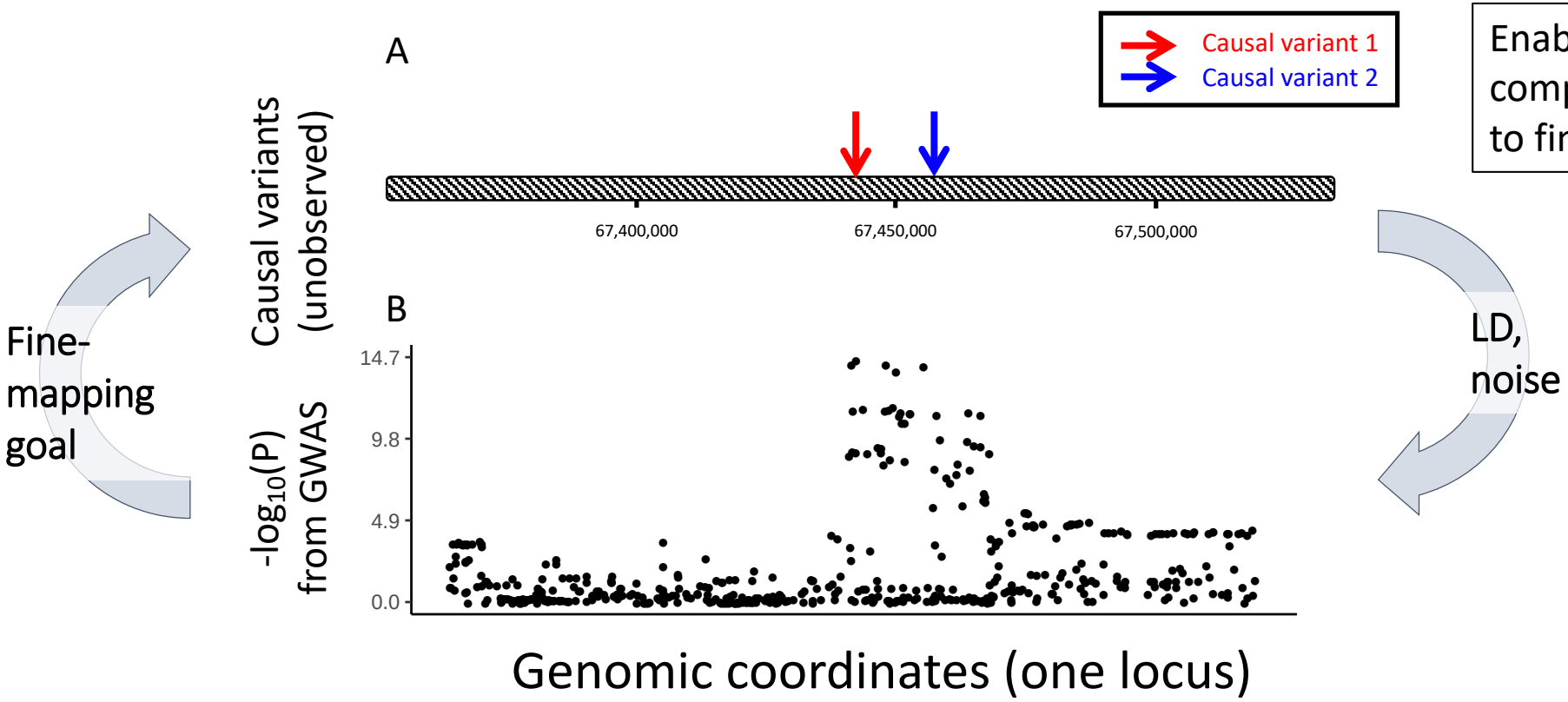
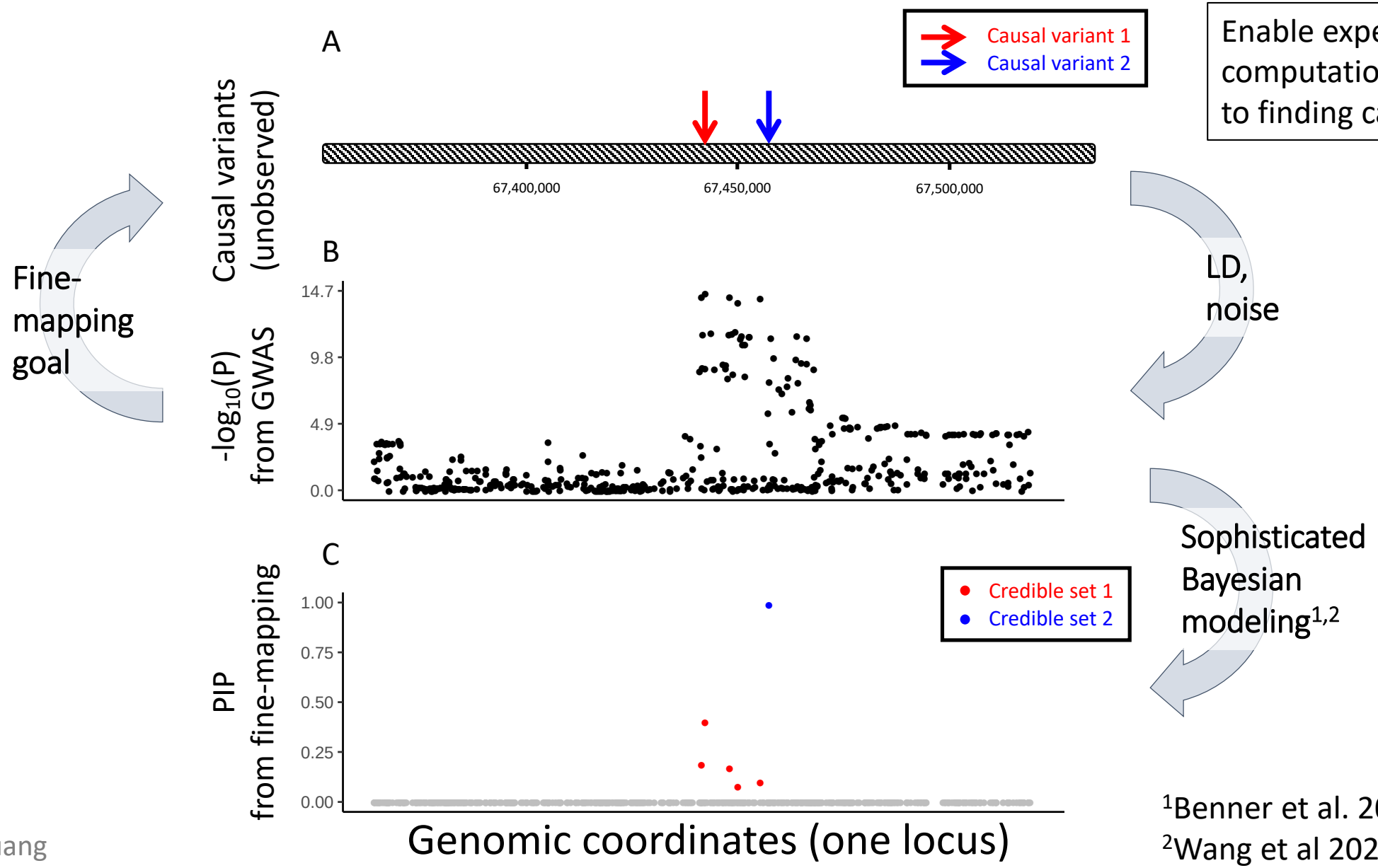


Enable experimental and computational approaches to finding causal genes

Bayesian fine-mapping outputs PIPs and credible sets



Enable experimental and computational approaches to finding causal genes

[1]Benner et al. 2016 *Bioinformatics*
[2]Wang et al 2020 *J R Stat Soc B*

We performed fine-mapping in three biobanks

Biobank Japan (BBJ)
79 complex traits

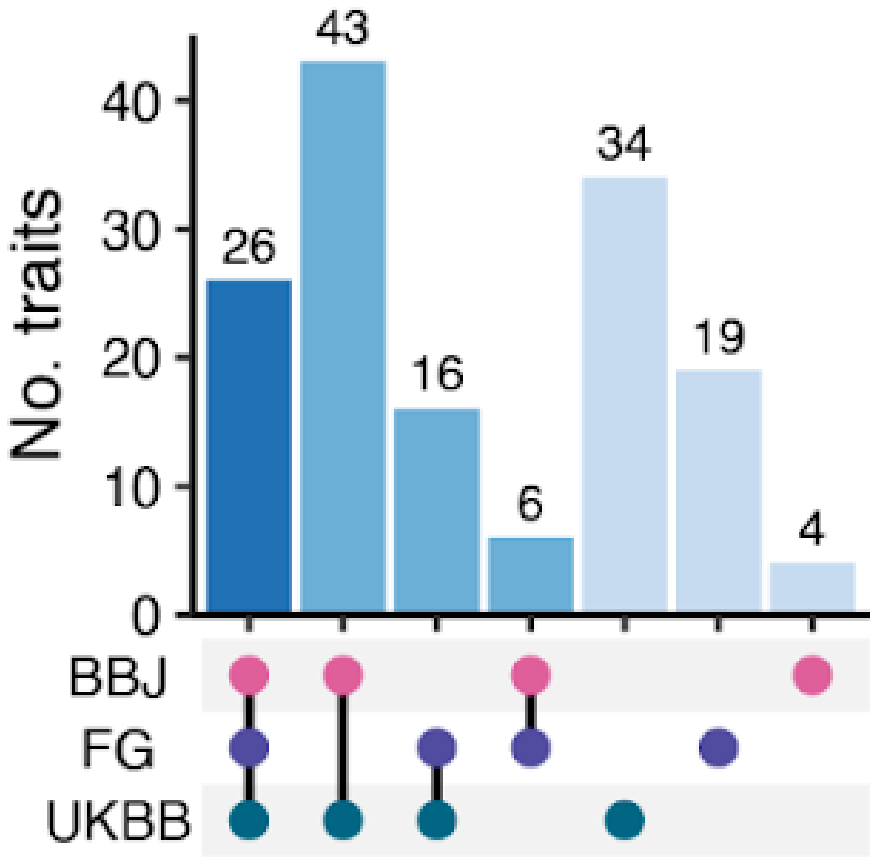
Japanese
(*n* = 178,726)

FinnGen (FG) release 6
67 complex traits

Finnish
(*n* = 271,341)

UK Biobank (UKBB)
119 complex traits

White British
(*n* = 361,194)



Masahiro Kanai

Our pipeline

- *Association*: mixed linear models
- *Fine-mapping:* FINEMAP[1] and SuSiE[2]
- *Simulations* first to set parameters

[1]Benner et al. 2016 *Bioinformatics*
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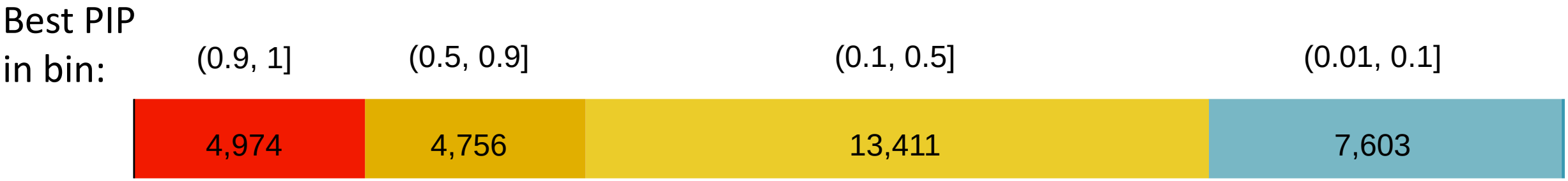
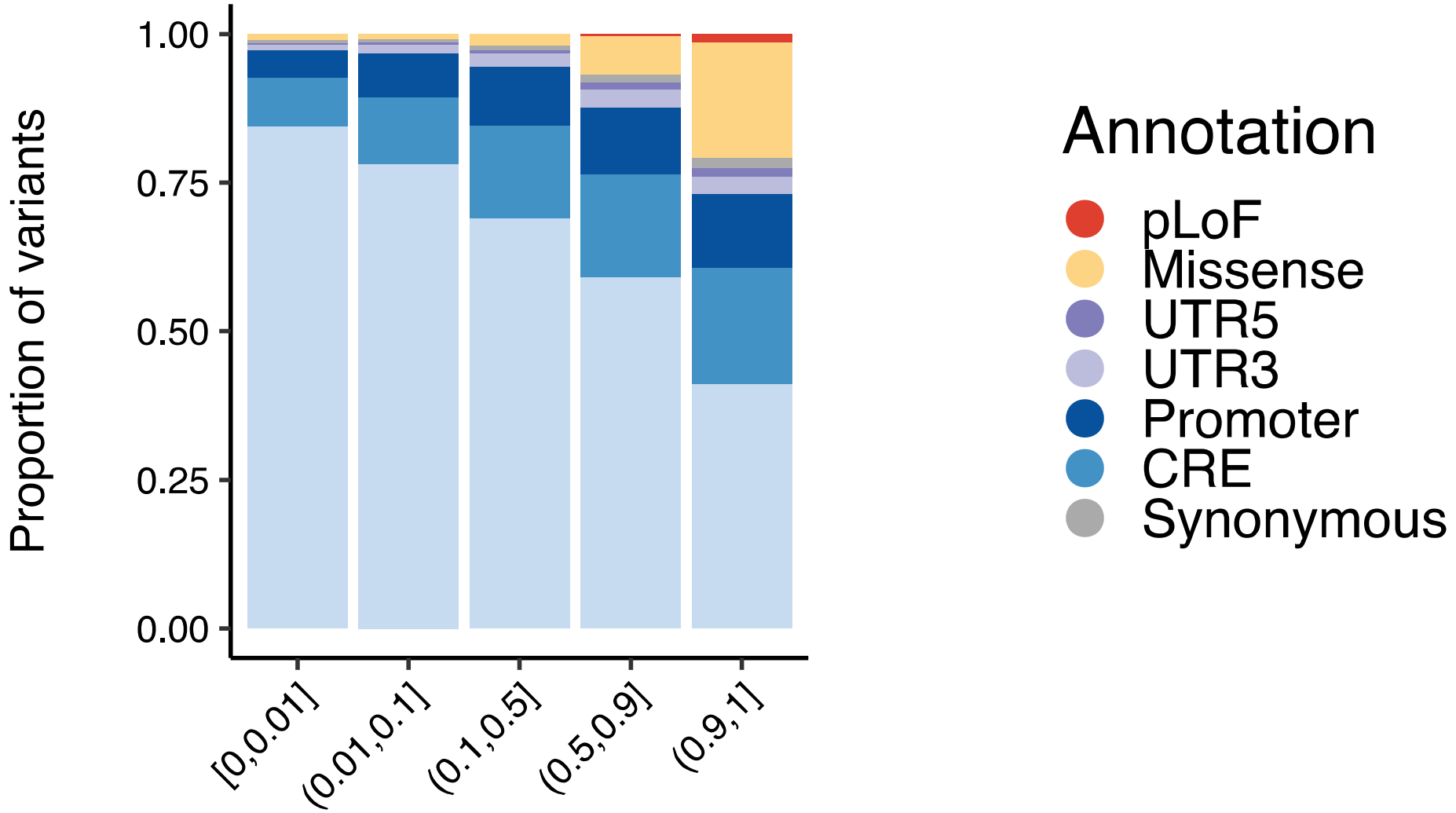
Kanai et al. 2021 medRxiv

We identified 30,812 credible sets



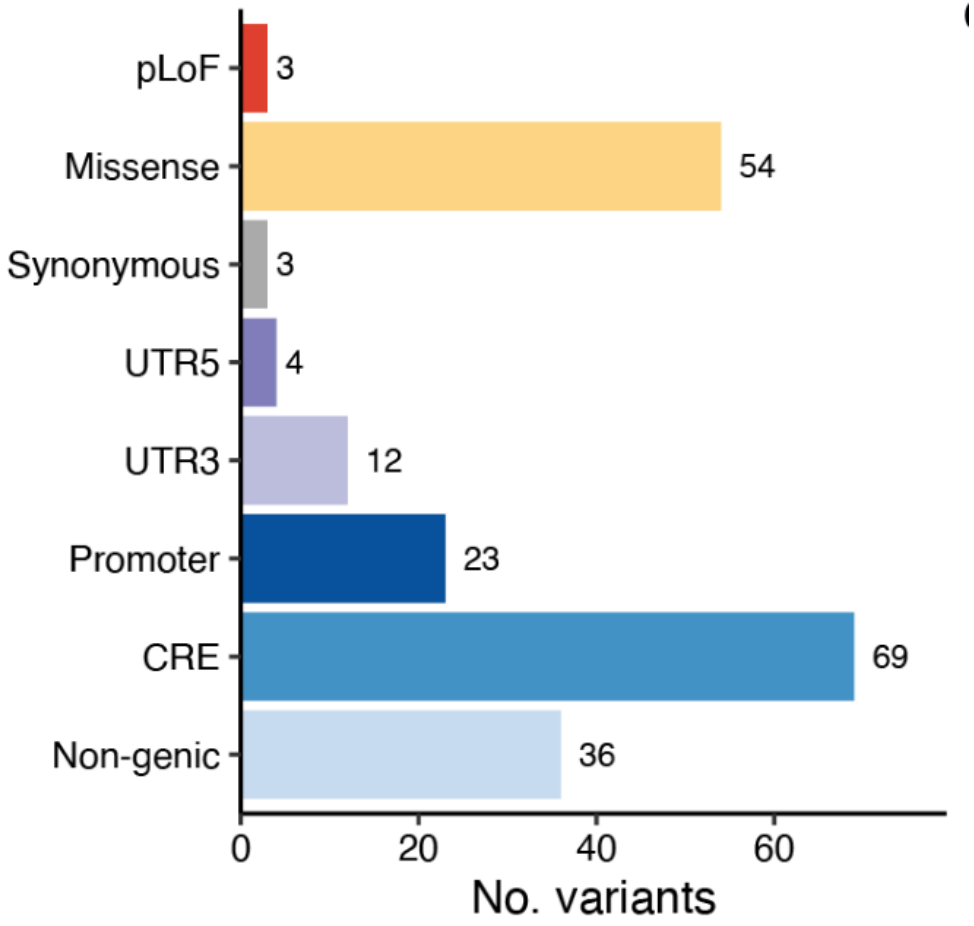
- 75% have at least one variant with PIP>0.1
- 16% have at least one variant with PIP>0.9

We found thousands of high-PIP variants, enriched for functional annotations



Kanai et al. 2021 medRxiv

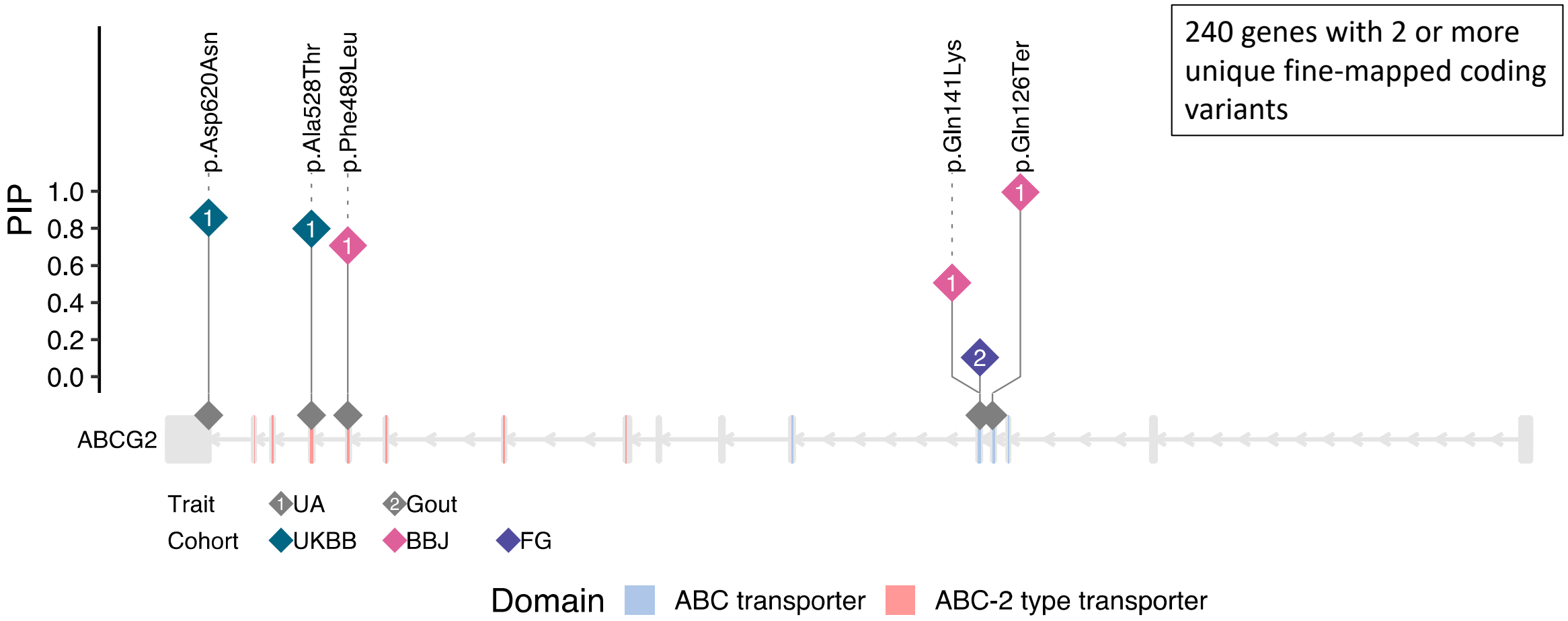
We identified 285 high-confidence putative causal variants that replicate across biobanks



Kanai et al. 2021 medRxiv

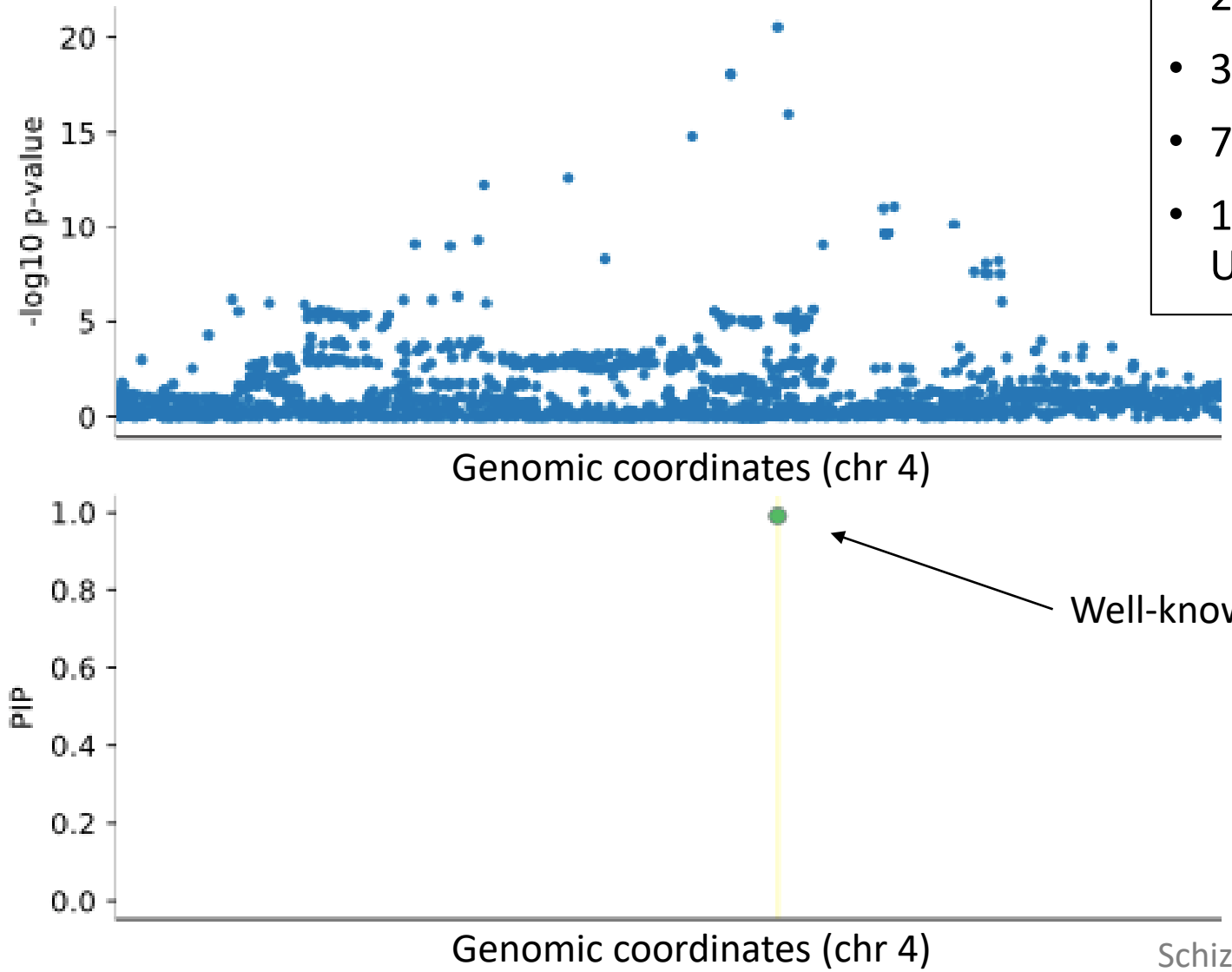
Why so few? Details in our preprint.

Fine-mapping in multiple populations identifies allelic series



Kanai et al. 2021 medRxiv

The PGC has performed fine-mapping for SCZ



- 288 credible sets
- 32 credible sets have 5 or fewer SNPs
- 7 SNPs with PIP>0.95
- 19 genes with fine-mapped coding or UTR variant

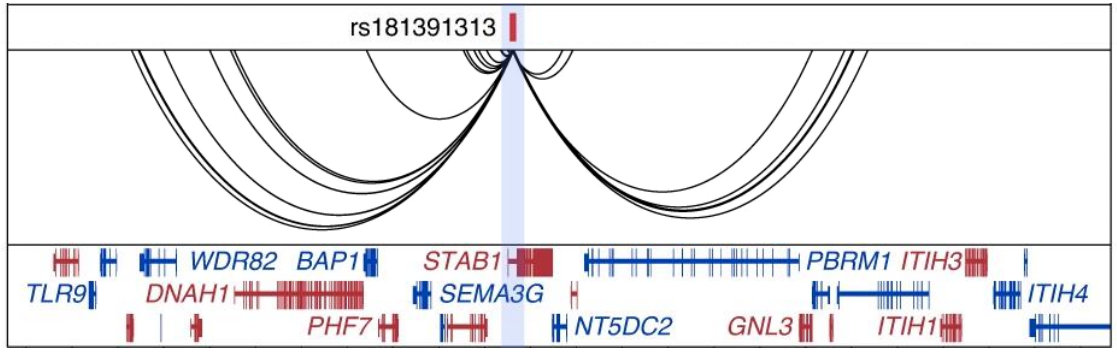
Well-known missense variant in SLC39A8

Schizophrenia Working Group of the PGC, 2020 *medRxiv*

Fine-mapping aids gene prioritization and benchmarking

Many ways to nominate a gene:

- Coding variant
- Local epigenetics
- eQTL-based analysis
- Closest gene
- Similarity-based

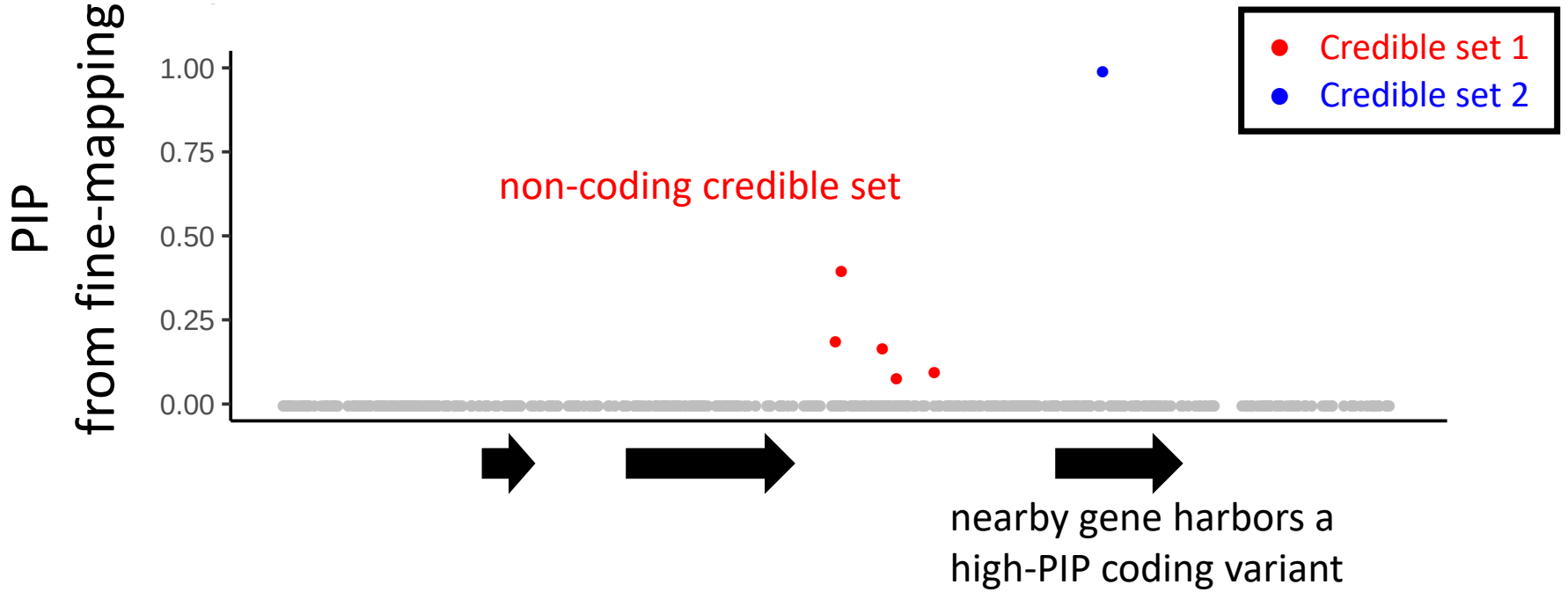


Corces et al. 2020 Nat Genet

E.g.: deLeeuw et al. 2015 *PLoS Comp Bio,* Ulirsch et al. 2019 *Nat Genet*, The FANTOM Consortium et al. 2014 *Nature,* Liu et al 2017 *Genome Biol,* Jung et al. 2019 *Nat Genet,* Javierre et al. 2016 *Cell,* Fulco et al. 2019 *Nat Genet,* Gusev et al. 2016 *Nat Genet,* Hormozdiari et al. 2016 *Am J Hum Genet,* Corces et al. 2020 Nat Genet, Pers et al. 2015 *Nat Commun*, Stacey et al. 2018 *Nucleic Acids Res*, Greene et al 2015 *Nat Genet,* Pers et al 2015 Nat Commun, Greene et al. 2015 *Nat Genet*, …

Large-scale fine-mapping in UKBB provides a new evaluation set of genes

Jesse Engreitz



>1K cases of a non-coding credible set near a gene with a high-PIP coding variant

We can estimate precision and recall with our new evaluation set

Q1: How confident should we be in what we prioritize?

A1:

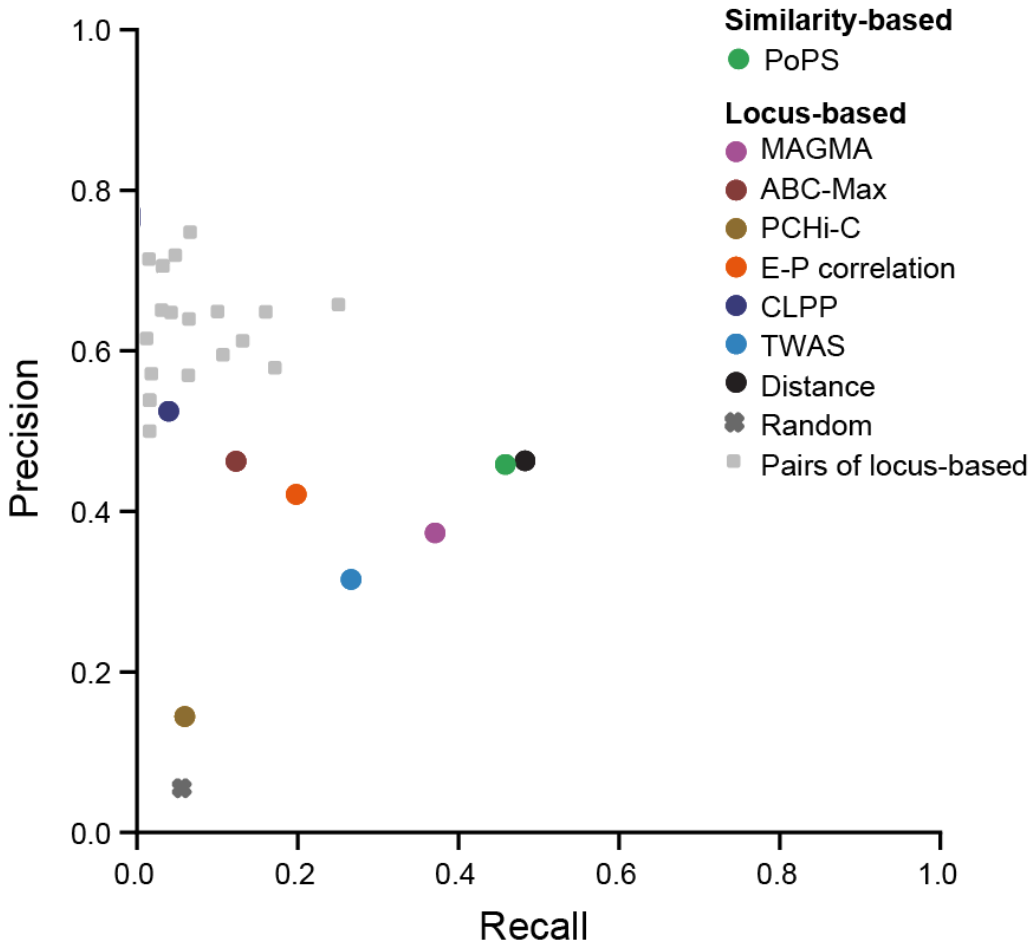
$$\text{Precision} = \Pr(\text{in the evaluation set} \mid \text{prioritized})$$

Q2: How much do we find?

A2:

$$\text{Recall} = \Pr(\text{prioritized} \mid \text{in the evaluation set})$$

No individual method achieves very high precision or recall

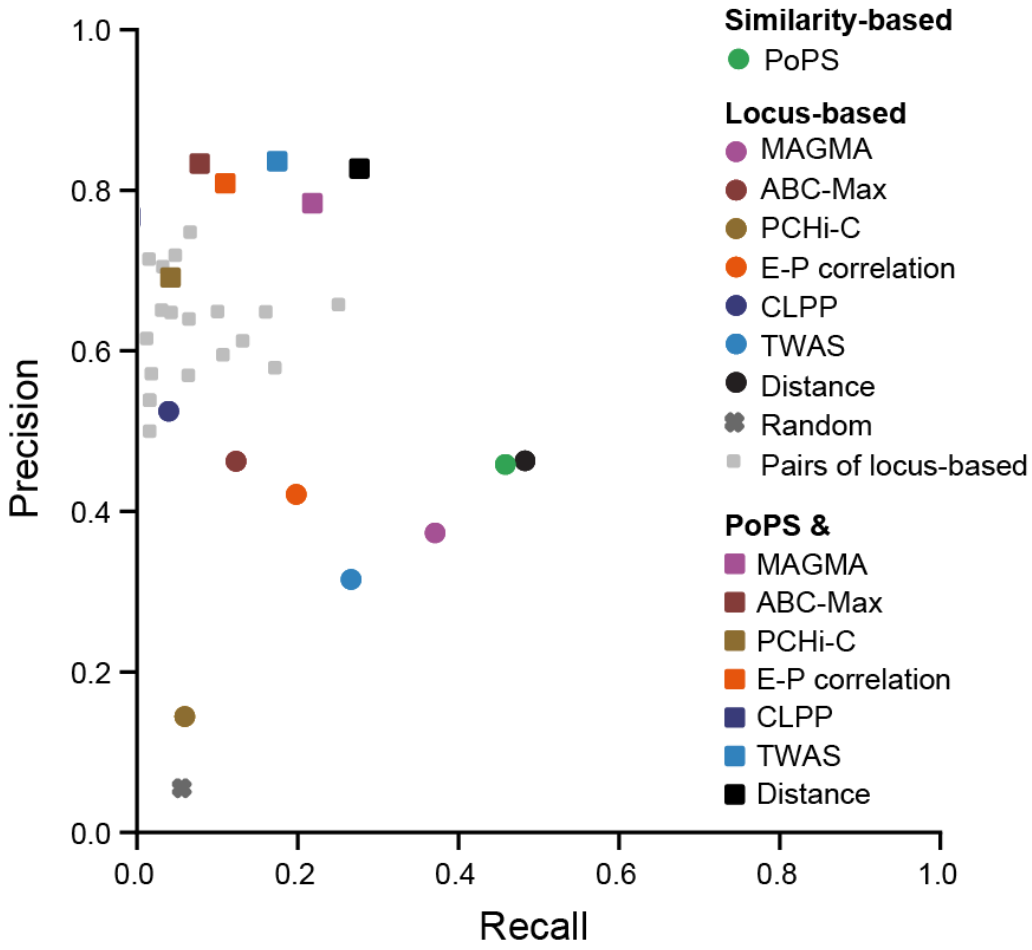


Uses expression, pathways, etc

Use local GWAS signal: proximity, eQTLs, or epigenetics

Weeks et al. 2020 medRxiv

Combining similarity-based and locus-based methods increases precision



Uses expression, pathways, etc

Use local GWAS signal: proximity, eQTLs, or epigenetics

Require both types of evidence

Weeks et al. 2020 medRxiv

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