



Original article

# Gliome database: a comprehensive web-based tool to access and analyze glia secretome data

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## Abstract

Glial cells are phenotypically heterogeneous non-neuronal components of the central and peripheral nervous systems. These cells are endowed with diverse functions and molecular machineries to detect and regulate neuronal or their own activities by various secreted mediators, such as proteinaceous factors. In particular, glia-secreted proteins form a basis of a complex network of glia–neuron or glia–glia interactions in health and diseases. In recent years, the analysis and profiling of glial secretomes have raised new expectations for the diagnosis and treatment of neurological disorders due to the vital role of glia in numerous physiological or pathological processes of the nervous system. However, there is no online database of glia-secreted proteins available to facilitate glial research. Here, we developed a user-friendly ‘Gliome’ database (available at [www.gliome.org](http://www.gliome.org)), a web-based tool to access and analyze glia-secreted proteins. The database provides a vast collection of information on 3293 proteins that are released from glia of multiple species and have been reported to have differential functions under diverse experimental conditions. It contains a web-based interface with the following four key features regarding glia-secreted proteins: (i) fundamental information, such as signal peptide, SecretomeP value, functions and Gene Ontology category; (ii) differential expression patterns under distinct experimental conditions; (iii) disease association; and

(iv) interacting proteins. In conclusion, the Gliome database is a comprehensive web-based tool to access and analyze glia-secretome data obtained from diverse experimental settings, whereby it may facilitate the integration of bioinformatics into glial research.

**Database URL:** [www.gliome.org](http://www.gliome.org)

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## Introduction

Glial cells are the most abundant non-neuronal cells in the nervous system. They are a heterogeneous class of cells, comprising astrocytes, microglia, oligodendrocytes and ependymal cells in the central nervous system and Schwann and satellite glial cells in the peripheral nervous system. Glial cells mainly function in the homeostasis and surveillance of neurons and also support and nurture them (1–5). Accumulated evidence has shown that they actively regulate neuronal activity and morphology (6). Glia also participate in synapse remodeling, blood–brain barrier, neurogenesis and neuroinflammation (7, 8).

Glial cells communicate with each other or neurons through the release of signaling molecules, predominantly secretory proteins. Glial secretory proteins play essential roles in mediating various biological processes under healthy or diseased conditions. For example, these proteins initiate intracellular signaling cascades leading to changes in gene expression and inducing cellular processes that include proliferation, differentiation, migration and protein secretion (1, 9).

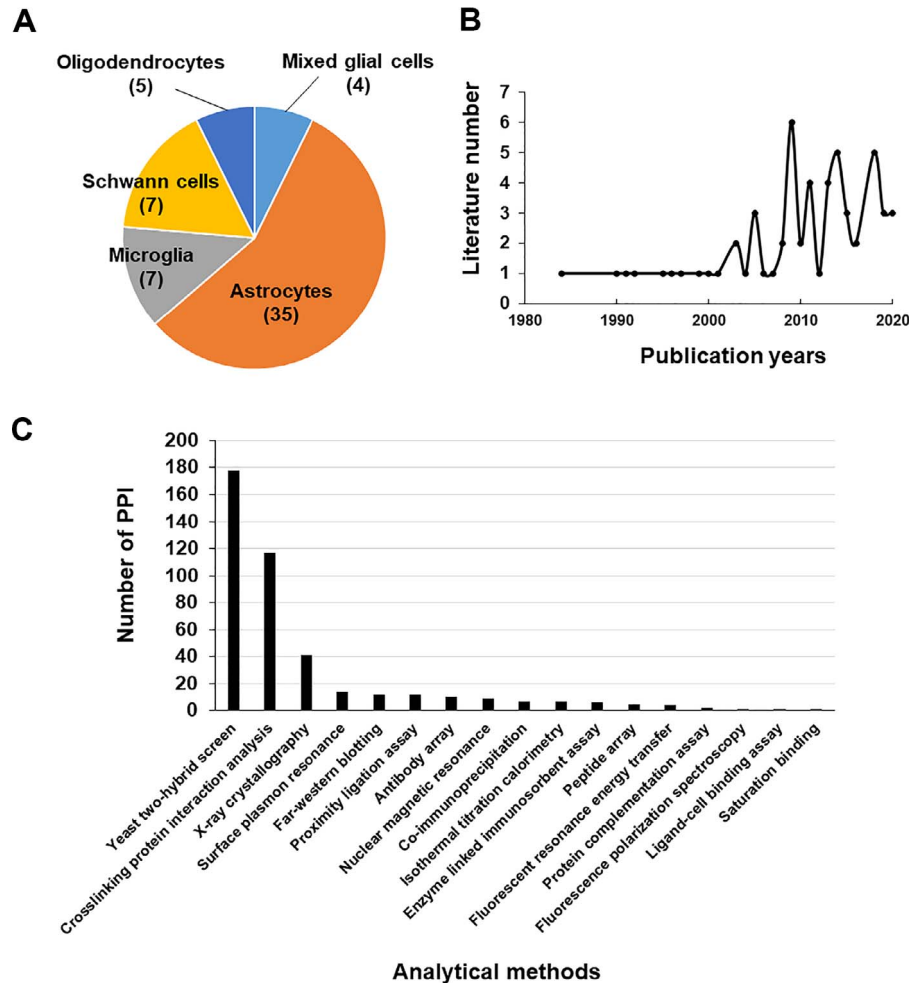
Secretome is a term that denotes all the factors secreted by cells, such as soluble proteins, cytokines (10), growth factors (11), extracellular matrix proteins (12) and shed membrane receptors (13). The secretory proteins typically include a hydrophobic signal peptide at the N-terminus undergo their journey along the biosynthetic-secretory pathway through the endoplasmic reticulum and Golgi apparatus. These are eventually secreted into the extracellular space via the classical, non-classical, extracellular membrane vesicular (14) or exosomal pathways (15). Secretomics is a sub-field of proteomics that involves the analysis of the secretome including the liquid chromatography–mass spectrometry (LC-MS/MS) analysis, enzyme-linked immunosorbent assay (ELISA) or protein array (16, 17). Since secretome plays a myriad of roles ranging from homeostasis to biological regulation, such as intercellular cross-talk (12), coordination of biological activity (18) and disease development (19), secretomics has been a good source for characterizing and quantifying proteins secreted by a given cell under specific experimental conditions and a powerful strategy for discovering disease biomarkers (20–22).

Glial secretome refers to the full set of proteins secreted by glial cells. Currently, glial secretome has been a topic of active interest in biomarker discovery (17, 23, 24). Accordingly, a number of proteomics studies have identified numerous secretory proteins related to various neurological disorders (19, 25–29). For instance, amyloid peptides and their precursors, tau proteins (30), have been identified as potential biomarkers for Alzheimer's disease and alpha-synuclein (31) and apolipoprotein H (32) for Parkinson's disease (33). Nevertheless, there are many hurdles regarding glial secretome analysis. First, secretome analysis can typically be compromised due to contaminations with proteins from cell debris or culture supplements and result in false identification. Second, it is hard to predict whether a protein is secreted or not, since proteins can be secreted via two pathways, by either the canonical (through an N-terminal signal peptide) or non-canonical secretion pathway (34, 35). To overcome these limitations, several bioinformatics tools, such as SignalP (36), SecretomeP (37), TMHMM (38) and WoLFPSORT (39), have been developed that can predict secretory proteins. However, these tools show varying reliabilities of detection in secretome analysis and can be biased. Therefore, a considerable amount of time and effort should be invested to confirm the results. To our knowledge, no specific database for glial secretome presently exists. Thus, a systematic and curated database that can manage the glial secretome data is in high demand. To fill this important gap, we generated the 'Gliome' database, a web-based tool to access and analyze glia-derived secretory proteins. The database provides a set of information about manually curated glia-based experiments as well as the disease associations and protein–protein interactions (PPIs) of glia-secreted proteins. It integrates a diffused glial secretome data and provides a comprehensive platform for glial research.

## Materials and Methods

### Data collection and pre-processing

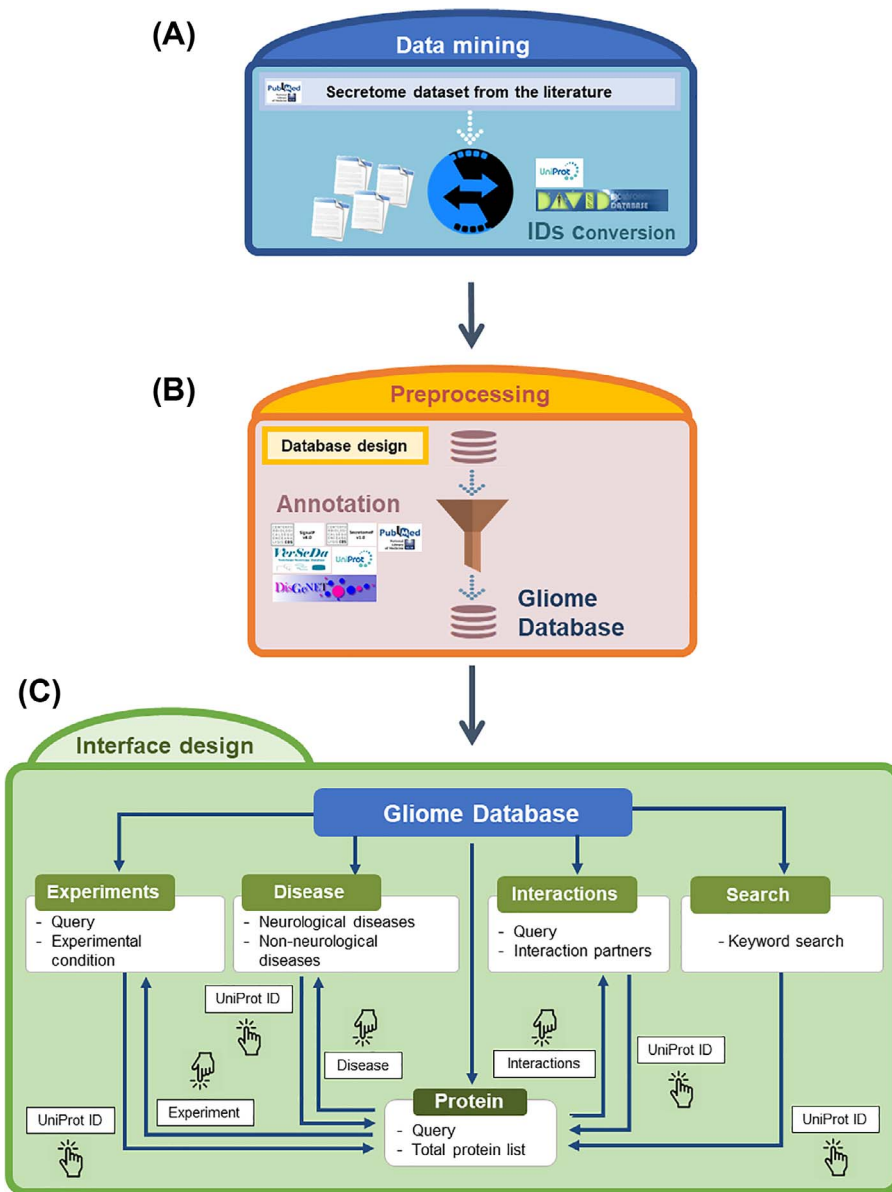
The data in the Gliome database were manually obtained through a comprehensive literature search at the Google Scholar, Scopus and PubMed databases using general keywords, namely 'glia, astrocyte, microglia, oligodendrocyte,



**Figure 1.** Literature used in the Gliome database. (A, B) The distribution of the literature according to glial cell type (A) or the publication year (B). (C) The number of PPIs classified by analytical methods.

Schwann cell, secretome and secretory protein'. To collect all the relevant data, literatures were searched by the following selection criteria: (i) main or supplementary tables containing detailed information on glial proteins, which were identified by secretomic analysis such as LC-MS/MS analysis, ELISA or protein array; (ii) differential expression of glia-secreted proteins under specific stimulation conditions; (iii) experiments related to specific secretory proteins; and (iv) molecular/clinical validation experiments have been performed for the identified biomarkers (glia-secreted proteins). These criteria were used to gather information of secretome analysis, expression level under a certain stimulation, experimental design and relevance to clinical use. Applying these criteria, 58 publications were selected as the data source to collect the relevant data (Figure 1). All the glial secretory proteins found through the literature search were compiled for the generation of the Gliome database (Figure 2). For ID mapping, different types of protein IDs (such as the International Protein Index) were unified to the UniProt ID using UniProtKB (40) and the ID conversion

tool of the Database for Annotation, Visualization and Integrated Discovery (DAVID) Bioinformatics Resources (41). The basic information [such as signal peptide (a discrimination score obtained using the SignalP. Y indicates discrimination score greater than 0.45; N, discrimination score lesser than 0.45). Secretory proteins are indicated by Y.), SecretomeP value (neural network score obtained using the SecretomeP. Non-classically secreted proteins are predicted based on a score greater than 0.5), functions and Gene Ontology functions] about the glial secretory proteins was annotated using the public databases VerSeDa (42), UniProtKB, PubMed, DisGeNet, Scopus and DAVID (Table 1). For searching the publications regarding the PPIs of the glial secretory proteins, all the synonyms for each protein at UniProtKB and Entrez Gene (43) were used. For PPI detection methods, we used the standard nomenclature in two highly verified databases, International Molecular Exchange (<http://imex.sourceforge.net/>) and the PSI-MI controlled vocabulary (<https://www.ebi.ac.uk/ols/ontologies/mi>). Using various combinations of protein names,



**Figure 2.** Overview of the Gliome database. **(A)** Data mining step to obtain the glia secretome information. The obtained protein names are converted into UniProt ID. **(B)** Information is entered according to the database format so that users can browse various types of information. At this step, various external databases were used alongside ours. **(C)** A diagram of navigation at the Gliome database. The protein identifiers of any types were converted into official gene name/UniProt ID.

their synonyms and PPI detection methods, we searched the literature for the physical interactors of glia-secreted proteins. The PubMed and Scopus databases were manually screened for the experimental information related to PPI, whereby 137 articles were identified (Figure 1).

#### Database architecture and web interface

The Gliome database used a MySQL database server version 5.7.22 to store and query the collected data. The web interface was implemented by Ruby on Rails version 5.1.4, a server-side web application framework written in Ruby programming language. The system runs on a Phusion

Passenger application server version 5.2.3 and an Nginx HTTP server version 1.12.2 hosted on an Ubuntu Linux server version 16.04.2 LTS. HTML5, CSS and JavaScript were used for building the client-side user interfaces. We also utilized jQuery 3.2, Semantic UI version 2.3.1 and Font Awesome version 4.7.0 to generate a user-friendly interface.

#### Results

##### The structure of the Gliome database

The Gliome database was structured to provide the following: (i) a straightforward searchable depository for glial

**Table 1.** The websites of the public databases used in this work

Database	URL	Description
Google Scholar	<a href="https://scholar.google.com/">https://scholar.google.com/</a>	Google Scholar provides a simple way to broadly search for scholarly literature.
Scopus	<a href="https://www.scopus.com">https://www.scopus.com</a>	Scopus is an extensive, multidisciplinary database of peer-reviewed literature.
PubMed	<a href="https://www.ncbi.nlm.nih.gov/pubmed/">https://www.ncbi.nlm.nih.gov/pubmed/</a>	PubMed is a free search engine to access primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.
SignalP	<a href="http://www.cbs.dtu.dk/services/SignalP/">http://www.cbs.dtu.dk/services/SignalP/</a>	The SignalP 5.0 server predicts the presence of signal peptides and the location of their cleavage sites in proteins.
SecretomeP	<a href="http://www.cbs.dtu.dk/services/SecretomeP/">http://www.cbs.dtu.dk/services/SecretomeP/</a>	The SecretomeP 2.0 server performs <i>ab initio</i> prediction of classical vs. non-classical secretion.
DisGeNet	<a href="https://www.disgenet.org/">https://www.disgenet.org/</a>	DisGeNet is a discovery platform containing one of the largest publicly available collections of genes and variants associated with human diseases.
DAVID	<a href="https://david.ncifcrf.gov/">https://david.ncifcrf.gov/</a>	DAVID provides a comprehensive set of functional annotation tools for investigators to understand the biological roles of a large list of genes.
IMEx	<a href="http://imex.sourceforge.net/">http://imex.sourceforge.net/</a>	IMEx is a consortium that makes a data resource, which enables the user to download, combine, visualize and analyze data in a single format from multiple resources.
PSI-MI CV	<a href="https://www.ebi.ac.uk/ols/ontologies/mi">https://www.ebi.ac.uk/ols/ontologies/mi</a>	PSI-MI CV is a structured and controlled vocabulary for the annotation of experiments concerned with PPIs.
VerSeDa	<a href="http://genomics.cicbiogune.es/VerSeDa/index.php">http://genomics.cicbiogune.es/VerSeDa/index.php</a>	VerSeDa has been developed to accelerate the prediction process for whole secretomes (the full set of secreted proteins by a given organism).
UniProtKB	<a href="https://www.uniprot.org/">https://www.uniprot.org/</a>	The UniProtKB is the central hub for the collection of functional information on proteins, with accurate, consistent and rich annotation.

DAVID indicates Database for Annotation, Visualization and Integrated Discovery Bioinformatics Resources; IMEX, International Molecular Exchange; PSI, Proteomics Standards Initiative; MI, Molecular Interactions; CV, controlled vocabulary; VerSeDa, Vertebrate Secretome Database; UniProt Knowledgebase, UniProtKB.

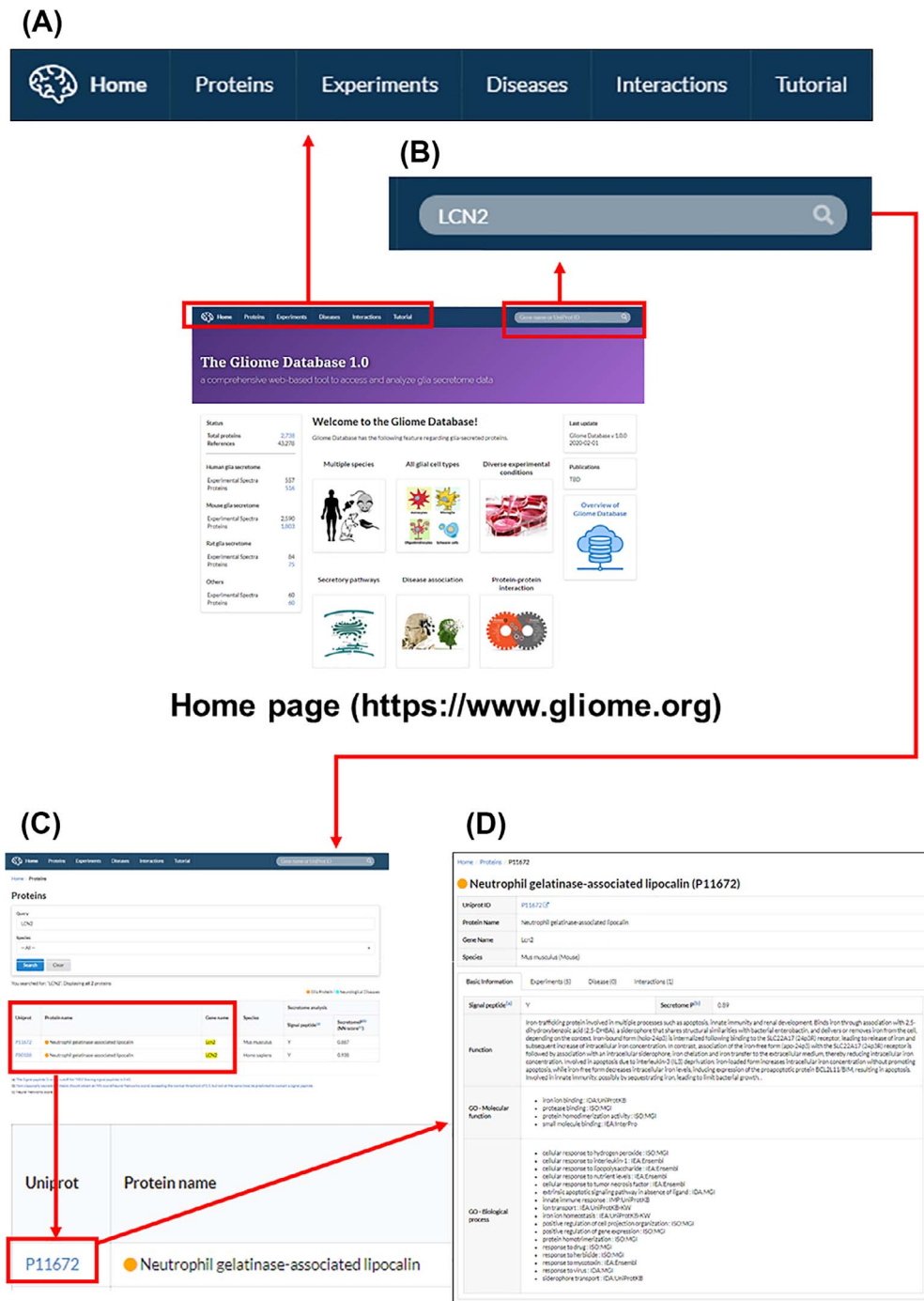
secretory proteins and basic information about them, such as secretory pathway and functions; (ii) information across different secretome measurements; (iii) disease relevance; and (iv) prediction of the protein interactors of each glial secretory protein. Therefore, the Gliome database comprises glial secretory proteins characterized in various studies and provides information about the annotation of these proteins and predictions about their functions.

### Web interface

The Gliome database home page includes database status and a brief introduction of the database within four major lines: (i) information retrieval about glia-secreted proteins, (ii) analysis of differential protein expression under specific conditions, (iii) disease associations of glia-secreted proteins and (iv) PPIs of glia-secreted proteins (Figures 2 and 3). On top of the home page, we implemented the query window that allows users for a quick protein search (Figure 3). To query, the users first need to specify a gene

name or UniProt ID. Entering a search term (gene name or UniProt ID) opens the list table that contains the search term in any field. When users click the UniProt ID in the table, the detailed information about the queried protein appears.

The Gliome database contains four main tabs designed for different purposes. Users can utilize the database by clicking ‘Proteins’, ‘Experiments’, ‘Diseases’ and ‘Interactions’ (Figure 4). The Gliome database also provides instructions in the ‘Tutorial’ section. The browser that appears after clicking ‘Proteins’ tab includes a query box and the whole protein list. Users can choose species using the optional drop-down menu. If users enter a gene name or UniProt ID on the query box and select species using the drop-down menu, a result table will be displayed. By clicking the UniProt ID, users can browse the summary table of basic protein information, including existence (Y)/non-existence (N) of a signal peptide, SecretomeP value, general function and GO functions. At the same time, users can access associated experiments, disease or



**Figure 3.** The main page and appearance of the Gliome database. (A) Main tabs, (B) quick search window, (C) protein list, (D) protein information. When a user enters a protein name, such as ‘LCN2’, on the quick search window, the page of LCN2 protein appears. By clicking the UniProt ID, the relevant detailed information can be obtained.

protein interactions using beside tabs. ‘Experiments’ tab at the top of the main page shows the page of drop-down menus and a complete list of experiments. This page was designed to allow users to browse through the experiments associated with the protein of interest or to simulate an experiment. Users can select a glial cell

type and experimental stimulus and browse glial secretory proteins under a selected experimental condition. Clicking the UniProt ID or References returns to the page of protein information or publication at the PubMed database. The ‘Diseases’ tab provides a list of the proteins associated with the queried disease of interest. Entering a disease name

# Proteins

# Experiments

Home Proteins Experiments Diseases Interactions Tutorial

Home Proteins

Query:

Species:

Search Clear

Displaying proteins 1 - 25 of 2564 total

UniProt	Protein name	Gene name	Species	Secretion analysis
P00075	① Dihydropyridase	DHP	Mus musculus	N
P00087	① NADH dehydrogenase [ubiquinone]	ND5B3	Homo sapiens	N
P00090	① Succinate dehydrogenase, mitochondrial	SDH	Homo sapiens	N
P00411	① Succinyl-CoA lyase [Co-2S]	SCL1	Homo sapiens	N
P00412	① Hippocampine gamma-aminobutyrate lyase	Hprt1	Mus musculus	N
P00522	① Epidermal growth factor receptor	EGFR	Homo sapiens	N
P00663	① Ribonuclease pancreatic	RNase1	Mus musculus	Y
P00667	① Alpha-amylase 1	Amy1	Mus musculus	Y
P00790	① Tissue-type plasminogen activator	PLAT	Homo sapiens	Y
P00798	① Pro-cathepsin H	Csh	Rattus norvegicus	Y

Home Proteins Experiments Diseases Interactions Tutorial

Home Experiments

UniProt ID:

Stimulation:

Search Clear

Displaying experiments 1 - 25 of 2293 total

UniProt ID	Protein Name	Gene name	Species	Sample type	Sample type for Analysis	Stimulation	Treatment Duration (hr)	Mass Spectrometry Platform	Ratio change (RelativeAbundance)	References
P00002	① Fucosyl transferase alpha-L	Ablcc	Mouse	BV-2 microglia	CM	LPS-100 ng/ml + IFN-gamma-100 U/ml	12	Fragstar L20 linear ion trap mass spectrometer	0.0	Kim, S. et al. J Neurochem, 2007,107
Q10815	① AMP deaminase 2	Ampd2	Mouse	BV-2 microglia	CM	LPS-100 ng/ml + IFN-gamma-100 U/ml	12	Fragstar L20 linear ion trap mass spectrometer	0.0	Kim, S. et al. J Neurochem, 2007,107
P00007	① Complement C3	C3	Mouse	BV-2 microglia	CM	LPS-100 ng/ml + IFN-gamma-100 U/ml	12	Fragstar L20 linear ion trap mass spectrometer	0.0	Kim, S. et al. J Neurochem, 2007,107
P00160	① Complement factor B	Cfb	Mouse	BV-2 microglia	CM	LPS-100 ng/ml + IFN-gamma-100 U/ml	12	Fragstar L20 linear ion trap mass spectrometer	0.0	Kim, S. et al. J Neurochem, 2007,107



Home Proteins Experiments Diseases Interactions Tutorial

Home Diseases

Search:

Displaying entries 1 - 25 of 142 total

Protein Name	Gene Name	UniProt ID	Disease Name	References
① Neocentropomyx-like associated complex subunit alpha, muscle specific, form	Nxa	P70670	Alzheimer's Disease	Kim, S. H. et al. J Invertebr Med, 2002
① Neocentropomyx-like associated complex subunit alpha	Nxa	Q10817	Alzheimer's Disease	Kim, S. H. et al. J Invertebr Med, 2002
① Phosphatase-related protein 2	Prr2	Q12240	Alzheimer's Disease	Lubin, W. S. et al. J Neurosci Res, 1997
① Low-density lipoprotein receptor-related protein 8	Lrp8	Q80172	Alzheimer's Disease	De Paoli, G. V. et al. Physiol Nat Acad Sci 10131A, 2007; Alesson, M. A. et al. Neurobiol Aging, 2013
① C1s related factor	C1s1	Q80992	Alzheimer's Disease	Gao, Q. et al. Neurobiol Aging, 2012
① NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8, mitochondrial	ND6P8	Q10605	Alzheimer's Disease	Frank, S. M. et al. J Alzheimer Dis, 2004
① Superficial domain [Co-2S]	Scl1	P00229	Alzheimer's Disease	Kim, G. E. et al. Drug Metab Res, 1999 and 20 others
① Carcinoembryonic antigen	Ce	P13435	Alzheimer's Disease	Squitti, R. et al. J Neural Transm (Vienna), 2007 and 11 others
① Carcinoembryonic antigen	Ce	Q81147	Alzheimer's Disease	Squitti, R. et al. J Neural Transm (Vienna), 2007 and 11 others
① Haptoglobin	Hp	Q13444	Alzheimer's Disease	Toussaint, M. S. et al. ACS Chem Neurosci, 2015; Elstner, R. et al. J Clin Pathol, 2006, 59:6

Home Proteins Experiments Diseases Interactions Tutorial

Home Interactions

Search:

Displaying interactions 1 - 25 of 122 total

Secreted protein	Interaction protein						
UniProt ID	Protein name	Gene name	UniProt ID	Protein name	Gene name	Method	References
A20358	① Titin	Ttn	Q10C42	① Actin-binding domain-containing protein 1	Ankrd1	Yeast two-hybrid screen	Almouzni, G. et al. J Cell Biol, 2006
Q00353	① Dihydropyridase-related protein 2	Dhp2	Q10G24	① Dihydropyridase-related protein 5	Dhp5	Yeast two-hybrid screen	Sakaki, M. et al. J Biol Chem, 2003
Q00709	① Peroxisomal protein 6	Pp6b	Q10000	① Nuclear receptor core coactivator 3	Nco3	Yeast two-hybrid screen	Perez-Ferns, M. et al. 2004
Q00549	① Heterogeneous nuclear ribonucleoproteins A2/B1	Hnpa2b1	P04154	① Major prion protein	Prnp	far western blotting	Strick, A. et al. J Proteomics, 2006
P00492	① Hippocampine gamma-aminobutyrate lyase	Hprt1	P00493	① Hippocampine gamma-aminobutyrate lyase	Hprt1	Yeast two-hybrid screen	Suh, K. H. et al. J Neurochem, 2002
P00007	① Complement C3	C3	Q10C02	① Autochaperonin-related protein 16-1	Atp161	Co-immunoprecipitation	Soriano, M. et al. J Cell Mol Med, 2005
P00468	① Lamrin subunit gamma 1	Lam1	P00493	① Nidogen-1	Nid1	X-ray crystallography	Tang, J. J. J Biol Chem, 2000

# Diseases

# Interactions

**Figure 4.** Gliome database navigation. The main tab at the top of the homepage is hyperlinked with four major informative browsers including protein information ('Proteins'), experiments ('Experiments'), associated diseases ('Diseases') and PPI ('Interactions').

(auto-completion) displays the protein names, UniProt IDs and References. The 'Interactions' page offers a manually curated protein interaction of each protein and related analytical methods.

## Discussion

The goal of the Gliome database is to answer several important questions. (i) Is the protein of interest secreted? (ii) What is the cellular origin of the secretory protein of interest? (iii) Has the secretory protein of interest been experimentally investigated? (iv) Is the protein of interest relevant to human diseases? (v) Is there any protein that interacts with the secretory protein of interest?

Our database provides well-summarized fundamental information on glia-secreted proteins. The basic information may be useful to predict the biological functions of novel glial proteins and to determine whether a protein of interest has a canonical or non-canonical secretory pathway. Secretory proteins were grouped according to glial cell types and stimulation conditions in the 'Experiments' tab so that one can easily identify the glial cell type and experimental condition from which a particular protein of interest was derived. Moreover, as the glial secretome reflects various states of the nervous system under a given condition in real time (24), it is a potentially rich source of biomarkers. Accordingly, a set of glial secretory proteins associated with diseases may be a fundamental source for disease-specific

biomarkers or therapeutic targets (44). Recently, the role of glia-derived exosome or extracellular vesicle (EV) proteins in neuron–glia communication and neurological disease has been emerging (45, 46). EVs from ALS patients and animal models contained many misfolded proteins mainly released by astrocytes, implying the deleterious role of astrocytes in ALS pathology (47), and the stimulation of astrocytes with proinflammatory or anti-inflammatory cytokines results in the release of neurotoxic or neuroprotective proteins in EVs, respectively (48). Therefore, our database provides information about a broad range of glial secretome.

Furthermore, our database provides information about the PPIs of glia-secreted proteins. PPI plays a fundamental role in virtually all biological processes. The identification of the interacting proteins of specific glia-secreted proteins may deepen our understanding of the mechanisms by which the glial proteins act and glia regulate the nervous system. This will lead to the discovery of mechanism-based drug targets and the optimization of treatment strategies (49). In our database, the manually curated PPI information was included together with other public PPI databases, such as IntAt, MINT and STRING, to provide high-confident experimental information. Therefore, the Gliome database is equipped with more accurate PPI information of glia-secreted proteins, which may be helpful for clinical usage in the future.

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*Conflict of interest.* The authors declare no competing interest.

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