THE UNIVERSITY OF QUEENSLAND
AUSTRALIA
CREATE CHANGE

Fine-Mapping

Genetics & Genomics Winter School

Module 1

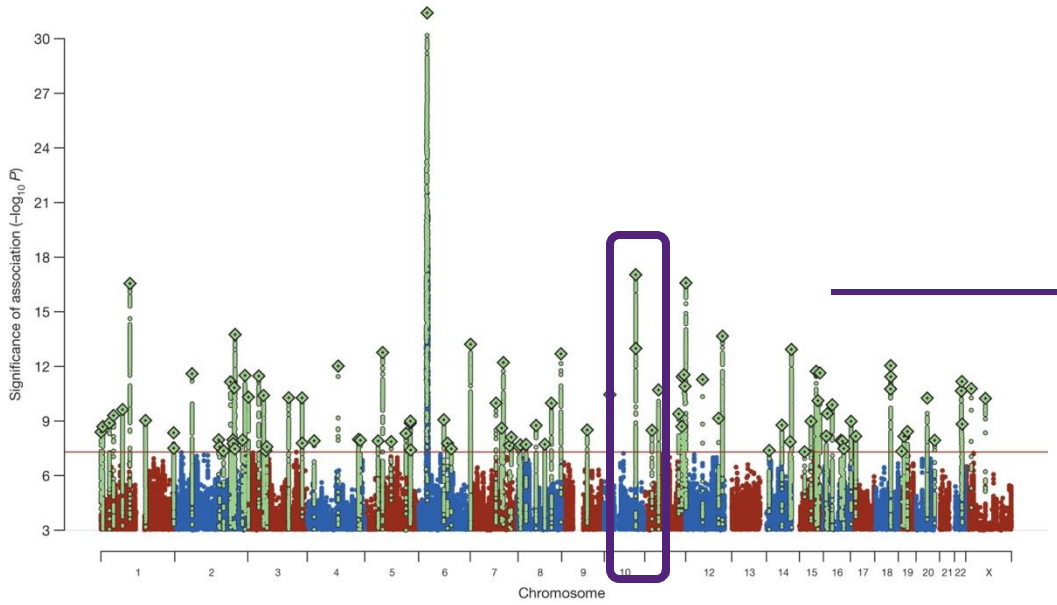
Alesha Hatton

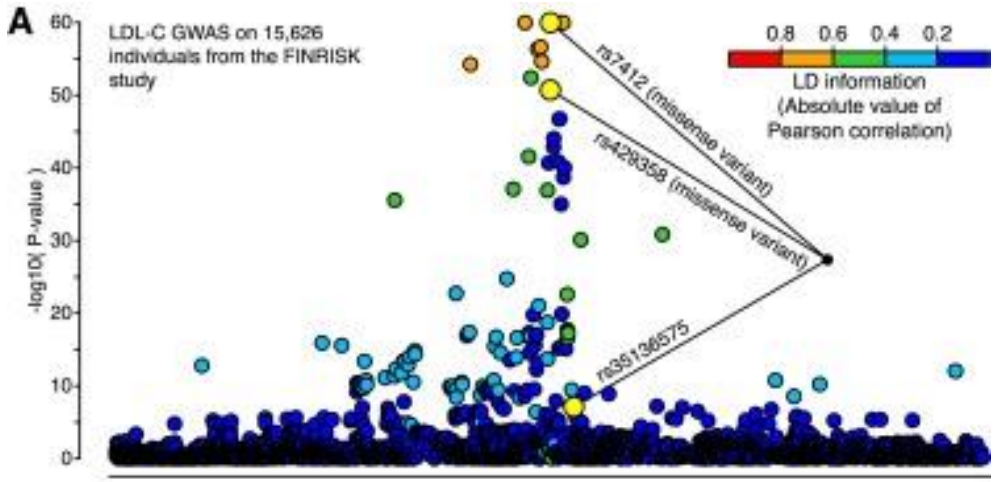
8/7/2025

What is fine-mapping?

An approach to identify and prioritise SNPs driving GWAS association signals

We want to understand the mechanisms by which genetic variants impact associated traits





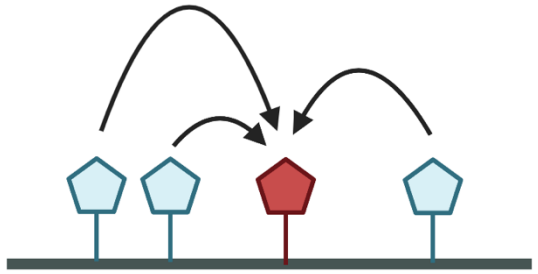
S Ripke et al. *Nature* (2014)

Benner et al. *AJHG*, 2017

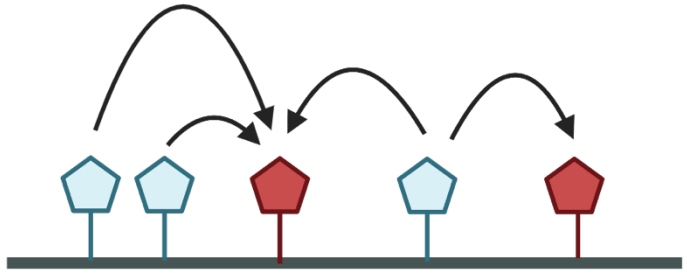
Why don’t we take the top associated SNP?

Red – causal variant

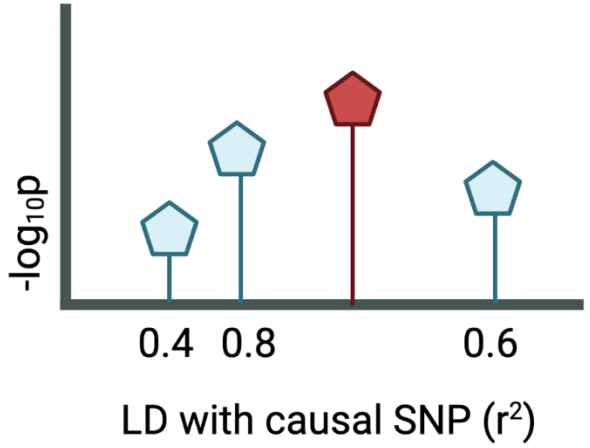
Single causal variant



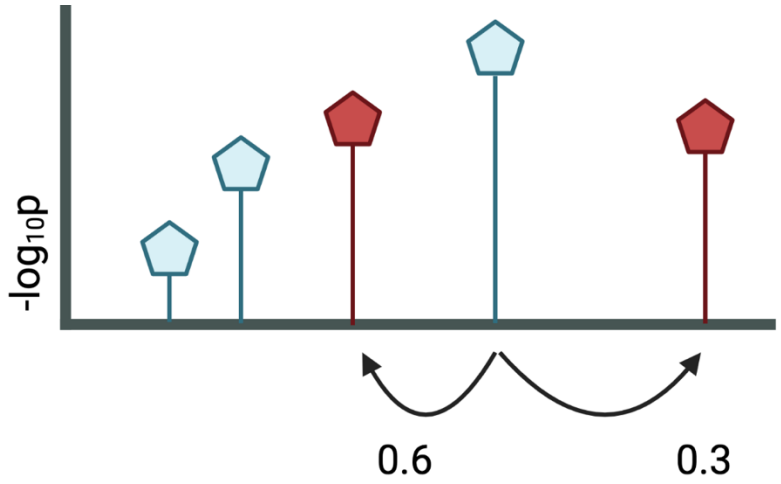
What about when there is ≥ 1 causal variant



GWAS result

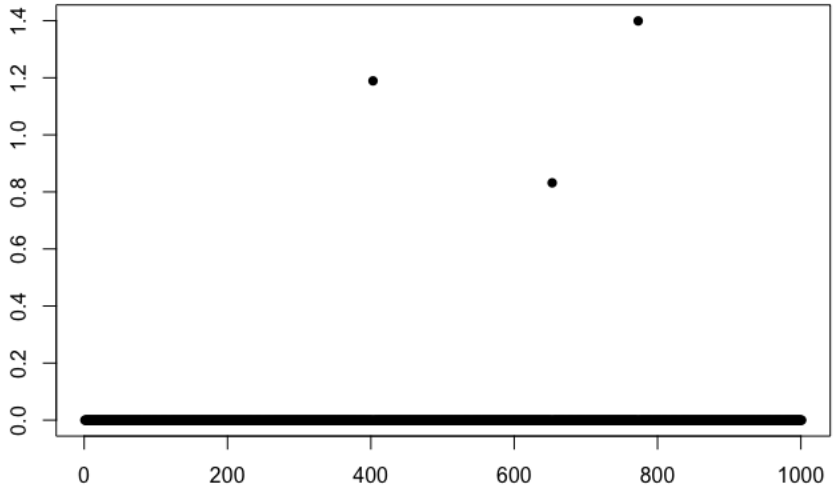


GWAS result

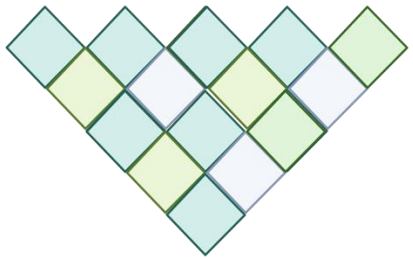


Simplistic fine-mapping example

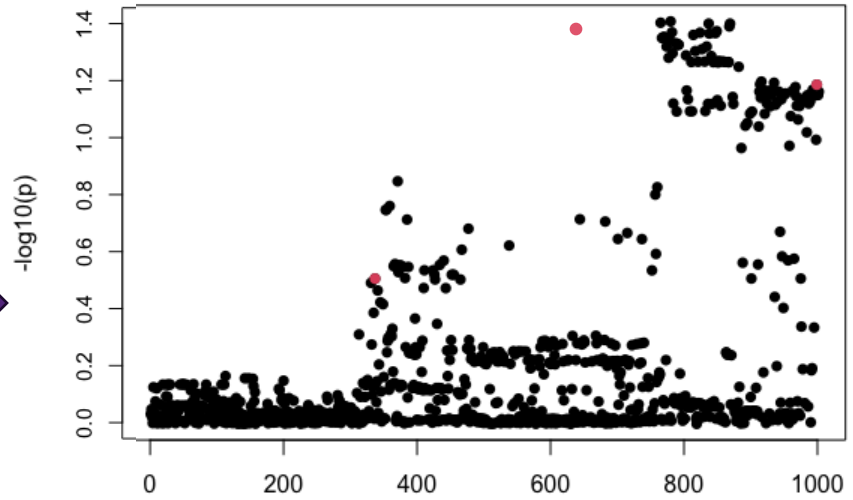
True effects



+ LD, noise



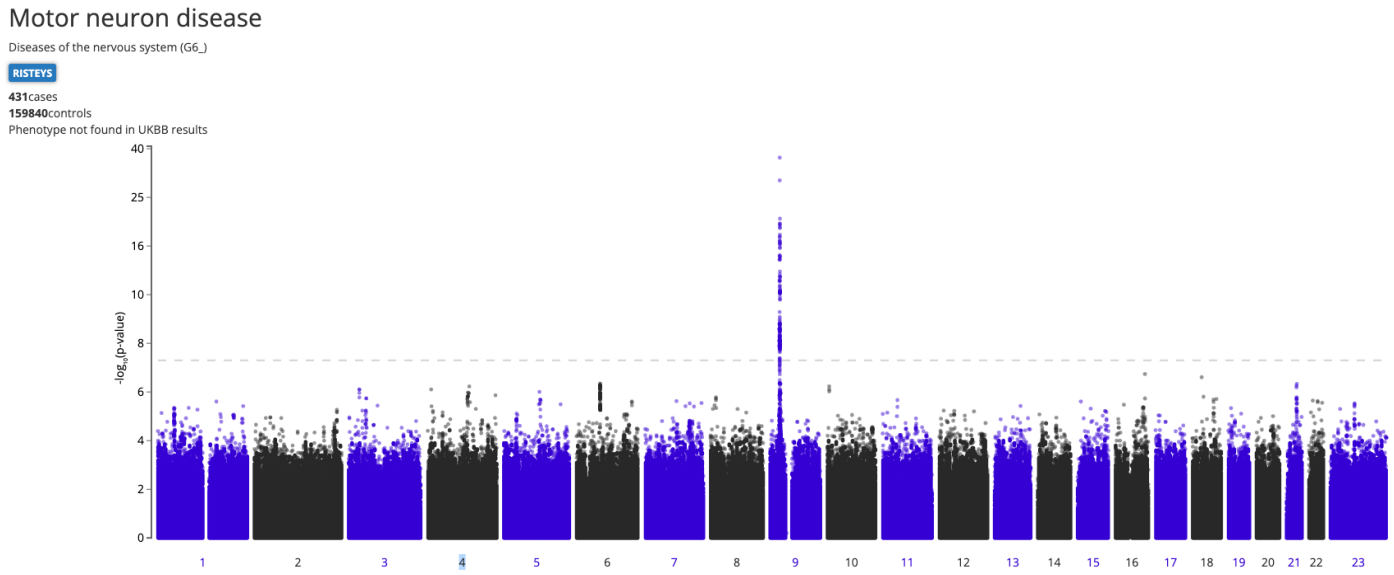
Estimated effect



Fine mapping attempts to do the reverse..

Fine mapping assumes the causal variant has been measured!

- This is a big assumption!
- For example, FinnGen provides publicly available fine-mapping results
  - For ALS they report two credible sets.
  - The top variant in one of the sets had a PIP of 1.00 – that is equivalent to the fine mapping method reporting 100% certainty this is the causal variant.
  - However, it is unlikely causal - there is a C9orf72 repeat expansion that is in strong LD with the SNP



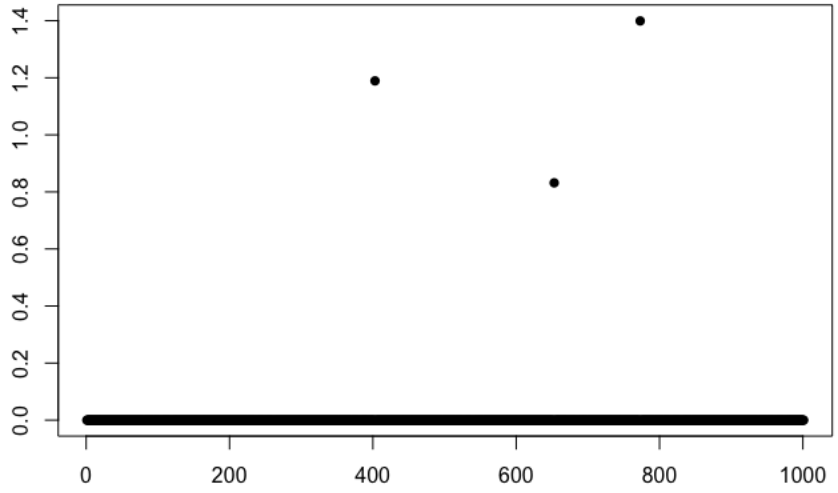
https://r8.finngen.fi/pheno/G6_ALS

Many fine-mapping methods

Majority of methods follow a Bayesian framework

- prior × data = posterior

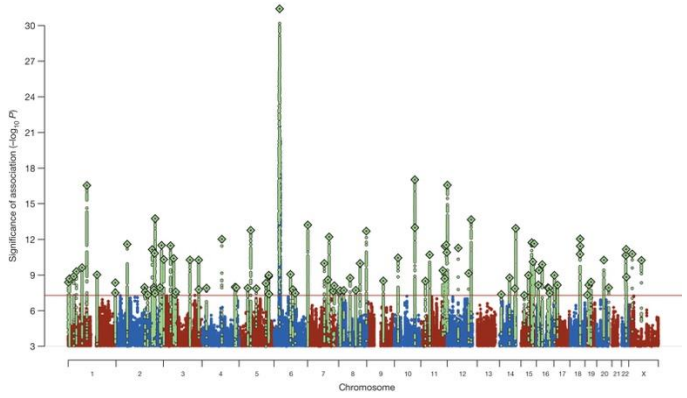
E.g. Prior knowledge of distribution of true SNP effects

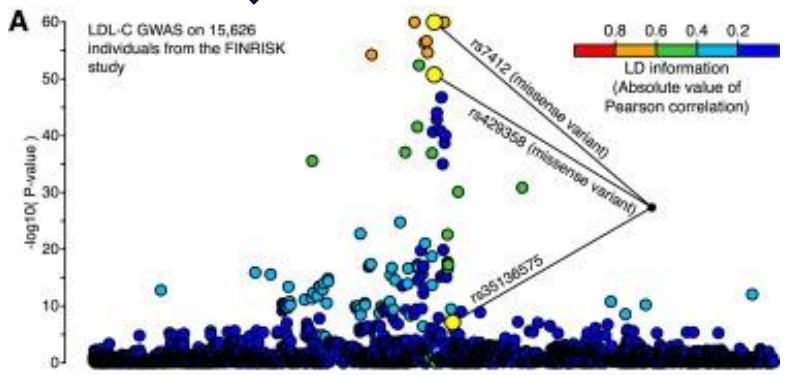


Methods

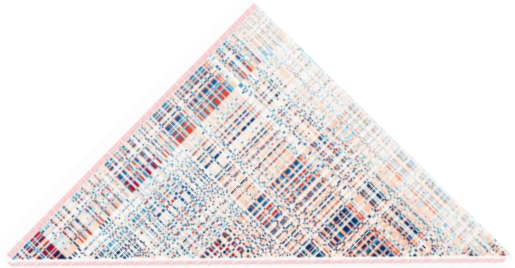
- BIMBAM (Servin and Stephens, 2007)
- CAVIAR (Hormozdiari, 2014)
- PAINTOR (Kichaev, 2014)
- CAVIARBF (Chen, 2015)
- FINEMAP (Benner, 2016)
- SuSiE (Wang, 2020)
- Susie-inf & FINEMAP-inf (Cui, 2024)
- SBayesRC (Wu, 2025 biorxiv)

How does this work?





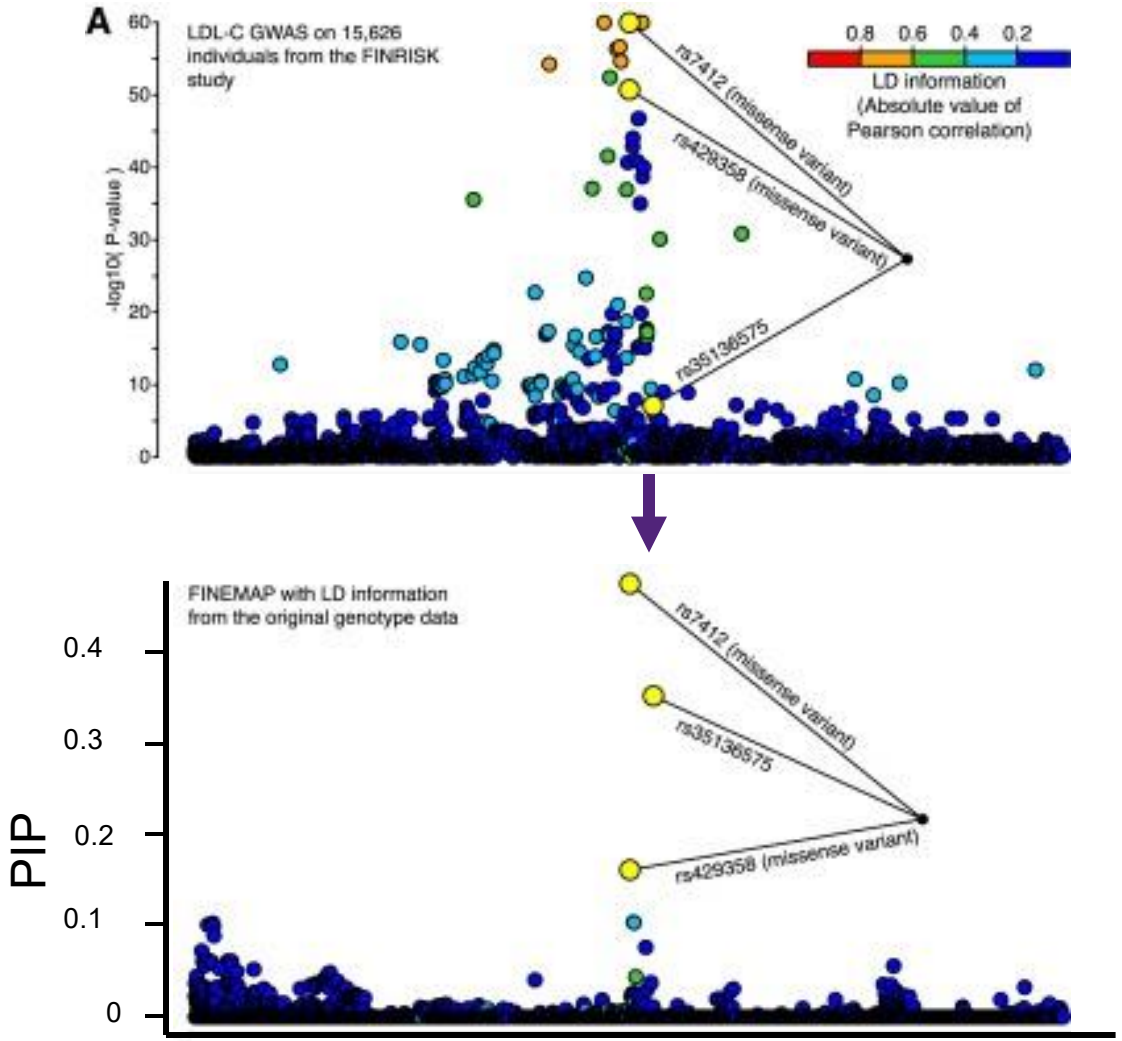
Prior
- Each SNP has equal probability of being causal
- Joint SNP effects are sparse



Probability of causality for each SNP

Benner et al. The American Journal of Human Genetics, 2017

Posterior inclusion probability (PIP)



Benner et al. The American Journal of Human Genetics, 2017

Probability (according to the model) the variant is casual

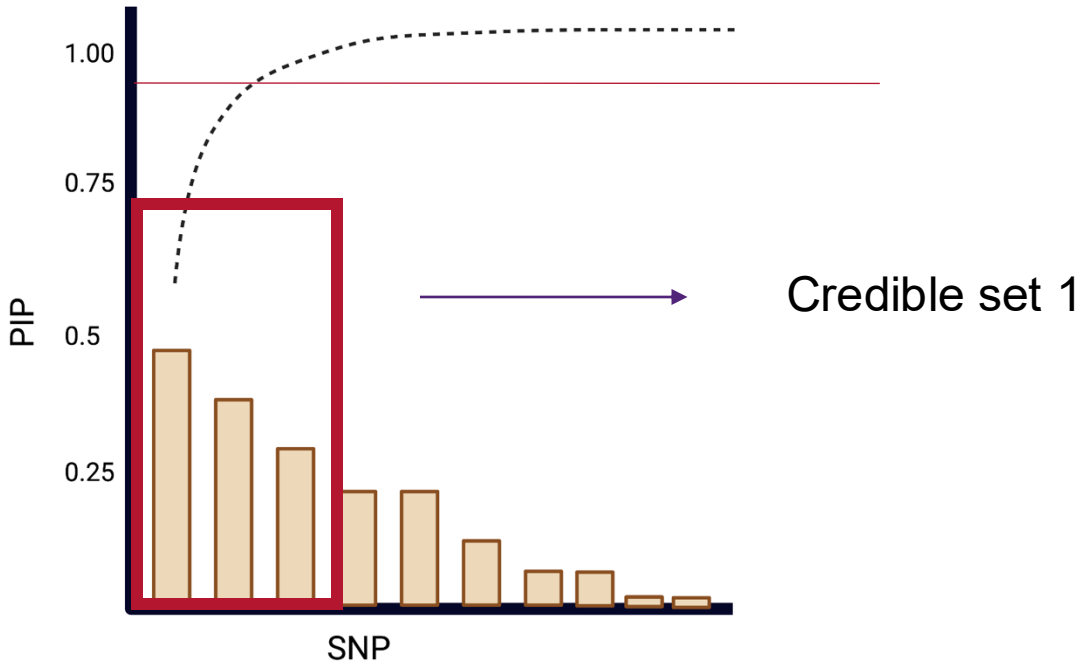
$$\mathrm{PIP_i} = \Pr(b_j \neq 0 \,|\, X, Y)$$

⇧ PIP = more confidence

⇩ PIP = less likely to be driving signal

Maller et al. Nature Genetics (2012)

Credible Sets (CS)



Threshold	0.95
Size	0.97

A set of putative causal variants for further investigation.

- Sorting PIP for each SNPs in descending order
- Cumulatively sum until reach the threshold

Formal Definition

Smallest set of SNPs with >95% probability of containing a single causal variant

Multiple causal variants

Most newer methods allow for the assumption of multiple causal variants

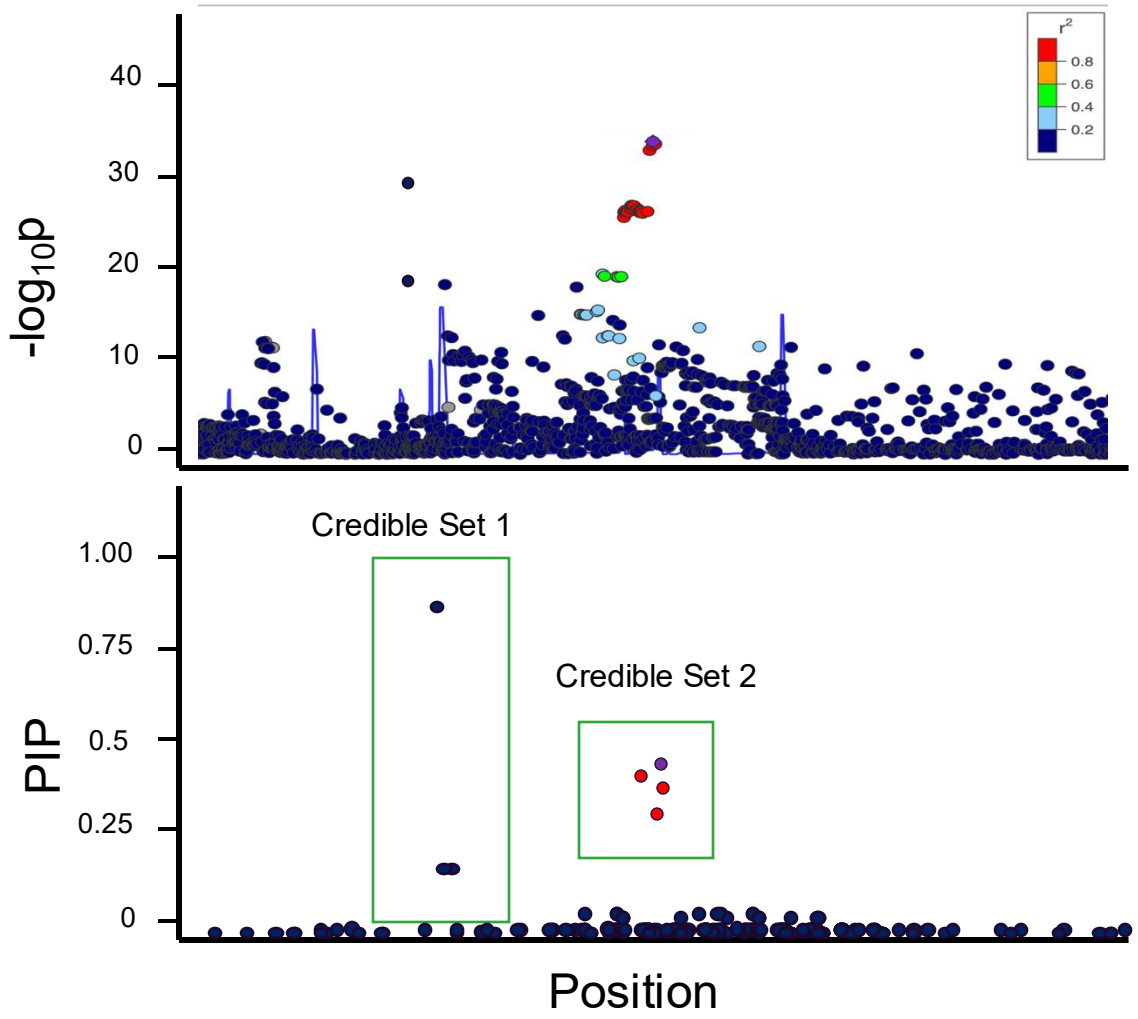
Some assuming **infinitesimal model** - a small number of larger effects, large number of infinitesimal effects (e.g. Susie-INF)

Multiple credible sets

- Smallest set of SNPs with >95% probability of containing a single causal variant

In general, the more independent signals, the less statistical power to detect credible sets

Specify minimum correlation between SNPs allowed within a credible set



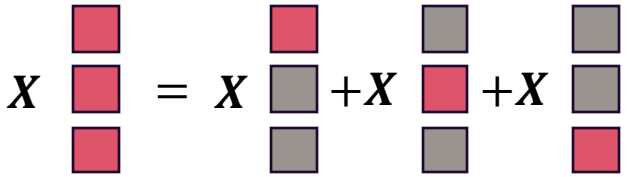
Sum of Single Effects (SuSiE)

Method for fine-mapping multiple causal variants

For each causal variant $\boldsymbol{b_i} = (b_{l1}, \ldots, b_{lJ})$ single effect vector

For multiple causal variants, sums over multiple vectors of single effects

$\boldsymbol{b} = \sum \boldsymbol{b_i}$



Iterative Bayesian stepwise selection

- Can quantify uncertainty in variables selected

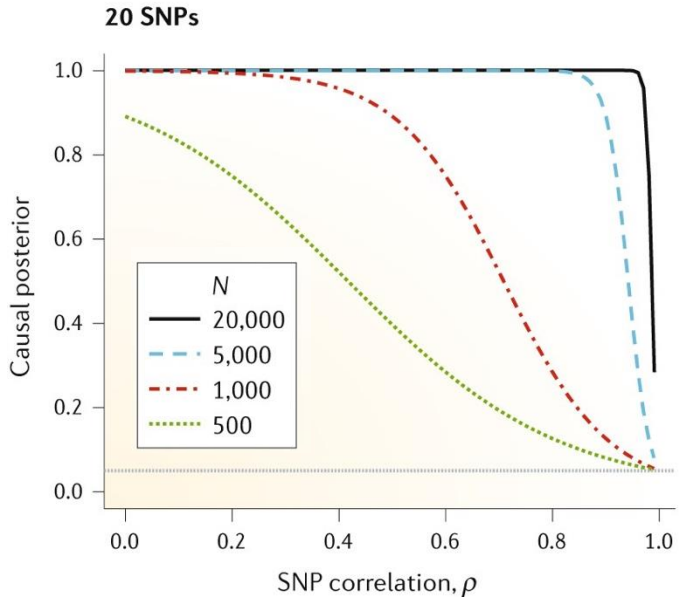
Outputs 95% credible sets with PIPs for each SNP

Wang 2020
Zou 2022

Factors influence fine-mapping performance

- The local LD structure
- Sample size
- SNP density

- Number of causal SNPs in a region
- Effect sizes
- LD reference matches the data
- Whether the causal variants are measured



Example:
- 20 SNPs
- All SNPs have equal LD (x-axis)
- One causal SNP (R^2 1%)
- PIP of causal SNP on yaxis

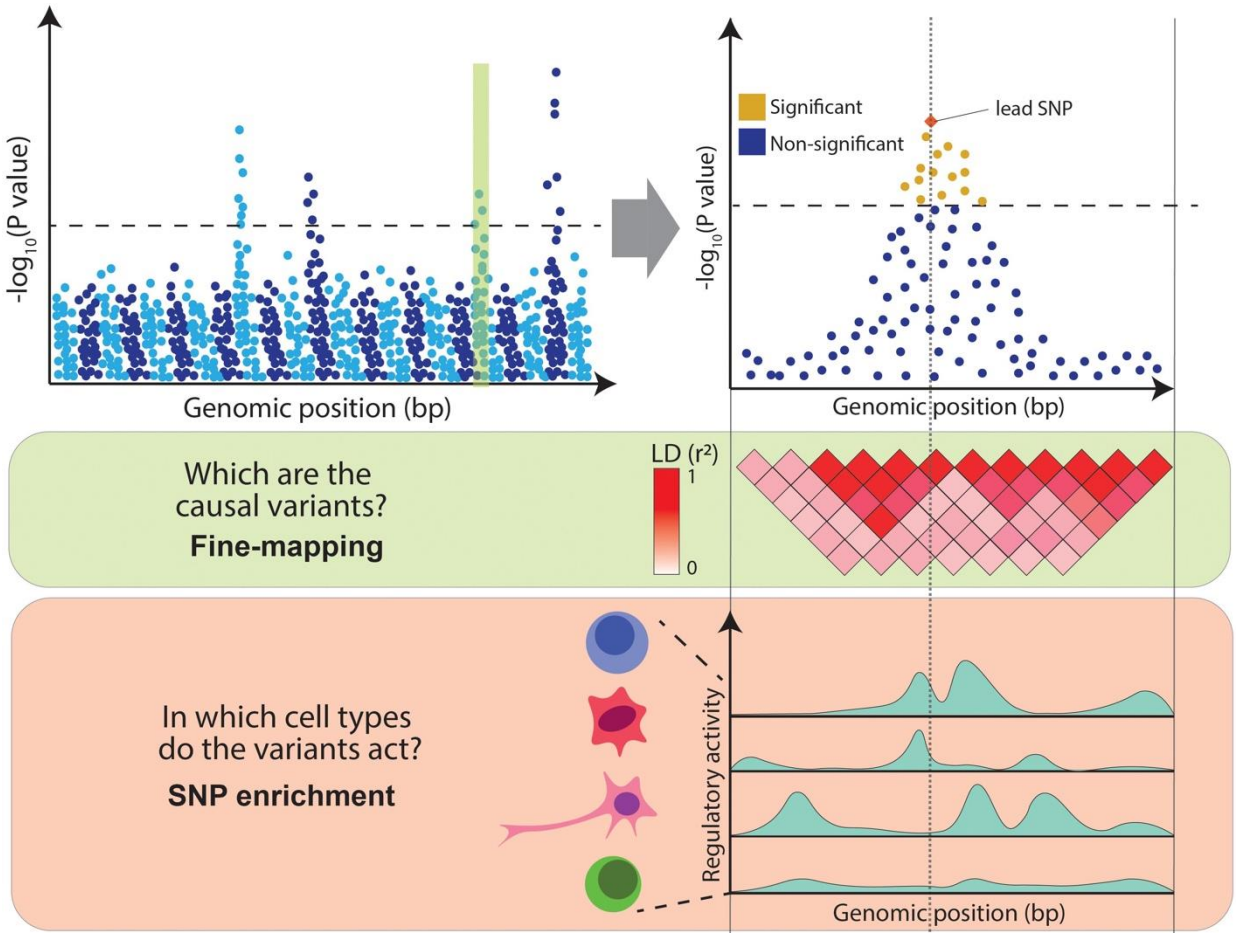
Schaid, 2018 Nature Reviews Genetics

Integrate functional annotation

Use our “prior” knowledge about the SNPs

1. Estimates prior causal probabilities for all SNPs using functional annotations
2. Perform fine-mapping using these prior causal probabilities.

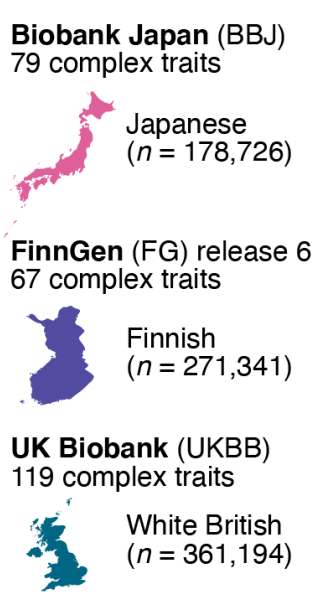
Methods: SBayesRC, PolyFun, PAINTOR, fastPAINTOR, CAVIARBF

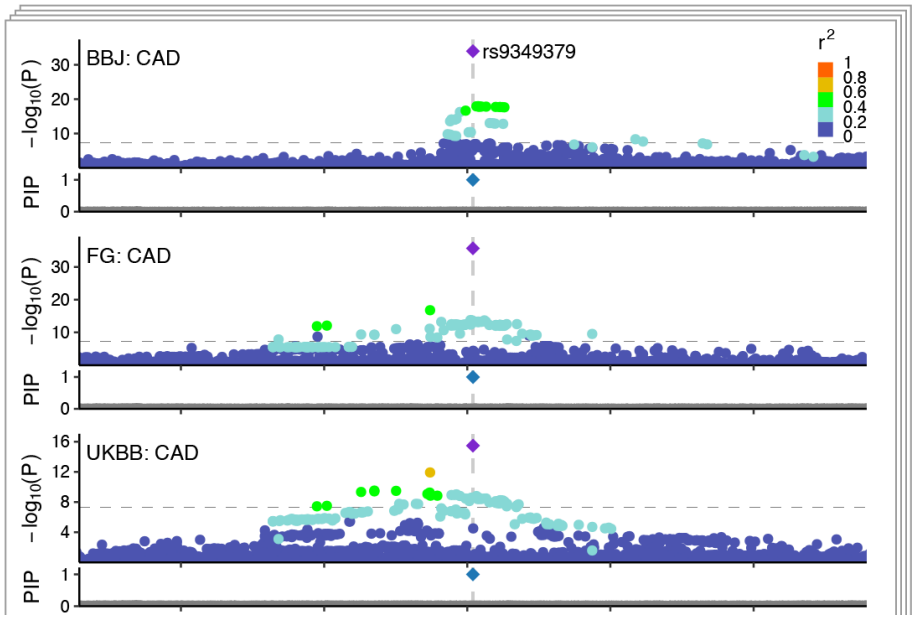


Cano-Gamez et al. Frontiers in Genetics (2020)

Cross-ancestry fine-mapping

- Utilise populations of different ancestries to prioritise SNPs
- Relies on the assumption that causal variants are shared between populations (generally supported in literature).
- Leveraging differences in LD between populations
- Methods: SuSiEx, MS-Caviar





Kanai et al, medRxiv (2021)

Use caution when applying fine-mapping

- Beware of reference LD, follow Weissbrod et al. 2020 NG guidelines.
  - Recommend using in-sample LD from the GWAS target sample
- Meta-analysis fine-mapping is tricky, see Kanai et al. 2022 Cell Genomics.
- Don’t forget to use covariate-adjusted LD when the cohort has more complex population structure, e.g. admixture. See Pan-UKBB LD documents.
- Keep in mind that model misspecifications and missing causal variants exist in real data applications. Use caution when interpreting fine-mapping results.
- Run different methods if you can.

Slide from Ran Cui (IBG workshop 2025)

Fine-mapping resources

Published fine-mapping results by large studies:

FinnGen: https://finngen.gitbook.io/documentation/methods/finemapping

UK Biobank: https://www.finucanelab.org/data

PGC Schizophrenia study: Supplementary Table 11

LD resources:

PolyFun published UK Biobank LD matrices.

Pan-UKBB published multi ancestry LD matrices.

Fine-mapping pipelines:

FinnGen pipeline: https://github.com/FINNGEN/finemapping-pipeline

UK Biobank pipeline: https://github.com/mkanai/finemapping-pipeline

Practical

- Use SuSiE to investigate the genetic effects underlying height.
- We will use summary statistics from Wood et al (2014) and perform fine-mapping in the regions surrounding some of the GWAS 'hits' to identify SNPs that are most likely to be causal (or in LD with causal variants).
- The practical html can be found on the website

  https://cnsgenomics.com/data/teaching/GNGWS25/module1/9_FineMappingPrac.html
- The data can be found on the cluster

  /data/module1/9_FineMappingPrac