cnvGSA Package Introduction

Joseph Lugo
The Centre for Applied Genomics
joseph.r.lugo@gmail.com

May 1, 2024

cnvGSA is an R package for testing the gene-set rare variant burden in case-control studies of copy number variation (CNV).

Only rare CNV (e.g. at frequency <1%) should be present in the input data. Gene-sets need to be pre-compiled based on user-curated data or publicly available gene annotations like **Gene Ontology** or pathways.

"Competitive" gene-set over-representation tests are commonly used to analyze differentially gene expressed genes (e.g. Fisher's Exact Test, GSEA), but they are not suitable for rare CNV; the most appropriate choice for rare CNV is a "self-contained" burden test with global burden correction implemented by cnvGSA or other tools.

Global burden correction is very important. For many disorders (including autism and schizophrenia), the disease-affected subjects (i.e. cases) are enriched in large, recurrent CNV. Those CNV are not observed (or observed at very low frequency) in controls and only a minority of their genes may contribute to disease risk. In the absence of global burden correction, many gene-sets would present a biologically unspecific burden, uniquely driven by those larger and recurrent CNV. Global burden correction thus helps identifying specific pathways and functional categories implicated in disease risk by rare CNVs.

In cnvGSA, subjects are treated as statistical sampling units. Subject-level covariates that may act as confounders can be provided by the user (e.g. sex, ethnicity, CNV genotyping platform, CNV genotyping site, array quality metrics, etc.). The gene-set burden is tested using a logistic regression approach. Two logistic regression models are fit: model A includes the subject-level covariates and a variable quantifying global CNV burden for each subject (total CNV length, or total number of CNV-overlapped genes per subject, etc.); model B includes all variables present in model A, plus the number of CNV-overlapped genes that are members of the gene-set being tested. Presence of significantly higher burden in cases compared to controls for the gene-set of interest is then tested by comparing the two models using a deviance chi-square test, as implemented by anova.glm.