across studies, thereby removing non-causal signals more effectively and improving the assessment of causal consistency across studies.

At the same time, MsCAVIAR places higher demands on the data. It depends on the completeness and comparability of multi-study datasets, and because it combines statistical information across several studies, its computational burden is also substantially increased. MsCAVIAR can therefore be regarded as a cross-study model that extends the scope of causal inference and improves identifiability through cross-study information.

(4) Colocalization methods: inference of cross-trait causal consistency
Colocalization methods, such as COLOC and eCAVIAR, extend the inferential target from a single phenotype to multiple phenotypes, focusing on whether different phenotypes share the same causal variant and thereby enabling probabilistic modeling of cross-trait causal consistency (Giambartolomei et al., 2013; Hormozdiari et al., 2016). Whereas fine-mapping primarily concerns locus-level causal probabilities, colocalization methods further expand the inferential target to shared causal probability, allowing GWAS signals to be connected more directly to molecular mechanisms.

The performance of these methods, however, is typically influenced by the quality of downstream molecular QTL data and the degree of matching across tissues and cell types. For this reason, colocalization methods are best understood as a framework for causal inference at the cross-trait level.

6.2 A layer-based decision strategy

In practical research, method selection is better organized according to inferential layers rather than based on empirical preference alone. Different stages of analysis address different questions, and the methods used should accordingly change with the inferential goal.

(1) Genome-wide scanning stage
At the genome-wide scanning stage, the main objective is usually to narrow the candidate space as quickly as possible in order to complete an initial screen in large-scale datasets. In this context, fastPAINTOR is often an appropriate choice. Its use presupposes access to high-quality functional annotation information. By leveraging annotation-informed prioritization, the method can balance efficiency with candidate-space reduction in high-throughput analysis settings (Kichaev et al., 2016; Zou et al., 2021).

(2) Regional fine-resolution stage
Once the analysis enters the stage of fine-scale dissection of candidate regions, the focus shifts from broad screening to the robust identification of sets of causal variants. At this stage, CAVIAR is often more advantageous. Especially when functional annotations are insufficient or local LD structure is complex, its independence from prior information allows its robustness to become more evident (Schaid et al., 2018).

(3) Cross-study integration stage
When the research goal further shifts to evaluating causal consistency across studies or ancestries, MsCAVIAR becomes more suitable. It can exploit LD differences across studies to enhance identification, thereby improving both causal consistency assessment and localization resolution in multi-cohort or multi-ancestry studies (Lapierre et al., 2020).

(4) Mechanistic interpretation stage
At the stage of mechanistic interpretation, the focus is no longer limited to locating causal variants, but rather to linking genetic variants with molecular functional processes. At this point, colocalization analysis combined with TWAS can more effectively evaluate cross-trait causal consistency and connect GWAS findings with potential molecular mechanisms (Giambartolomei et al., 2013; Okamoto et al., 2023).

6.3 A unified strategy: hierarchical inference pipeline

Integrating the above considerations, method selection in complex trait genetics can be summarized as a unified inferential pipeline:

GWAS→fine-mapping→colocalization→TWAS/functional validation