Title: NIAGADS Alzheimer's GenomicsDB: A resource for exploring Alzheimer's Disease genetic and genomic knowledge

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Abstract

INTRODUCTION:

The NIAGADS Alzheimer's Genomics Database (GenomicsDB) is an interactive knowledgebase for Alzheimer's disease (AD) genetics that provides access to GWAS summary statistics datasets deposited at NIAGADS, a national genetics data repository for AD and related dementia (ADRD).

METHODS:

The website makes available >70 genome-wide summary statistics datasets from GWAS and genome sequencing analysis for AD/ADRD. Variants identified from these datasets are mapped to up-to-date variant and gene annotations from a variety of resources and linked to functional genomics data.

The database is powered by a big data optimized relational database and ontologies to consistently annotate study designs and phenotypes, facilitating data harmonization and efficient real-time data analysis and variant or gene report generation.

RESULTS:

Detailed variant reports provide tabular and interactive graphical summaries of known ADRD associations, as well as highlight variants flagged by the Alzheimer's Disease Sequencing Project (ADSP). Gene reports provide summaries of co-located ADRD risk-associated variants and have been expanded to include meta-analysis results from aggregate association tests performed by the ADSP allowing us to flag genes with genetic evidence for AD.

DISCUSSION:

The GenomicsDB makes available >150 million variant annotations, including ~30 million (5 million novel) variants identified as AD-relevant by ADSP, for browsing and real-time mining via the website. With a newly redesigned, efficient, search interface and comprehensive record pages linking summary statistics to variant and gene annotations, this resource makes these data both accessible and interpretable, establishing itself as valuable tool for AD research.

1 Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects 5.8 million people in US in 2018, is effectively untreatable, and invariably progresses to complete incapacitation and death 10 or more years after onset. Early work in the 1990s identified mutations in the amyloid precursor protein (APP) gene, presenilins 1 and 2 that cause AD, and alleles of the apolipoprotein E gene (APOE) that increase (ε4) or decrease (ε2) susceptibility to late-onset Alzheimer's disease (LOAD). Heritability of AD is high, ranging from near 60% to 80% in the best fitting model [1,2]. However, apart from APOE, there is no simple pattern of inheritance for LOAD. Instead, it is likely caused by a complex combination of common, polygenic variants [3] acting together with a small number of rare variants with a large effect [4,5].

Our current understanding of genetic risk for AD has resulted mainly from massive genotyping and sequencing efforts such as the Alzheimer's Disease Genetics Consortium (ADGC), the International Genomics of Alzheimer's Project (IGAP), and the Alzheimer's Disease Sequencing Project (ADSP). Large-scale genome wide association studies (GWAS) and GWAS-derived meta-analyses have been performed by each of these groups [4–7], the results of which are deposited at the National Institute of Aging (NIA) Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) at the University of Pennsylvania [8]. NIAGADS is an NIA-designated essential national infrastructure, providing a one-stop access portal for Alzheimer's disease 'omics datasets. Qualified investigators can submit data use requests to access protect personal genetic information. NIAGADS also disseminates unrestricted meta-analysis results and GWAS summary statistics to promote data reuse, allowing researchers to explore known evidence for AD genetic risk. However, substantive bioinformatics expertise and compute power are required to annotate and mine these datasets, which are significant hurdles for many researchers planning to explore this large and ever-increasing volume of data. Assembly of unrestricted genomic knowledge into an integrated, interactive web resource would help overcome this barrier.

Here, we introduce the NIAGADS Alzheimer's Genomics Database (GenomicsDB), which was developed in collaboration with the ADGC and ADSP with this goal in mind. The GenomicsDB is a user-friendly workspace for data sharing, discovery, and analysis designed to facilitate the quest for better understanding of the complex genetic underpinnings of AD neurodegeneration and accelerate the progress of research on AD and AD related dementias (ADRD). It accomplishes this by making summary genetic evidence for AD/ADRD both accessible to and interpretable by molecular biologists, clinicians and bioinformaticians alike regardless of computational skills.

2 Methods

2.1 Genomics Datasets

2.1.1 NIAGADS GWAS summary statistics

As of December 2020, the NIAGADS GenomicsDB provides unrestricted access to genome-wide summary statistics *p*-values from >70 GWAS and ADSP meta-analysis. Summary statistic results are linked to >150 million ADSP annotated single-nucleotide variants (SNVs) and indels. GWAS summary statistics datasets deposited at NIAGADS are integrated into the GenomicsDB as they become publicly available via publication or permission of the submitting researchers. These include studies that focus specifically on AD and late-onset AD (LOAD), as well as those on ADRD-related neuropathologies and biomarkers. A full listing of the summary statistics datasets currently available through the NIAGADS GenomicsDB is provided in **Supplementary Table S1**.

Prior to loading in the database, the datasets are annotated (e.g. provenance, phenotypes, study design) and variant representation normalized to ensure consistency with ADSP analysis pipelines and facilitate harmonization with third-party annotations. To ensure the privacy of personal health information, the NIAGADS GenomicsDB website only makes *p*-values from the summary statistics available for browsing (on dataset, gene, and variant reports and as genome browser tracks) and analysis. Access to the full summary statistics (including genome-wide allele frequencies and effect sizes) and corresponding GWAS or sequencing results is managed via formal data-access requests made to NIAGADS. All datasets included in the GenomicsDB are properly credited to the submitting researchers or sequencing project.

2.1.2 NHGRI-EBI GWAS Catalog

Variants and summary statistics curated in the NHGRI-EBI GWAS catalog [9] are listed in NIAGADS GenomicsDB variant reports and a track is available on the genome browser. Variants linked to AD/ADRD are highlighted.

2.1.3 ADSP meta-analysis results

The NIAGADS GenomicsDB has recently expanded its scope to include meta-analysis results offering genetic evidence for gene-level and single-variant risk associations for AD. Currently available are case/control association results recently published by the ADSP [7] and deposited at NIAGADS (Accession No. NG00065).

2.2 Variant annotation

2.2.1 Variant identification

Single nucleotide polymorphisms (SNPs) and short-indels are uniquely identified by position and allelic variants. This allows accurate mapping of risk-association statistics to specific mutations and to external variant annotations from resources such as gnomAD (https://gnomad.broadinstitute.org/) [10] and GTex (https://www.gtexportal.org/home/) [11]. All variants are mapped to dbSNP (https://www.ncbi.nlm.nih.gov/snp/) [12] and linked to refSNP identifiers when possible.

2.2.2 ADSP variant annotations

Annotated variants in the NIAGADS GenomicsDB include the >29 million SNPs and ~50,000 short-indels identified during the ADSP Discovery Phase whole-genome (WGS) and whole-exome sequencing (WES) efforts [13]. These variants are highlighted in variant and dataset reports and their quality control status is provided. As part of this sequencing effort, the ADSP developed an annotation pipeline that builds on Ensembl's VEP software [14] to efficiently integrate standard annotations and rank potential variant impacts according to predicted effect (such as codon changes, loss of function, and potential deleteriousness) [13,15]. Variant tracks annotated by these results are available for both the WES and WGS variants on the GenomicsDB genome browser.

The pipeline has been applied to all variants in the GenomicsDB. These annotations can be browsed on variant reports or used to filter search results. User uploaded lists of variants are automatically annotated in real-time.

2.2.3 Allele frequencies

The NIAGADS GenomicsDB includes allele frequency data from 1000 Genomes (phase 3, version 1) (https://www.internationalgenome.org/home) [16], ExAC (http://exac.broadinstitute.org/) [17], and gnomAD [10].

2.2.4 Linkage disequilibrium

Linkage-disequilibrium (LD) structure around annotated variants is estimated using phase 3 version 1 (11 May 2011) of the 1000 Genomes Project [16]. LD estimates were made using PLINK v1.90b2i 64-bit [18]. Only LD-scores meeting a correlation threshold of $r^2 \geq 0.2$ are stored in the database. *Locuszoom.js* [19,20] is used to render LD-scores in the context of the GWAS summary statistics datasets.

2.3 Gene and transcript annotation

2.3.1 Gene identification

Gene and transcript models are obtained from the GENCODE Release 19 (GRCh37.p13) reference gene annotation [21]. A GRCh38 version of the NIAGADS GenomicsDB is planned for 2021. Standard gene nomenclature is imported from the HUGO Gene Nomenclature Committee at the European Bioinformatics Institute [22] and used to link annotated genes to external resources such as UniProt (https://www.uniprot.org/) [23], the UCSC Genome Browser (http://genome.ucsc.edu)[24], and Online Mendelian Inheritance in Man (OMIM) database (https://omim.org/) [25,26].

2.3.2 Functional annotation

Annotations of the functions of genes and gene products are taken from packaged releases of the Gene Ontology (GO; http://geneontology.org) and GO-gene associations [27] and are updated regularly. GO-gene associations are reported in summary tables on gene reports and include details on annotation sources, as well as new information from the GO causal modeling (GO-CAM) framework that allows better understanding of how different gene products work together to effect biological processes [28].

Users can run functional enrichment analysis on gene search results or uploaded gene lists. Geneset enrichment and semantic similarity scores are calculated using the *goatools* Python library for GO analysis [29].

2.4.3 Pathways

Gene membership in molecular and metabolic pathways is provided from the Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.genome.jp/kegg/) [30] and Reactome (https://reactome.org/) [31]. Users can run pathway enrichment analysis on gene search results or uploaded gene lists. Pathway enrichment statistics are calculated using a multiple hypothesis corrected Fisher's exact test implemented using the *SciPy*, *pandas*, and *statsmodels* Python packages.

2.4 Functional genomics

Hundreds of functional genomics tracks have been integrated into the NIAGADS GenomicsDB and mapped against AD/ADRD-associated variants. These tracks are queried from the NIAGADS Functional genomics repository (FILER), which provides harmonized functional genomics datasets that have been GIGGLE indexed [32] for quick lookups [33]. FILER tracks made available through the GenomicsDB have been pulled from established functional genomics resources, including the Encyclopedia of DNA Elements (ENCODE) [34,35], the Functional Annotation of the Mouse/Mammalian Genome (FANTOM5) enhancer atlas [36], and the NIH Roadmap Epigenomics Mapping Consortium [37]. Genome browser tracks are available for all functional genomics datasets and are organized by data source, biotype (e.g., cell, tissue, or cell line), type of functional annotation (e.g., expressed enhancers, transcription factor binding sites, histone modifications) and platform or assay type to facilitate track selection.

2.5 Overview of database design

An overview of the NIAGADS GenomicsDB systems architecture is provided in **Figure 1**. The GenomicsDB is powered by a PostgreSQL relational database system that has been optimized for parallel big data querying, allowing for efficient real-time data mining. Data are organized using the modular Genomics Unified Schema version 4 (GUS4), designed for scalable integration and dissemination of large-scale 'omics datasets. Loading of all data is managed by the GUS4 application layer (https://github.com/VEuPathDB/GusAppFramework), which ensures the accuracy of data integration.

2.6 Overview of website design and organization

The NIAGADS GenomicsDB is powered by an open-source database system and web-development kit (WDK; https://github.com/VEuPathDB/WDK) developed and successfully deployed by the Eukaryotic Pathogen, Vector and Host Informatics (VEuPathDB) Bioinformatics Resource Center [38,39]. The VEuPathDB WDK provides a query engine that ties the database system to the website via an easily extensible XML data model. The data model is used to automatically generate and organize searches, search results, and reports, with concepts and data organized by topics from the EMBRACE Data And Methods (EDAM) ontology, which defines a comprehensive set of concepts that are prevalent within bioinformatics [40]. This facilitates updates of third-party data and rapid integration of new datasets as they become publicly available.

The WDK also provides a framework for lightweight Java/Jersey representational state transfer (REST) services for data querying. This allows search results and reports to be returned in multiple file formats (e.g., delimited-text, XML, and JSON) in addition to browsable, interactive web pages. This new feature of GenomicsDB has enabled the inclusion of sophisticated visualizations for summarizing search results and annotations in gene and variant reports. API development is still undergoing, with plans to develop a flexible API that allows researchers to integrate GenomicsDB datasets and annotations into analysis pipelines. The GenomicsDB uses a combination of an in-house JavaScript genomics visualization toolkit and established third-party visualization tools, including the *HighCharts.js* (https://www.highcharts.com/) charting library for rendering scatter, pie, and bar charts, *ideogram.js* (https://github.com/eweitz/ideogram) for chromosome visualization, *LocusZoom.js* for rendering LD structure in the context of NIAGADS GWAS summary statistics datasets, and an *IGV.js* powered genome browser [41].

All code used to generate the WDK website, including the JavaScript genomics visualizations are available on GitHub (https://github.com/NIAGADS).

2.7 Overview of the NIAGADS genome browser

The NIAGADS genome browser enables researchers to visually inspect and browse GWAS summary statistics datasets in a genomic context. The genome browser allows users to compare NIAGADS GWAS summary statistics tracks to each other, against annotated gene or variant tracks, or to the functional genomics tracks from the NIAGADS FILER functional genomics repository. This tool is powered by *IGV.js*, with track data queried in real-time by NIAGADS GenomicsDB REST services. The browser also provides a track selection tool that allows users to easily find tracks of interest by keyword search, data source, biotype (e.g., cell, tissue, or cell line) or type of functional annotation (**Fig. 2**).

3. Results

The NIAGADS Alzheimer's GenomicsDB creates a public forum for sharing, discovery, and analysis of genetic evidence for Alzheimer's disease that is made accessible via an interface designed for easy mastery by biological researchers, regardless of background. The GenomicsDB provides four main routes for data exploration and mining. First, detailed reports compile all available data concerning summary statistics datasets and genetic evidence linking AD/ADRD to genes and variants. Second, datasets can be mined in real-time to isolate a refined set of variants that share biological characteristics of interest. Third, visualization tools such as *LocusZoom.js* and the NIAGADS Genome Browser offer the ability to quickly view and draw conclusions from comparisons of summary statistics or ADSP annotated variants to different types of sequence data in a genomic area of interest. Fourth, and finally, tools such as enrichment analyses offer opportunities for users to link variants to biological processes via impacted genes.

3.1 Finding variants, genes, and datasets

The GenomicsDB homepage and navigation menu contain a site search allowing users to quickly find variants, genes, and datasets of interest by identifier or keyword. This search is paired with interactive graphics found throughout the site that provide shortcuts to resources and annotations of interest to the AD/ADRD research community (**Fig. 3A, B**). The GenomicsDB also provides a dataset browser that allows users to search for GWAS summary statistics datasets by AD/ADRD phenotype, population, genotype, attribution, and sequencing center.

3.2 Browsing and mining NIAGADS GWAS summary statistics

A detailed report is provided for each of the GWAS summary statistics and ADSP meta-analysis datasets in the NIAGADS GenomicsDB (**Fig. 4A**). These reports allow users to browse the genetic variants with genome-wide significance in the dataset (p-value $\leq 5 \times 10^{-8}$ to account for false positives due to testing associations of millions of variants simultaneously) via tables and interactive plots that provide an overview of the distribution and potential functional or regulatory impacts of the top variants (and proximal gene-loci) across the genome. All genes and variants listed in a dataset report are linked to reports in the GenomicsDB that provide detailed information about genetic evidence for AD for the sequence feature (see next sections). Dataset reports also provide quick links back to their parent accession in the NIAGADS repository where users can download the complete p-values or make formal data access requests for the full summary statistics, related GWAS, expression, or sequencing data associated with the accession. The reports also provide an inline search allowing users to mine the summary statistics in real-time via the website, setting their own p-value cut-off (see section 3.5 for more information).

3.3 Detailed variant reports

Variant reports include a basic summary about the variant (alleles, variant type, flanking sequence, genomic location) and a graphical overview of NIAGADS GWAS summary statistics datasets in which the variant has genome-wide significance (**Fig. 5A**). All other information in

the report is subdivided into multiple sections that can be expanded or hidden at the user's discretion. These sections include sub-reports on genetic variation (e.g., allele population frequencies and LD), function prediction determined via the ADSP annotation pipeline (incl. transcript and regulatory consequences), and comprehensive listings of GWAS inferred disease or trait associations from both NIAGADS summary statistics and the NHGRI-EBI GWAS Catalog. Tables listing summary statistics results can be dynamically filtered by *p*-value, dataset, phenotypes, or covariates, and the filtered results are downloadable. Links to the source datasets for each reported statistic are also provided, leading to detailed dataset reports (e.g., NIAGADS GWAS summary statistics) or to the source publication (e.g., curated variant catalogs). These tables are paired with browsable *LocusZoom.js* views of the LD structure surrounding the variant in the context of selected GWAS summary statistics datasets. Links to the NIAGADS Alzheimer's Disease Variant Portal (ADVP) and external resources for additional information (e.g., dbSNP, ClinVar) are also provided.

3.4 Detailed gene reports

Like the variant reports, gene reports provide basic summary information about the gene (nomenclature, gene type, genomic span) and a graphical overview of NIAGADS GWAS summary statistics-linked variants proximal to or within the footprint of the gene (**Fig.5B**). Two types of gene-linked genetic evidence for AD are provided in the GenomicsDB gene reports. First, we have surveyed the top risk-associated variants from the NIAGADS GWAS summary statistics datasets and provide a comprehensive listing of and links to those contained within ±100kb of each gene (**Fig. 5C**). Second, we report meta-analysis results from gene-based rare variant aggregation tests performed as part of the ADSP discovery phase case/control analysis [42]. Genes found to have a significant *p*-value in these results are flagged as being associated with genetic-evidence for AD. Also provided on the gene report are sections reporting function prediction (Gene Ontology associations and evidence) and pathway membership (KEGG and Reactome). Tables reporting these results or annotations can be dynamically filtered or downloaded. Links to the NIAGADS ADVP and to external resources (e.g., UniprotKB, OMIM, and ExAC) are also provided.

3.5 Workspaces

The GenomicsDB provides an interactive workspace for exploring a dataset in more depth. As an example, dataset reports provide an inline search allowing users to mine the summary statistics. Variants meeting the search criterion are reported in an interactive workspace that includes both tabular and graphical summaries. Users are initially presented with a table that can be sorted or filtered by annotations (e.g., variant type, predicted effect, deleteriousness) (**Fig. 4B**). A per-chromosome genome view is also available allowing users to explore an interactive ideogram depicting the distribution of variants meeting the search and filter criteria across the genome and allowing inspection of LD structure among proximal variants (**Fig. 4C**).

Tables of results can be downloaded or requested via the API for programmatic processing. Registered users also have the option to save and share search results both privately and

publicly; publicly shared search results are assigned a stable URL that can be referenced in publications.

3.6 Genome Browser

The NIAGADS genome browser can be used to visually inspect any of the NIAGADS GWAS summary statistics datasets in a broader genomic context and compare against annotated ADSP variant tracks or other 'omics tracks in the GenomicsDB or FILER (see section 2.7, **Fig. 2B**).

4 Discussion

The NIAGADS Alzheimer's Genomics Database is a user-friendly platform for interactive browsing and real-time in-depth mining of published genetic evidence and genetic risk-factors for AD. It provides open, real-time access to summary statistics datasets from genome-wide association analysis (GWAS) of Alzheimer's disease and related neuropathologies.
Flexible search options allow users to easily retrieve AD risk-associated variants, conditioned on phenotypes such as ethnicity and age of onset. Users can compare the NIAGADS datasets against personal gene or variant lists.

Every entry in the GenomicsDB has been linked with relevant external resources and functional genomics annotations to supply further information and assist researchers in interpreting the potential functional or regulatory role of risk-associated variants and susceptibility loci. The GenomicsDB is updated periodically with enhanced features and new datasets and annotations when they are reported. The AD research community is actively encouraged through outreach and collaboration to submit data to NIAGADS to keep this public platform updated and timely.

The GenomicsDB is integrated with other resources available at NIAGADS. Users can follow links back to the NIAGADS repository to view comprehensive details about all GWAS summary statistics datasets from NIAGADS accession or request access to the primary data. The REST services used to query the database and generate data or feature reports provide the foundation of an API that allows programmatic access to the database, which we plan to integrate with cloud based NIAGADS analysis pipelines.

The GenomicsDB is regularly updated to keep up with advances in Alzheimer's disease genomics research. New AD-related GWAS summary statistics datasets and meta-analysis results from the ADSP are added as they become available. Reference databases are updated yearly. All genomics data in the current version of the GenomicsDB are aligned and mapped to the GRCh37.p13 genome build. A GRCh38 version of the database is planned for release in early 2021, which will include variants from the ongoing ADSP sequencing effort, including 20K WES in 2020 and 17K WGS in 2021.

GenomicsDB is a potent platform for the AD genetics community to host comprehensive AD genetic and genomic findings. It uses the latest web and database technologies to allow integration with new tools, and NIAGADS is constantly improving. As more data and tools

become available the NIAGADS Alzheimer's Genomics Database will become a central hub for AD/ADRD research and data analysis.

5 Conflicts of Interest

The authors have no financial interests to disclose.

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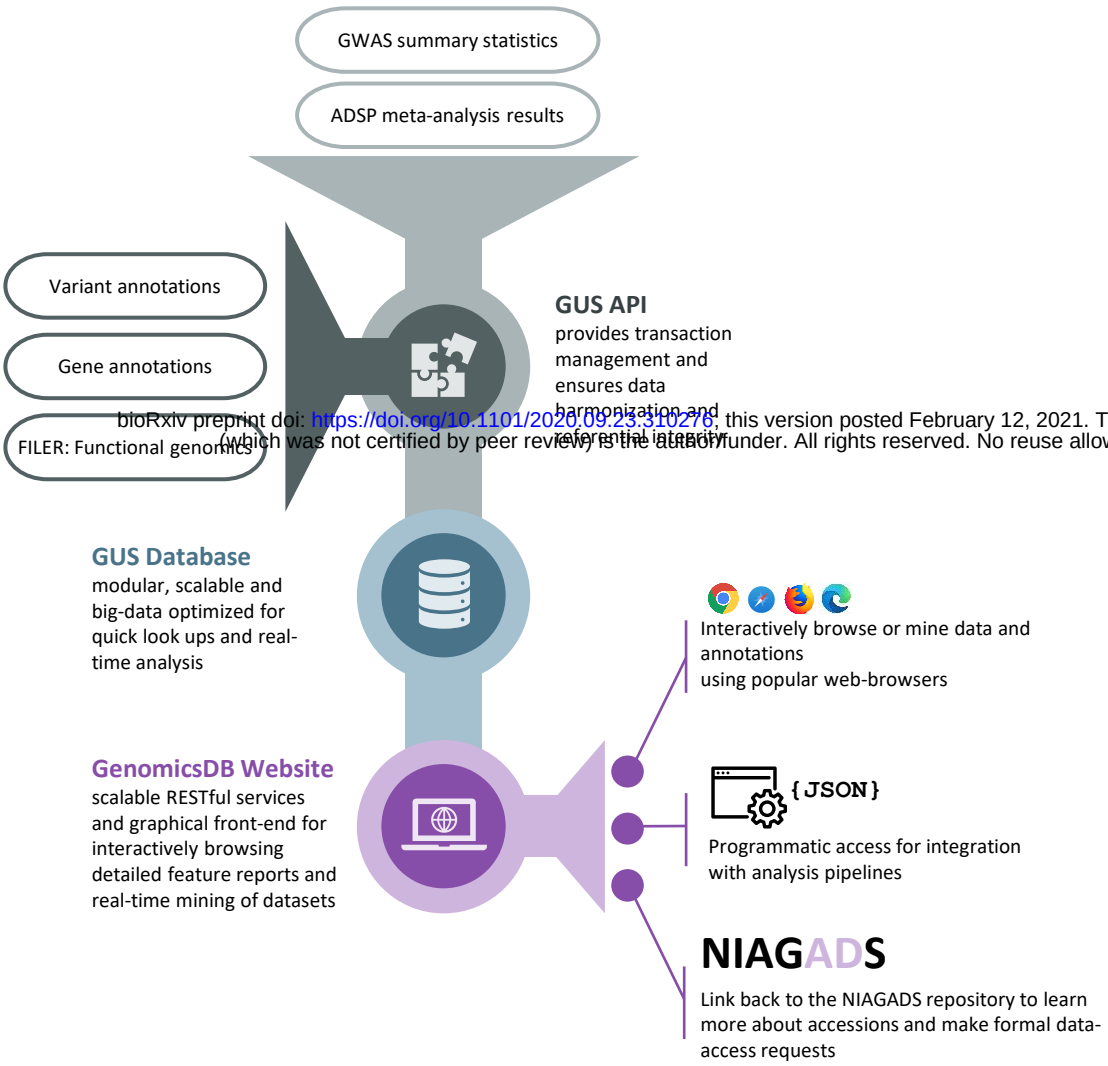
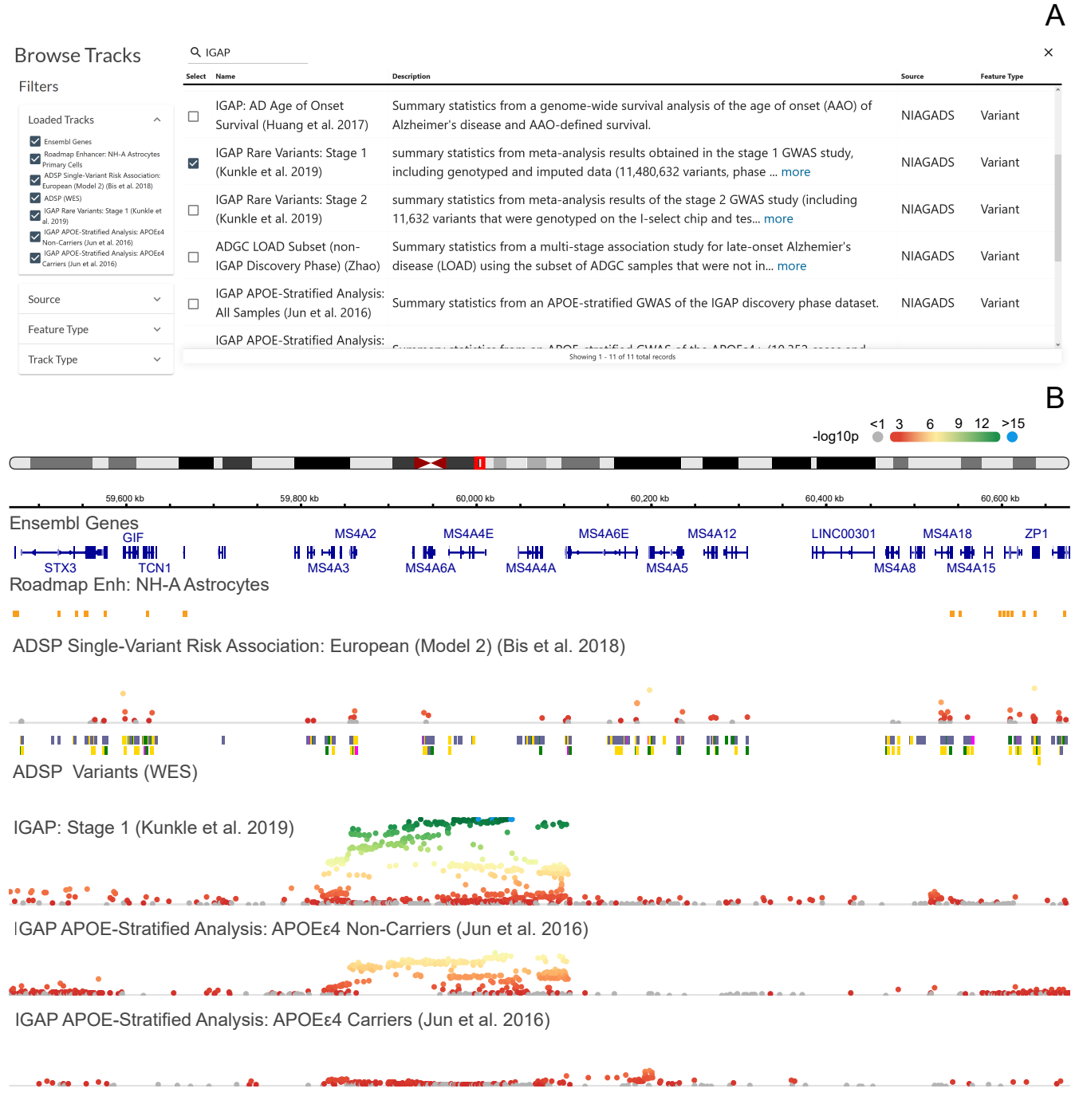
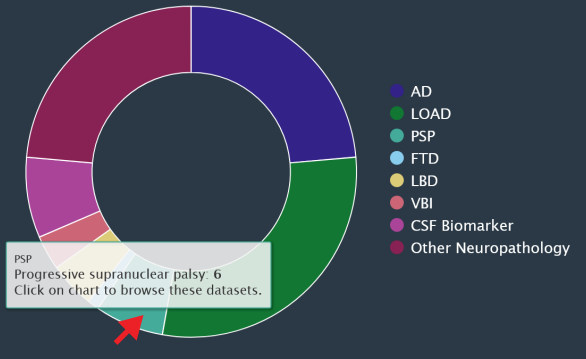



A
Browse Tracks
IGAP
Filters
Loaded Tracks
Ensembl Genes
Roadmap Enhancer: NH-A Astrocytes Primary Cells
ADSP Single-Variant Risk Association: European (Model 2) (Bis et al. 2018)
ADSP (WES)
IGAP Rare Variants: Stage 1 (Kunkle et al. 2019)
IGAP APOE-Stratified Analysis: APOEε4 Non-Carriers (Jun et al. 2016)
IGAP APOE-Stratified Analysis: APOEε4 Carriers (Jun et al. 2016)
Source
Feature Type
Track Type
Select
Name
Description
Source
Feature Type
IGAP: AD Age of Onset Survival (Huang et al. 2017)
Summary statistics from a genome-wide survival analysis of the age of onset (AAO) of Alzheimer's disease and AAO-defined survival.
NIAGADS
Variant
IGAP Rare Variants: Stage 1 (Kunkle et al. 2019)
summary statistics from meta-analysis results obtained in the stage 1 GWAS study, including genotyped and imputed data (11,480,632 variants, phase ... more
NIAGADS
Variant
IGAP Rare Variants: Stage 2 (Kunkle et al. 2019)
summary statistics from meta-analysis results of the stage 2 GWAS study (including 11,632 variants that were genotyped on the I-select chip and tes... more
NIAGADS
Variant
ADGC LOAD Subset (non-IGAP Discovery Phase) (Zhao)
Summary statistics from a multi-stage association study for late-onset Alzhemier's disease (LOAD) using the subset of ADGC samples that were not in... more
NIAGADS
Variant
IGAP APOE-Stratified Analysis: All Samples (Jun et al. 2016)
Summary statistics from an APOE-stratified GWAS of the IGAP discovery phase dataset.
NIAGADS
Variant
IGAP APOE-Stratified Analysis:
Showing 1 - 11 of 11 total records
B
-log10p
<1 3 6 9 12 >15
59,600 kb
59,800 kb
60,000 kb
60,200 kb
60,400 kb
60,600 kb
Ensembl Genes
GIF
STX3
TCN1
MS4A2
MS4A3
MS4A4E
MS4A6A
MS4A6E
MS4A4A
MS4A12
MS4A5
LINC00301
MS4A8
MS4A18
MS4A15
ZP1
Roadmap Enh: NH-A Astrocytes
ADSP Single-Variant Risk Association: European (Model 2) (Bis et al. 2018)
ADSP Variants (WES)
IGAP: Stage 1 (Kunkle et al. 2019)
IGAP APOE-Stratified Analysis: APOEε4 Non-Carriers (Jun et al. 2016)
IGAP APOE-Stratified Analysis: APOEε4 Carriers (Jun et al. 2016)

A

NIAGADS
Alzheimer's Genomics Database

An interactive knowledgebase for Alzheimer's disease (AD) genetics that provides a platform for data sharing, discovery, and analysis to help advance the understanding of the complex genetic underpinnings of AD neurodegeneration and accelerate the progress of research on AD and AD related dementias (ADRD).



PSP

NG00040: Multi-ethnic exome array: AD, FTP, and PSP (Chen et al. 2015) *...xome array: AD, FTP, and PSP*

NG00045: Progressive Supranuclear Palsy (PSP) (Hoglinger et al. 2011) *...sive Supranuclear Palsy (PSP)*

FDPSP1 *FDPSP1*

FDPSP2 *FDPSP2*

FDPSP3 *FDPSP3*

...and 23 more *click to view full results*

Search Results

28 results were found for the search **PSP**

20 Genes

2 NIAGADS Accessions

6 Summary Statistics Datasets

Genes

FDPSP1

Gene // pseudogene // farnesyl diphosphate synthase pseudogene 1 // Also Known As: CHR39A, FPSL1, FDPSL1 // Location: 1q31.1

FDPSP2

Gene // pseudogene // farnesyl diphosphate synthase pseudogene 2 // Also Known As: FPSL2, FDPSL2, FDPSL2A, TCAG_1641456 // Location: 7q11.23

B

6 Datasets Revise this search

Summary Statistics Dataset Report Results

Rows per page: 20

Download | Add Columns

Dataset	Name	Attribution	Description	Accession	Mine Dataset
Multi-ethnic exome array: PSP	Multi-ethnic exome array: PSP	Chen et al. 2015	a multi-ethnic exome array study to identify low-frequency coding variants that affect susceptibi...	NG00040	View top variants
PSP Europeans: Stage 1	PSP Europeans: Stage 1	Hoglinger et al. 2011	summary statistics from stage 1 (autopsy cases) of a GWAS study of Progressive Supranuclear Palsy...	NG00045	View top variants
PSP Europeans: Stage 2	PSP Europeans: Stage 2	Hoglinger et al. 2011	summary statistics from stage 2 (majority clinically diagnosed) of a GWAS study of Progressive Su...	NG00045	View top variants
PSP Europeans: Stages 1 and 2	PSP Europeans: Stages 1 and 2	Hoglinger et al. 2011	summary statistics from combined stage 1 (autopsy cases) and stage 2 (clinically diagnosed cases)...	NG00045	View top variants
PSP: Stage 1	PSP: Stage 1	Hoglinger et al. 2011	summary statistics from stage 1 (autopsy cases) of a GWAS study of Progressive Supranuclear Palsy...	NG00045	View top variants
PSP: Stages 1 and 2	PSP: Stages 1 and 2	Hoglinger et al. 2011	summary statistics from the combined stage 1 (autopsy cases) and stage 2 (clinically diagnosed ca...	NG00045	View top variants

A

Add to favorites | Download Summary Statistics Dataset Report

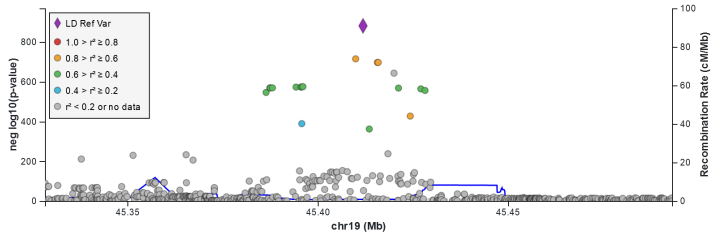
IGAP Rare Variants: Stage 1 (Kunkle et al. 2019)

summary statistics from meta-analysis results obtained in the stage 1 GWAS study, including genotyped and imputed data (11,480,632 variants, phase 1 integrated release 3, March 2012) of 21,982 Alzheimer's disease cases and 41,944 cognitively normal controls. The meta-analysis examined SNPs genotyped or imputed in at least 30% of the AD cases and 30% of the control samples across all datasets.

Category: Summary Statistics Dataset Report
Explore related datasets: NG00075

Top Hits

APOE
APOC1
TOMM40
rs6733839
rs4663105
rs11680911
CLU
rs1582763
CR1
rs201153362



Mine this dataset

1

p-value ≤ 5e-8 Search

B

1,514 Variants Revise this search

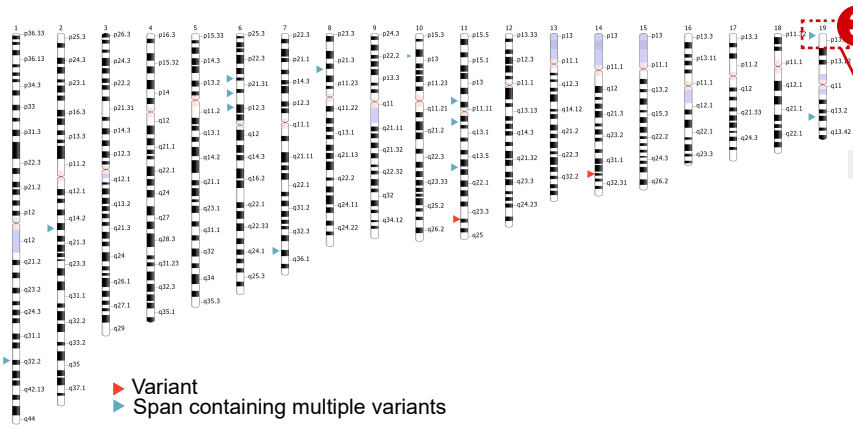
Variant Results | Genome View 2

1 2 3 ... 76 Rows per page: 20

Download Add to Basket Add Columns

Variant	p-value	ADSP Variant?	RefSNP ID	Variant Class	Allele	Consequence	Impacted Gene	Consequence Impact	Coding?
19:45420082:A:C	7.04e-643	✔	rs73052335	SNV	A>C	intron_variant	APOC1	MODIFIER	N/A
19:45396144:C:T	6.15e-575	✔	rs11556505	SNV	C>T	synonymous_variant	TOMM40	LOW	✔Coding
19:45395909:C:G	3.34e-574	✔	rs34404554	SNV	C>G	intron_variant	TOMM40	MODIFIER	N/A
19:45394336:T:C	2.25e-573	✔	rs71352238	SNV	T>C	intron_variant	TOMM40	MODIFIER	N/A
19:45395619:A:G	6.64e-573	✔	rs2075650	SNV	A>G	intron_variant	TOMM40	MODIFIER	N/A
19:45387459:C:G	9.86e-569	✔	rs12972156	SNV	C>G	intron_variant	PVRL2	MODIFIER	N/A
19:45387596:G:A	9.33e-569	✔	rs12972970	SNV	G>A	intron_variant	PVRL2	MODIFIER	N/A
19:45388130:G:A	5.73e-569	✔	rs34342646	SNV	G>A	intron_variant	PVRL2	MODIFIER	N/A
19:45421254:G:A	2.37e-568	✔	rs12721046	SNV	G>A	intron_variant	APOC1	MODIFIER	N/A
19:45427125:T:A	4.13e-564	✔	rs111789331	SNV	T>A	upstream_gene_variant	APOC1P1	MODIFIER	N/A
19:45428234:G:A	4.27e-556	✔	rs66626994	SNV	G>A	upstream_gene_variant	APOC1P1	MODIFIER	N/A
19:45386467:G:GTAA	9.70e-546	N/A	rs142042446	INS	insTAA	intron_variant	PVRL2	MODIFIER	N/A

C



basket favorites Variant

19:45411941:T:C

rs429358

Has this variant been flagged by the ADSP? ✔ Yes

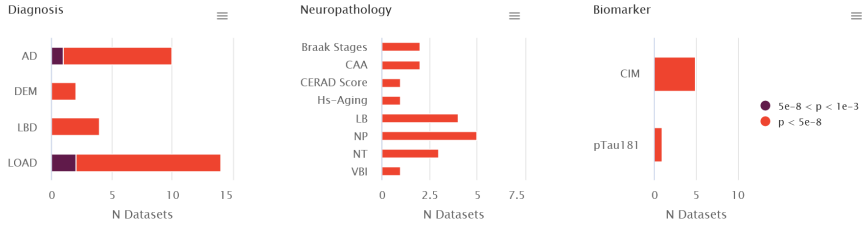
WES PASS: pass in both GATK and ATLAS

WGS PASS: present in both, passed in GATK, failed in ATLAS

Consequence: missense_variant ✔Coding
Impact: MODERATE
Amino Acid Change: C/R
Codon Change: Tgc/Cgc
Impacted Gene: APOE
Impacted Transcript: ENST00000252486

Summary of AD/ADRD associations for this variant: Browse the association evidence ↴

A



Show Contents

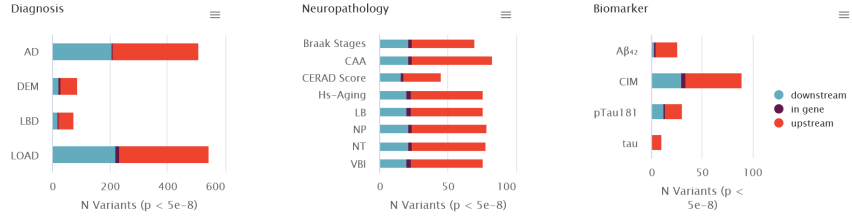
Add to basket Add to favorites Download Gene

APOE - ENSG00000130203

apolipoprotein E
Also known as: AD2
Gene Type: protein coding
Location: chr19:45409011-45412650:+ / 19q13.32

Summary of AD/ADRD associations for this variants proximal to APOE: Browse the association evidence ↴

B

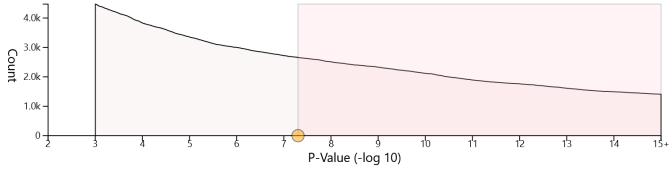


1.1 NIAGADS GWAS

C

Alzheimer's Disease

Download Search table



Current p-value: 5e-8
New p-value: 5e-8
Update
Close P-value Filter

Relative Position	Variant	RefSNP ID	ADSP?	Test/Minor Allele	p-value	Track	Accession
in gene	19:45411941:T:C		✔	T	1.17e-881	IGAP Rare Variants: Stage 1	NG00075
in gene	19:45410002:G:A		✔	A	7.52e-715	IGAP Rare Variants: Stage 1	NG00075
downstream	19:45415713:G:A		✔	A	1.74e-697	IGAP Rare Variants: Stage 1	NG00075
downstream	19:45415935:G:T		✔	T	7.52e-697	IGAP Rare Variants: Stage 1	NG00075
downstream	19:45420082:A:C		✔	A	7.04e-643	IGAP Rare Variants: Stage 1	NG00075
upstream	19:45392254:C:T		✔	T	2.50e-575	IGAP: Stage 1	NG00036
upstream	19:45396144:C:T		✔	T	6.15e-575	IGAP Rare Variants: Stage 1	NG00075
upstream	19:45395909:C:G		✔	C	3.34e-574	IGAP Rare Variants: Stage 1	NG00075
upstream	19:45394336:T:C		✔	T	2.25e-573	IGAP Rare Variants: Stage 1	NG00075
upstream	19:45395619:A:G		✔	A	6.64e-573	IGAP Rare Variants: Stage 1	NG00075