

Bottom line analysis

Meta-analysis of genetic association studies provides an estimate of the effect of a genetic variant on a phenotype by pooling information across multiple studies with similar designs and sampling.

One potential complication in performing meta-analysis is when samples overlap between the studies. Failing to account for this overlap can lead to inflated type 1 error (incorrectly identifying variants as associated with a phenotype when in fact they are not.)

Our bottom line analysis estimates the sample overlap between each pair of studies/datasets and accounts for it when weighting each study's contribution to the final effect estimate. The method is implemented in METAL (documented [here](#)) and was developed at the University of Michigan. The procedure for performing this analysis in the Knowledge Portals is outlined below.

Please note that this method as instantiated in the Knowledge Portals is experimental; be sure to compare the results with those from individual datasets. We are happy to provide help in evaluating these results; please [contact us](#).

Bottom line analysis in the Knowledge Portals

Partitioning Variants

For each dataset, the variants are first filtered and then partitioned by:

1. Ancestry
2. Minor allele frequency (common/rare)

In the filter step, the following variants are removed from the meta-analysis:

- Multi-allelic variants
- Variants with missing p-value or beta/OR

Running Meta-Analysis

The meta-analysis is broken up into 2 steps: ancestry-specific and trans-ethnic.

Ancestry-Specific Analysis

If more than one ancestry is present for the phenotype, then - if present - the "Mixed" ancestry is removed from further analysis.

Then, for each ancestry, the following analysis is performed:

1. METAL is run over common variants from each dataset with OVERLAP ON.
2. The output is then unioned with the rare variants from all datasets.
3. In the event that a variant exists as both common and rare (from differing datasets), only the variant with the largest, total N across all datasets is kept.

Trans-Ethnic Analysis

After each ancestry has been processed, METAL is run across all the ancestries with OVERLAP OFF. If the only ancestry present was "Mixed" then this should result in an identity operation.

Loading Results

Only the final results of the trans-ethnic analysis are loaded into the database as "bottom line" results.