Integrative Genomics Analyses using the *gact* and *qgg* R packages

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Why Integrate Diverse Data Sources?

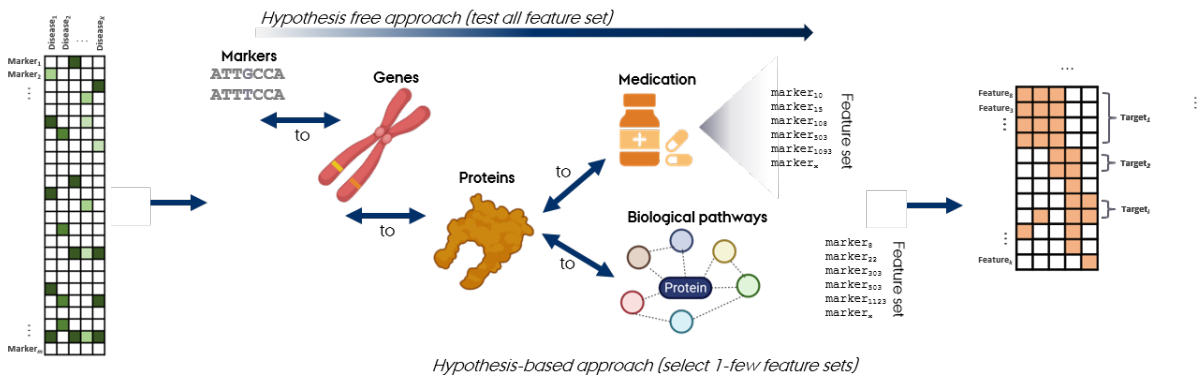
- Complex traits arise from **interacting molecular layers** — genetic, transcriptomic, proteomic, and metabolic.
- Single data types provide only **partial insights** complex biological systems (**GWAS: DNA → disease phenotype**)
- Integration connects **variants → genes → pathways → phenotypes** may help reveal molecular mechanisms that drive traits and diseases.
- Enables **functional interpretation**, **better prediction**, and **new discoveries** across molecular systems.

From Data Integration to Discovery

BLR Adjusted GWAS summary statistics

Link genetic markers to information in biological databases

Functional marker sets enriched for disease association



"*Utilising cleaner and stronger marker signals linked to functional marker information and jointly analysing multiple functional marker sets and diseases may help better understand disease biology and subsequently be used to identify novel drug targets.*"

The *gact* R Package

gact provides an infrastructure for efficient processing of large-scale genomic association data, with core functions for:

- Establishing and populating a database of genomic associations
- Downloading and processing biological databases
- Handling and processing GWAS summary statistics
- Linking genetic markers to genes, proteins, metabolites, and biological pathways
- Integrates with statistical machine learning tools in the **qgg** R package

gact is intended to serve as **a practical implementation of integrative genomics**, bridging **statistical modeling** and **biological interpretation**, and supporting **reproducible** and **extensible** workflows.

Integrating Data with *gact*

The `gact()` function is a single R command that creates and populates the *Genomic Association of Complex Traits (GACT)* database.

It automates three main tasks:

- **Infrastructure creation** – sets up a structured folder-based database
  (`glist`, `gstat`, `gsets`, `marker`, `gtex`, `download`, etc.)
- **Data acquisition** – downloads and organizes multiple biological data sources
  (e.g., GWAS Catalog, Ensembl, GTEx, Reactome, STRING, STITCH, DGIdb)
- **Marker and feature set generation** - integrates data across sources to create curated genomic feature sets that form the basis for the integrative genomic analyses.

Biological Databases Used by *gact*

gact constructs gene and marker sets from a wide range of curated biological databases:

- **Ensembl** — genes, transcripts, and proteins
- **Ensembl Regulation** — regulatory genomic features
- **GO**, **Reactome**, **KEGG** — ontology and pathway sets
- **STRING**, **STITCH** — protein and chemical complexes
- **DrugBank**, **ATC** — drug–gene and drug-class associations
- **DISEASE** — disease–gene associations
- **GTEx** — eQTL-based gene sets
- **GWAS Catalog** — trait-associated variants and genes
- **VEP** — functional variant annotations

We plan to add additional biological resources in **gact**.

From Database to Model Inputs

The *gact* R package includes utility functions to extract and structure data from the GACT database into analysis-ready inputs — $\mathbf{Y}$ (e.g., summary statistic outcomes) and $\mathbf{X}$ (genomic or biological features).

- `getMarkerStat()` — retrieve GWAS summary statistics (**Y's**)
- `getFeatureStat()` — extract gene-, protein-, or pathway-level results (**Y's**)
- `getMarkerSets()` — define biological groupings (basis for **X's**)
- `designMatrix()` — build feature matrices (**X**) linking variants or genes to biological feature sets

Together, these functions form a **reproducible workflow** for generating **standardized input data** for **Bayesian Hierarchical Models** and other **machine learning** approaches.

The *qgg* R Package

qgg provides tools for statistical modeling and analysis of large-scale genomic data, including:

- Fine-mapping of genomic regions using **Bayesian Linear Regression (BLR) models**
- Polygenic scoring using **Bayesian Linear Regression (BLR) models**
- Gene set enrichment analysis using **Bayesian Linear Regression (BLR) models**

qgg handles large-scale genomic data through **efficient algorithms** and **sparse matrix techniques**, combined with **multi-core processing** using **OpenMP**, **multithreaded matrix operations** via **BLAS** libraries (e.g., OpenBLAS, ATLAS, or MKL), and **fast, memory-efficient batch processing** of genotype data stored in binary formats such as **PLINK `.bed` files**.

Tutorials using the *qgg* and *gact* R packages

- Gene analysis using VEGAS: Gene analysis using the VEGAS (Versatile Gene-based Association Study) approach using the 1000G LD reference data processed above,
- Gene set analysis using Bayesian MAGMA: Pathway prioritization using a single and multiple trait Bayesian MAGMA models and gene-level statistics derived from VEGAS (Gholipourshahraki et al.2024).
- Gene ranking using PoPS: Polygenic Prioritization Scoring (PoPS) using BLR models and gene-level statistics derived from VEGAS (work in progress).
- Finemapping using BLR models: Finemapping of gene and LD regions using single trait Bayesian Linear Regression models (Shrestha et al.2025).
- Polygenic scoring using BLR models: Polygenic scoring (PGS) using Bayesian Linear Regression models and biological pathway information (work in progress).

From Data Integration to Modeling

The *gact* and *qgg* R packages bridges data integration, statistical modeling and biological interpretation, enabling reproducible and extensible workflows.

- **Integrates biological information** across molecular layers — from **genome** to **pathways**, **complexes**, and **drug–gene interactions**
- **Uses structured priors and hierarchical modeling** to share information, regularize effect estimates, and quantify uncertainty
- **Enables data-driven discovery and prediction**

Next Steps

- Apply the framework to new and relevant use cases
- Expand integration with more biological data resources
- Incorporate additional statistical and machine learning methods

Further Reading and Collaboration

We are open to collaboration!

If you're interested in applying **BLR methods** or contributing to the **gact** framework, please reach out.

Further Reading

- **Bayesian Linear Regression** – teaching materials
- **gact** – R package documentation
- **qgg** – R package documentation