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PROTOCOLS AND METHODS

ABCD: Alzheimer's disease Biomarkers Comprehensive Database

Ashwani Kumar[1] · **Ankush Bansal**[1] · **Tiratha Raj Singh**[1]

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Abstract
Alzheimer's disease (AD) is an age-related, non-reversible, and progressive brain disorder. Memory loss, confusion, and personality changes are major symptoms noticed. AD ultimately leads to a severe loss of mental function. Due to lack of effective biomarkers, no effective medication was available for the complete treatment of AD. There is a need to provide all AD-related essential information to the scientific community. Our resource Alzheimer's disease Biomarkers Comprehensive Database (ABCD) is being planned to accomplish this objective. ABCD is a huge collection of AD-related data of molecular markers. The web interface contains information concerning the proteins, genes, transcription factors, SNPs, miRNAs, mitochondrial genes, and expressed genes implicated in AD pathogenesis. In addition to the molecular-level data, the database has information for animal models, medicinal candidates and pathways involved in the AD and some image data for AD patients. ABCD is coupled with some major external resources where the user can retrieve additional general information about the disease. The database was designed in such a manner that user can extract meaningful information about gene, protein, pathway, and regulatory elements based search options. This database is unique in the sense that it is completely dedicated to specific neurological disorder i.e. AD. Further advance options like AD-affected brain image data of patients and structural compound level information add values to our database. Features of this database enable users to extract, analyze and display information related to a disease in many different ways. The database is available for academic purpose and accessible at http://www.bioinfoindia.org/abcd.

Keywords Dementia · Alzheimer's disease · Database · Gene expression · Pathways

Introduction

Social development, better living conditions, and medical advances lead to the fact that more people have the opportunity to live longer than in the past. The aging population is a characteristic feature of demographic trends in developed countries. This trend is closely linked with the issue of increasing number of diseases in old age. The most frequently mentioned diseases in old age include dementia (Odle 2003). Dementia could be a syndrome, sometimes of a chronic or progressive nature, caused by the spread of brain disorder that have an effect on memory, thinking, and behavior to perform everyday activities. Alzheimer's disease (AD) is the most common form of dementia (Román 2002).

AD is characterized by an incurable progressive decline in psychological activities. Current treatment for the disease prescribed by food and drug administration (FDA) is basically symptomatic and relies on three enzyme inhibitors which are donepezil, rivastigmine, and galantamine, affecting acetylcholine-based system, whereas memantine, affecting the glutamatergic system (Hogan 2007). Since 2003, no new medicines are being approved by FDA for the treatment of AD. Mostly AD targeted the individuals aged higher than 65 years (Hung and Fu 2017). AD research is going on from long time, still there is no permanent cure that stops or reverses the progression of the disease which ultimately worsens the situation, and afterward results in the death of sufferers (Foley et al. 2019). Presently, there is no specific biomarker available which can be considered as medicinal drug target for AD identification and diagnosis that may make sure with a 100% certainty regarding AD identification. The challenges in front of scientific community include understanding of abnormalities in gene regulation, protein–protein interactions, and the consequent alterations

✉ Tiratha Raj Singh
tiratharaj@gmail.com

[1] Department of Biotechnology and Bioinformatics, Jaypee University of Information Technology, Waknaghat, Solan, Himachal Pradesh 173234, India

in signaling and metabolic pathways result in AD (Vasaikar et al. 2013). Advancement in medical technology cause better health conditions as a consequence of which number of people of old age increases and dementia like conditions arises. Amyloid precursor protein (APP), Presenilin-1 (PS-1), Presenilin-2 (PS-2), and Apolipoprotein E-e4 (APOE4) are few key genes that are known to be involved in AD progression (McKhann et al. 2011), but their overall contribution is very little or too little in relation to available dementia data. There is an urgent need for substantial advances in the research area of biomarkers for assessment of risk, identification of causal factors, and disease progression monitoring (Privitera et al. 2015). Continuing efforts are still going on to achieve success, this includes developing medicines that would slow progression, halt, or prevent AD. Current studies on AD are underway to spot biomarkers for diagnosing and new medical specialty to hinder disease progression. Acceleration in the biomarker identification, disease prognosis, and diagnosis has been observed through the development of various specific repositories as the information provided can be helpful in planning the experiments. Therefore, our objective was to collect and consolidate this data in a single repository for assessing different AD biomarkers (Kinoshita and Clark 2007). Keeping in view of the above studies and available data, we designed and developed Alzheimer's Disease comprehensive database (ABCD); which may be a fully AD dedicated online information portal for storing and retrieving varied elements within the type of information to researchers, academicians, doctors, and caregivers. The amount and type of data available in ABCD is of high quality as all the data are being manually curated for the final compilation and storage. Most of the data are experimentally either computationally validated or experimentally verified as collected from the authentic published biomedical literature.

Exponential growth of biological experimental data and the development of new tools made it easier for the research community to analyze AD data (de la Torre 2004; Panigrahi and Singh 2013; Kumar and Singh 2017; Panigrahi et al. 2018). The bottleneck of AD study lies in data analysis, because the complexity of data analysis depends on multitude of databases, tools, and heterogeneity of data involved in the study (Thangam and Gopal 2015). We have a tendency to collate associated data related to AD that is scattered in various web-based resources and literature for the analysis of increasingly massive biological information of AD.

The information in the form of data available in ABCD is open access to all except image section which can be accessed only by the user after accepting some term and condition and allows user to easily browse the data associated with AD and their related molecular consequences. In addition, network-level understanding of pathways using concrete information can help scientific community to pave a path to resolve AD complexity. Molecular-level information retrieval portal can interrogate the information from user-friendly interface. ABCD database management system architecture is shown in Fig. 1. Its comprehensiveness, standardization, free availability, ease of accessibility use, and support of different user profiles make ABCD a resource of choice to the scientific community.

Materials and methods

ABCD is fabricated as a relational database implemented in MySQL language with a web interface that was developed in PHP using phpMyAdmin platform and hosted through Apache http server (Meloni 2012). Figure 2 shows the manually designed entity–relationship (ER) model for ABCD to establish causal relation between different entities of AD. Figure 3 represents the architecture of ABCD which describes that data extraction from literature and other external resources and their in-between association which allows user to access and retrieve information in an easy way.

Large data collection from standard resource in ABCD

The data stored in ABCD database have been collected from literature and online resources like PubMed, PMC, Google Scholar, Medical Literature Analysis and Retrieval System Online (MEDLINE), and NCBI (National Center for Biotechnology Information) (Greenhalgh 1997). ABCD contains genes, proteins, SNPs, and microRNAs (miRNAs) which collaboratively provide gene regulatory information to the researcher. For miRNA-related data, the user may get verified information from miRBASE (Kozomara and Griffiths-Jones 2014), an archive of annotated microRNA sequence. A custom PHP script, utilizing the Entrez API, helped us to retrieve molecular data from NCBI resources (Maglott et al. 2011). Information about drugs was retrieved from Chembank (Seiler et al. 2008) and other resources. In addition, ABCD includes manually curated data extracted from the published research articles. The data available in the current version of the ABCD cover 843 publications reporting 499 genes and 767 miRNAs as well as 404 drugs.

ABCD external links

To enrich the contents of ABCD, association with various external databases was established, which includes (1) World health Expectancy for statistics of AD and other diseases, medical subject heading (MESH) (Lipscomb 2000) for medical literatures related to AD; (2) National cell repository for AD (NCRAD) to retrieve genes that increase risk for AD and dementia funded by National

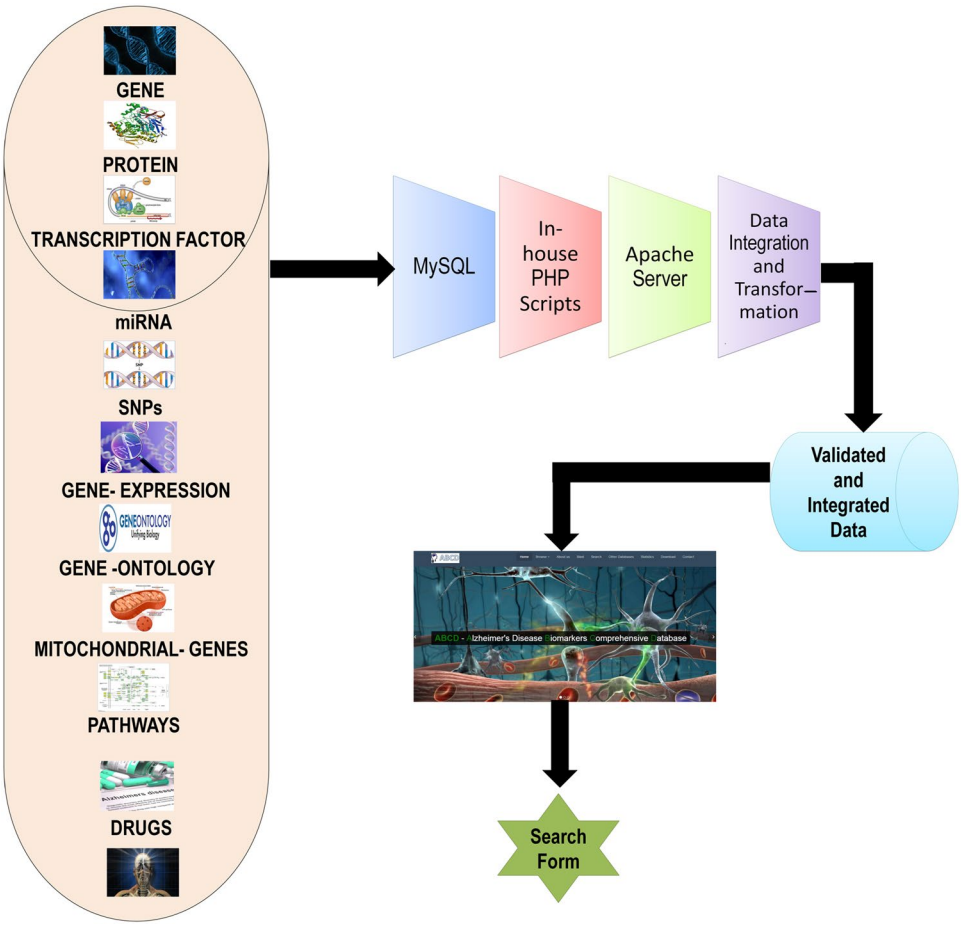


Fig. 1 Workflow for data storage, processing, and searching of useful information for Alzheimer's disease through ABCD platform. It involves GUI through Web technologies [HTML, Java Script, and Cascading Style Sheet (CSS)] and server side technologies along with database systems as Apache, PHP, and MySQL, respectively. Information flow is also being represented to complete the ABCD information architecture

Institute of Ageing (NIA) (Vardarajan et al. 2014). (3) Alzheimer's association is the leading health organization in AD care, support, and research to have information about causes, risk factors, diagnosis, and clinical trials studies such as pharmaceutical categories and therapy indications (McKhann et al. 2011); (4) Alzforum portal contain repository of biomarkers, literature, risks, antibodies, animal model, mutation studies, and therapeutics (Kinoshita and Clark 2007), National Institute of health (NIH), an American department of health for human services have quick link to several institutes under NIH (Strimbu and Tavel 2010). miRBase has more research material linked with miRNAs and endogenous molecules (Griffiths-Jones et al. 2006). In addition, Alzheimer's and related Disorders Society of India (ARDSI) link was also connected with ABCD; which is a body to improve quality of life of people who sufferers of dementia and maintain a record of the people affected by AD in India (Varghese 2012). Apart from the above-mentioned data source, some are also need to mention here like MADAM, MOLGEN, and ICHOLM database from there we collected or cross-checked different molecular entities for AD (Potter 1998; Cruts et al. 2012).

Data interface

The main ABCD interface modules are genes' search, proteins search, gene regulatory information related search, and advanced search. All types of searches in ABCD are of independent types. These allow (1) to navigate in the database by searching genes and proteins by their name and ids. All information related to protein-coding genes is also retrievable by searching protein name or ids. In advanced search, users can search SNPs regions and mitochondrial gene in molecular search option, whereas transcription factors and the co-expressed gene under gene regulatory information search. Drug details, pathway catalogs, and image information of AD-affected brain were provided separately. For each search type, ABCD guides the user by providing sample input to avoid misspelled entries. There are two levels of control checking on inputs, a client side and a server side by applying suitable PHP script. The input nomenclature is based on the official scientific standard commonly used by online databases. The statistics on the ABCD data are reported together with a brief documentation on the usage of the database content.

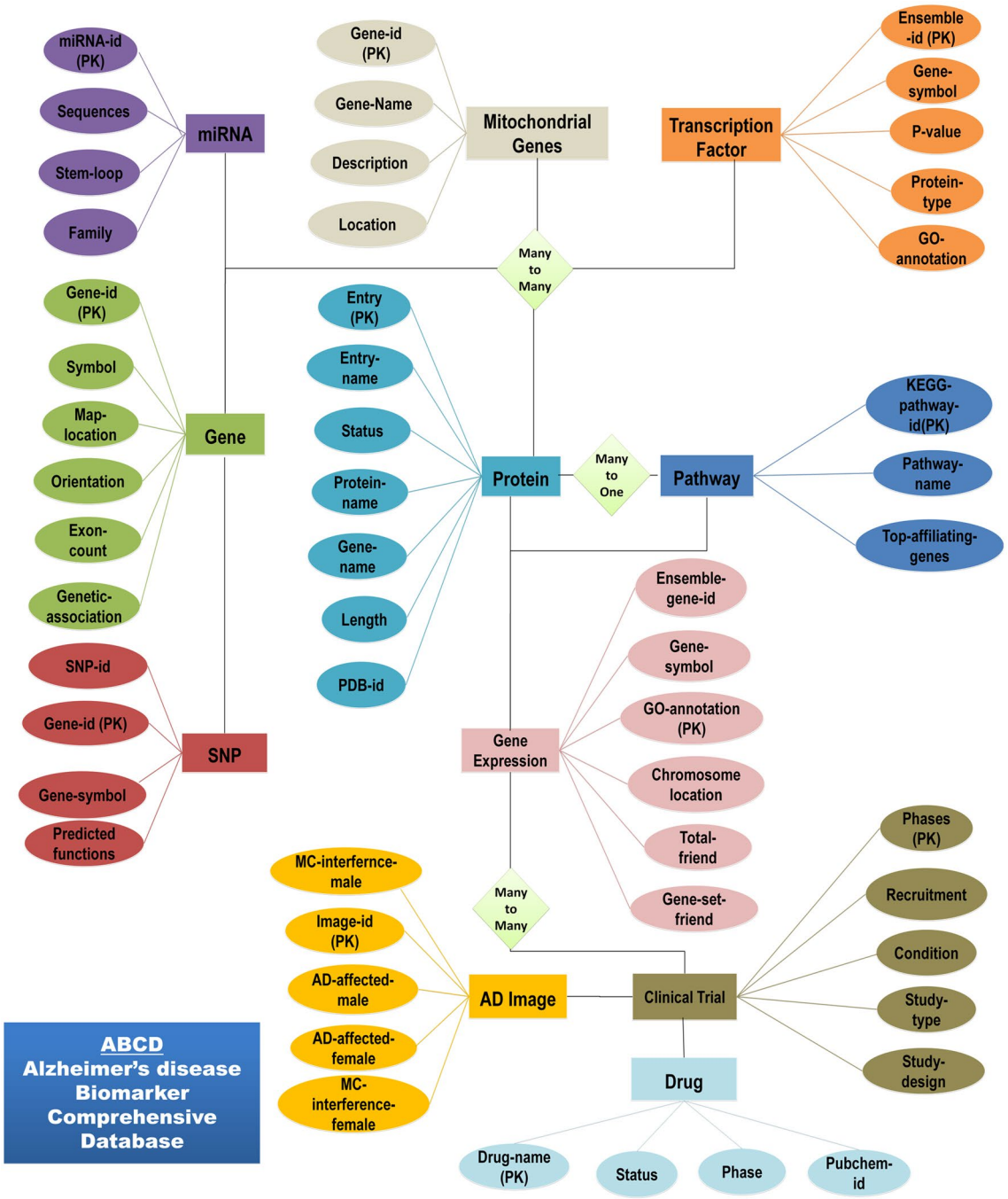
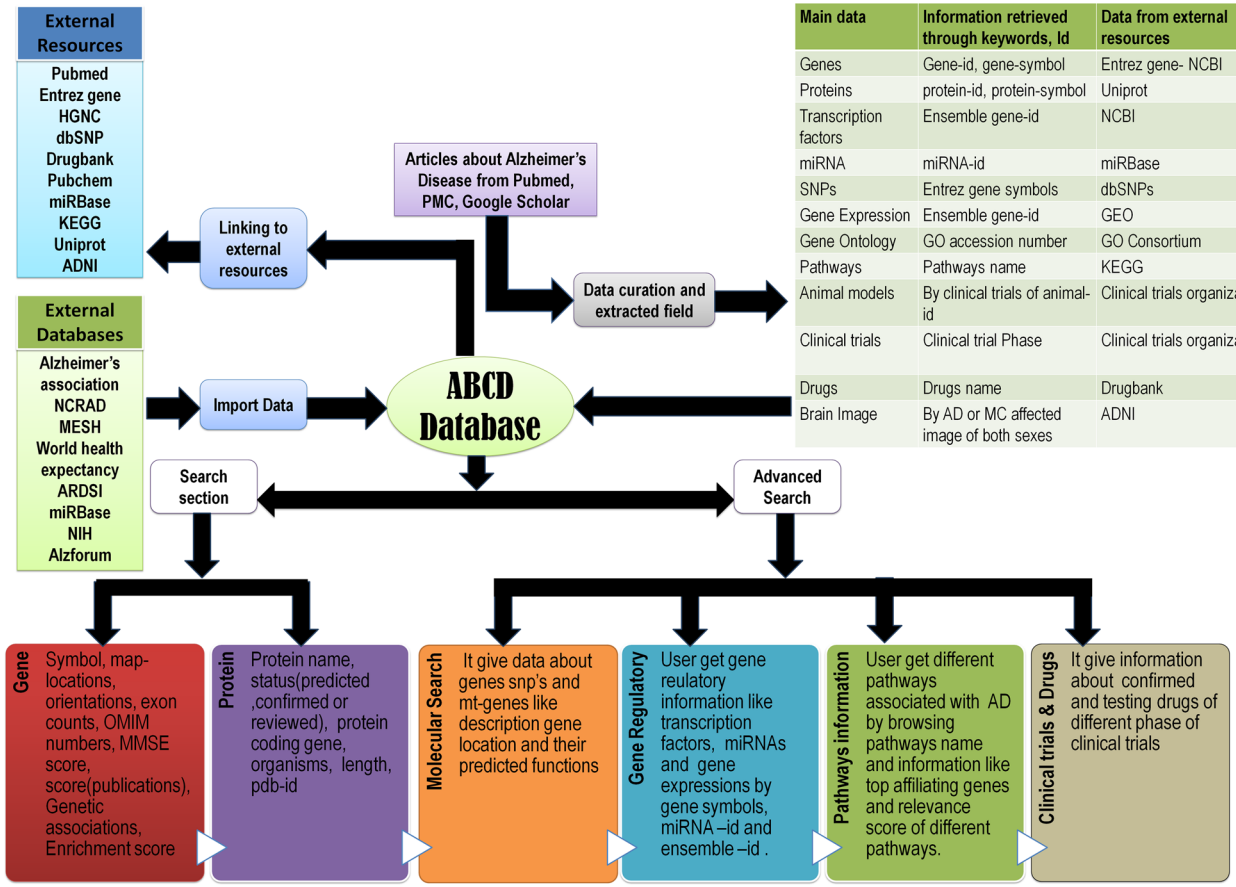


Fig. 2 Entity–Relationship (E–R) diagram for ABCD. Information about the tables and their relationships is being represented through ER diagram. Interconnectivity of biological parameters is elaborated through standard relation parameters of ER representations

Search and advanced search

The search section allows users to query the system by genes and proteins. In the Advanced Search, users can query ABCD by mitochondrial gene, co-expressed gene, SNPs, Transcription factors (TF), miRNA, pathways, and drug target. The drug target section points to genes that are targets of drugs used in the treatments. Genes are specified using the nomenclature of HGNC (Bruford et al. 2008) and Entrezgene by NCBI (Maglott et al. 2011). Drugs are asserted by their names as reported in Chembank (Seiler et al. 2008). SNPs are inserted by rs# number corresponding to the nomenclature in dbSNP (Sherry et al. 2001). Mitochondrial gene, co-expressed gene, and SNPs are also sub-leveled in advanced search option in gene category. Major categories of ABCD are listed as below.



Main data	Information retrieved through keywords, Id	Data from external resources
Genes	Gene-id, gene-symbol	Entrez gene- NCBI
Proteins	protein-id, protein-symbol	Uniprot
Transcription factors	Ensemble gene-id	NCBI
miRNA	miRNA-id	miRBase
SNPs	Entrez gene symbols	dbSNPs
Gene Expression	Ensemble gene-id	GEO
Gene Ontology	GO accession number	GO Consortium
Pathways	Pathways name	KEGG
Animal models	By clinical trials of animal-id	Clinical trials organization
Clinical trials	Clinical trial Phase	Clinical trials organization
Drugs	Drugs name	Drugbank
Brain Image	By AD or MC affected image of both sexes	ADNI

Fig. 3 ABCD architecture, which represents the main features of the ABCD platform. The information type to be searched and explored through ABCD is indicated through hierarchical representations along with basic and advanced search options

Genes

Genes' search shows the location of genes on chromosome and number of exon count with their genetic association and enrichment score describe the overrepresentation of gene from gene set and association with disease phenotype (Hertz et al. 2015). It also reports the co-expressed gene which is expressed in symbiosis and encodes the role of genes.

Proteins

Proteins' search provides important information about protein's physiochemical properties with their structure and function related to AD (Bairoch et al. 2005).

Transcription factor

The transcription factor-related information is being completed for our gene set using DAVID (Dennis et al. 2003).

SNPs

SNPs' search shows the SNPs present in the genes and respective SNP-id is also linked to dbSNP. If the item is not a gene, ABCD shows also the gene name linked to Entrez-gene card or the microRNAs' (miRNAs) access number containing the SNP (Johnson et al. 2008).

miRNA

miRNAs are a family of short, single-stranded 21–22 nucleotides-long non-coding RNAs, constituting about 1% of all human genes and the most abundant class of small RNAs in animals. miRNA option provides information about non-coding gene of AD with chromosomal location and family information about respective miRNA.

Drugs

Drug search shows the gene as a target and also linked to DrugBankV4.2 together with its type and a description, if available. The data are extracted from DrugBank (targets,

transporters, and enzymes) or computed by the DT-Hybrid algorithm (Wishart et al. 2006). For all other data, this section report details on drugs (if any) that have been associated with the searched item. In details, there are gene names linked to Entrez by NCBI (Maglott et al. 2011), endogenous molecules involved, and the actions that the drugs has on the targets. The information about the therapeutical indications, pharmacodynamics, pharmacological action, and eventually the effects of drug on AD, extracted from the indexed articles (Kumar et al. 2019 and references therein), will also be available.

Clinical trials

It contains information about drugs candidates, their descriptions, clinical testing starting–closing dates, stages of phase trials, etc. (Jadad et al. 1996).

Pathways

Pathways gives the list of pathways involved in AD in which top affiliating genes are involved (Mi et al. 2007; Mudunuri et al. 2009).

Image data

AD-affected brain image data are displayed on the basis of patient-id of both male and female (Petersen et al. 2010). Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD.

For each specific data available in the database, users can visualize all details and relations with the genetic elements of which would be reported in the results by clicking search options.

Statistics

Statistics section reports the amount of data by category and Fig. 4 shows the ABCD statistics. The number concerning the manually curated data is the following: 499 genes, 259 proteins, 66 SNPs, 404 drugs, 1608 drug entries for clinical trials data, etc. Here, we also consider mitochondrial genes along with different speciation genes, because epigenetic changes in mitochondrial genes are somehow linked to early onset AD (Johannsen and Ravussin 2009). The data presented in ABCD enriched using external sources like Alzforum, NIH, miRBASE, etc. In addition, the graphical representation of number of death and population subdivided into different age groups affected by AD was shown. Hence, the data collected would be a unified information portal for the AD research community.

Data maintenance

ABCD will be continuously updated, through manual screenings of new publications on PubMed. Therefore, the manual procedures will extract and evaluate genetic- and network-level information which will be incorporated in ABCD at regular intervals. In addition, researchers can suggest new or missing findings to be inserted in the database by contacting authors by filling policy agreement form and send directly to database team in our 'Contact us' page. Agile approach has been adopted in designing; therefore, it is easy to update ABCD at any point of time.

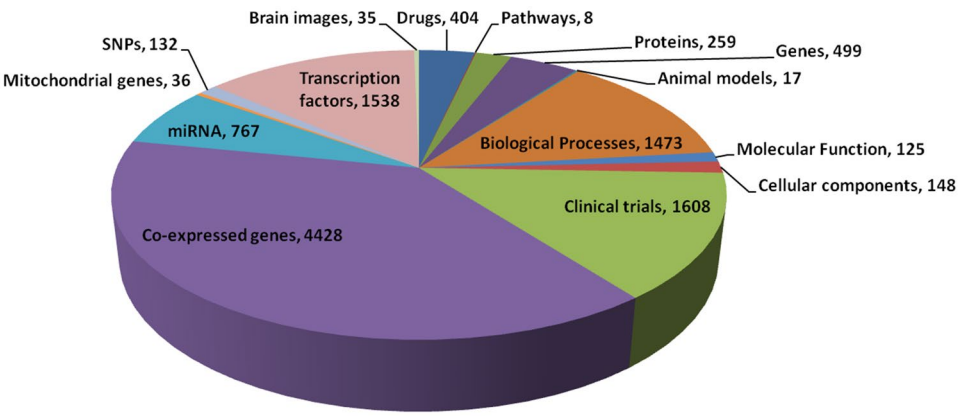


Fig. 4 Data distribution of ABCD, represented through a pie-chart. Here, major types used for the data collection are mentioned along with their respective count as stored in the database

Data distribution

The whole database was developed through standard RDBMS technology with the MySQL and Apache server and is available on http://www.bioinfoindia.org/abcd. Search results (i.e., by gene, protein, MT gene, SNPs, transcription factor, co-expressed genes, drugs, clinical trials, image, and pathways) can be visualized in HTML format through the browse and search section of the menu. Once data are available on HTML page, it can be copied to a relevant source for further usage.

Conclusion

Manual screening of literature and information retrieval from online resources was the major source of data for on fact that ABCD presents solid and reliable information resource for AD. Till date, in molecular level, most studies are conducted on genes and proteins; therefore, the limited biomarkers are available for AD. It joins bits of missing information scattered publicly in the archives and associated publications, into an identical, simply accessible, and often updated information resource. Our resource ABCD will facilitate to offer a comprehensiveness concerning the most genes, proteins, SNPs, drugs, or miRNAs associated within the pathology for AD. These entities are extremely necessary for complicated biological queries underlying AD pathology. Our results show that the number of data that are scattered in numerous resources needs in depth manual effort to be captured at a single platform. In addition, we tend to report that even with comprehensive manual gather; we were not able to capture 100% of information to fill for the fundamental annotation fields. Subsequently, we commit to extend the curation pipeline by adding a lot of options in the form of information for AD particularly. Special feature as raw brain image information was also incorporated for the researcher linked to biomedical neuroimaging. We would like to comprehend our database in future, so that it will cover all the relevant RNA-sequence studies and gene expression analysis, since their massive storage space has contributed to disperse nature of the marker information. The presented database offers great potentials to the scientific world and it is anticipated that ABCD will help the mankind through information dissemination for worldwide monitoring and effective biomarkers search for AD.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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