Association testing with GENESIS

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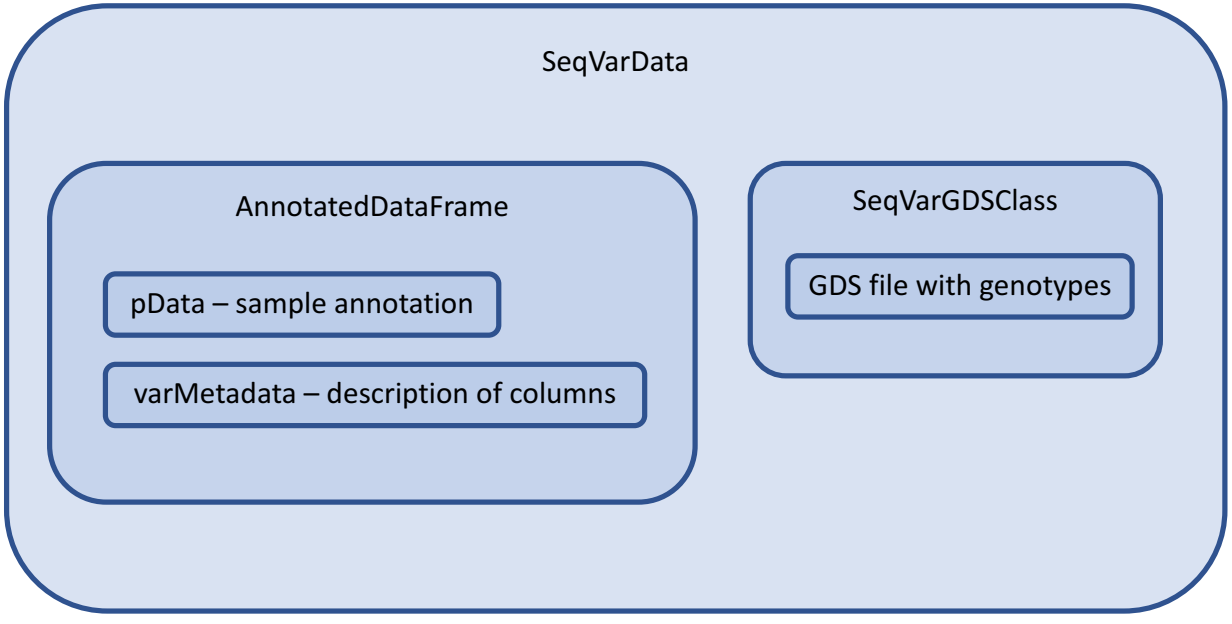
Essential R objects

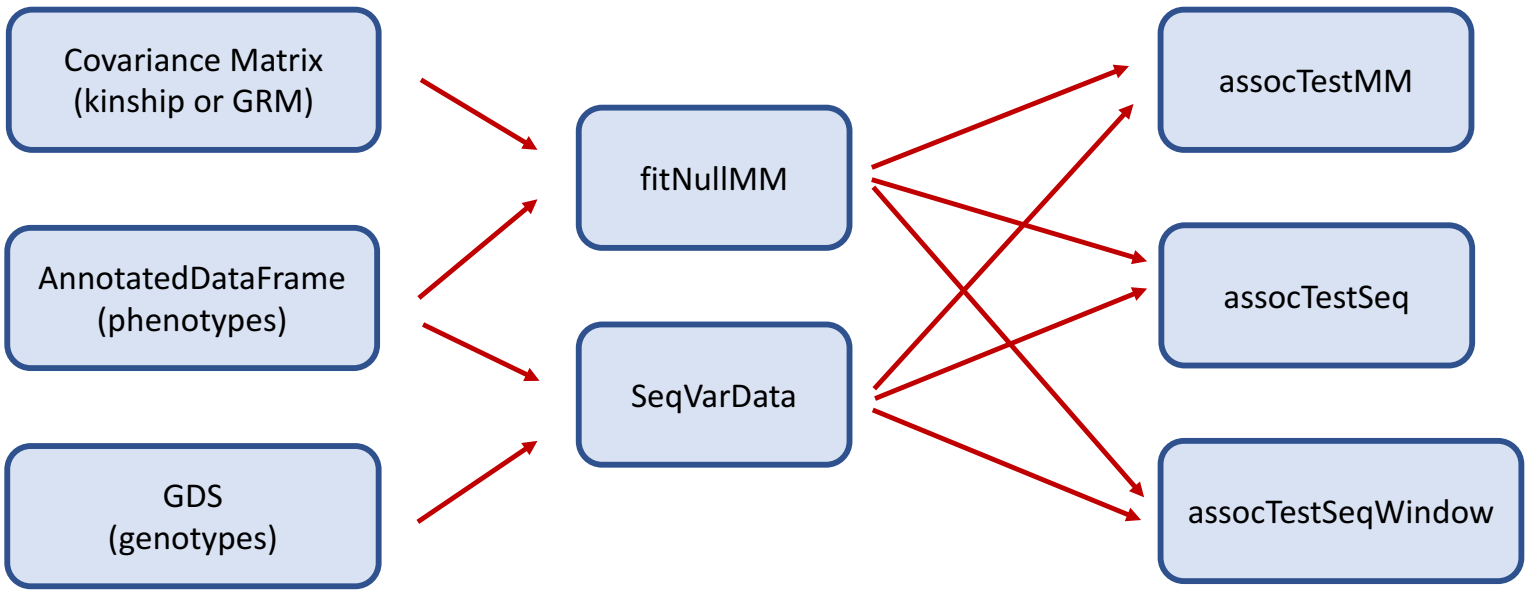
Object	Package	Description
AnnotatedDataFrame	Biobase	R data.frame with metadata describing each column
SeqVarGDSClass	SeqArray	Object providing access to a GDS file
SeqVarData	SeqVarTools	Object linking a GDS file to sample annotation



GENESIS key functions

Function	Description
fitNullMM	Fit a null mixed model with fixed effects and one or more random effects (e.g., kinship, GRM)
assocTestMM	Single-variant test using null mixed model
assocTestSeq	Rare variant test (burden or SKAT) with user-defined aggregation units (e.g., genes)
assocTestSeqWindow	Rare-variant test (burden or SKAT) with a sliding window

Association testing flow chart



Fitting the null model

When combining samples from groups with different variances for a trait (e.g., study or ancestry group), it is recommended to allow the null model to fit heterogeneous variances by group using the parameter `group.var`.

1. Fit null mixed model including covariates (as fixed effects) and kinship/GRM (as random effect)
2. For each group separately:
   - 2.1 Inverse normal transform marginal residuals
   - 2.2 Rescale variance to match original
3. For all samples together:
   - 3.1 Fit null mixed model using transformed residuals as outcome
   - 3.2 Allow heterogeneous variance by `group.var`
   - 3.3 Include covariates as fixed effects
   - 3.4 Include kinship/GRM as random effect

The analysis pipeline implements this procedure.