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# Investigating drug–target interactions in frontotemporal dementia using a network pharmacology approach

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## Abstract

**Background:** Frontotemporal dementia (FTD) is the second most common type of dementia in individuals aged below 65 years with no current cure. Current treatment plan is the administration of multiple medications. This has the issue of causing adverse effects due to unintentional drug–drug interactions. Therefore, there exists an urgent need to propose a novel targeted therapy that can maximize the benefits of FTD-specific drugs while minimizing its associated adverse side effects.

In this study, we implemented the concept of network pharmacology to understand the mechanism underlying FTD and highlight specific drug–gene and drug–drug interactions that can provide an interesting perspective in proposing a targeted therapy against FTD.

**Results:** We constructed protein–protein, drug–gene and drug–drug interaction networks to identify highly connected nodes and analysed their importance in associated enriched pathways. We also performed a historeceptomics analysis to determine tissue-specific drug interactions.

Through this study, we were able to shed light on the APP gene involved in FTD. The APP gene which was previously known to cause FTD cases in a small percentage is now being extensively studied owing to new reports claiming its participation in neurodegeneration. Our findings strengthen this hypothesis as the APP gene was found to have the highest node degree and betweenness centrality in our protein–protein interaction network and formed an essential hub node between disease susceptibility genes and neuroactive ligand–receptors.

Our findings also support the study of FTD being presented as a case of substance abuse. Our protein–protein interaction network highlights the target genes common to substance abuse (nicotine, morphine and cocaine addiction) and neuroactive ligand–receptor interaction pathways, therefore validating the cognitive impairment caused by substance abuse as a symptom of FTD.

**Conclusions:** Our study abandons the one-target one-drug approach and uses networks to define the disease mechanism underlying FTD. We were able to highlight important genes and pathways involved in FTD and analyse their relation with existing drugs that can provide an insight into effective medication management.

**Keywords:** FTD, Network pharmacology, Drug–gene network, Historeceptomics, Substance abuse, APP gene

## 1 Background

Frontotemporal dementia (FTD) is a term given to a group of multi-factorial disorders responsible for young-onset dementia varied by their pathological, genetic and clinical heterogeneity [1]. These disorders result in pathogenic protein accumulation in tiny structures called Pick

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bodies resulting in selective destruction of brain networks, hence giving it the name Pick's disorder [2]. There is no holistic explanation for the variations in FTD but recent studies suggest that mutations in different genes result in behavioural changes, impaired judgment and lack of empathy which varies on a case-to-case basis [3].

Based on the clinical presentation and mutational status, FTD can be classified into 3 distinct types: behavioural variant FTD (bvFTD) [4], semantic variant primary progressive aphasia (svPPA) and nonfluent variant primary progressive aphasia (nfvPPA) [5].

In a FTD patient, the current treatment plan is the administration of multiple medications to manage the physically visible symptoms. This approach is not suitable to many patients and has various drawbacks primarily due to unintentional drug–drug interactions. In the past two decades, the pharmaceutical industry has developed and tested several drugs for psychiatric disorders, including FTD, but it still remains largely unclear the interactions between the drugs and their targeted genes and the possible adverse side effects caused by the interaction between the drugs themselves [6]. In this regard, our study aims to explore the mechanism of drug–gene and drug–drug interactions in FTD to suggest a novel targeted gene therapy. We used the principle of network pharmacology [7] to construct protein–protein, drug–gene and drug–drug interaction networks. We also identified FTD-specific hub nodes, deciphered enriched pathways, isolated potential gene biomarkers and elucidated possible off-target effects.

This study is important as it identifies specific cognitive, behavioural and genetic biomarkers responsible for FTD [8]. This can help future investigators in designing clinical trials and in the recommendation of precision medicine. Based on the type of FTD presented, a physician can suggest an effective treatment that takes into account genetic variability and individual neuropathology.

## 2 Methods

### 2.1 Data retrieval

The DrugBank database (version 5.1.8) [9] is a comprehensive drug database that provides information about drugs and their associated gene targets, indications and pathways. Other relevant information such as the chemical, pharmaceutical, mechanism of action, pharmacodynamics, toxicity, clinical trials and absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of drugs are also listed.

To identify drugs related to FTD, "frontotemporal dementia" was used as a search term. For each drug, the information about its Food and Drug Administration (FDA) status, number of targets, target genes, Universal

Protein Resource (UniProt) ID of the target genes and DrugBank ID was retrieved.

NeuroDNet [10] an open-source platform that hosts a collection of disease models was used to collect the list of susceptible genes, their UniProt IDs and associated disorders linked to these genes.

### 2.2 Functional enrichment analysis

Functional enrichment analysis is a method used to identify pathways of statistical significance. This method recognizes the overrepresented genes and the sub-systems associated with it. This gives us a biological insight into the intersecting pathways that could be affected when a drug is administered. WebGestalt, a Web-based Gene Set Analysis Toolkit [11] was used to interpret and analyse the significantly enriched molecular pathways associated with the target genes.

To perform enrichment analysis, the following steps were followed:

- Homo sapiens, overrepresentation analysis (ORA), pathway and Kyoto Encyclopedia of Genes and Genomes (KEGG) were chosen as the organism of interest, method of enrichment analysis, functional database category and functional database name, respectively. Gene symbol was chosen as the gene ID type, and the list of target genes retrieved from DrugBank was imported into WebGestalt in Text (tab-delimited) format.

- Protein coding genome was selected as the reference gene set for enrichment analysis.

- The Benjamini–Hochberg (BH) procedure was used to control the false discovery rate (FDR) at 0.05.

The enrichment results were displayed in the form of a bar chart (default) and a table in the decreasing order of enrichment ratio. The p-value and FDR values were set to 0.05 as a threshold for significance. The volcano plot is a  $-\log_{10}$  FDR v/s  $+\log_2$  enrichment value plot that can be downloaded to visualize the significantly enriched gene sets. Each gene set from the table was then downloaded in the form of a.csv file for further analysis.

### 2.3 Protein–protein interaction using STRING

To analyse the biological interaction between the target genes and the disease susceptibility genes, protein–protein interaction (PPI) network was constructed using the STRING (Search Tool for the Retrieval of Interacting Genes) v11 database. STRING is a biological database consisting of physical and functional protein–protein interactions derived from public text collections, experimental data, co-expression and genomic context predictions. A text file containing the gene targets (DrugBank) and the disease susceptibility genes (NeuroDNet) was imported into STRING [12].

The network was constructed based on the interaction data provided from text mining, experiments, databases, co-expression, neighbourhood, gene fusion and co-occurrence. The target genes of the drugs represent the nodes and the interactions between them represent the edges in the PPI network. STRING also provides the functional enrichments in a network that include a list of biological processes, molecular functions, cellular components, protein domains, etc. Each function is also provided with a count in the network, strength of interaction and the FDR. The Network Stats provided by STRING consists of the number of nodes, number of edges, average node degree, average local clustering coefficient, expected number of edges and the PPI enrichment *p*-value. A very low *p*-value indicates statistical significance. The biological significance of the network can be assessed by comparing the observed number of edges and the expected number of edges with a *p* value of 0.05 as threshold. If the observed edge count is way higher than the expected edge count, it indicates that the proteins are biologically connected as a group and do not belong to a random set of proteins of similar size.

The interaction network obtained was updated by removing disconnected nodes and by increasing the confidence score to 0.700 (high confidence) to reduce the number of false positives. The resulting network was imported into Cytoscape [13] and was analysed based on the node degree and betweenness centrality values using the network analyser plug-in of Cytoscape.

A high node degree represents a greater interaction with other nodes, and a high betweenness centrality (based on shortest paths) indicates a better reach and connection within the network. These nodes can be classified as hub nodes that form bridges between clusters in a network. These hub nodes play an important role in network architecture and targeting them can result in the impairment of the entire network.

#### 2.4 Drug–gene network analysis and visualization using Cytoscape

Cytoscape 3.8.2 is an open-source, publicly available tool written in Java that is used for network representation and analysis.

To visualize the drug–target interactions for the enriched categories, a Python script was written to read the.csv files downloaded for each enriched gene set from WebGestalt as mentioned earlier. The script mapped the UniProt IDs from each gene set with the respective target drugs from DrugBank as columns into individual.csv files. Each resultant.csv file was imported as networks into Cytoscape. The genes were chosen as source nodes and the drugs as target nodes. The edges correspond to the interaction between the nodes. The individual

networks were merged and analysed based on the node degree and betweenness centrality. The "Style" option was used to change the shape of the drugs and gene targets to ellipse and round rectangle, respectively. The node colour was changed to match the node degree based on continuous mapping. The darker-coloured nodes represented a higher node degree while the lighter-coloured nodes represented a lower node degree.

#### 2.5 Historeceptomics approach

To further evaluate the region of action of multi-target drugs and multi-drug combinations, a historeceptomics analysis was performed. Historeceptomics is a bioinformatics method that integrates tissue specificity with drug–target data.

One can narrow down the common tissues targeted by the FTD drugs and make an educated guess about possible drug–drug interaction at the tissue level using the historeceptomics profiler. Historeceptomics profiler [14] is a tool that assigns a historeceptomics (HR) score to each target–tissue pair of the input drug and ranks them based on the drug's likeness to elicit a phenotype in that tissue. The top five drugs with the highest node degrees were fed as input to the tool. The output table lists the possible targets (proteins/drug receptors) for the specific drug, corresponding tissues displaying the drug activity, target gene, its UniProt ID and the source of the drug (ChEMBL/DrugBank). The score section of the table consists of the Z-score (observed gene expression value in said tissue when compared with the mean of the gene expression values in other tissues), intensity (raw gene expression value), HR score (an amalgamation of drug–target affinity and tissue expression values, a higher score indicates the higher likeness of the drug to bind to that tissue) and the *p* value of the HR score. The common target tissues of the five drugs were tabulated and taken forward for further analysis.

#### 2.6 Drug–drug association network

To analyse the adverse drug–drug interactions among the FTD drugs, drug interactions for each drug were collected from the Drug Interaction Lookup tool by DrugBank.

A Python script was written to extract only the interactions with the FTD drugs present in our drug list. The results were used to construct a drug–drug interaction network in Cytoscape. The drugs depicted as nodes while the edges depicted the adverse drug–drug interactions. The colours of the nodes were changed to reflect the node degree. The darker-coloured nodes represented more interactions in the network while the lighter-coloured nodes represented fewer interactions in the network.

### 3 Results

From the DrugBank database, 55 FTD-related drugs along with their 87 gene targets were retrieved. Among these 55 drugs, 31 drugs are approved, 40 are still in the investigational stage, 2 are in the experimental stage and 3 are withdrawn. The details of the 55 FTD-related drugs, their DrugBank IDs, FDA approval status and the number of targets are given in Table 1. Based on the frequency of interaction, ACHE, DRD2, ADRA1A, HRH1 and BCHE were the top five target genes interacting with the largest number of FTD-related drugs.

From NeuroDNet, a list of 7 FTD susceptible genes were retrieved. Among these, the most prevalent are Microtubule Associated Protein Tau (MAPT) and Granulin Precursor (GRN) as they represent the autosomal dominant inheritance of FTD as given in Table 2.

Using WebGestalt, top 10 enriched pathways were generated. Based on the enrichment ratio, nicotine addiction (ratio=55.419) had the highest overlap between the observed and expected genes, followed by neuroactive ligand–receptor interaction (ratio=18.889) and cocaine addiction (ratio=18.096), whereas based on the expect value, neuroactive ligand–receptor interaction ranked 1. Out of the 10 pathways, 3 pathways were related to substance abuse (nicotine, morphine and cocaine addictions) which suggests that substance abuse and prescription medications such as antinicotinic medication may act on pathways that contribute to cognitive impairment and result in symptoms of dementia and its sub-types [15]. A study also highlighted that exposure to multiple types of strong anticholinergic drugs is associated with an increased risk of dementia [16].

Neuroactive ligand–receptor interaction had the most number of genes (59) as it is involved in neuronal development. The  $p$  values range from (0.00 to  $1.0915 \times 10^{-10}$ ) and FDR values from (0.00 to  $3.5582 \times 10^{-9}$ ). The FDR correction factor removes the false positives. The very low  $p$ -values for the 10 biological pathways indicate that the genes grouped into them are not random but specific to the pathway. These pathways can be viewed in the KEGG database. The result of the enrichment analysis is given in Table 3.

The false discovery rate (FDR) and  $p$ -values were estimated by the Benjamini–Hochberg procedure. The enrichment ratio is calculated as the number of observed genes by the number of expected genes in each of the individual enriched gene sets obtained from KEGG.

To evaluate whether our genes in the PPI network were related, we compared the expected number of edges with the observed number of edges. The observed value (404) was significantly higher than the expected value (55) with the PPI enrichment  $p$  value  $< 1.0 \times 10^{-16}$ , indicating that

the target genes were interconnected and not by random chance.

Protein–protein interaction network showed that the disease susceptibility genes such as MAPT and PSEN1 interact with APP with a high confidence score of 0.949 and 0.998, respectively. MAPT in turn interacts with the rest of the disease susceptibility genes (C9orf72, CHMP2B, GRN, PSEN1, TARDBP and VCP) making APP an essential link between disease susceptibility genes and drug target genes, especially neuroactive ligand–receptors. The target genes common to substance abuse (nicotine, morphine and cocaine addiction) and neuroactive ligand–receptor interaction pathways are the GABAergic genes and ionotropic glutamate receptor genes as shown in Fig. 1.

On analysing the network in Cytoscape, it was found that the APP gene had the highest node degree (31) and betweenness centrality (0.45) and formed an important PPI hub in the network. Other genes with high node degrees include HTR3A, DRD2, HTR1A, CHRM2 and GABRG2.

The individual drug–gene tables created for each of the 10 enriched pathways were imported and merged as networks in Cytoscape. From the Style settings, the gene target and drug node shapes were changed to round rectangle and ellipse, respectively, via discrete mapping. On analysing the merged network, few important statistics are as follows: number of nodes=89, number of edges=149 and average number of neighbours=3.641.

It was observed that the drugs memantine (node degree=29, BC=0.54) and quetiapine (node degree=26, BC=0.39) had the highest node degree and betweenness centrality and hence, stood out in the merged network. Other drugs with high node degree include clonazepam, donepezil, risperidone, propiomazine and trazodone.

Two distinct clusters were identified with donepezil as the bridge drug between the two. Donepezil is an essential enzyme blocker used as a drug to restore the balance of neurotransmitters. It is one of the popular drugs, in combination with memantine, to treat dementia-related disorders. Clonazepam and memantine act as source drugs for GABA and GRN genes. GABA genes are inhibitory neurotransmitters while GRN genes are involved in neuronal proliferation and development. Heterozygous mutations in the GRN genes are a primary cause of FTD. Quetiapine, risperidone, propiomazine and trazodone form the source nodes for many target genes like the adrenergic, serotonergic and acetylcholine receptors. These drugs play a primary role in treating the neuropsychiatric symptoms in dementia and observing their interactions with target genes would be helpful in proposing a novel targeted gene therapy. The drug–target gene interaction network is displayed in Fig. 2.

**Table 1** Summary of frontotemporal dementia drugs, FDA status and number of targets based on DrugBank annotation

Sl. No	DrugBank ID	Generic name	FDA status	# Targets
1	DB00556	Perflutren	Approved	-
2	DB12401	Bromperidol	Approved, investigational	No annotation
3	DB01043	Memantine	Approved, investigational	7
4	DB00372	Thiethylperazine	Approved, withdrawn	1
5	DB00699	Nicergoline	Approved, investigational	1
6	DB01381	Ginkgo biloba	Approved, investigational, nutraceutical	6
7	DB01068	Clonazepam	Approved, illicit	3
8	DB00777	Propiomazine	Approved	6
9	DB00656	Trazodone	Approved, investigational	8
10	DB00620	Triamcinolone	Approved, vet approved	1
11	DB08842	Acetylcarnitine	Approved, investigational	-
12	DB00674	Galantamine	Approved	4
13	DB00382	Tacrine	Approved, investigational, withdrawn	3
14	DB06016	Cariprazine	Approved, investigational	6
15	DB12710	Perazine	Approved, investigational	No annotation
16	DB12867	Benperidol	Approved, investigational	No annotation
17	DB01121	Phenacemide	Approved	1
18	DB00377	Palonosetron	Approved, investigational	1
19	DB00122	Choline	Approved, nutraceutical	8
20	DB00889	Granisetron	Approved, investigational	1
21	DB08870	Brentuximab vedotin	Approved, investigational	1
22	DB00904	Ondansetron	Approved	5
23	DB00433	Prochlorperazine	Approved, vet approved	4
24	DB00843	Donepezil	Approved	8
25	DB00989	Rivastigmine	Approved, investigational	2
26	DB01209	Dezocine	Approved, investigational	2
27	DB11584	Pipradrol	Approved	1
28	DB01224	Quetiapine	Approved	24
29	DB00734	Risperidone	Approved, investigational	13
30	DB09210	Piracetam	Approved, investigational	-
31	DB11239	Aluminium sulphate	Approved	-
32	DB13668	Ipidacrine	Experimental	No annotation
33	DB12969	Methylinositol	Investigational	No annotation
34	DB11756	Solanezumab	Investigational	No annotation
35	DB12034	Gantenerumab	Investigational	No annotation
36	DB04859	Zanapezil	Investigational	1
37	DB13084	Pyritinol	Investigational	No annotation
38	DB12958	Prothipendyl	Investigational	No annotation
39	DB06106	AIT-034	Investigational	No annotation
40	DB12311	CP1-1189	Investigational	No annotation
41	DB05432	DAS-431 IV	Investigational	1
42	DB12930	Opipramol	Investigational	No annotation
43	DB12555	Nelotanserin	Investigational	1
44	DB16214	Landipirdine	Investigational	No annotation
45	DB06504	S-8510	Investigational	No annotation
46	DB11758	Cenicriviroc	Investigational	No annotation
47	DB05180	LX6171	Investigational	-
48	DB06465	FK-960	Investigational	No annotation
49	DB08831	2-deoxyglucose	Experimental, investigational	-

**Table 1** (continued)

Sl. No	DrugBank ID	Generic name	FDA status	# Targets
50	DB06247	CX516	Investigational	1
51	DB05814	GPI-1485	Investigational	1
52	DB05450	Smilagenin	Investigational	No annotation
53	DB12613	Davunetide	Investigational	No annotation
54	DB04892	Phenserine	Investigational	3
55	DB12129	Tideglusib	Investigational, withdrawn	1

**Table 2** Summary of frontotemporal dementia susceptible genes and their associated disorders retrieved from NeuroDNet

FTD susceptible genes	Associated disorders	UniProt ID
C9orf72	Amyotrophic lateral sclerosis (OMIM: 105400) Frontotemporal dementia (OMIM: 600274)	Q96LT7
CHMP2B	Frontotemporal dementia (OMIM: 600274)	Q9UQN3
GRN	Multiple sclerosis (OMIM: 126200) Frontotemporal dementia (OMIM: 600274)	P28799
MAPT	Supranuclear palsy (OMIM: 601104) Dementia, frontotemporal (OMIM: 600274) Dementia (OMIM: 600,274) Supranuclear palsy, progressive atypical (OMIM: 260,540), Pick disease (OMIM: 172,700), Parkinson disease (OMIM: 168,600), tauopathy and respiratory failure (OMIM: 157,140), amyotrophic lateral sclerosis (OMIM: 105,400) Frontotemporal dementia (OMIM: 600274)	P10636
PSEN1	Frontotemporal dementia (OMIM: 600274) Disease (OMIM: 172700) Amyotrophic lateral sclerosis (OMIM: 105400) Alzheimer disease (OMIM: 104300) Cardiomyopathy dilated 1U (OMIM: 613694) Acne inversa (OMIM: 613737) Frontotemporal dementia (OMIM: 600274)	P49768
TARDBP	Amyotrophic lateral sclerosis (OMIM: 105400) Frontotemporal dementia (OMIM: 600274) Frontotemporal dementia (OMIM: 600274)	Q13148
VCP	Frontotemporal dementia (OMIM: 600274) Amyotrophic lateral sclerosis (OMIM: 105400)	P55072

**Table 3** Enriched KEGG pathways in target genes of FTD drugs as identified by WebGestalt

Gene Set	Description	Size	Expect	Ratio	p value	FDR
hsa04080	Neuroactive ligand–receptor interaction	277	2.9	19.9	0	0
hsa04024	cAMP signalling pathway	199	2.1	10.3	0	0
hsa04020	Calcium signalling pathway	183	1.9	11.2	0	0
hsa05032	Morphine addiction	91	0.9	18.4	0	0
hsa05033	Nicotine addiction	40	0.4	58.3	0	0
hsa04727	GABAergic synapse	88	0.9	16.9	4.4E–16	2.4E–14
hsa04726	Serotonergic synapse	115	1.2	12.9	4.0E–14	1.9E–12
hsa04723	Retrograde endocannabinoid signalling	148	1.6	10.7	1.5E–13	6.2E–12
hsa04742	Taste transduction	83	0.9	13.5	5.1E–11	1.8E–09
hsa05030	Cocaine addiction	49	0.5	19.0	6.5E–11	2.1E–09



(See figure on next page.)

**Fig. 1** Protein–protein interaction (PPI) network created using STRING. The nodes represent proteins and the edges represent protein–protein association. The edge confidence is set to high (0.700), and disconnected nodes are hidden in the network. The nodes common to the most enriched pathways, i.e., substance abuse receptors and neuroactive ligand–receptors, are highlighted. Nodes in blue represent nicotine addiction, nodes in green represent cocaine addiction, nodes in yellow represent morphine addiction and nodes in red represent neuroactive ligand–receptor interaction. The edges are coloured based on the following types of interactions: known interactions (turquoise—from curated databases, purple—experimentally determined), predicted interactions (bright green—gene neighbourhood, red—gene fusions, dark blue—gene co-occurrence) and others (yellow—text mining, black—co-expression, light blue—protein homology). The filled nodes show that the 3D structure of the protein is known or predicted

The top 5 drugs with the highest node degree in the drug–target gene interaction network were subjected to historeceptomics analysis and the results were analysed as given in Table 4. It was found that memantine and clonazepam primarily target different regions of the brain such as the amygdala, cerebellum and occipital lobe, while quetiapine and donepezil target the heart and the skeletal muscles. Risperidone, on the other hand, targeted the thymus and the cells of the immune system.

Using the Drug Interaction Lookup tool from Drug-Bank, drug–drug interactions were visualized in Cytoscape. Based on the highest node degree, quetiapine (58), propiomazine (52), ondansetron (48), trazodone (46), risperidone (46) and donepezil (46) were the drugs with the highest interaction. This indicates that a combination of these drugs taken together could result in multiple adverse drug–drug interactions and severe side effects.

Another cause of concern is off-target effects. Off-target effects refer to adverse effects as a result of drugs binding to an unrelated region of interest either due to resemblance to the predicted target or by modulating other targets. The top 6 hub drugs bind to various regions in the body: quetiapine, donepezil and propiomazine (skeletal and heart muscles), ondansetron and risperidone (thymus and liver) and trazodone (brain and liver) and when administered as a combination may result in off-target effects. Therefore, a thorough understanding of the mechanism of each drug and its interaction with other drugs is required to minimize adverse effects and to maximize the efficacy of the drugs. The drug–drug interaction network is displayed in Fig. 3.

#### 4 Discussion

Out of the 55 FTD-related drugs retrieved from Drug-Bank, the drugs with the highest interaction with target genes were memantine, quetiapine, donepezil, risperidone and clonazepam. The expression of these target genes was significantly enriched in the brain, lymph, thymus, heart, liver and thyroid indicating the multi-target effect of these drugs. With the use of multi-target drugs comes the drawback of off-target effects. For effective drug management, it is crucial to select the

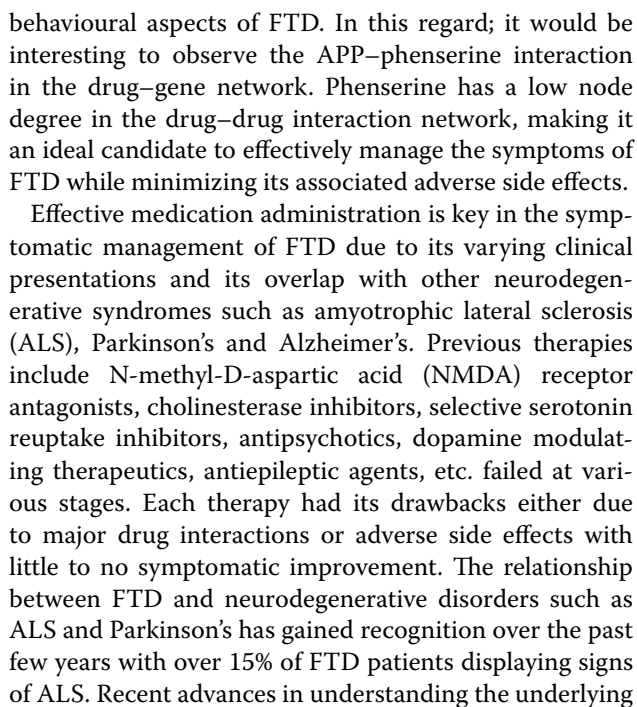
right combination of target drugs and achieve the right balance between them while eliminating undesired target activity, especially in the case of targets belonging to the same family (kinase inhibitors) or having the same functional domain [17].

We performed pathway enrichment analysis to generate the top 10 enriched pathways of which 3 belonged to substance abuse. We also generated a PPI network that displayed the target genes common to substance abuse (nicotine, morphine and cocaine addiction) and neuroactive ligand–receptor interaction pathways to understand the relation between the pathways. The common target genes were the GABAergic and ionotropic glutamate receptor genes primarily responsible for cognition and behaviour. Our findings suggest that certain characteristics of the behavioural variant FTD (bvFTD) such as behavioural disinhibition and impulsivity could be manifested by substance misuse. Previous studies show alcohol and drug use as components preceding, following or accompanying bvFTD, thus substantiating our hypothesis. The past decade has seen a rise in substance abuse in the older population prone to cognitive disorders ranging from prescription misuse to illegal substance use. Clinical treatment providers are therefore being encouraged to monitor substance use patterns in all FTD sub-types [18].

Our study also highlights the importance of the APP gene in FTD which forms an essential link between disease susceptibility genes and drug target genes. Earlier studies restricted the role of the APP gene to inherited FTDs but are now being extensively studied with new reports claiming its participation in neurodegeneration and cognitive impairment. A reduction in APP-derived peptides is now known to affect the amyloidogenic pathway, neuropsychological performance, cortical thickness and cortical gene expression profiles in frontotemporal lobar degeneration [19]. Our findings strengthen this hypothesis as the APP gene was found to have the highest node degree (31) and betweenness centrality (0.45) in our PPI network connecting various cholinergic, dopamine, opioid and adreno receptors that play an important role in neurodegeneration. The APP gene also behaves as a biomarker in identifying specific cognitive and

**Fig. 1** (See legend on previous page.)





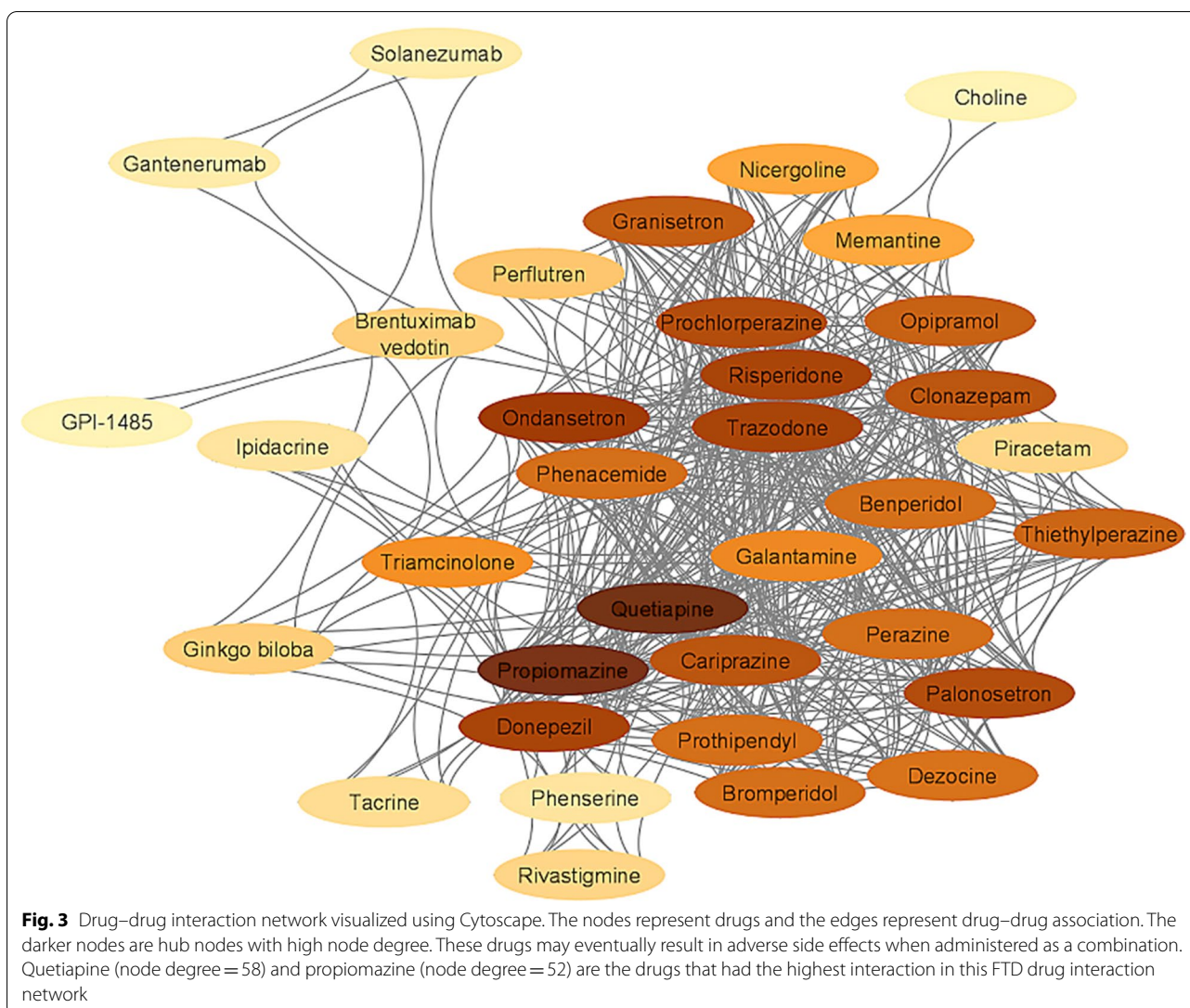
mechanism behind FTD have led to the development of novel targeted therapies at the gene level. Mutations in MAPT (tau) and GRN (progranulin) genes are responsible for FTD-associated Parkinsonism while mutations in the C9orf72 gene are responsible for FTD-ALS. As emphasized earlier, our findings display the APP gene as an important hub linking disease susceptible genes (C9orf72, CHMP2B, GRN, MAPT, PSEN1, TARDBP and VCP) with neuroactive ligand receptors making it an important gene to be targeted in developing a potentially disease-modifying FTD therapy [20].

A major limitation in clinical trials is the lack of information on genetic variability and drug–gene interactions. In the current world of polypharmacy, developing physiologically based pharmacokinetic (PBPK) and drug–drug–gene interaction (DDGI) models can help in the real-time prediction of drug interactions and their possible outcomes [21]. Our study can assist future investigators in incorporating these factors in building reliable models to test clinical studies.

With the advancement in precision medicine, attempts on targeted therapeutics are made based on

**Table 4** Historeceptomics analysis displaying target regions of the top 5 drugs in the drug-gene network

Drug	Tissue	Gene symbol
Memantine	Adrenal cortex, appendix, cardiac myocytes, cd33 myeloid, heart, liver, occipital lobe, pituitary, prefrontal cortex, skeletal muscle, skin, thyroid, whole brain	CDKL3, DRD2, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, GLRA1, GLRA2, GLRA3, GLRB, HTR3A
Quetiapine	Adipocyte, cardiac myocytes, cd33 myeloid, foetal brain, foetal liver, heart, liver, lymph node, pineal, prefrontal cortex, skeletal muscle, superior cervical ganglion, uterus, whole brain	ADRA1D, ADRA2A, CHRM2, CHRM3, CHRM5, DRD5, HTR1B, HTR1D, HTR1E, HTR3A
Donepezil	Amygdala, bdca4, dendritic cells, cd33 myeloid, cd4t cells, cingulate cortex, foetal brain, heart, liver, occipital lobe, skeletal muscle, smooth muscle, superior cervical ganglion, thyroid, uterus, whole blood	GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, HTR2A, IL1B, NFKB1, NFKB2, NOS1, TNFAIP6
Risperidone	Adrenal cortex, bronchial epithelial cells, cd14 monocytes, cd33 myeloid, cd34, cd56 NK cells, cerebellum, cerebellum peduncles, foetal brain, heart, kidney, liver, lung, pancreas, pineal, pituitary, placenta, prostate, retina, thyroid, whole blood, whole brain	ADRB2, APOD, BCL6, BRD3, BRD4, CDC42, CDKL2, CETP, DCK, ERBB2, FKBP4, GLTP, GRM1, GSTA1, GSTP1, MET, MIF, NQO2, OGG1, PARP1, SRC, SRK10TNKS2, VDR, ZAP70
Clonazepam	Amygdala, appendix, cardiac myocytes, cerebellum, cerebellum peduncles, heart, liver, medulla oblongata, occipital lobe, pancreas, pituitary, placenta, prefrontal cortex, skeletal muscle, skin, superior cervical ganglion, trachea, whole brain	GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ



an individual's genetic risk variant and type of FTD [22]. These include tau-targeting therapy for bvFTD patients, progranulin-related therapies for GRN mutation, antisense therapeutics to reduce C9orf72 repeat expansions, etc. On the clinical forefront, a future perspective of this study could involve the use of neuroimaging alongside specific biomarkers in classifying homogenous groups for testing targeted therapies [23].

With the increase in drug databases, future work can also involve the creation of a custom database that is regularly updated on FDA-approved drugs. Additionally, study can be expanded from FTD-related drugs to other related disorders such as ALS, Parkinson's and Alzheimer's to observe the similarity in the drug–gene network and identify sub-phenotypes.

## 5 Conclusions

Recent advances in the understanding of FTD have shown genetic factors to play an important role in its onset and progression. A complete framework of drug–gene and drug–drug interactions can help in the identification of potential biomarkers for innovative clinical trials. In this regard, our study gives an insight into the underlying mechanism of frontotemporal dementia-related drugs, their mode of action on target genes and possible drug–drug interactions.

We identified 55 FTD-related drugs, 87 gene targets and 7 FTD susceptible genes from databases such as DrugBank and NeuroDNet. An enrichment and PPI network analysis revealed the gene targets overrepresented in neuroactive ligand–receptors and substance abuse systems (nicotine,

cocaine and morphine) demonstrating that neuropsychiatric drugs do not function independently but rather forms an interacting network. We also identified the APP gene as an important hub node that forms an essential link between disease susceptibility genes and drug target genes.

In addition, we proved the off-target effects commonly seen in neuropsychiatric drugs by displaying their multi-target behaviour via a historeceptomics analysis. Our study shows that the network-based method is useful and might help in the development of an effective drug management approach from a computational biology perspective.

### Abbreviations

FTD: Frontotemporal dementia; APP: Amyloid precursor protein; bvFTD: Behavioural variant FTD; svPPA: Semantic variant primary progressive aphasia; nfvPPA: Nonfluent variant primary progressive aphasia; ADMET: Absorption, distribution, metabolism, excretion and toxicity; FDA: Food and Drug Administration; UniProt: Universal Protein Resource; WebGestalt: Web-based Gene Set Analysis Toolkit; ORA: Overrepresentation analysis; KEGG: Kyoto Encyclopedia of Genes and Genomes; BH: Benjamini–Hochberg; FDR: False discovery rate; PPI: Protein–protein interaction; STRING: Search Tool for the Retrieval of Interacting Genes; HR: Historeceptomics; MAPT: Microtubule-Associated Protein Tau; GRN: Granulin Precursor; OMIM: Online mendelian inheritance in man; ALS: Amyotrophic lateral sclerosis; NMDA: *N*-Methyl-D-aspartic acid.

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### Authors' contributions

AB had contributed to conceptualization, methodology, investigation and writing draft manuscript; RS was involved in conceptualization, methodology, investigation and writing draft manuscript. JC took part in conceptualization, supervision and manuscript finalization. All authors have read and approved the final manuscript.

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#### Consent for publication

Not applicable.

#### Availability of data and materials

The datasets generated and/or analysed during the current study are available in the [<http://www.drugbank.ca/>, <https://bioschool.iitd.ac.in/NeuroDNet/>, <http://www.webgestalt.org/>, <https://historeceptomics.com>, [https://go.drugbank.com/interax/drug\\_lookup](https://go.drugbank.com/interax/drug_lookup)].<sup>[19–21, 14]</sup>

#### Competing interests:

The authors declare that they have no competing interests.

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### References

- Waldö ML (2015) The frontotemporal dementias. *Psychiatr Clin North Am* 38(2):193–209
- Sivasathiseelan H, Marshall CR, Agustus JL, Benhamou E, Bond RL, van Leeuwen JEP, Hardy CJD, Rohrer JD, Warren JD (2019) Frontotemporal Dementia: A Clinical Review. *Semin Neurol* 39(2):251–263
- Maxime M, Brambati SM, Luisa G-T, Raffaella M (2018) Clinical, Anatomical, and Pathological Features in the Three Variants of Primary Progressive Aphasia: A Review. *Front Neurol* 9:692. <https://doi.org/10.3389/fneur.2018.00692>
- Lanata SC, Miller BL (2016) The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. *J Neurol Neurosurg Psychiatry* 87(5):501–511
- Bang J, Spina S, Miller BL (2015) Frontotemporal dementia. *Lancet* 386(10004):1672–1682
- Panza F, Lozupone M, Seripa D, Daniele A, Watling M, Giannelli G, Imbimbo BP (2020) Development of disease-modifying drugs for frontotemporal dementia spectrum disorders. *Nat Rev Neurol* 16(4):213–228
- Chandran U, Mehendale N, Patil S, Chaguturu R, Patwardhan B (2017) Network Pharmacology. *Innovative Approaches in Drug Discovery*:127–164. doi:<https://doi.org/10.1016/B978-0-12-801814-9.00005-2>.
- Tsai RM, Boxer AL (2016) Therapy and clinical trials in frontotemporal dementia: past, present, and future. *J Neurochem* 138:211–221
- Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Lynkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C, Wilson M (2017) DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* 46(D1):D1074–D1082.
- Vasaikar, S.V., Padhi, A.K., Jayaram, B. James Gomes (2013) NeuroDNet - an open source platform for constructing and analyzing neurodegenerative disease networks. *BMC Neurosci*, 14, Article Number 3.
- Liao Y, Wang J, Jaehnic EJ, Shi Z, Zhang B (2019) WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs. *Nucleic Acids Res* 47(W1):W199–W205
- Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, HuertaCepas J, Simonovic M, Doncheva NT, Morris JH, Bork P, Jensen LJ, Mering C (2019) STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res* 47(D1):D607–D613
- Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 13(11):2498–2504
- Shmelkov E, Grigoryan A, Swetnam J, Xin J, Tivon D, Shmelkov S, Cardozo T (2015) Historeceptomic fingerprints for drug-like compounds. *Front Physiol* 6:371. <https://doi.org/10.3389/fphys.2015.00371>
- Reddy PV, Anuroop L, Shetageri V, Kumar RK, Gopalakrishnan G (2019) A Case of Frontotemporal Dementia Presenting as Nicotine Dependence and Carbohydrate Craving. *Indian J Psychol Med* 41(4):391–393
- Coupland CAC, Hill T, Denning T, Morris R, Moore M, Hippisley-Cox J (2019) Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. *JAMA Intern Med* 179(8):1084–1093
- Decker M (2017) Design of hybrid molecules for drug development. Elsevier, Amsterdam
- Kalapathu RK, Delucchi KL, Wang S, Harbison JD, Nelson EE, Kramer JH (2016) Substance use history in behavioral-variant frontotemporal dementia versus primary progressive aphasia. *J Addict Dis* 35(1):36–41. <https://doi.org/10.1080/10550887.2015.1102026>
- Illán-Gala I, Pegueroles J, Montal V, Alcolea D, Vilaplana E, Bejanin A, Borrego-Écija S, Sampedro F, Subirana A, Sánchez-Saudinós MB, Rojas-García R, Vanderstichele H, Blesa R, Clarimón J, Antonell J, Lladó A, Sánchez-Valle R, Fortea J, Lleó A (2019) APP-derived peptides reflect neurodegeneration in frontotemporal dementia. *Ann Clin Transl Neurol* 6(12):2518–2530. <https://doi.org/10.1002/acn3.50948>
- Boxer AL, Mackenzie IR, Boeve BF, Baker M, Seeley WW, Crook R, Feldman H, Hsiung GY, Rutherford N, Laluz V, Whitwell J, Foti D, McDade E, Molano J, Karydas A, Wojtas A, Goldman J, Mirsky J, Sengdy P, Dearmond S, Miller BL, Rademakers R (2011) Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family. *J Neurol Neurosurg Psychiatry* 82(2):196–203
- Malki MA, Pearson ER (2020) Drug-drug-gene interactions and adverse drug reactions. *Pharmacogenomics J* 20(3):355–366

22. Liu MN, Lau CI, Lin CP (2019) Precision Medicine for Frontotemporal Dementia. *Front Psychiatry* 10:1–13
23. Borroni B, Benussi A (2019) Recent advances in understanding frontotemporal degeneration. *F1000Res* 8:F1000

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