Analyzing bivariate cross-trait genetic architecture in GWAS summary statistics with the BIGA cloud computing platform

Running title: BIGA GWAS cloud platform

Yujue Li[1], Fei Xue[1], Bingxuan Li[2], Yilin Yang[3], Zirui Fan[4], Juan Shu[1], Xiyao Wang[2], Jinjie Lin[5], Carlos Copana[1], and Bingxin Zhao[4]*

[1]Department of Statistics, Purdue University, West Lafayette, IN 47907, USA.

[2]Department of Computer Science, Purdue University, West Lafayette, IN 47907, USA.

[3]Department of Computer and Information Science and Electrical and Systems Engineering, School of Engineering & Applied Science, University of Pennsylvania, Philadelphia, PA 19104, USA.

[4]Department of Statistics and Data Science, University of Pennsylvania, Philadelphia, PA 19104, USA.

[5]Yale School of Management, Yale University, New Haven, CT 06511, USA.

**Corresponding to*:

Bingxin Zhao

413 Academic Research Building

265 South 37th Street, Philadelphia, PA 19104.

E-mail: bxzhao@upenn.edu Phone: (215) 898-8222

Abstract

As large-scale biobanks provide increasing access to deep phenotyping and genomic data, genome-wide association studies (GWAS) are rapidly uncovering the genetic architecture behind various complex traits and diseases. GWAS publications typically make their summary-level data (GWAS summary statistics) publicly available, enabling further exploration of genetic overlaps between phenotypes gathered from different studies and cohorts. However, systematically analyzing high-dimensional GWAS summary statistics for thousands of phenotypes can be both logistically challenging and computationally demanding. In this paper, we introduce BIGA (http://bigagwas.org/), a website that offers unified data analysis pipelines and centralized data resources for cross-trait genetic architecture analyses using GWAS summary statistics. We have developed a framework to implement statistical genetics tools on a cloud computing platform, combined with extensive curated GWAS data resources. Through BIGA, users can upload data, submit jobs, and share results, providing the research community with a convenient tool for consolidating GWAS data and generating new insights.

Keywords: GWAS; Cross-trait analysis; Cloud computing; Online platform.

The rapid development of biobank-scale biomedical databases, encompassing phenotyping and genomic data, has occurred globally[1]. Numerous genome-wide association studies (GWAS) have been conducted to determine the genetic architecture underlying a wide range of complex traits and clinical outcomes, with the aim of improving disease prevention and treatment[2]. Publicly available GWAS summary-level data (or GWAS summary statistics) encompass thousands of phenotypes[3-8]. These summary statistics, derived from large-scale studies, provide valuable opportunities for in-depth investigations into genetic overlaps and shared architectures between phenotypes across studies and cohorts. Several statistical genetic tools have been developed to analyze GWAS summary statistics and examine the shared genetic components between pairs of phenotypes, including LDSC[9], LAVA[10], Coloc[11], and Mendelian randomization[12]. These methods offer insights into genetic links from various perspectives and have been widely applied to clinical biomarkers and outcomes[13,14].

However, implementing and batch-running these tools often requires robust computing and data infrastructure, which may not always be available to all researchers. Consequently, systematic bivariate cross-trait analyses using massive GWAS summary statistics for thousands of phenotypes can be logistically and computationally challenging. As more complex and deep phenotyping data are obtained from biobanks[15], addressing these limitations becomes increasingly urgent. For example, the UK Biobank (UKB) imaging study[16] collected multimodal brain imaging data, generating over 5,000 imaging-derived phenotypes using different imaging modalities and processing pipelines[17-21]. Researchers interested in a specific disease and its genetic connections with imaging biomarkers have traditionally downloaded all the GWAS summary statistics for over 5,000 imaging biomarkers from the Oxford BIG40 Project (http://big.stats.ox.ac.uk) and the BIG-KP project (https://bigkp.org/), and run their statistical tools in local clusters, which can be inefficient. Several online research platforms based on cloud computing have been developed, most of which focus on one database (such as the UKB study, https://ukbiobank.dnanexus.com/), univariate trait GWAS analysis (such as FUMA[22]), or single data analysis method/function (such as LD Hub[23] and Locus Compare[24]). Developing an integrated platform for cross-trait analyses of GWAS summary data resources will make existing large-scale GWAS summary data more accessible to researchers.

To address these limitations, we developed BIGA (http://bigagwas.org/), an online cloud-based platform that offers unified data analysis pipelines and centralized data resources for cross-trait analyses using GWAS summary statistics. BIGA aims to provide various tools for quantifying cross-trait genetic architectures, such as genome-wide genetic correlation methods (e.g., LDSC[9], Popcorn[25], and SumHer[26]), polygenic overlap estimation between two traits (e.g., MiXeR[27]), genomic structural equation modeling (e.g., GenomicSEM[28]), local genetic correlation analysis (e.g., LAVA[10]), Mendelian randomization (e.g., MR-Base[29], MR-RAPS[30], DIWV[31], and GRAPPLE[32]), and colocalization (e.g., Coloc[11]). We have also aggregated and preprocessed GWAS summary statistics from various resources (e.g., the UKB[15], GWAS Atlas[4], FinnGen[6], Biobank Japan[8], BIG-KP[18,19,21], and Oxford BIG40[17,20]) and provided curated datasets. Our framework can easily be extended to incorporate additional methods and GWAS summary statistics.

Figure 1 provides an overview of the BIGA architecture. We offer users several options for inputting GWAS summary statistics data, including uploading their own data, querying harmonized data from public databases (such as the IEU OpenGWAS[7] and Pan-UK Biobank, https://pan.ukbb.broadinstitute.org/), and querying data from the BIGA in-house database. Users can specify the tools and job types they are interested in and submit their request. After submission, the job request will be passed to the back-end and executed on our cloud computing platform using the specified tools and datasets. Once completed, the results will be presented to the user through the front-end interface. Users have the option to share their results and/or data with our public database.

Here we present an LDSC data analysis example for schizophrenia[33]. Specifically, we investigated the genetic correlation between schizophrenia and complex traits and diseases available in our current curated datasets. These datasets include 4,575 UKB phenotypes provided by the Neale Lab (http://www.nealelab.is/uk-biobank), 3,095 clinical outcomes from FinnGen[6], 199 brain-related phenotypes in GWAS Atlas[4], 3,905 brain imaging phenotypes from the Oxford BIG40[17,20], and 3,016 multi-organ imaging phenotypes from the BIG-K[18,19,21]. **Figure S1** displays the job information for these LDSC data analyses, including Job ID, Job Name, Job Type, Status, Download Link, Result link,

and a link to share your results with the public. Once the job is complete, users can either download the full set of results or view them in our online table. For example, among the 199 brain-related phenotypes in GWAS Atlas[4], we discovered that the top-ranking phenotypes exhibiting strong genetic correlations with schizophrenia included neuroticism and its subclusters, daytime napping, and daytime sleepiness (**Fig. S2**). These results can be effortlessly shared on our Public Results Portal (**Fig. S3**). This data analysis demonstrates that our platform facilitates rapid analysis of extensive GWAS summary statistics and enables seamless result sharing with the community.

In summary, our platform enables researchers to easily perform multiple cross-trait analyses without needing access to a local research computing cluster, implementing methods locally, or downloading large datasets. BIGA will help reduce the imbalance in the research community caused by unequal computing resources. The source code to build the BIGA platform will be made publicly available on GitHub, which can serve as an example for creating more cloud computing-based genomic data analysis websites. The BIGA website welcomes user feedback and requests, which aids in improving the project and implementing new tools and functions to better meet the needs of the research community.

ADDITIONAL INFORMATION

One supplementary information pdf file is available, where the figures of an example data analysis using BIGA are displayed.

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AUTHOR CONTRIBUTIONS

Y.L. and B.Z. designed the study, developed the BIGA website, and wrote the manuscript with feedback from all authors. B.L. helped with the implementation of statistical genetic methods and website functions. Y.Y., Z.F., J.S., X.W., B.L., and C.C. processed the GWAS summary statistics, developed the curated datasets, and contributed to the development of the website. F.X. and J.L. provided feedback on the study design and website.

CORRESPONDENCE AND REQUESTS FOR MATERIALS should be addressed to B.Z.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Code availability

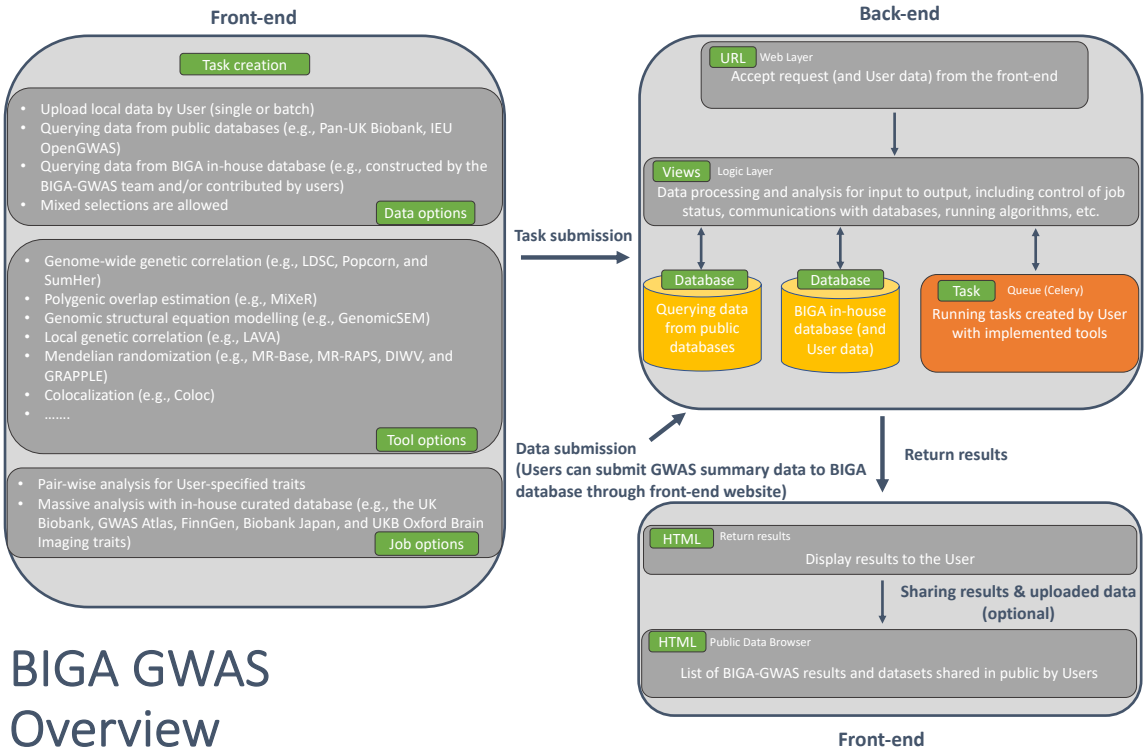
All source code and related information for the BIGA platform will be made publicly available on the BIGA GitHub repository. The statistical genetics tools and methods implemented in the BIGA platform are also open source, and their source code has already been made available to the public by their authors.

Data availability

GWAS summary statistics used in the BIGA platform are publicly available and can be found in several public databases, such as the
Pan-UK Biobank (https://pan.ukbb.broadinstitute.org/),
IEU OpenGWAS (https://gwas.mrcieu.ac.uk/),
GWAS Atlas (https://atlas.ctglab.nl/),
FinnGen (https://www.finngen.fi/en/access_results),
Biobank Japan (https://pheweb.jp/),
BIG-KP (https://bigkp.org/), and
Oxford BIG40 (https://open.win.ox.ac.uk/ukbiobank/big40/).

1 **Figure Legend**

2 **Fig. 1 Overview of BIGA GWAS online platform.**



BIGA GWAS Overview

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