AlzGPS: A Genome-wide Positioning Systems Platform to Catalyze Multi-omics for Alzheimer's Therapeutic Discovery

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Abstract

Background: Over 15 million family members and caregivers have expended $220 billion for care of patients with AD and other dementias, and the attrition rate for AD clinical trials (2002-2012) is estimated at 99.6%. While recent DNA/RNA sequencing and other multi-omics technologies have advanced the understanding of the biology and pathophysiology of AD, no effective disease-modifying or preventive therapies, for AD have emerged in the past two decades. A new approach to integration of the genome, transcriptome, proteome, and human interactome in the drug discovery and development process is essential for this endeavor.

Methods: In this study, we developed AlzGPS (Genome-wide Positioning Systems platform for Alzheimer's Therapeutic Discovery, https://alzgps.lerner.ccf.org), a comprehensive systems biology tool to enable searching, visualizing, and analyzing multi-omics, various types of heterogeneous biological networks, and clinical databases for target identification and effective prevention and treatment of AD.

Results: Via AlzGPS: (1) we curated more than 100 AD multi-omics data sets capturing DNA, RNA, protein, and small molecules’ profiles underlying AD pathogenesis (e.g., early vs. late stage and tau vs. amyloid endophenotype); (2) we constructed endophenotype disease modules by incorporating multi-omics findings and human protein-protein interactome networks; (3) we identified repurposable drugs from ~3,000 FDA approved/investigational drugs for AD using state-of-the-art network proximity analyses; (4) we curated 300 literature references for highly repurposable drugs; (5) we included information from over 200 ongoing AD clinicals noting drug mechanisms and primary drug targets, and linking them to our integrated multi-omics view for targets and
network analyses results for the drugs; (6) we implemented a highly interactive web-
interface for database browsing and network visualization.

**Conclusions:** Network visualization enabled by the AlzGPS includes brain-specific
neighborhood networks for genes-of-interest, endophenotype disease module networks
for data sets-of-interest, and mechanism-of-action networks for drugs targeting disease
modules. By virtue of combining systems pharmacology and network-based integrative
analysis of multi-omics data, the AlzGPS offers actionable systems biology tools for
accelerating therapeutic development in AD.

**Keywords:** Alzheimer’s disease, network medicine, database, drug repurposing, clinical
trial, transcriptomics

**Background**
Alzheimer’s disease (AD) is a progressive neurodegenerative disorder accounting for
60-80% of dementia cases (1). In addition to cognitive decline, AD patients have
extensive neuropathological changes including deposition of extracellular amyloid
plaques, intracellular neurofibrillary tangles, and neuronal death (2, 3). It is estimated
that the number of AD patients will reach 16 million by 2050 in the United States alone
(4, 5). Effective treatments are needed, as there are no disease-modifying treatments
for AD and no new drugs have been approved since 2003 by the US Food and Drug
Administration (FDA). There are several possible explanations for the high failure rate in
AD drug discovery. For example, transgenic rodent models used to test drugs may not
fully represent human AD pathobiology (6). Also, there is a lack of sensitive measures for outcomes in clinical trials. Other potential immediate causes for clinical trial failures include targeting the wrong pathobiological or pathophysiological mechanisms, attempted intervention at the wrong stage (too early or too late), unfavorable pharmacodynamic and pharmacokinetic characteristics of the drug (e.g., poor brain penetration), lack of target engagement by drug candidates, and hypothesis that fail to incorporate the great complexity of AD (6, 7).

Multiple types of omics data have greatly facilitated our understanding of the pathobiology of AD. For example, using single-cell RNA-seq, a novel microglia type (termed disease-associated microglia, DAM) was discovered to be associated with AD, understanding of whose molecular mechanism could offer new therapeutic targets (8). Using large-scale genome-wide association studies (GWAS), twenty loci showed genome-wide significant association with Alzheimer's disease, among which 11 were newly discovered (9). A recent study using deep profiling of proteome and phosphoproteome prioritized proteins and pathways associated with AD, and it was shown that protein changes and their corresponding RNA levels only partially coincide (10). The large amount of multi-omics data and recent advances in network-based methodologies for drug repurposing today present unprecedented opportunities for accelerating target identification for drug discovery for AD, and this potential has also been demonstrated in other complex diseases as well, such as cancer (11), cardiovascular disease (12), and schizophrenia (13), and are beginning to be exploited in AD (6, 14). Drug repurposing offers a rapid and cost-effective solution for drug discovery for complex disease, such as the current global pandemic of coronavirus.
disease 2019 (COVID-19) (15, 16) and AD (6). The central idea of network-based drug repurposing is that for a drug to be able to affect a disease, the drug targets must directly overlap with or be in the immediate vicinity of the disease modules, which can be identified using the vast amount of high-throughput sequencing data (Figure 1A). Our recent efforts using network-based methodologies and AD omics data have led to the discovery of two drugs that show efficacy in network models in AD: sildenafil and pioglitazone (14). Network analysis provides potential mechanisms for these drugs and facilitates experimental validation. Therefore, we believe posit that a comprehensive systems biology tool in the framework of network-based multi-omics analysis could inform Alzheimer's patient care and therapeutic development.

To this end, we present a new freely-available database and tool, named AlzGPS (A Genome-wide Positioning Systems platform for Alzheimer's Therapeutic Discovery), for target identification and drug repurposing for AD. AlzGPS was built with large scale diverse information, including multi-omics (genomics, (bulk and single cell) transcriptomics, proteomics, and interactomics) of human and other species, drug-target network, literature-derived evidence, AD clinical trials information, and network proximity analysis (Figure 1B). Our hope is that AlzGPS will be a valuable resource for the AD research community for several reasons. First, AlzGPS contains abundant multi-domain information types all coalesced in one location. The manually curated data, such as the literature-derived information for the most promising repurposable drugs and more than 100 multi-omics AD data sets, are of high quality and relevance. Second, using state-of-the-art network proximity approaches, AlzGPS provides a systemic evaluation of 3000 FDA approved or investigational drugs against the AD data sets. These results (along
with various network visualizations) will provide insights for potential repurposable drugs with clear network-based footprints in the context of the human protein interactome. The drug-data set associations can be further explored in AlzGPS for individual drug targets or genes associated with AD. Lastly, AlzGPS offers a highly interactive and intuitive modern web interface. The relational nature of these data was embedded in the design to help the user easily navigate through different types of information. In addition, AlzGPS provides three types of network visualizations for the tens of thousands of networks in the database, including brain-specific neighbor networks for genes, disease modules for data sets, and inferred mechanism-of-action (MOA) networks for drugs and data set pairs with significant proximity. AlzGPS is freely available to the public without registration requirement at https://alzgps.lerner.ccf.org.

Methods

Data collection and preprocessing

**AD data sets.** A data set is defined as either (1) genes/proteins/metabolites that are differentially expressed in AD patients/mice versus controls; or (2) genes that have known associations with risks of AD from literature or other databases. We retrieved expression data sets underlying AD pathogenesis capturing transcriptomics (microarray, bulk or single-cell RNA-Seq) and proteomics across human, mouse, and model organisms (e.g. fruit fly and *C. elegans*). All the samples of the data sets were derived from total brain, specific brain regions (including hippocampus, cortex, and cerebellum), and brain-derived single cells, such as microglial cells. For some of the expression data
sets, the differentially expressed genes/proteins were obtained from the original publications (from main tables or supplemental tables). For other data sets that did not have such differential expression results available, the original brain microarray/RNA-Seq data were obtained from Gene Expression Omnibus (GEO) (17) and differential expression analysis was performed using the tool GEO2R (18). GEO2R performs the differential expression analysis for the sample groups defined by the user using the limma R package (19). All differentially expressed genes identified in mouse were further mapped to unique human-orthologous genes using the NCBI HomoloGene database (https://www.ncbi.nlm.nih.gov/homologene). The details for all the data sets, including organism, genetic model (for mouse), brain region, cell type (for single-cell RNA-Seq), PubMed ID, GEO ID, and the sources (e.g., supplemental table or GEO2R), etc., can be found in Table S1.

Genes and Proteins. We retrieved the gene information from the HUGO Gene Nomenclature Committee (HGNC, https://www.genenames.org/) (20), including gene symbol, name, type (e.g., coding and non-coding), chromosome, synonyms, and identification (ID) mapping in various other databases such as National Center for Biotechnology Information (NCBI) Gene, ENSEMBL, and UniProt. All proteins from the AD proteomics data sets were mapped to genes using the mapping information from HGNC.

Single-nucleotide polymorphisms (SNPs). We found 3,321 AD-associated genetic records for 1,268 genes mapped to 1,629 SNPs, by combining results from GWAS Catalog (https://www.ebi.ac.uk/gwas/) (21) using the trait “Alzheimer's disease” and published studies. The PubMed IDs for the genetic evidence are provided on AlzGPS.
**Tissue expression specificity.** We downloaded RNA-Seq data (Reads Per Kilobase Million [RPKM] value) of 32 tissues from GTEx V6 release (accessed on April 01, 2016, https://gtexportal.org/home/). We defined the genes with RPKM≥1 in over 80% of samples as tissue-expressed genes and the other genes as tissue-unexpressed. To quantify the expression significance of tissue-expressed gene i in tissue t, we calculated the average expression \( \langle E(i) \rangle \) and the standard deviation \( \delta_E(i) \) of a gene’s expression across all included tissues. The significance of gene expression in tissue t is defined as

\[
z_E(i, t) = \frac{E(i, t) - \langle E(i) \rangle}{\delta_E(i)}
\]

**Drugs.** We retrieved drug information from the DrugBank database (v4.3) (22), including name, type, group (approved, investigational, etc.), Simplified Molecular-Input Line Entry System (SMILES) and Anatomical Therapeutic Chemical (ATC) code(s). We also evaluated the pharmacokinetic properties (such as blood–brain barrier [BBB] penetration) of the drugs using admetSAR (23, 24).

**Drug literature information for AD treatment.** For the top 300 repurposable drugs (i.e., drugs with the highest number of significant proximities to the AD data sets), we manually searched and curated the literature for their therapeutic efficacy against AD using PubMed. In addition to the title, journal, and PubMed ID, we summarized the types (clinical and non-clinical), experimental settings (e.g., mouse/human and transgenic line for non-clinical studies; patient groups, randomization type, length, and control type of clinical studies), and results of these studies. In total, we found 292 studies for 147 drugs.
**Drug-target network.** To build a high-quality drug-target network, several databases were accessed, including the DrugBank database (v4.3) (22), Therapeutic Target Database (TTD) (25), PharmGKB database, ChEMBL (v20) (26), BindingDB (27), and IUPHAR/BPS Guide to PHARMACOLOGY (28). Only biophysical drug-target interactions involving human proteins were included. To ensure data quality, we kept only interactions that have inhibition constant/potency \((K_i)\), dissociation constant \((K_d)\), median effective concentration \((EC_{50})\), or median inhibitory concentration \((IC_{50})\) ≤ 10 µM. The final drug-target network contains 21,965 interactions among 2,892 drugs and 2,847 human genes.

**Clinical trials.** The AD intervention clinical trials were retrieved from Cummings et al. 2018 (29) & 2019 (30). Information including phase, posted date, status, and agent(s) was obtained from https://clinicaltrials.gov. Drugs were mapped to the DrugBank IDs. Proposed mechanism and therapeutic purpose were from Cummings et al. 2018 (29) & 2019 (30).

**Human protein interactome.** We used our previously built high-quality comprehensive human protein interactome which contains 351,444 unique protein-protein interactions (PPIs, edges) among 17,706 proteins (nodes) (11, 12, 31, 32). Briefly, five types of evidence were considered for building the interactome: physical PPIs from protein three-dimensional (3D) structures, binary PPIs revealed by high-throughput yeast-two-hybrid (Y2H) systems, kinase-substrate interactions by literature-derived low-throughput or high-throughput experiments, signaling networks by literature-derived low-throughput experiments, and literature-curated PPIs identified by affinity purification followed by
mass spectrometry (AP-MS), Y2H, or by literature-derived low-throughput experiments. No inferred PPIs were included.

**Network proximity quantification of drugs and AD data sets**

To quantify the associations between drugs and AD-related gene sets from the data sets, we adopted the “closest” network proximity measure:

\[ \langle d_{AB} \rangle = \frac{1}{|A| + |B|} \left( \sum_{a \in A} \min_{b \in B} d(a, b) + \sum_{b \in B} \min_{a \in A} d(a, b) \right) \]  \hspace{1cm} (2)

where \(d(a, b)\) is the shortest path length between gene \(a\) and \(b\) from gene list \(A\) (drug targets) and \(B\) (AD genes), respectively. To evaluate whether such proximity was significant, we performed z score normalization using a permutation test of 1,000 repeats. In each repeat, two randomly generated gene lists that have similar degree distributions to \(A\) and \(B\) were measure for the proximity. The z score was calculated as:

\[ z_d = \frac{d - \bar{d}}{\sigma_d} \]  \hspace{1cm} (3)

P value was calculated according the permutation test. Drug-data set pairs with \(Z < -1.5\) and \(P < 0.05\) were considered significantly proximal. In addition to network proximity, we calculated two additional metrics, overlap coefficient \(C\) and Jaccard index \(J\), to quantify the overlap and similarity of \(A\) and \(B\):

\[ C = \frac{|A \cap B|}{\min(|A|, |B|)} \]  \hspace{1cm} (4)

\[ J = \frac{|A \cap B|}{|A \cup B|} \]  \hspace{1cm} (5)
**Generation of networks**

We offer three types of networks on AlzGPS: brain-specific neighborhood (EGO) network for the genes, largest connected component (LCC) network for the data sets, and inferred MOA network for significantly proximal drug-data set pairs. The three networks differ by inclusion criteria of the nodes (genes/proteins). The edges are PPIs colored by their types (e.g., 3D, Y2H, and literature). All networks are colored by whether they can be targeted by the drugs in our database.

For the EGO networks, we filtered genes by their brain expression specificity and generated only the network for those with positive brain specificity. We used the `ego_graph` function from NetworkX (33) to generate the EGO networks. The networks are centered around the genes-of-interest. An LCC network was generated for each AD data set using the `subgraph` function from networkx. For MOA, we examined the connections (PPIs) among the drug targets and the data sets.

**Website implementation**

AlzGPS was implemented with the Django v2.2.2 framework (www.djangoproject.com). The website frontend was implemented with HTML, CSS, and JavaScript. The frontend was designed to be highly interactive and integrative. It uses AJAX to asynchronously acquire data in JSON format based on user requests to dynamically update the frontend interface. This architecture can therefore be integrated into end users’ own pipelines.

Network visualizations were implemented using Cytoscape.js (34).
Results and Discussion

Information architecture and statistics

One key feature of AlzGPS is the highly diverse yet interconnected data types (Figure 1). The three main data types are genes, drugs, and AD-relevant omics data sets. More than 100 omics data sets were processed, including 84 expression data sets (Table S1) from AD transgenic animal models or patient-derived samples and 27 data sets from the literature or acquired from other databases. The expression data sets contain transcriptomic and proteomic data of human and rodent samples. Comparative sample groups were available in these data sets, such as early stage vs. late stage, healthy vs. AD. The differentially expressed genes/proteins were calculated for each data set.

The statistics and relations of the database are shown in Figure 1B. We collected and processed all the basic information (see Methods) and then constructed the relationships among the data types. For example, for genes and drugs, the relationship is drugs targeting proteins (genes); for gene and data set, the relationship is genes being differentially expressed in the expression data sets or included in other types of data sets, such as literature-based; for drug and data set, the proximity between each pair was calculated (see Methods) to identify the drugs that are significantly proximal to a data set, and vice versa.

Additional data types were collected or generated. For genes, these included genetic evidence (variants associated with AD) and tissue expression specificity to provide additional information for target gene identification. For drugs, we collected the data from ongoing clinical trials, including the proposed mechanism and therapeutic purpose (29) & (30). The trials were mapped to drugs. The BBB probability was

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computed (23, 24). For the top 300 drugs with the highest number of significant proximities to all the data sets, we manually curated the available literature. A total of 292 studies were found for 147 drugs (49%) that reported the associations of the drugs and AD. We grouped these studies into clinical and non-clinical, and extracted trial information for clinical type and experimental setting (number and type of patients) for both types. We also summarized and provide the study results.

Web interface and network visualizations

A highly interactive web interface was implemented (Figure 2). On the home page (Figure 2A), the user can search for drugs, genes, metabolites, and gene variants. The user can directly list all drugs by their first-level ATC code, all AD data sets available, and all the ongoing clinical trials (Figure 2B). The search results are displayed in the “DATA TABLE” tab and switched with their associated buttons in the “RESULT” section on the left. Each data entity has its own data table for the associated information in the “DATA TABLE” tab. For example, on the gene page of APP (Figure 2B) is the basic information (green rows), such as name, type, chromosome, and synonym; descriptions for the derived data (purple rows), such as tissue specificity and number of genetic records; and external links (red row). Data for the relations of APP and other entities can be loaded by clicking the button in “DETAIL” (blue row). For example, the expression data sets in which APP is differentially expressed can be found by clicking the “Dataset” button (Figure 2B). Any data loaded will be added to the same explorer. The buttons in the “RESULT” are organized in trees. For example, APP is included in the “V1 AD-seed” data set, which contains 144 AD-associated genes with strong
literature evidence. When the user clicks this data set in the APP gene table, a new data table for the “V1 AD-seed” data set will replace the the APP gene page, and a new button with indentation will appear below the APP button in “RESULT” (Figure 2B).

An all-in-one interactive explorer that minimizes the need for navigation of information using the relational nature of these data is a major feature of the web interface. Another major feature is the network visualizations. We offer three types of networks, (1) the brain-specific neighborhood network (EGO) for a gene-of-interest that shows the PPIs with its neighbors (Figure 2C); (2) the largest connected component (LCC) network for a data set that shows the largest module formed by the genes in this data set (Figure 2D); and (3) inferred MOA network for a significantly proximal drug-data set pair, which is illustrated in the case studies below.

Case study – target identification

Generally, using AlzGPS for AD target identification starts with selecting one or a set of data sets (Figure 2B, “DATASET” tab). Users can select a data set based on organisms, methods (e.g., single-cell/nuclei RNA-Seq), brain regions, and comparisons (e.g., early-onset AD vs healthy control) for the expression data sets. Additionally, we have collected data sets from the literature, other databases, or computationally predicted results. Here, we use the “V1 AD-seed” data set as a starting point. This data set was from our recent study which contains 144 AD-associated genes based on literature-derived evidence. We found that 118 genes were differentially expressed as shown in at least one data set. By browsing these genes, we selected four examples, microtubule associated protein tau (MAPT), bridging integrator 1 (BIN1), apolipoprotein
E (APOE), and β-secretase 1 (BACE1) based on positive brain expression specificity and number of data sets that include them.

**MAPT.** MAPT encodes the tau protein, modification of which is one of the main neuropathological hallmarks of AD (35, 36). Mutations and alternative splicing of MAPT are associated with risk of AD (37). MAPT is differentially expressed in five expression data sets (Figure 3A) and has high brain specificity. Five pieces of genetic evidence were found for MAPT. MAPT can be targeted by 27 drugs. In addition, many of its direct PPI neighbors are targetable, suggesting a potential treatment strategy by targeting MAPT and its neighbors.

**BIN1.** BIN1 is one of the most important susceptibility genes for late-onset AD (38), and can modulate tau pathology (39). Higher levels of BIN1 expression are associated with a delayed age of AD onset (40). Differentially manifested in five data sets, BIN1 has 47 genetic record associations (Figure 3B). Although no drugs are known to target BIN1, many of the BIN1’s PPI neighbors can be targeted.

**APOE.** The ε4 allele of APOE is the main genetic risk factor of AD (41). Apolipoprotein E ε4 plays an important role in Aβ deposition (41), a major pathological hallmark of AD. APOE is differentially expressed in 22 data sets (Figure 3C). It has a high number of associated genetic records – 91. Both APOE and its PPI partners can be targeted.

**BACE1.** β-secretase 1 (BACE1) cleaves APP and generates amyloid-β peptides (42), whose aggregation is another pathological hallmark of AD. The inhibition of BACE1 has been a popular target for AD drug development. Shown in Figure 3D, BACE1 is differentially expressed in 4 data sets.
Case study – drug repurposing

In this section, we use sildenafil and pioglitazone as two examples. In our recent studies, we found that both sildenafil and pioglitazone were associated with a reduced risk of AD using network proximity analysis and retrospective case-control validation (14). Mechanistically, *in vitro* assays showed that both drugs were able to downregulate cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3 beta (GSK3B) in human microglia cells. These drugs were discovered using different data sets. Sildenafil was found using a high-quality literature-based AD endophenotype module (available as AlzGPS data set “V1 AD-seed”) containing 144 genes. Pioglitazone was found using 103 high-confidence AD risk genes (available as AlzGPS data set “V4 AD-inferred-GWAS-risk-genes”) identified by GWAS (13).

AlzGPS provides a list-view of the network proximity results of all the drugs organized by their first-level ATC code, which can be found in the “DRUG CLASS” tab (Figure 2B). The drugs are ranked by the number of significant proximities to the data sets. Sildenafil is the top four of the 148 drugs under the ATC code G “Genito-urinary system and sex hormones” with network proximity results, the top three being vardenafil, ibuprofen, and gentian violet cation. Pioglitazone is the top sixth of the 226 drugs under the ATC code A “Alimentary tract and metabolism”, following tetracycline, human insulin, epinephrine, cholecalciferol, and teduglutide. Both drugs achieved high numbers of significant proximities to the expression data set. Next, we examined the basic information of these drugs (Figure 4A and 4E). Both drugs are predicted to be BBB penetrable. Sildenafil has 20 known targets and is significantly proximal to 27 of the 111 data sets (Figure 4A). We found one non-clinical study that reported that
sildenafil treatment improves cognition and memory of vascular dementia in aged rats (43) (Figure 4C). As noted, we identified the potential of sildenafil against AD using the AD endophenotype module (Figure 4B, Z = -2.44, P = 0.003). Then, clicking the corresponding “MOA (mechanism-of-action)” button opened the inferred MOA network for sildenafil and the data set (Figure 4D). Although sildenafil does not target the genes in the data set (green) directly, it can potentially alter them through PPIs with its targets (blue).

Pioglitazone has 8 known targets and is significantly proximal to 34 data sets (Figure 4E). Five studies, containing both clinical and non-clinical data were found to be related to treating AD with pioglitazone. For example, a clinical study showed that pioglitazone can improve cognition in AD patients with type II diabetes (44) (Figure 4G). Similarly, network results and associated MOA networks suggested that pioglitazone can affect AD risk genes through PPIs (Figure 4F and Figure 4H).

Validation studies

Once candidate agents are identified on AlzGPS, a variety of validation steps can be pursued (6). The agent can be tested in animal model systems of AD pathology to evaluate the predicted MOA of behavioral and biological effects. Since these are repurposed agents and have been used for other indications in human healthcare, electronic medical records can be interrogated to determine if there are notable effects on AD incidence, prevalence, or rate of progression. Both these methods are imperfect since animal models have rarely been predictive of human response, and doses and duration of exposures may be different for indications of other then AD in which the
candidate agents are used. The ultimate assessment that could make an agent available for human care is success in a clinical trial and nominated agents must eventually be submitted to trials. If repurposed agents are not entered into trials because of intellectual property limitations or other challenges, the information from AlzGPS may be useful in identifying druggable disease pathways or providing seed structures that provide a basis for creation of related novel agents with similar MOAs.

Conclusions

AlzGPS contains rich and diverse information connecting genes, AD data sets, and drugs for AD target identification and drug repurposing. It utilizes multiple biological networks and omics data such as genomics, transcriptomics, and proteomics, and provides network-based drug repurposing results with network visualizations. AlzGPS will be a valuable resource to the AD research community. We will continue to add more types of omics data and update AlzGPS annually or when a large amount of new data is available. In summary, AlzGPS presents the first comprehensive in silico tool for human genome-informed precision medicine drug discovery for AD. From a translational perspective, if broadly applied, AlzGPS will offer a powerful tool for prioritizing biologically relevant targets and clinically relevant repurposed drug candidates for multi-omics-informed therapeutic discovery in AD and other neurodegenerative diseases.

Declarations

Ethics approval and consent to participate

Not applicable
**Consent for publication**

Not applicable

**Availability of data and materials**

All the data in AlzGPS can be freely accessed without registration requirement at [https://alzgps.lerner.ccf.org](https://alzgps.lerner.ccf.org).

**Competing interests**

Dr. Cummings has provided consultation to Acadia, Actinogen, Alkahest, Alzheon, Annovis, Avanir, Axsome, Biogen, BioXcel, Cassava, Cerecin, Cerevel, Cortexyme, Cytox, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Karuna, Merck, Novo Nordisk, Otsuka, Resverlogix, Roche, Samumed, Samus, Signant Health, Suven, Third Rock, and United Neuroscience pharmaceutical and assessment companies. Dr. Cummings has stock options in ADAMAS, AnnovisBio, MedAvante, BiOasis. Dr Cummings is supported by Keep Memory Alive (KMA); NIGMS grant P20GM109025; NINDS grant U01NS093334; and NIA grant R01AG053798.

**Funding:** This work was supported by the National Institute of Aging (NIA) under Award Number R01AG066707 and 3R01AG066707-01S1 to F.C. This work was supported in part by the NIA under Award Number R56AG063870 (L.B.) and P20GM109025 (J.C.). A.A.P., L.B., J.C., J.B.L., and F.C. are supported together by the Translational Therapeutics Core of the Cleveland Alzheimer's Disease Research Center (NIH/NIA: 1
P30 AG062428-01). A.A.P. is also supported by the Brockman Foundation, Project 19PABH134580006-AHA/Allen Initiative in Brain Health and Cognitive Impairment, the Elizabeth Ring Mather & William Gwinn Mather Fund, S. Livingston Samuel Mather Trust, G.R. Lincoln Family Foundation, Wick Foundation, Gordon & Evie Safran, the Leonard Krieger Fund of the Cleveland Foundation, the Maxine and Lester Stoller Parkinson’s Research Fund, and Louis Stokes VA Medical Center resources and facilities.

Authors’ contributions
F.C. conceived the study. Y.Z. constructed the database and developed the website. J.F., Y.Z., and Y.H.K. performed data gathering and processing. L.B., A.A.P., J.B.L., and J.C. discussed and interpreted all results. Y.Z., F.C., and J.C. wrote and all authors critically revised the manuscript and gave final approval.

Acknowledgements
We thank the Lerner Research Institute Computing Services for hosting AlzGPS.

References
1. 2020 Alzheimer’s disease facts and figures. Alzheimer’s & Dementia.
2. 2020;16(3):391-460.
3. Long JM, Holtzman DM. Alzheimer Disease: An update on pathobiology and treatment strategies. Cell. 2019;179(2):312-39.
4. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nat Rev Dis Primers. 2015;1:15056.
4. Kodamullil AT, Zekri F, Sood M, Hengerer B, Canard L, McHale D, et al. Trial watch: Tracing investment in drug development for Alzheimer disease. Nat Rev Drug Discov. 2017;16(12):819.

5. Alteri E, Guizzaro L. Be open about drug failures to speed up research. Nature. 2018;563(7731):317-9.

6. Fang J, Pieper AA, Nussinov R, Lee G, Bekris L, Leverenz JB, et al. Harnessing endophenotypes and network medicine for Alzheimer’s drug repurposing. Med Res Rev. Published online 2020 Jul 13. doi: 10.1002/med.21709.

7. Cummings J, Feldman HH, Scheltens P. The "rights" of precision drug development for Alzheimer's disease. Alzheimers Res Ther. 2019;11(1):76.

8. Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, et al. A unique microglia type associated with restricting development of Alzheimer's disease. Cell. 2017;169(7):1276-90 e17.

9. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013;45(12):1452-8.

10. Bai B, Wang X, Li Y, Chen PC, Yu K, Dey KK, et al. Deep multilayer brain proteomics identifies molecular networks in Alzheimer's disease progression. Neuron. 2020;105(6):975-91 e7.

11. Cheng F, Lu W, Liu C, Fang J, Hou Y, Handy DE, et al. A genome-wide positioning systems network algorithm for in silico drug repurposing. Nat Commun. 2019;10(1):3476.

12. Cheng F, Desai RJ, Handy DE, Wang R, Schneeweiss S, Barabasi AL, et al. Network-based approach to prediction and population-based validation of in silico drug repurposing. Nat Commun. 2018;9(1):2691.

13. Wang Q, Chen R, Cheng F, Wei Q, Ji Y, Yang H, et al. A Bayesian framework that integrates multi-omics data and gene networks predicts risk genes from schizophrenia GWAS data. Nat Neurosci. 2019;22(5):691-9.

14. Fang J, Zhang P, Wang Q, Zhou Y, Chiang WC, Cheng R, et al. Network-based translation of GWAS findings to pathobiology and drug repurposing for Alzheimer's
1. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov. 2020;6:14.

2. Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. The Lancet Digital Health. in press. doi: https://doi.org/10.1016/S2589-7500(20)30192-8

3. Edgar R, Domrachev M, Lash AE. Gene Expression Omnibus: NCBI gene expression and hybridization array data repository. Nucleic Acids Res. 2002;30(1):207-10.

4. Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets--update. Nucleic Acids Res. 2013;41(Database issue):D991-5.

5. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015;43(7):e47.

6. Braschi B, Denny P, Gray K, Jones T, Seal R, Tweedie S, et al. Genenames.org: the HGNC and VGNC resources in 2019. Nucleic Acids Res. 2019;47(D1):D786-D92.

7. Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res. 2019;47(D1):D1005-D12.

8. Law V, Knox C, Djoumbou Y, Jewison T, Guo AC, Liu Y, et al. DrugBank 4.0: shedding new light on drug metabolism. Nucleic Acids Res. 2014;42(Database issue):D1091-7.

9. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, et al. admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. J Chem Inf Model. 2012;52(11):3099-105.
24. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, et al. Correction to "admetSAR: A Comprehensive Source and Free Tool for Assessment of Chemical ADMET Properties". J Chem Inf Model. 2019;59(11):4959.

25. Yang H, Qin C, Li YH, Tao L, Zhou J, Yu CY, et al. Therapeutic target database update 2016: enriched resource for bench to clinical drug target and targeted pathway information. Nucleic Acids Res. 2016;44(D1):D1069-74.

26. Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, Hersey A, et al. ChEMBL: a large-scale bioactivity database for drug discovery. Nucleic Acids Res. 2012;40(Database issue):D1100-D7.

27. Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK. BindingDB: a web-accessible database of experimentally determined protein-ligand binding affinities. Nucleic Acids Res. 2007;35(Database issue):D198-D201.

28. Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP, et al. The IUPHAR/BPS Guide to PHARMACOLOGY: an expert-driven knowledgebase of drug targets and their ligands. Nucleic Acids Res. 2014;42(Database issue):D1098-D106.

29. Cummings J, Lee G, Ritter A, Zhong K. Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement (N Y). 2018;4:195-214.

30. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. Alzheimers Dement (N Y). 2019;5:272-93.

31. Cheng F, Kovacs IA, Barabasi AL. Network-based prediction of drug combinations. Nat Commun. 2019;10(1):1197.

32. Smith IN, Thacker S, Seyfi M, Cheng F, Eng C. Conformational dynamics and allosteric regulation landscapes of germline PTEN mutations associated with autism compared to those associated with cancer. Am J Hum Genet. 2019;104(5):861-78.

33. Hagberg AA, Schult DA, Swart PJ. Exploring network structure, dynamics, and function using NetworkX. Proceedings of the 7th Python in Science Conference (SciPy2008). 2008:11-5.

34. Franz M, Lopes CT, Huck G, Dong Y, Sumer O, Bader GD. Cytoscape.js: a graph theory library for visualisation and analysis. Bioinformatics. 2016;32(2):309-11.
35. Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci U S A. 1986;83(11):4044-8.

36. Goedert M, Wischik CM, Crowther RA, Walker JE, Klug A. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. Proc Natl Acad Sci U S A. 1988;85(11):4051-5.

37. Kovacs GG. Invited review: Neuropathology of tauopathies: principles and practice. Neuropathol Appl Neurobiol. 2015;41(1):3-23.

38. Tan MS, Yu JT, Tan L. Bridging integrator 1 (BIN1): form, function, and Alzheimer's disease. Trends Mol Med. 2013;19(10):594-603.

39. Chapuis J, Hansmannel F, Gistelinck M, Mounier A, Van Cauwenberghe C, Kolen KV, et al. Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. Mol Psychiatry. 2013;18(11):1225-34.

40. Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C, Goate AM. Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. PLoS One. 2012;7(11):e50976.

41. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106-18.

42. Cai H, Wang Y, McCarthy D, Wen H, Borchelt DR, Price DL, et al. BACE1 is the major beta-secretase for generation of Abeta peptides by neurons. Nat Neurosci. 2001;4(3):233-4.

43. Venkat P, Chopp M, Zacharek A, Cui C, Landschoot-Ward J, Qian Y, et al. Sildenafil treatment of vascular dementia in aged rats. Neurochem Int. 2019;127:103-12.

44. Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging. 2011;32(9):1626-33.
**Figure Legends**

**Figure 1. The architecture of AlzGPS.**

(A) AlzGPS is built on three main data entities (genes, drugs, and omics layers) and their relationships. The multi-omics data (genomics, transcriptomics (bulk and single-cell/single-nucleus, and proteomics) in AlzGPS help identify likely causal genes/targets that are associated with Alzheimer's disease (AD) and disease modules in the context of human protein-protein interactome. Then, via network proximity measure between drug-target networks and disease modules in the human interactome, drugs can be prioritized for the potential to alter the genes in the module, for potential treatment of AD. (B) Detailed statistics of the entities and relations in AlzGPS. EGO – brain-specific neighborhood network (ego network); LCC – largest connected component network; MOA – mechanism-of-action network.

**Figure 2. Web interface overview.**

(A) The home page provides access to searching, listing entries, and viewing brain-specific gene/target networks. User will be redirected to the interactive explorer (B), in which all information are then dynamically loaded and added to the same web page. Each data entity has its own basic information page under the “DATA TABLE” tab. Additional information regarding the relations (e.g., proximity results) can be loaded by clicking the corresponding button in the “DETAIL” section. (C) An example brain-specific neighborhood network using APOE. (D) An example largest connected component network using data set “V2”.

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**Figure 3. Case study – target identification.**

Four genes, MAPT (A), BIN1 (B), APOE (C), and BACE1 (D) are used as examples to show the gene page. On the gene page, we show a summary of several statistics of the gene in AlzGPS, including the number of drugs that can target it, number of data sets of omics in which the target/protein coding gene is differentially expressed, number of genetic records, and the brain-expression specificity. Detailed information can be loaded by clicking corresponding buttons. Examples of detailed differential expression results and genetic records are shown for these four genes. In addition, a brain-specific neighborhood network is available that centers around the gene-of-interest and show the targetability of its neighborhood.

**Figure 4. Case study – drug repurposing.**

Sildenafil and pioglitazone are used as examples to demonstrate how to use AlzGPS for drug repurposing. (A) Basic information for sildenafil. (B) Network proximity results for sildenafil. (C) Literature evidence for sildenafil. (D) Inferred mechanism-of-action for sildenafil targeting the “V1 AD-seed” data set, which contains 144 high-quality literature-based Alzheimer’s disease (AD) endophenotype genes. (E) Basic information for pioglitazone. (F) Network proximity results for pioglitazone. (G) Five studies were found that were related to treating AD with pioglitazone. (H) Inferred mechanism-of-action for pioglitazone targeting the “V4 AD-inferred-GWAS-risk-genes” data set which contains 103 high-confidence AD risk genes identified using genome-wide association studies.
Figure 1. The architecture of AlzGPS.

A

Human protein interactome

Multi-omics data sets

Drug repurposing

Target identification

Disease module identification

B

| Entities | Statistics | Relations with other entities |
|----------|------------|-------------------------------|
| Drug     | 13,339 drugs, 2,892 with target information, 2,892 with screening results, 16,465 screening results have MOA, 147 with manually curated literature evidences | Drug target, Screening results vs. all datasets, Inferred MOA network |
| Gene     | 41,725 genes, 11,727 in expression datasets, 1,268 with genetic evidence, 2,847 targetable, 10,035 with tissue specificity, 4,164 with EGO network | Drugs that target this gene, Datasets that contains this gene, Genetic evidence, Metabolite evidence, Brain specific neighborhood network (EGO) |
| Dataset  | 84 expression datasets, 4 datasets curated from literature, 23 datasets from misc. databases, 78 with LCC network, 12,226 genes covered | Differentially expressed / disease genes, Screening results vs. all drugs, Inferred MOA network, Network of the genes in this dataset (LCC) |
| Clinical Trial | 161 ongoing AD clinical trials, 93 with associated drug information | Drug in this trial |
| SNP      | 1,629 AD-related, 3,321 SNP-Gene mapping | Mapped genes |
| Metabolite | 2,118 metabolites, 45,203 metabolite-Gene mapping, 58 differentially expressed from literature | Mapped genes, Differentially expressed in datasets |
Figure 2. Web interface overview.

1. Search for
   - Drugs (by name or DrugBank ID)
   - Genes (by Entrez ID or symbol)
   - Metabolites (by name or PubChem/HMDB ID)
   - Variants (by variant ID)

2. List entries
   - Drugs by first-level ATC
   - AD data sets
   - AD clinical trials (ongoing)

3. Net visualization

Gene - APP (ID: 351)

- **Symbol**: APP
- **Name**: amyloid beta precursor protein
- **Type**: Protein-coding gene
- **Chromosome**: 21q13.3
- **Target by**: APP is a known target of 11 drugs.
- **Expression Score**: APP is differentially expressed in 30 of the 84 expression datasets.
- **Genetic Evidence**: APP has 8 genetic records.

Net visualization with nodes and edges representing different biological entities and relationships.
Figure 3. Case study – target identification.
Figure 4. Case study – drug repurposing.

A. Drug - Sildenafil

- **NAME**: Sildenafil
- **TYPE**: Small molecule
- **GROUP**: Approved, investigational
- **SMILES**: CCC1=NC(2=C=NC=O)C1=CC(=C=O)C1=C(C=C(=C1)S(=O)(=O)N)
- **ATC**: G01AE10 - Genito-urinary system and sex hormones
- **G04BE03 - Genito-urinary system and sex hormones**
- **AD TRIAL (ONGOING)**: No
- **TARGET**: Sildenafil has 20 known targets
- **PROXIMITY SCORE**: Sildenafil has significant proximity to 27 of the 111 datasets
- **LITERATURE EVIDENCE**: We found 1 literature evidence
- **BBB**
  - **(p = 0.646)**
- **DETAIL**
  - Target
  - Proximity
  - Literature
- **EXTERNAL LINK**
  - admetsAR: Predict ADMET properties
  - admetsAR: Structural similarity search
  - DrugBank: DB00203
  - DrugCentral: 2441

B. VARIOUS DATASET

| ID | Name       | Z  | P    | N  | J  | C  | Open | MOA |
|----|------------|----|------|----|----|----|------|-----|
| V1 | AD-seed    | -2.44 | 0.003 | 0  | 0  | 0  | 0    |     |
| V3 | Tau-seed   | -2.34 | 0.023 | 0  | 0  | 0  | 0    |     |
| V5 | Harmonicine-AD01 | -2.65 | 0.000 | 1  | 0  | 0  | 0    |     |
| V7 | Harmonicine-AD03 | -2.22 | 0.008 | 1  | 0  | 0  | 0    |     |

C. Sildenafil treatment of vascular dementia in aged rats.

*Neurochem Int.* 2019

**TYPE**: Non-clinical

**SETTING**: A mouse model of mild Alzheimer disease (AD) with Aβ1-40 and Aβ1-42 deposits and elevated LRP1 expression in the hippocampus.

**RESULT**: Sildenafil treatment of vascular dementia significantly improved cognition and memory at 1 month after MI and it also increased axon and myelin density, increased tyrosine phosphorylation expression, decreases autophagic activity and exerts anti-inflammatory effects which in concert may contribute to cognitive improvement in aged rats subjected to MI.

D. NODE LEGEND

- Yeast 2-hybrid
- Complex
- Kinase-substrate
- Signaling
- Literature

E. Drug - Pioglitazone

- **NAME**: Pioglitazone
- **TYPE**: Small molecule
- **GROUP**: Approved, investigational
- **SMILES**: CCC1=NC(2=C=NC=O)C1=CC(=C=O)C1=C(C=C(=C1)S(=O)(=O)N)
- **ATC**: A10B009 - Alimentary tract and metabolism
- **A10B003 - Alimentary tract and metabolism**
- **A10B005 - Alimentary tract and metabolism**
- **A10B006 - Alimentary tract and metabolism**
- **A10B012 - Alimentary tract and metabolism**
- **AD TRIAL (ONGOING)**: No
- **TARGET**: Pioglitazone has 17 known targets
- **PROXIMITY SCORE**: Pioglitazone has significant proximity to 34 of the 111 datasets
- **LITERATURE EVIDENCE**: We found 5 literature evidences
- **BBB**
  - **(p = 0.875)**
- **DETAIL**
  - Target
  - Proximity
  - Literature
- **EXTERNAL LINK**
  - admetsAR: Predict ADMET properties
  - admetsAR: Structural similarity search
  - DrugBank: DB01132
  - DrugCentral: 2179

F. VARIOUS DATASET

| ID | Name       | Z  | P    | N  | J  | C  | Open | MOA |
|----|------------|----|------|----|----|----|------|-----|
| V1 | AD-seed    | -2.17 | 0.007 | 2  | 0.01| 0.25|     |
| V4 | AD-inferred-GWAS-risk-genes | -1.55 | 0.048 | 0  | 0  | 0  |     |
| V7 | Harmonicine-AD03 | -2.36 | 0.005 | 0  | 0  | 0  |     |
| V8 | Harmonicine-AD04 | -2.67 | 0.002 | 0  | 0  | 0  |     |

G. Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease.

*Neurobiol Aging.* 2011

**TYPE**: Clinical

**SETTING**: Patients with mild Alzheimer disease (AD) accompanied with type 1 diabetes mellitus

**RESULT**: Pioglitazone exhibited cognitive and functional improvements, and stabilization of the disease in diabetic patients with AD

**LOW DOSE PIOGLI TAZONE**

- Low-dose pioglitazone can ameliorate learning and memory impairment in a mouse model of mild Alzheimer disease by increasing LRP1 expression in the hippocampus.

H. NODE LEGEND

- Yeast 2-hybrid
- Complex
- Kinase-substrate
- Signaling
- Literature
## Table S1. All data sets in AlzGPS.

| Dataset ID | Taxon: Human | Omic: Transcriptome | Method: Microarray | Region: Brain | Group (sample): | Criteria: | GEO: | PMID: | Note: | Source: |
|------------|--------------|---------------------|--------------------|---------------|----------------|-----------|------|-------|-------|--------|
| E1         |              |                     |                    |               | 30 EAD vs. 173 controls | FDR < 0.01, | GSE48350 | 23273601 | EAD, Braak III or IV | GEO2R |
| E2         |              |                     |                    |               | 180 EAD vs. 214 controls | FDR < 0.01, | GSE84422 | 27799057 | EAD, Probable AD (Braak III or IV) | GEO2R |
| E3         |              |                     |                    |               | 180 EAD vs. 214 controls | FDR < 0.01, | GSE84422 | 27799057 | EAD, Probable AD (Braak III or IV) | GEO2R |
| E4         |              |                     |                    |               | 6 EAD vs. 8 controls | p<0.01 (Paper) | GSE12685 |       |       | GEO2R |

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PMID: 19295912
Note: controls (MMSE 30-25) and "Incipient AD" (MMSE 21-26, with MCI 24-26 and mild AD 21-23)
Source: Table S2

Dataset ID: E5
Taxon: Human
Omic: Transcriptome
Method: Microarray
Region: Hippocampus
Group (sample): 31 LAD vs. 32 controls
Criteria: FDR < 0.01, |FC| > 1.2
GEO: GSE29378
PMID: 23705665
Note: LAD, Braak V or VI
Source: GEO2R

Dataset ID: E6
Taxon: Human
Omic: Transcriptome
Method: Microarray
Region: Brain
Group (sample): 42 LAD vs. 173 controls
Criteria: FDR < 0.01, |FC| > 1.2
GEO: GSE48350
PMID: 23273601
Note: LAD, Braak V or VI
Source: GEO2R

Dataset ID: E7
Taxon: Human
Omic: Transcriptome
Method: Microarray
Region: Brain
Group (sample): 328 LAD vs. 214 controls
Criteria: FDR < 0.01, |FC| > 1.2
GEO: GSE84422
PMID: 27799057
Note: LAD, Definite AD (Braak V or VI)
Source: GEO2R

Dataset ID: E8
Taxon: Human
Omic: Transcriptome
Method: Microarray
Region: Brain
Group (sample): 328 LAD vs. 214 controls
Criteria: FDR < 0.01, |FC| > 1.2
GEO: GSE84422
PMID: 27799057
Note: LAD, Definite AD (Braak V or VI)
Source: GEO2R

Dataset ID: E9
Taxon: Human
Omic: Transcriptome
Method: Bulk RNA-seq
Region: Hippocampus
Group (sample): 4 LAD vs. 4 controls
Criteria: PFP<0.1 (Paper)
GEO: GSE67333
PMID: 26402107
Note: LAD, Braak V or VI
Source: File S2

Dataset ID: E10
Taxon: Human
Omic: Transcriptome
Method: Bulk RNA-seq
Region: Hippocampus
Group (sample): 6 LAD vs. 6 controls
Criteria: |log2(FC)|> 1 and corrected P value < 0.05 (Paper)
PMID: 29523845
Note: LAD, Braak V or VI
Source: Table S2

Dataset ID: E11
Taxon: Human
Omic: Transcriptome
Method: Bulk RNA-seq
Region: Hippocampus
Group (sample): 20 LAD vs. 10 controls
Criteria: DE score >0.1
PMID: 30497016
Note: LAD, Braak V or VI
Source: Table S1

Dataset ID: E12
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Excitatory neurons (Ex)
Group (sample): 24 AD vs. 24 controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: A spectrum of mild to severe Aβ and other pathologies (AD-pathology)
Source: Table S2

Dataset ID: E13
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Inhibitory neurons (In)
Group (sample): 24 AD vs. 24 controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: A spectrum of mild to severe Aβ and other pathologies (AD-pathology)
Source: Table S2

Dataset ID: E14
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Astrocytes (Ast)
Group (sample): 24 AD vs. 24 controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: A spectrum of mild to severe Aβ and other pathologies (AD-pathology)
Source: Table S2

Dataset ID: E15
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Oligodendrocytes (Oli)
Group (sample): 24 AD vs. 24 controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: A spectrum of mild to severe Aβ and other pathologies (AD-pathology)
Source: Table S2

Dataset ID: E16
Taxon: Human
Omic: Transcriptome
Method: Single Cell  
Region: Brain  
Cell type: Microglia (Mic)  
Group (sample): 24 AD vs. 24 controls  
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05  
PMID: 31042697  
Note: A spectrum of mild to severe Aβ and other pathologies (AD-pathology)  
Source: Table S2  

Dataset ID: E17  
Taxon: Human  
Omic: Transcriptome  
Method: Single Cell  
Region: Brain  
Cell type: Oligodendrocyte precursor cells (OPC)  
Group (sample): 24 AD vs. 24 controls  
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05  
PMID: 31042697  
Note: A spectrum of mild to severe Aβ and other pathologies (AD-pathology)  
Source: Table S2  

Dataset ID: E18  
Taxon: Human  
Omic: Transcriptome  
Method: Single Cell  
Region: Brain  
Cell type: Excitatory neurons (Ex)  
Group (sample): EAD vs. controls  
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05  
PMID: 31042697  
Note: EAD, amyloid burden, but modest neurofibrillary tangles and cognitive impairment  
Source: Table S2  

Dataset ID: E19  
Taxon: Human  
Omic: Transcriptome  
Method: Single Cell  
Region: Brain  
Cell type: Inhibitory neurons (In)  
Group (sample): EAD vs. controls  
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05  
PMID: 31042697  
Note: EAD, amyloid burden, but modest neurofibrillary tangles and cognitive impairment  
Source: Table S2  

Dataset ID: E20
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Astrocytes (Ast)
Group (sample): EAD vs. controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: EAD, amyloid burden, but modest neurofibrillary tangles and cognitive impairment
Source: Table S2

Dataset ID: E21

Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Oligodendrocytes (Oli)
Group (sample): EAD vs. controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: EAD, amyloid burden, but modest neurofibrillary tangles and cognitive impairment
Source: Table S2

Dataset ID: E22

Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Microglia (Mic)
Group (sample): EAD vs. controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: EAD, amyloid burden, but modest neurofibrillary tangles and cognitive impairment
Source: Table S2

Dataset ID: E23

Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Oligodendrocyte precursor cells (OPC)
Group (sample): EAD vs. controls
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: EAD, amyloid burden, but modest neurofibrillary tangles and cognitive impairment
Source: Table S2
Dataset ID: E24
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Excitatory neurons (Ex)
Group (sample): LAD vs. EAD
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: LAD, higher amyloid, and also elevated neurofibrillary tangles, global pathology, and cognitive impairment
Source: Table S2

Dataset ID: E25
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Inhibitory neurons (In)
Group (sample): LAD vs. EAD
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: LAD, higher amyloid, and also elevated neurofibrillary tangles, global pathology, and cognitive impairment
Source: Table S2

Dataset ID: E26
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Astrocytes (Ast)
Group (sample): LAD vs. EAD
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: LAD, higher amyloid, and also elevated neurofibrillary tangles, global pathology, and cognitive impairment
Source: Table S2

Dataset ID: E27
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Oligodendrocytes (Oli)
Group (sample): LAD vs. EAD
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: LAD, higher amyloid, and also elevated neurofibrillary tangles, global pathology, and cognitive impairment
Source: Table S2

Dataset ID: E28
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Microglia (Mic)
Group (sample): LAD vs. EAD
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: LAD, higher amyloid, and also elevated neurofibrillary tangles, global pathology, and cognitive impairment
Source: Table S2

Dataset ID: E29
Taxon: Human
Omic: Transcriptome
Method: Single Cell
Region: Brain
Cell type: Oligodendrocyte precursor cells (OPC)
Group (sample): LAD vs. EAD
Criteria: FDR < 0.01, |FC| > 1.2, Poisson mixed-model FDR < 0.05
PMID: 31042697
Note: LAD, higher amyloid, and also elevated neurofibrillary tangles, global pathology, and cognitive impairment
Source: Table S2

Dataset ID: E30
Taxon: Human
Omic: Transcriptome
Method: Microarray
Region: Human fibroblasts cell
Cell type: Neural progenitor cells
Group (sample): 5 sporadic AD vs. 5 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE117589
PMID: 30699343
Note: Sporadic AD
Source: Table S3
Dataset ID: E31
Taxon: Human
Omic: Transcriptome
Method: Microarray
Region: Human fibroblasts cell
Cell type: Neural cells
Group (sample): 6 sporadic AD vs. 5 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE117589
PMID: 30699343
Note: Sporadic AD
Source: Table S4

Dataset ID: E32
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: HO-TASTPM
Age: 4 months
Region: Hippocampus
Group (sample): 4 AD mice vs. 9 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E33
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: HO-TASTPM
Age: 8 months
Region: Hippocampus
Group (sample): 4 AD mice vs. 9 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E34
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: HO-TASTPM
Age: 18 months
Region: Hippocampus
Group (sample): 4 AD mice vs. 9 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E35
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: HO-TASTPM
Age: 4 months
Region: Frontal cortex
Group (sample): 4 AD mice vs. 9 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E36
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: HO-TASTPM
Age: 8 months
Region: Frontal cortex
Group (sample): 4 AD mice vs. 9 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E37
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Zhou et al. 2020

Genetic BG: C57Bl/6J
Model: HO-TASTPM
Age: 18 months
Region: Frontal cortex
Group (sample): 3 AD mice vs. 7 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E38
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: APP/PS1
Age: 8 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): 5 AD mice vs. 5 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE65067
PMID: 25728668
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E39
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: APP/PS1
Age: 5 months
Region: Frontal cortex
Group (sample): 9 AD mice vs. 12 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE74438
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E40
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: APP/PS1
Age: 5 months
Region: Hippocampus
Group (sample): 9 AD mice vs. 12 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE74438
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E41
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: APP/PS1
Age: 5 months
Region: Hippocampus
Group (sample): 8 AD mice vs. 11 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE74437
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E42
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: APP/PS1
Age: 5 months
Region: Frontal cortex
Group (sample): 8 AD mice vs. 11 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE74437
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E43
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: A cross between C57BL/6J and C3H/HeJ
Model: APP/PS1
Age: 15-18 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): 7 AD mice vs. 7 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE74615
PMID: 25002035
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E44
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA)
Model: rTg4510
Age: 4 months
Region: Hippocampus
Group (sample): 4 AD mice vs. 4 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE53480
PMID: 25069841
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E45
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA)
Model: rTg4510
Age: 4-6 months
Region: Hippocampus
Group (sample): 16 AD mice vs. 20 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE56772
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E46
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA)
Model: rTg4510
Age: 6 months
Region: Hippocampus
Group (sample): 17 AD mice vs. 17 controls
Criteria: FDR < 0.05, |FC| > 1.5
Dataset ID: E47
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: Tau P301L
Age: 18 months
Region: Hippocampus
Group (sample): 3 AD mice vs. 7 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E48
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: Tau P301L
Age: 18 months
Region: Frontal cortex
Group (sample): 3 AD mice vs. 7 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R

Dataset ID: E49
Taxon: Mouse
Omic: Transcriptome
Method: Microarray
Genetic BG: C57Bl/6J
Model: Tau P301L
Age: 18 months
Region: Cerebellum
Group (sample): 3 AD mice vs. 7 controls
Criteria: FDR < 0.05, |FC| > 1.5
GEO: GSE64398
PMID: 25620700
Note: Mouse genes converted to human orthologs
Source: GEO2R
Dataset ID: E50
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6J females (B6) and C3H/HeJ males (C3)
Model: TgCRND8
Age: 1.5 months
Region: Cortex
Group (sample): 4 AD mice vs. 6 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E51
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6J females (B6) and C3H/HeJ males (C3)
Model: TgCRND8
Age: 3 months
Region: Cortex
Group (sample): 6 AD mice vs. 6 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E52
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6J females (B6) and C3H/HeJ males (C3)
Model: TgCRND8
Age: 4.5 months
Region: Cortex
Group (sample): 3 AD mice vs. 4 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E53
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6Boy mice to SJL/J mice
Model: Tg2576
Age: 3 months
Region: Cortex
Group (sample): 4 AD mice vs. 4 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E54
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: C57Bl/6J
Model: 5XFAD
Age: 3-6 months
Region: Brain
Group (sample): Young WT vs. young 5XFAD
Criteria: FDR < 0.05, |FC| > 1.5
PMID: 24795628
Note: Mouse genes converted to human orthologs
Source: Table 2

Dataset ID: E55
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: C57Bl/6J
Model: APP_PS1KI
Age: 6 months
Region: Brain
Group (sample): 5 AD mice vs. 5 controls
Criteria: FDR < 0.05
PMID: 26639971
Note: Mouse genes converted to human orthologs
Source: Table S2

Dataset ID: E56
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6J females (B6) and C3H/HeJ males (C3)
Dataset ID: E57
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6Boy mice to SJL/J mice
Model: Tg2576
Age: 6 months
Region: Cortex
Group (sample): 4 AD mice vs. 4 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E58
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: C57Bl/6J
Model: APP/PSEN1
Age: 8 months
Region: Prefrontal cortex
Group (sample): 4 AD mice vs. 4 controls
Criteria: FDR < 0.05, |FC| > 1.2
PMID: 30283032
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E59
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: C57Bl/6J
Model: 5xFAD
Age: 6 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): Amyloid plaque-containing (XO4+) vs non-containing (XO4-) microglia
Criteria: FDR < 0.05, |FC| > 1.2
Note: Mouse genes converted to human orthologs
Source: doi.org/10.1101/639054

Dataset ID: E60
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6Boy mice to SJL/J mice
Model: Tg2576
Age: 9 months
Region: Cortex
Group (sample): 4 AD mice vs. 4 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E61
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6J females (B6) and C3H/HeJ males (C3)
Model: TgCRND8
Age: 10 months
Region: Cortex
Group (sample): 7 AD mice vs. 6 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E62
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6Boy mice to SJL/J mice
Model: Tg2576
Age: 12 months
Region: Cortex
Group (sample): 4 AD mice vs. 4 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1
Dataset ID: E63
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between C57BL/6Boy mice to SJL/J mice
Model: Tg2576
Age: 15 months
Region: Cortex
Group (sample): 4 AD mice vs. 4 controls
Criteria: T-test, P < 0.01
PMID: 30189875
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E64
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: C57Bl/6J
Model: 5XFAD
Age: 12 months
Region: Brain
Group (sample): Aged WT vs. aged 5XFAD
Criteria: FDR < 0.05, |FC| > 1.5
PMID: 24795628
Note: Mouse genes converted to human orthologs
Source: Table 5

Dataset ID: E65
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: C57Bl/6J
Model: Tg4_42
Age: 12 months
Region: Brain
Group (sample): Aged WT vs. aged Tg4–42
Criteria: FDR < 0.05, |FC| > 1.5
PMID: 24795628
Note: Mouse genes converted to human orthologs
Source: Table 3

Dataset ID: E66
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA)
Model: rTg4510
Age: 2 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): 4 AD mice vs. 4 controls
Criteria: FDR<0.05 and |FC|>1.5
GEO: GSE123467
PMID: 30558641
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E67
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA)
Model: rTg4510
Age: 4 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): 3 AD mice vs. 3 controls
Criteria: FDR<0.05 and |FC|>1.5
GEO: GSE123467
PMID: 30558641
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E68
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA)
Model: rTg4510
Age: 6 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): 4 AD mice vs. 4 controls
Criteria: FDR<0.05 and |FC|>1.5
GEO: GSE123467
PMID: 30558641
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E69
Taxon: Mouse
Omic: Transcriptome
Method: Bulk RNA-seq
Genetic BG: A cross between FVB/N(TRE-Tau) and 129S6(CaMKIIα-tTA) Model: rTg4510
Age: 8 months
Region: Brain
Cell type: Microglia (Mic)
Group (sample): 3 AD mice vs. 3 controls
Criteria: FDR<0.05 and |FC|>1.5
GEO: GSE123467
PMID: 30558641
Note: Mouse genes converted to human orthologs
Source: Table S1

Dataset ID: E70
Taxon: Mouse
Omic: Proteome
Method: 10-plex tandem mass tag
Genetic BG: Crossing the 5XFAD strain with JNPL3 tau animals
Model: ADLPAPT
Age: 4 months
Region: Hippocampus
Group (sample): 3 AD mice vs. 3 controls
Criteria: p-value<0.05 for the Student’s t-test; FDR<0.05 for the ANOVA test.
PMID: 29338754
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes
Source: Table S3

Dataset ID: E71
Taxon: Mouse
Omic: Proteome
Method: 10-plex tandem mass tag
Genetic BG: Crossing the 5XFAD strain with JNPL3 tau animals
Model: ADLPAPT
Age: 7 months
Region: Hippocampus
Group (sample): 3 AD mice vs. 3 controls
Criteria: p-value<0.05 for the Student’s t-test; FDR<0.05 for the ANOVA test.
PMID: 29338754
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes
Source: Table S3

Dataset ID: E72
Taxon: Mouse
Omic: Proteome
Method: 10-plex tandem mass tag
Genetic BG: Crossing the 5XFAD strain with JNPL3 tau animals
Model: ADLPAPT
Age: 10 months
Region: Hippocampus
Group (sample): 3 AD mice vs. 3 controls
Criteria: p-value<0.05 for the Student’s t-test; FDR<0.05 for the ANOVA test.
PMID: 29338754
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes
Source: Table S3

Dataset ID: E73
Taxon: Mouse
Omic: Proteome
Method: 10-plex tandem mass tag
Genetic BG: C57BL6
Model: 5XFAD
Age: 4 months
Region: Hippocampus
Group (sample): 3 AD mice vs. 3 controls
Criteria: p-value<0.05 for the Student’s t-test; FDR<0.05 for the ANOVA test.
PMID: 29338754
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes
Source: Table S3

Dataset ID: E74
Taxon: Mouse
Omic: Proteome
Method: 10-plex tandem mass tag
Genetic BG: C57BL6
Model: 5XFAD
Age: 7 months
Region: Hippocampus
Group (sample): 3 AD mice vs. 3 controls
Criteria: p-value<0.05 for the Student’s t-test; FDR<0.05 for the ANOVA test.
PMID: 29338754
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes
Source: Table S3

Dataset ID: E75
Taxon: Mouse
Omic: Proteome  
Method: 10-plex tandem mass tag  
Genetic BG: C57BL6  
Model: 5XFAD  
Age: 10 months  
Region: Hippocampus  
Group (sample): 3 AD mice vs. 3 controls  
Criteria: p-value<0.05 for the Student’s t-test; FDR<0.05 for the ANOVA test.  
PMID: 29338754  
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes  
Source: Table S3

Dataset ID: E76  
Taxon: Mouse  
Omic: Proteome  
Method: Tandem mass spectrometry  
Genetic BG: C57BL6  
Model: 5XFAD  
Age: 3 months  
Region: Brain  
Group (sample): 5XFAD_3M vs controls_3M  
Criteria: FDR < 0.05  
PMID: 29186695  
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes  
Source: Integrated DEPs from 5XFAD-3M-Hip, 5XFAD-3M-Cere, and 5XFAD-3M-FC. (Table S2)

Dataset ID: E77  
Taxon: Mouse  
Omic: Proteome  
Method: Tandem mass spectrometry  
Genetic BG: C57BL6  
Model: 5XFAD  
Age: 12 months  
Region: Brain  
Group (sample): 5XFAD_12M vs controls_12M  
Criteria: FDR < 0.05  
PMID: 29186695  
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes  
Source: Integrated DEPs from 5XFAD-12M-Hip, 5XFAD-12M-Cere, and 5XFAD-12M-FC. (Table S2)

Dataset ID: E78
Taxon: Mouse  
Omic: Proteome  
Method: Tandem mass spectrometry  
Genetic BG: C57BL6  
Model: hAPP  
Age: 3 months  
Region: Brain  
Group (sample): hAPP_3M vs controls_3M  
Criteria: FDR < 0.05  
PMID: 29186695  
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes  
Source: Integrated DEPs from hAPP-3M-Hip, hAPP-3M-Cere, and hAPP-3M-FC. (Table S1)

Dataset ID: E79  
Taxon: Mouse  
Omic: Proteome  
Method: Tandem mass spectrometry  
Genetic BG: C57BL6  
Model: hAPP  
Age: 12 months  
Region: Brain  
Group (sample): hAPP_12M vs controls_12M  
Criteria: FDR < 0.05  
PMID: 29186695  
Note: Mouse genes converted to human orthologs. Differentially expressed proteins represented by genes  
Source: Integrated DEPs from hAPP-12M-Hip, hAPP-12M-Cere, and hAPP-12M-FC. (Table S1)

Dataset ID: E80  
Taxon: Fruit fly  
Omic: Transcriptome  
Method: Microarray  
Criteria: FDR < 0.05  
GEO: GSE48681  
PMID: 24336499  
Note: Fruit fly genes converted to human orthologs  
Source: Table S1, 233 (day-matched) and 636 (survival-matched) DEGs, with a total of 712 genes combined

Dataset ID: E81  
Taxon: Fruit fly  
Omic: Transcriptome  
Method: Bulk RNA-seq
Group (sample): eGRL_Aβ42 vs eGRL_Control
Criteria: FDR < 0.05, |FC| > 1.5
PMID: 29598827
Note: Fruit fly genes converted to human orthologs
Source: eGRL_Aβ42 vs eGRL_Control, Table S1

Dataset ID: E82
Taxon: Fruit fly
Omic: Transcriptome
Method: Bulk RNA-seq
Group (sample): GGRL_Tau vs GGRL_Control
Criteria: FDR < 0.05, |FC| > 1.5
PMID: 29598827
Note: Fruit fly genes converted to human orthologs
Source: GGRL_Tau vs GGRL_Control, Table S1

Dataset ID: E83
Taxon: C. elegans
Omic: Transcriptome
Method: Bulk RNA-seq
Criteria: FDR < 0.05, |FC| > 2
PMID: 28982592
Note: C. elegans genes converted to human orthologs
Source: Significant differential expressed genes between N2 and UM0002 (Aβ1–42 + anti-aggregating tau), Table S3

Dataset ID: E84
Taxon: C. elegans
Omic: Transcriptome
Method: Bulk RNA-seq
Criteria: FDR < 0.05, |FC| > 2
PMID: 28982592
Note: C. elegans genes converted to human orthologs
Source: Significant differential expressed genes between N2 and UM0001(Aβ1–42 + pro-aggregating tau), Table S3

Dataset ID: V1
Note: These genes were composed of amyloid seed genes, tauopathy seed genes; late-onset AD common risk genes identified by large-scale genetic studies, and high quality disease gene integration.
Source: Literature

Dataset ID: V2
Note: These genes satisfied at least one of the following conditions: i) gene validation in large-scale amyloid GWAS studies; ii) in vivo experimental model evidence that knockdown or overexpression of the gene leads to AD-like amyloid pathology.
Source: Literature

Dataset ID: V3
Note: These genes satisfied at least one of the following conditions: i) gene validation in large-scale tauopathy GWAS studies; ii) in vivo experimental model evidence that knockdown or overexpression of the gene leads to AD-like tau pathology.
Source: Literature

Dataset ID: V4
Note: The 103 risk genes were predicted based on the hypothesis that the true risk genes are more densely linked with each other in a biological network. Nat Neurosci. 2019;22(5):691-699.
Source: Literature

Dataset ID: V5
Note: 404 genes co-occurring with the biological term Alzheimer in literature-supported statements describing functions of genes from the GeneRIF Biological Term Annotations dataset.
Source: GeneRIF-Biological-Term-Annotations

Dataset ID: V6
Note: 15 genes associated with Alzheimer's disease; Alzheimer's disease in GWAS and other genetic association datasets from the GAD Gene-Disease Associations dataset.
Source: GAD Gene-Disease Associations

Dataset ID: V7
Note: Alzheimer's Disease CNS - Brain - Hippocampus (MMHCC) GSE1297
Source: GEO Signatures of Differentially Expressed Genes for Diseases

Dataset ID: V8
Note: Alzheimer's Disease Entorhinal Cortex GSE5281
Source: GEO Signatures of Differentially Expressed Genes for Diseases

Dataset ID: V9
Note: 33 genes associated with Alzheimer's disease phenotype in GWAS datasets from the GWAS Catalog SNP-Phenotype Associations dataset.
Source: GWAS Catalog SNP-Phenotype Associations

Dataset ID: V10
Note: 34 genes associated with Alzheimer's disease (late onset) phenotype in GWAS datasets from the GWAS Catalog SNP-Phenotype Associations dataset.
Source: GWAS Catalog SNP-Phenotype Associations

Dataset ID: V11
Note: 41 genes associated with Alzheimer's disease (cognitive decline) phenotype in GWAS datasets from the GWAS Catalog SNP-Phenotype Associations dataset.
Source: GWAS Catalog SNP-Phenotype Associations

Dataset ID: V12
Note: 28 proteins participating in Alzheimer's disease pathway from the KEGG Pathways dataset.
Source: KEGG Pathways

Dataset ID: V13
Note: 55 proteins participating in Alzheimer's disease-amyloid secretase pathway from the PANTHER Pathways dataset.
Source: PANTHER Pathways

Dataset ID: V14
Note: 98 proteins participating in Alzheimer's disease-presenilin pathway from the PANTHER Pathways dataset.
Source: PANTHER Pathways

Dataset ID: V15
Note: 66 proteins co-occurring with the biological term Alzheimer in the abstracts of publications describing phosphosites from the Phosphosite Textmining Biological Term Annotations dataset.
Source: Phosphosite Text-mining Biological Term Annotations

Dataset ID: V16
Note: 226 proteins co-occurring with Alzheimer's disease specific cell type in the abstracts of biomedical publications describing phosphosites from the TISSUES Text-mining Tissue Protein Expression Evidence Scores dataset.
Source: TISSUES Text-mining Tissue Protein Expression Evidence Scores

Dataset ID: V17
Note: 79 proteins participating in Alzheimers Disease (Homo sapiens) pathway from the Wikipathways Pathways dataset.
Source: Wikipathways Pathways

Dataset ID: V18
Note: 73 proteins participating in Alzheimers Disease (Mus musculus) pathway from the Wikipathways Pathways dataset.
Source: Wikipathways Pathways

Dataset ID: V19
Note: 17 proteins associated with Alzheimer's disease from the curated PhosphoSitePlus Phosphosite-Disease Associations dataset.
Source: PhosphoSitePlus Phosphosite-Disease Associations

Dataset ID: V20
Note: Overall score>0.3 and S_literature>0. Retrieve on Nov 18th, 2019.
Source: Open Targets

Dataset ID: V21
Note: C0002395, Score_gda>0.3. Retrieve on Nov 18th, 2019.
Source: DisGenet

Dataset ID: V22
Note: C0494463, Score_gda>0.3. Retrieve on Nov 18th, 2019.
Source: DisGenet

Dataset ID: V23
Note: C0750901, Score_gda>0.3. Retrieve on Nov 18th, 2019.
Source: DisGenet

Dataset ID: V24
Note: C0276496, Score_gda>0.3. Retrieve on Nov 18th, 2019.
Source: DisGenet

Dataset ID: V25
Note: Retrieve on Nov 18th, 2019.
Source: ClinVar

Dataset ID: V26
Note: All genes have at least 3 related publications. Retrieve on Nov 18th, 2019.
Source: Phenopedia

Dataset ID: V27
Note: D000544, excluding the gene without direct evidence. Retrieve on Nov 18th, 2019.
Source: The Comparative Toxicogenomics Database (CTD)

Dataset ID: M1
Taxon: Human
Omic: Metabolomics
Method: UPLC-HRMS + HILIC
Region: Brain
Group (sample): 21 late AD vs 19 controls
Criteria: p < 0.05
PMID: 26717242
Note: Semi quantification

Dataset ID: M2
Taxon: Human
Omic: Metabolomics
Method: LC-MS/MS + C18
Region: Serum
Group (sample): 305 late AD vs 370 controls
Criteria: p < 0.05
PMID: 30337153
Note: Absolute quantification