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Functional Characterization of Neurodegenerative Disease Genes via Gene Ontology Enrichment Analysis

Sachintan Mohanty
sachintanm@gmail.com

ABSTRACT

Neurodegenerative disorders remain the leading cause of disability and illness worldwide; however a true cure that targets the progression and onset of these diseases has not yet been developed. I hypothesized that multiple genes frequently associated with Parkinson's, Alzheimer's, and dementia would share enrichment through overlapping biological processes and cellular components, despite having diverged molecular functions indicating shared neurodegenerative mechanisms with disease-specific effectors. I can report that many of the commonly associated genes with these disorders have similar roles in biological processes but are far more specialized in their individual molecular function, with little commonality in terms of cellular components. This holds promise to the future of research in this area, suggesting that broader research should target the processes they are responsible for, whereas disease specific research should focus on the functions they impact on a molecular level.

INTRODUCTION

Worldwide, over one in every three people are diagnosed with neurological conditions and disorders such as Parkinson's or ALS (Amyotrophic Lateral Sclerosis) (Steinmetz, 2024). Roughly 6.2 million people across the United States have Alzheimer's disease (Alzheimer's Association, 2023). Even some milder forms of Alzheimer's, such as dementia, are believed to have over 55 million patients worldwide, over 60% of whom live in low to middle-income countries(World Health Organization, 2023).Global estimates of Parkinson's disease in 2019 show that there are over 8.5 million diagnosed patients, resulting in 5.8 million Disability Adjusted Life Years (DALYs) (World Health Organization, 2023).

In terms of cures or therapies for these disorders, many only focus on symptomatic relief or the slowing of progression, rather than complete halting. Pharmacological treatments have been used for all three diseases with mixed success. When treating Alzheimer's, most treatments involve Cholinesterase inhibitors and NMDA receptor antagonists. The former, being used to briefly alleviate symptoms (Birks, 2018), and the latter the same but with some scope for limited influence on progression (Areosa, 2005).

In terms of pharmacological therapies for Parkinson's disease, dopaminergic therapy is the main method of management. It provides temporary motor symptom control, but can lead to long-term motor fluctuations and dyskinesias(Connolly, 2014). Many of these treatments are accompanied by standard antipsychotic medications in order to combat behavioral changes such as extreme aggression, such as but not limited to thioridazine, chlorpromazine, haloperidol, trifluoperazine, and risperidone to target psychotic episodes. Many of these can however result in various adverse effects such as weight gain, addiction, and withdrawal (Ballard, 2009).

While there is no complete cure for these types of diseases, understanding the commonalities in genes previously explored and thought to be involved, can provide an insight into the molecular functions and the specific biological processes that influence onset and progression. In order to better understand these factors, it is crucial to understand the genetic basis of these kinds of diseases. Knowing the genes associated with these diseases allows the exploration of the molecular and cellular underpinnings of these disease phenotypes. Here, I use genes which have been identified to be associated with the 3 most common neurodegenerative diseases (Alzheimer's, Parkinson's, and dementia) to perform a gene ontology (GO) enrichment analysis allowing me to explore the cellular and molecular underpinnings for neurodegenerative diseases, in order to understand the direction of future research in the field.

RESULTS

37 genes were associated with either Alzheimer's, Parkinson's, or Dementia (Table 1). The GO terms including all three categories (biological processes, cellular components, and molecular functions) had some level of significant term enrichment.

In terms of the biological processes, many of the results showed a significant correlation to the genes selected for the list. 10 of the 15 most significant GO terms were directly linked to cellular apoptosis, specifically in the brain. Cellular (specifically neural) apoptosis is the programmed method by which cells dismantle and destroy themselves to declining performance or identified maladaptive mutations. In neurodegenerative disorders, it should be eliminating potentially hazardous cells but is overactive and causes the widespread destruction of healthy neurons as well, contributing the overall neurodegeneration. Of those 10, the top 5 terms included two instances of neural apoptosis (Fig 1a).19 of the genes held connections to the same top 6 terms from Fig 1a, with the exclusion of direct macroautophagy (Fig 1b). Macroautophagy is the way that the cell destroys waste through the formation of double-membraned vesicles called autophagosomes that engulf these waste particulates and subsequently fuse with a lysosome in order to destroy the material. Neurodegenerative disorders see these macroautophagy systems degraded upon which toxic aggregates such as amyloid-beta and alpha-synuclein would accumulate rather than being cleared. Macroautophagy itself was a direct connection to 19 genes meaning that it most likely plays a role regulating the upstream or downstream segments of the neurodegenerative pathways. The genes PINK1 and PRKN had functions that were closely related to the majority of GO terms, with the exclusion of glial cell activation, autophagosome organization, and vacuole organization for PRKN (Fig 1c). Glial cell activation is the transition of cells into responsive states to injury, infection, or aggregation, but can drive neuroinflammation which contributes as an amplifier of pre-existing neurodegenerative

conditions. Autophagosome organization ties into macroautophagy and connects by organizing autophagosome for proper debris clearance. The vacuolar organization ties back to the pathways of storage and waste processing, similar to autophagosome and macroautophagy, but deals more heavily in lysosomal storage disorder and impaired protein degradation (including the degradation of both amyloid, synuclein, and tau proteins). This term holds particular interest as PRKN, a very well-researched and commonly associated gene, was not linked to vacuole organization but was linked to numerous other terms related to mitochondrial quality control, implying this gene could better inform mutation-specific research. Along with PRKN, PINK1 is also linked heavily to the regulation of autophagy for mitochondrion, also known as mitophagy, where damaged mitochondria are tagged for selective destruction. Mutations in either of these two genes prevent the destruction of dysfunctional mitochondria which accelerates neuronal death. Enrichment of reactive oxygen species metabolic process (Figure 1) reflects that many of the selected genes influence oxidative damage control which ends up contributing to larger accumulation pathways during mitochondrial failure.

In terms of cellular components, 7 of the 15 GO terms presented function solely in the brain (distal axon, growth cone, synaptic vesicle, neuron projection terminus, glial cell projection, axon terminus, and inclusion body), whereas the others are similar, but can be found elsewhere as well (Fig 2a). The top 3 GO terms, those being distal axon, transport vesicle, and site of polarized growth, as seen in Fig 2a, also hold strong connections with 10 of the genes, being linked to 6 or more of them (Fig 2b). Distal axons are metabolically distinct from the neuronal cell body and dependent upon axonal transport for proteins and organelles. In this case, PSEN1 ends up dysregulating APP cleavage which can produce potentially hazardous fragments that form plaques. Synaptic vesicles, membrane-bound transport sacs, represent another prominently enriched brain-specific term. The gene SNCA normally functions by regulating the clustering system of these vesicles, but misfolding and aggregation cause neurotransmitter release disruptions, connecting back to the general membrane trafficking machinery present in a number of selected genes. Fig 2c shows that many of the genes were associated with a wide variety of terms, most of which however were neural components (Fig 2c). Of particular significance among the cellular component terms are two protein aggregation-related components, being the inclusion body and aggresome. Inclusions bodies are the abnormal result of cellular clearance system malfunctions, resulting in many hallmarks such as Lewy bodies in Parkinson's disease. Aggresomes themselves are compartments in which misfolded proteins are concentrated prior to the autophagic clearance, and the enrichment implies that multiple genes in this study are involved in the triage of protein aggregation and subsequent mediation pathways. Together, these two terms imply that the biological processes illustrated in Figure 1 have direct physical manifestations in terms of their cellular effects; the autophagy failures end up having a direct physical result through the protein aggregate deposits of hallmark proteins that define neurodegenerative pathology. The presence of lysosomal membrane enrichment further reinforces this connection, as the terminal degradation compartment where autophagosomes normally conduct their roles, the enrichment suggests that multiple genes in this set influence not only the initiation of the process but also its completion, indicating lysosomal dysfunction as a common convergence point across these 3 diseases.

When considering molecular functions, there was a single very prominent result, that being that protein-folding chaperone binding stood out as the most noticeable GO term (Fig 3a). When considering

the top 5 terms used, all had links to at least 3 genes, with protein-folding chaperone binding having links with 5 (Fig 3b). Of the genes in the list, PRKN had the most connections with the GO terms, including protein-folding chaperone binding (Fig 3c). Alongside the chaperone binding, protease binding, heat shock protein binding, ubiquitin-specific protease binding, and aspartic-type endopeptidase activity were the next most enriched terms with multiple phosphatidylinositol phosphatase activity variants also appearing within the results. Chaperone binding itself refers to a proteins ability to interact with molecular chaperones in order to ensure accurate folding and aggregation prevention, but SNCA mutations can results in misfolding of a-synuclein as a result of chaperone-mediated autophagy failure resulting in toxic aggregates that are characteristic of Parkinson's disease. Heat shock protein binding reflects a stress-response mechanism whereby specialized chaperones are upregulated in response to detected protein aggregation, and their enrichment suggests several genes in this set interact with this compensatory defense system. Ubiquitin-specific protease binding is particularly relevant given PRKN's function as an E3 ubiquitin ligase, which tags damaged proteins and mitochondria for degradation, played a larger part in the protein clearance network. Aspartic-type endopeptidase activity encompasses much of the secretase enzymes responsible for cleaving APP to form amyloid-beta fragments implicating APP, PSEN1, and PSEN2, connecting their molecular function to biochemical operations driving neurodegeneration, more specifically in Alzheimer's disease. Phosphatidylinositol activity terms, driven by SYNJ1 and INPP5F reflect lipid signaling in neuronal membranes in regulating vesicle trafficking and autophagy initiation; meaning that these enzyme disruptions inevitably lead to the same downstream failures mentioned in the biological processes and cellular components.

DISCUSSION

Considering the results of the GO enrichment analysis, several conclusions can be drawn. The majority of the Biological Process GO terms were strongly focused on autophagy and apoptosis in neurons, with PINK1 and PRKN being associated with the highest number terms. This suggests that many of the genetic mutations involved in the neurodegenerative diseases explored share similarities in the processes they dictate. Both PINK1, PRKN, and other genes in the list, play key roles in autophagy, and when these genes are inactivated by mutation, their dysfunction has been observed in patient's brains with neurological disorders (Hamano, 2018). PINK1 stabilizes upon both damaged mitochondrial membranes and phosphorylates PRKN, activating the ubiquitin ligase function to trigger selective mitochondrial clearance. When either gene is mutated the process collapses, meaning that dysfunctional mitochondria persist creating the oxidative stress as shown in the ROS metabolic process GO terms. While autophagy dysfunction in neurodegeneration mechanisms are already established in identified literature, the co-enrichment of both apoptosis regulatory terms across the same gene set is notable as it positions these genes at the decision point between cellular-self-repair and cell destruction rather than remaining in exclusively one pathway. The breadth of the autophagy and apoptosis enrichment supports the hypothesis in that these processes represent shared upstream vulnerabilities versus disease-specific mechanisms between all three diseases.

Although the Cellular Component category yielded fewer significant results than Biological Processes, some noteworthy terms and correlations were identified. Of the 15 most significant terms, seven are

specifically involved in brain and neuronal function, while the others are more broadly expressed in both the brain and other tissues. The gene PSEN1 is highly associated with various cellular components, including the distal axon, along with other neurological components, such as synaptic vesicles. PSEN 1 has also been commonly noted with mutations in the brain of people with AD and EOAD (early-onset Alzheimer's disease) (Lladó, 2010). The enrichment of two terms, inclusion body and aggresomes, provides a structural explanation as to why many autophagy-related biological process terms were so prominent in the enrichment; they are the physical compartments in which autophagic failure becomes visible in the form of disease pathology. Lewy bodies, one of the defining pathological features of Parkinson's disease, are a type of inclusion body, meaning that the GO enrichment of this term in particular connects several genes to the observable neuropathology rather than abstract pathways. The enrichment of lysosomal membrane as a cellular component further reinforces that multiple genes influence the completion of autophagy rather than simply its initiation, indicating lysosomal dysfunction as a shared convergence point across all three diseases, consistent with the growing literature on lysosomal storage dysfunction in neurodegeneration.

The Molecular Function category yielded few significant results, and one term stood out with relatively high significance. Ɑ-synuclein, a neuronal protein found in presynaptic terminals and associated with distal reserve pools, is prone to misfolding due to improper chaperone binding. This misfolding results in the development of neurological disorders such as Parkinson's. Disruptions in processes like chaperon-mediated autophagy, specifically the failure to eliminate oligomers, results in a-synuclein-mediated toxicity, ultimately leading to disease onset (Lashuel, 2013). The enrichment of ubiquitin-specific protease binding as a molecular function term reinforces this protein clearance theme; PRKN's function as an E3 ubiquitin ligase and its connections to the highest number of molecular function GO terms suggests its role as a hub within the ubiquitin-proteasome clearance network, connecting multiple genes in this set to a shared degradation mechanism. Separately, the enrichment of aspartic-type endopeptidase activity directly implicates the secretase machinery of APP, PSEN1, and PSEN2, linking molecular functions to the amyloid-beta process that specifically drives Alzheimer's pathology. This represents one of the clearest examples in the dataset in which a molecular function terms that is disease-specific, supporting the divergence in molecular functions as predicted by the hypothesis.

The convergence of biological process terms revolving around autophagic processes, apoptosis, and oxidative stress across genes in this set from all three diseases indicates a shared therapeutic target, where interventions like autophagy enhancement or neuroinflammation reduction may have a broader scale of applicability across Parkinson's, Alzheimer's, and dementia. By contrast, the divergence seen with the molecular function enrichment, with chaperone-binding being most prominent for Parkinson's genes and aspartic-type endopeptidase activity selectively to Alzheimer's genes suggests that disease-specific treatments should prioritize the distinct molecular mechanisms downstream of these shared processes. Future work combining GO enrichment with protein-protein interaction networks or expression data could further inform which specific nodes within shared pathways represent the most viable therapeutic targets.

LIMITATIONS

The gene set involved in this study reflects a large publication bias towards more well-studied genes rather than an completely unbiased screen. GO annotation is also incomplete for more less-characterized genes such as RBMS3 which returned no enrichment. The set size could also be increased as it currently poses the risk of inflated significance for broader categorical terms and the study itself lacks mechanistic validation.

METHODS

To identify similarities, a comprehensive list of genes, previously determined by other research, associated with Parkinson's, Dementia, and Alzheimer's was compiled. Using databases such as Google Scholar and the National Library of Medicine, specific searches focused on exploring the relationship between specific genetic mutations and the onset or diagnosis of Alzheimer's, dementia, and Parkinson's, the three most prevalent diseases worldwide.

From this point, the resources were sorted by the times they were cited, and the top ten were analyzed for each query were used. The final gene list was developed from the data featured in these articles, and was then put through a gene ontology enrichment analysis in RStudio (v4.4.1) using the following packages via the bioconda installer: clusterProfiler (v4.12.2)(Xu, 2024), org.Hs.eg.db (v3.19.1)(Carlson, 2019), enrichplot (v1.24.2)(Yu, 2021), ComplexHeatmap (v2.20.0)(Gu, 2016), circlize (v0.4.16)(Gu, 2014), GOplot (v1.0.2)(Walter, 2015). Additional packages were included: Rcpp (v1.0.13)(Eddelbuettel, 2011), nloptr (v2.1.1)(Johnson, 2014), minqa (v1.2.7)(Bates, 2014), lme4 (v1.1.35.5)(Bates, 2014).

Next, a GO enrichment analysis was performed to identify similarities across three categories: Biological Process, Molecular Mechanism, and Cellular Component. The enrichGO command (Ferreira, 2006) was used for each GO term category, with corrections for multiple testing applied through the Benjamini-Hochberg method to minimize false positives. The gathered data was then visualized using dot plots, gene-concept networks, and heat maps.

Gene Symbol	**Full Name**	**Also Known As**
GBA1	glucosylceramidase beta 1	GBA; GCB; GLUC
LRRK2	leucine rich repeat kinase 2	PARK8; RIPK7; ROCO2; AURA17; DARDARIN
SNCA	synuclein alpha	PD1; NACP; PARK1; PARK4
GCH1	GTP cyclohydrolase 1	GCH; DYT5; DYT14; DYT5a; GTPCH1; HPABH4B; GTP-CH-1

MAPT	microtubule associated protein tau	TAU; MSTD; PPND; DDPAC; MAPTL; MTBT1; MTBT2; tau-40; FTDP-17; PPP1R103; Tau-PHF6
TMEM175	transmembrane protein 175	hTMEM175
VPS13C	vacuolar protein sorting 13 homolog C	BLTP5C; PARK23
TOX3	TOX high mobility group box family member 3	CAGF9; TNRC9
NEK1	NIMA related kinase 1	OFD2; ALS24; SRPS2; SRTD6; SRPS2A; NY-REN-55
FDFT1	farnesyl-diphosphate farnesyltransferase 1	SS; SQS; DGPT; ERG9; SQSD
PSD	pleckstrin and Sec7 domain containing	TYL; EFA6; PSD1; EFA6A
BAG3	BAG cochaperone 3	BIS; MFM6; BAG-3; CAIR-1
SLC2A13	solute carrier family 2 member 13	HMIT
CLCN3	chloride voltage-gated channel 3	CLC3; ClC-3; NEDSBA; NEDHYBA
CTSB	cathepsin B	KWE; APPS; CPSB; RECEUP
GBF1	golgi brefeldin A resistant guanine nucleotide exchange factor 1	CMT2GG; CMTDI2; CMTDIA; ARF1GEF
INPP5F	inositol polyphosphate-5-phosphatase F	SAC2; hSAC2; MSTP007; MSTPO47
RBMS3	RNA binding motif single stranded interacting protein 3	—
H2BC13	H2B clustered histone 13	H2B/c; H2BFC; HIST1H2BL; dJ97D16.4

TRIM40	tripartite motif containing 40	RNF35
EHMT2	euchromatic histone lysine methyltransferase 2	G9A; BAT8; GAT8; NG36; KMT1C; C6orf30
RPS12	ribosomal protein S12	S12; eS12
MICU3	mitochondrial calcium uptake family member 3	EFHA2
ITGA8	integrin subunit alpha 8	—
PRKN	parkin RBR E3 ubiquitin protein ligase	PDJ; AR-JP; LPRS2; PARK2
PINK1	PTEN induced kinase 1	BRPK; PARK6
PARK7	Parkinsonism associated deglycase	DJ1; DJ-1; GATD2; HEL-S-67p
ATP13A2	ATPase cation transporting 13A2	LN12; KRPPD; PARK9; SPG78; HSA9947
FBXO7	F-box protein 7	FBX; FBX7; PKPS; FBX07; PARK15
PLA2G6	phospholipase A2 group VI	GVI; PLA2; INAD1; NBIA2; iPLA2; NBIA2A; NBIA2B; PARK14; PNPLA9; CaI-PLA2; IPLA2-VIA; iPLA2beta
SYNJ1	synaptojanin 1	DEE53; EIEE53; INPP5G; PARK20
DNAJC6	DnaJ heat shock protein family (Hsp40) member C6	DJC6; PARK19
GRN	granulin precursor	GEP; GP88; PEPI; PGRN; CLN11; PCDGF

C9orf72	C9orf72-SMCR8 complex subunit	ALSFTD; DENND9; FTDALS; DENNL72; FTDALS1
APP	Amyloid Beta Protein Precursor	AAA; AD1; PN2; ABPP; APPI; CVAP; ABETA; PN-II; preA4; CTFgamma; alpha-sAPP
PSEN1	presenilin 1	AD3; FAD; PS1; PS-1; S182; PSNL1; ACNINV3
PSEN2	presenilin 2	AD4; PS2; AD3L; STM2; CMD1V

Table 1: All 32 genes selected with both the gene symbol, the full name of the gene, and other names by which the gene has been referenced as in published literature.

Figure 1. Gene Ontology (GO) enrichment analysis of Parkinson's disease-associated genes.

(a) Dot plot showing enriched biological process GO terms, with the x-axis representing the frequency of genes associated with each term. Dot size and color correspond to the adjusted p-value, indicating the statistical significance of enrichment. Terms related to autophagy, apoptosis, and reactive oxygen species metabolism are among the most significantly enriched.

(b) Binary matrix (presence/absence heatmap) showing the association between individual genes (columns) and enriched GO terms (rows). Black squares indicate that a gene is associated with the corresponding GO term, revealing the distribution of functional annotations across the gene set.

Figure 2. Gene Ontology (GO) enrichment analysis of Parkinson's disease-associated genes for cellular component terms.

(a) Dot plot displaying enriched molecular function GO terms, with the x-axis representing the frequency of genes associated with each term. Dot color indicates the adjusted p-value, with darker blue representing greater statistical significance. Terms related to phosphatidylinositol phosphatase activity, chaperone binding, and protease binding are among the most enriched.

(b) Binary matrix showing the association between individual genes (columns) and enriched molecular function GO terms (rows). Black squares indicate a gene is associated with the corresponding term, highlighting which genes drive the enrichment of specific molecular functions across the dataset.

Figure 3. Gene Ontology (GO) enrichment analysis of Parkinson's disease-associated genes for molecular function terms.

(a) Dot plot showing enriched molecular function GO terms plotted against the frequency of associated genes (x-axis). Dot color reflects the adjusted p-value, with darker blue indicating higher statistical

significance. Binding-related terms, including protein-folding chaperone binding, protease binding, heat shock protein binding, and phosphatidylinositol-related phosphatase activities, are prominently enriched.

(b) Binary matrix illustrating the gene-to-GO term associations, where black squares denote the presence of an association between a gene (columns) and a molecular function term (rows). The sparse but clustered pattern suggests that a subset of genes drives enrichment across multiple related phosphatidylinositol and chaperone binding terms.

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