across different functional regions, thereby extending the question from quantifying "the magnitude of heritability" to interpreting "the structural sources of heritability." This approach can not only reduce heterogeneity-related bias in overall estimates, but also substantially improve the biological interpretability of the results, allowing heritability estimates to be more closely aligned with functional genomic information (Finucane et al., 2015; Gazal et al., 2018).

In terms of methodological implementation, such models usually rely on existing functional annotation systems, in which genome-wide SNPs are classified into categories such as coding regions, regulatory regions, and conserved sequences. A genetic relationship matrix (GRM) is then constructed separately for each category. Subsequently, within an extended multi-GRM GREML framework, multiple variance components are introduced simultaneously to jointly estimate the genetic contributions of different functional regions (Finucane et al., 2015; Wei et al., 2019). A key assumption underlying this modeling strategy is that SNPs in different functional categories differ systematically in the distribution of their effect sizes and in their relationships with linkage disequilibrium (LD) structure, and that these differences can be statistically identified and quantified through partitioned modeling.

From the perspective of data suitability, this type of method places relatively high demands on sample size and annotation quality. A larger sample size helps stabilize the estimation of multiple variance components, while high-quality functional annotation is a prerequisite for ensuring that the partitioning results have biological meaning. The number of SNPs must also be sufficient to support multi-category partitioning; otherwise, model parameters may face identification difficulties. In human and crop genetic studies, this method is particularly appropriate when the research focus shifts from a single estimate of heritability to the analysis of genetic architecture, namely when attention is directed toward the relative importance of different functional regions in contributing to a trait.

It should be noted that functional partitioning of heritability is sensitive in practice to correlations among annotations. Because different functional categories often overlap in genomic space and may exhibit highly correlated LD structures, such multicollinearity can directly affect the identifiability of variance components, leading to unstable estimates or ambiguity in interpretation. Therefore, when interpreting the results, sensitivity analyses should be incorporated to evaluate model robustness, and conclusions regarding "enrichment" in any single region should be treated with caution. Statistical association should not be equated simplistically with clear biological causality (Gazal et al., 2018).

5.3 Bivariate and cross-trait genetic correlation

Under the single-trait GREML framework, researchers can estimate the genetic variance of a single phenotype with relative robustness. However, such models essentially remain confined to variance partitioning "within a trait" and are therefore limited in addressing the more biologically meaningful question of whether different traits share a common genetic basis. Against this background, bivariate and cross-trait GREML models have gradually become important extensions in the genetic analysis of complex traits. By jointly modeling multiple phenotypes, this approach not only improves the characterization of genetic covariance structures, but also enables the quantification of correlations between traits driven by shared genetic factors (Zhou et al., 2020).

Bivariate GREML is, in essence, an extension of the variance-covariance structure of the classical linear mixed model. Within the same statistical framework, the model simultaneously estimates the genetic variance and environmental variance of two traits, as well as the genetic covariance between them, from which the genetic correlation coefficient can be derived. Its validity depends on several key assumptions. First, the genetic effects of different traits should be representable by a common genomic relationship matrix (GRM). Second, the sample data should contain sufficient information to support effective identification of the covariance structure (Figure 2).

Ideally, the two traits should be measured in the same group of individuals or in highly overlapping samples, so that genetic and environmental effects can be partitioned within a unified reference framework. Adequate sample size is also particularly important for improving the precision of covariance estimation. In crop genetic