# Genetic approach for the discovery of novel therapeutics for Parkinson's Disease

Anwesha Soneja

## Abstract

Parkinson's disease (PD) is a multisystem disorder for which numerous genetic risk loci have been identified, however it is still not clear how these findings connect to the underlying biology or to realistic drug targets. This study brought together 122 genes associated with PD in genome-wide association studies (GWAS) and asked three questions: (1) which other diseases are they involved in, (2) which biological pathways they share and (3) whether they are already or a potential drug target for PD. Based on existing genetics studies, these PD associated genes influence multiple traits, commonly recurring in a wide range of neurological, psychiatric, metabolic, oncological and inflammatory conditions. Functional pathways analysis showed that despite this wide range of diseases, the genes share common key processes that affect dopamine, synapses, kinase signaling and calcium balance in the brain. Investigating drug data showed that many of the genes already have clinical stage or approved drugs, mostly for non-PD indications, while others belong to familiar druggable families but currently lack advanced modulators. These results reinforce the idea that PD is a disorder of vulnerable synapses that shares genetic risk with many other disorders and that it's risk genes cluster into a limited number of recurrent pathway networks. By viewing PD GWAS genes through this combined lens of disease links, pathways and druggability, this study highlights both short-term opportunities for rational drug repurposing and a set of promising genes that merit further studies as potential disease modifying targets.

## Keywords

Parkinson's disease, biological pathways, genome-wide association studies, genetic pleiotropy, pathway enrichment analysis, drug targets, target prioritization, drug repurposing, neurodegeneration.

## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder and a prevalent cause of chronic neurological disability in older adults worldwide.[1] Clinically, PD is characterized by its principal motor features including bradykinesia, muscular rigidity, resting tremor and postural instability. It is now acknowledged as a complex multisystem disorder with a broad spectrum of non-motor symptoms.[2] Rapid eye movement, sleep behavior disorders, autonomic dysfunction, hyposmia, mood and anxiety disorders, pain, fatigue and cognitive decline are all examples of non-motor symptoms.[3] These may appear well in advance of the motor symptoms or occur

alongside them. The combination of motor and non-motor symptoms lead to substantial impairment in quality of life, loss of independence and increased caregiver stress over its course.[4]

Biologically, PD is associated with a progressive destruction of dopaminergic neurons in the substantia nigra pars compacta region. It is also marked by the presence of Lewy bodies and Lewy neurites, which are intracellular inclusions mainly composed of misfolded and aggregated α-synuclein.[5] As a result of the damage done to nigrostriatal pathways, decreased levels of striatal dopamine contributes to many of the characteristic motor symptoms. However, α-synuclein pathology and neuronal loss are not confined to the nigrostriatal system and they often extend to brainstem nuclei, cortical areas and peripheral autonomic structures. This widespread involvement aligns with the broad range of non-motor symptoms seen in PD and supports the view that it is a diffuse synucleinopathy rather than solely being a basal ganglia disorder.[6]

Current therapeutic strategies for PD are predominantly symptomatic. Pharmacological treatment is centered on dopaminergic replacement or augmentation, mostly common with levodopa[7] in combination with peripheral decarboxylase inhibitors, dopamine agonists, monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors.[8] These agents can provide substantial and sustained improvement in bradykinesia and rigidity, particularly in the early stages of the disease. However, long-term dopaminergic therapy is associated with motor complications including dyskinesias, wearing-off phenomena and on-off fluctuations in mobility and it does not prevent progressive neuronal loss.[9] Deep brain stimulation and other neuromodulatory approaches have expanded the range of treatment options for selected patients with advanced cases. Nonetheless these interventions remain symptomatic and are not curative and many non-motor symptoms respond incompletely or not at all to dopaminergic therapies.

PD is a complex disorder in which genetic predisposition, environmental exposures and ageing-related processes are interconnected to determine individual susceptibility and disease trajectory. Over the past two decades, advances in human genetics have profoundly altered the understanding of PD. Initially, the discovery of rare, highly penetrant mutations in genes such as *SNCA, LRRK2, VPS35, PRKN, PINK1* and *DJ-1* established that monogenic forms of parkinsonism exist.[10] It also illuminated key pathogenic pathways, including α-synuclein aggregation, mitochondrial quality control and vesicular trafficking.[11] However, these mutations account for only a minority of PD cases, typically with familial or early-onset presentations. In most patients, Mendelian mutations are absent and in the more common sporadic form of PD, risk seems to arise from the combined influence of many small-effect genetic variants distributed throughout the genome.[12] Genome-wide association studies (GWAS) have identified dozens of loci associated with PD risk, and pathway-based analyses demonstrate that PD-associated genes are enriched in a limited number of biological processes such as autophagy-lysosomal function, mitochondrial function and synaptic vesicle cycling. Many important gaps still exist despite the fast development of PD genetics, including uncertainty about the causal gene or genes at

numerous loci and about whether disease risk is driven by increased or decreased activity of a gene and which specific cell types and neural circuits are implicated. Such doubts hinder the planning of precise treatments and highlight the challenge of converting genetic results into pharmaceutical targets, especially in the context of druggable genome and examples such as SNCA, very strong genetic relevance contrasts with difficult therapeutic tractability.

To answer this question, we have to think about these genes in three areas that are all connected. These areas are the diseases they are linked to; the paths they are a part of and if they can be used to make new treatments. Firstly, we examine all diseases and traits that are associated with genes implicated in Parkinson's disease. This can help us identify the genetic features that are shared across these conditions. It can also show us diseases that are linked and might have the basic reasons as to why they happen. Second, putting these genes onto curated pathway and ontology resources can reveal converging processes like dopamine biosynthesis, axon guidance, synaptic structure, kinase signaling cascades or calcium homeostasis which could be key vulnerability points in PD. Third, combining information on existing drugs with development pipelines and molecular tractability will show where genetic evidence coincides with pharmacological opportunity as well as where they do not coincide. Starting from genes associated with PD in GWAS, the current work focuses on clarifying how these genes distribute across other human diseases, which shared and distinct biological pathways they occupy and to what extent they fall within the currently druggable or potentially druggable space. By approaching PD GWAS findings through this integrated lens, the study aims to contribute to a more refined understanding of how human genetic data can inform the rational selection and prioritization of targets for disease modifying therapies in Parkinson's disease.

## Methods

The overall methodological workflow for PD GWAS gene prioritization and druggability assessment is summarized in Figure 1 along with the detailed procedures in the following sections.

*GWAS data, gene prioritization and disease associations*

Genome-wide association data for PD was first compiled from a curated GWAS resource by selecting all studies annotated to the trait 'Parkinson disease'. For each eligible study, all loci reported as 'genome-wide significant' were extracted and mapped genes assigned to each locus were collected.

A non-redundant list of 122 unique genes was queried in a comprehensive genetics and target-annotation database, Open Targets Platform[13], to identify all additional diseases and phenotypes

with genetic support. A reoccurrence count was calculated for every disease as the number of distinct PD-associated genes linked to that condition, providing a quantitative measure of how frequently each comorbid or pleiotropic trait appeared across the PD gene set.

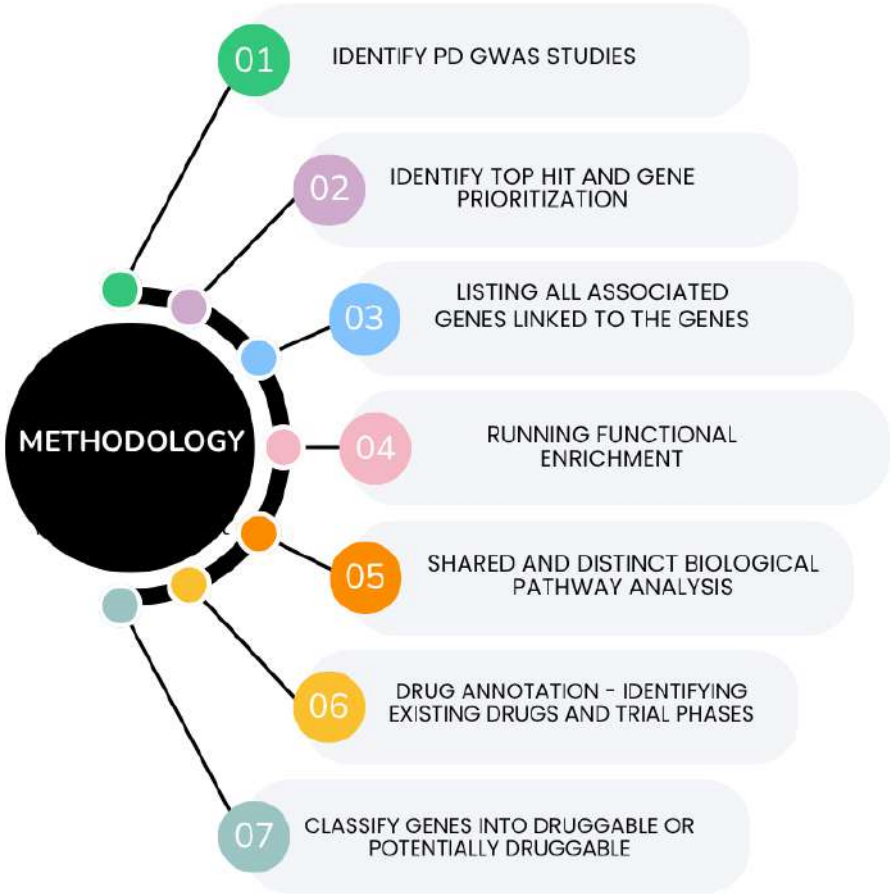


**Figure 1**: Stepwise methodological framework to investigate PD genetics, associated biological pathways, and potential drug targets.

*Biological pathway analysis*

The biological pathways that underlie the functions described by the GWAS-enriched genes were elucidated using an established functional annotation tool. Functional enrichment was performed in the Gene Ontology terms of molecular function, biological process and cellular component as well as curated pathways from sources like g: Profiler[14] and Reactome[15] using default parameters and correcting for multiple testing. Significant enrichments along with adjusted p-values and

overlapping genes were noted and organized according to higher order pathways. Genes that had annotations for PD in the disease association databases were segregated from those associated with other diseases, and comparisons made on pathway enrichment to note similarities and differences between sets.

*Drug targets assessment*

Therapeutic tractability of the PD-associated genes was assessed by systematically retrieving drug information for each gene from the same integrated genetics and pharmacology platform. For every gene, all pharmacological agents acting directly on the encoded protein, including small molecules, monoclonal antibodies and other modalities were identified. For each drug-gene pair, the drug name, highest clinical development phase (Unknown, Preclinical, IND, Early phase I, Phase I, Phase I/II, Phase II, Phase II/III, Phase III, Preapproval, Approval or Phase IV) and a brief mechanism-of-action description were recorded in a structured table. At the gene level, targets were classified as druggable if at least one agent modulating that gene had entered clinical development (Phase I-III) or obtained regulatory approval for any indication, irrespective of whether the indication was PD.

Genes encoding canonical druggable protein families, such as kinases, receptors, ion channels or enzymes or those with early-stage or indirect modulators were categorized as potentially druggable.[16] A brief description of biological functions was included for some genes based on their involvement in lysosome/autophagy signaling, dopamine biosynthesis, neurotransmission or other mechanisms relevant to PD pathogenesis. The two-level categorization into ‘druggable’ and ‘potentially druggable’ genes helped to present an overall picture of the status of therapeutic approaches and promising candidates for further research.

## Results

*Gene prioritization and disease association with PD*

From PD-GWAS, 122 independent genes were prioritized as reported or mapped candidates at genome-wide significant loci. This set included established loci (for example *SCARB2, CTSB, TMEM175, BST1, LRRK2, GCH1, KANSL1, RIT2, WNT3, MAPT-AS1, DNM1L, VAMP4, BAG3* and *RAB29*) together with additional genes emerging from larger meta-analyses. Systematic disease-association profiling (Appendix 1) showed that these genes exhibit extensive pleiotropy[17]. Top co-occurring conditions included bradykinesia (39 genes), neoplasm and obesity (35 genes), epilepsy (33 genes), REM sleep behavior disorder (31 genes), carcinoma (27 genes), schizophrenia and anxiety (26 genes), diabetes mellitus, dementia and neurodegenerative

disease (23 genes), Alzheimer's disease (20 genes), glioma (15 genes), Crohn's disease (13 genes) and ataxia (9 genes).

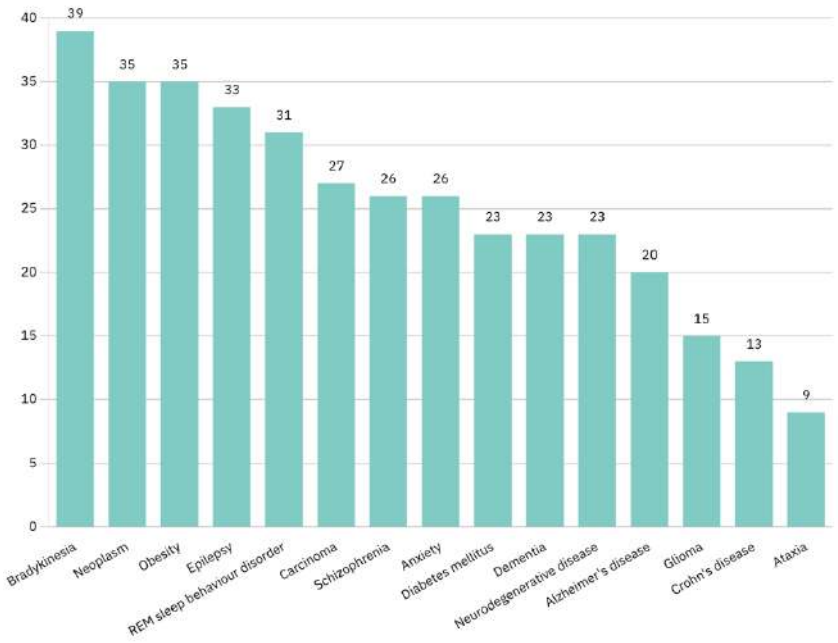


**Figure 2**: Bar plot showing the number of genes shared between Parkinson's disease and other neurological, psychiatric, metabolic and inflammatory conditions.

*Shared and distinct biological pathways*

Functional enrichment of the 122 gene list (Figure 3) identified significant enrichment of multiple pathway groups. When grouped into higher order themes, the main categories were dopamine biosynthesis, axon guidance and synaptic structure, protein phosphorylation and regulation, MAPK signaling and related stress-response cascades, calcium signaling pathways and neuroactive ligand-receptor interaction. Detailed analysis results are provided in Appendix 2.

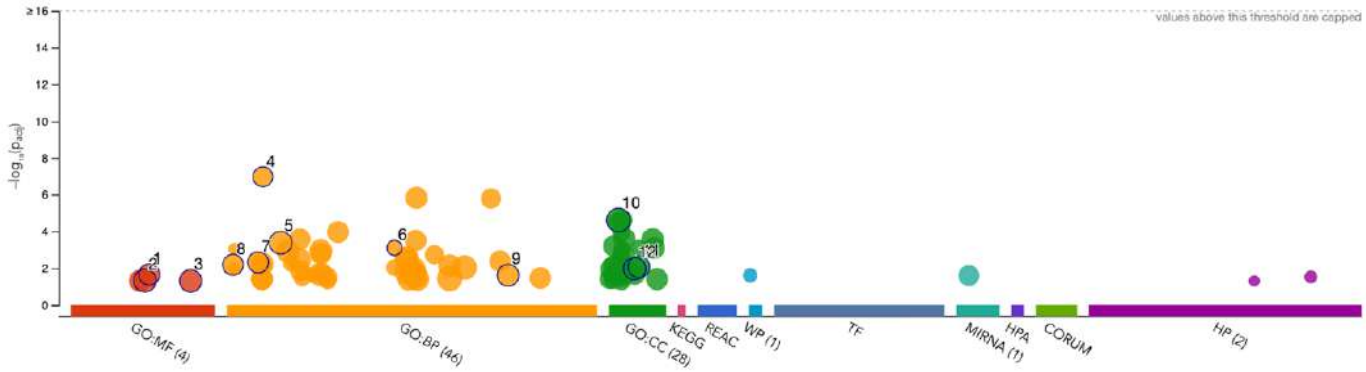


***Figure 3**: Functional enrichment profiling of genes prioritized in PD GWAS*

Figure 4 shows 21 genes directly annotated with PD and 101 genes primarily annotated with non-PD traits converge on seven shared pathway groups. This pattern indicates that genes not classically labelled as PD genes participate in the same core biological processes as established PD loci, suggesting broader pathway level convergence than gene-level labels alone imply. The specific 21 genes associated with PD taking part in the biological pathways are listed in detail in Appendix 3.

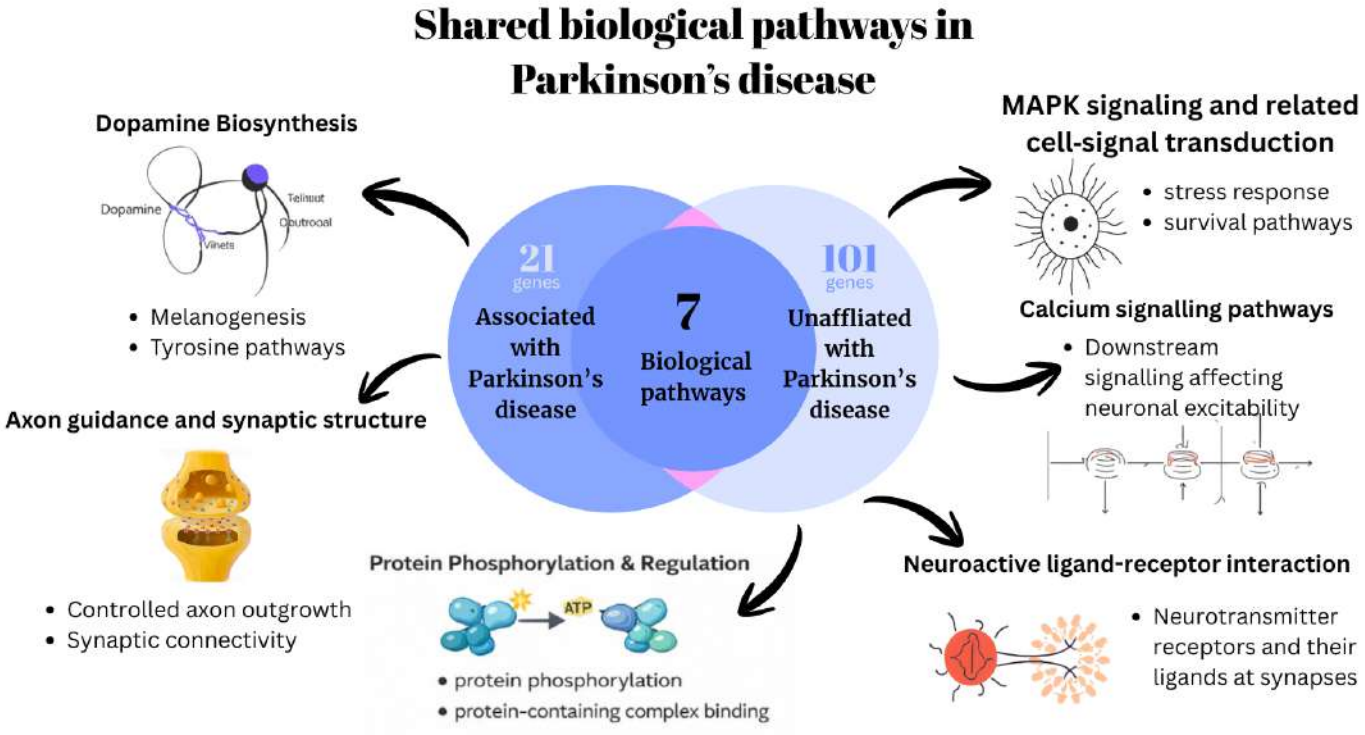


**Figure 4**: Shared biological pathways enriched amongst 122 PD GWAS-associated genes

*Drug targets available and under development*

Drug-annotation analysis showed that 9 of the 122 PD-associated genes already have at least one clinical-stage or approved pharmacological agent. For detailed analysis refer Appendix 4. Examples include α-synuclein-directed antibodies such as Cinpanemab (BIIB054) and Prasinezumab for *SNCA*; immune-modulating agents targeting *HLA-DRB1* and *HLA-DQA1*; multiple oncology drugs directed at *GPNMB* and *CD19* and neuromuscular blocking or channel-modulating agents acting on ion-channel and receptor genes such as *KCNS3* and *CHRNB1*.

These data demonstrate that a sizeable fraction of GWAS-prioritized genes falls within the existing drug-development landscape, although most associated agents have been developed for indications other than PD.

*Potential drug targets*

Assessment of tractability beyond existing drugs identified 113 genes as potentially druggable. These genes currently lack phase I-III or approved agents but belong to standard druggable protein classes or have early-stage or indirect modulators. These include *SCARB2, CTSB* and *TMEM175* which suggest roles for lysosomal and autophagy pathways; *LRRK2*, a kinase that has been replicated many times as a PD risk locus; *GCH1*, which links genetic risk to dopamine biosynthesis and *BAG3, RAB29, FCGR2A* and *SIPA1L2*, which implicate proteostasis, vesicular trafficking and immune signaling respectively. Overall, the 9 druggable genes and 113 potentially druggable genes represent a wide landscape of current and future targets for therapy. These relationships also highlight those genes of central biological importance, such as *SNCA*, which are not always the easiest targets for pharmacological modulation.[18] In this study eleven specific functional genes were identifies as potential drug targets as illustrated in Appendix 5.

## Discussion

This study reveals that the GWAS of Parkinson's disease have generated large numbers of 'candidate genes.' However, by themselves, these candidate genes do not provide an explanation for the clinical heterogeneity of PD[19] or help select realistic drug targets. The current study has revealed that when the 122 candidate genes identified through GWAS are taken collectively, they point to a disease that is highly interlinked genetically with multiple other diseases and revolves around a few key biological processes rather than being associated with independent genetic changes. The frequent occurrence of bradykinesia, dementia and neurodegeneration-related terms is not surprising. What is surprising is the frequent occurrence of cancerous processes, obesity, epilepsy, schizophrenia, anxiety, diabetes, glioma and Crohn's disease. It can be safely

inferred that genes associated with PD have pleiotropic effects, with the underlying biology involving neuronal metabolism, immune function, proliferation and not only dopaminergic cell degeneration. Frequencies underlying the bar plot of prevalent diseases showing these results reveal that PD GWAS genes overlap broadly with motoric, neurodegenerative, metabolic, oncological, inflammatory and psychiatric phenotypes

*Biological insights from genetics of PD*

Pathway analysis provides an additional level of mechanistic information for this pathway network. Noting the repeated emergence of dopamine biosynthesis, axon guidance and synapse assembly, protein kinase signaling, *MAPK* signaling, calcium signaling and neuroactive ligand-receptor interaction pathways from the same group of 122 genes is striking. Collectively, these findings refine the conceptual framework of PD, supporting its classification as a multifactorial synaptopathology arising within a vulnerable dopaminergic system.[20] Importantly, while these pathways include genes with explicit associations to PD within database listings, they also involve genes that have their strongest annotations to other phenotypes. Thus, limiting analysis of the disease solely to those genes that are annotated with PD in databases would result in ignoring many biological processes involved in modulating disease risk and pathogenesis.

*Drug target assessment against literature*

Considering specific genes in this context clarifies why some have received extensive drug development focus whereas others have not been as intensively studied. *LRRK2, GBA, SCARB2, TMEM175* and *CTSB* are backed up by both genetics and their location in lysosome autophagy signaling related modules[21], encoding proteins with structural druggability. *GCH1* connects the genetic and pharmaceutical approaches by providing a link between the risk of PD and the process of dopamine production. Synaptic genes including *RIT2, VAMP4* and *SH3GL2* stress the need to maintain neuronal structures intact not only as the outcome of the disease but due to their genetically predisposed vulnerability. *SNCA* provides a contrasting example, since being essential for the etiology of PD, it encodes a protein with poor druggability. It is one of the main reasons why therapies directed against α-synuclein failed so far.[22] On the other hand, the tractability landscape emphasizes the extensive opportunities that exist. With 9 genes showing clinical evidence or having approved drugs, there are several chances for repurposing combination therapies or biomarker-based trials, even if the indications for these agents happen to be unrelated to neurology. With 113 potentially druggable targets identified, there is also considerable discovery space where basic target validation, chemistry and modelling studies might generate the next wave of therapies for PD.

*Limitations*

This study has a few limitations. First, the relationship between GWAS signals and genes is incomplete, with some causative targets possibly omitted or incorrectly labelled. Second, the disease and drug annotations are biased toward areas that have been studied intensively, rather than reflecting their biological significance. Furthermore, the findings of enrichment analysis rely on the ever-evolving databases of pathways. Third, the distinction of a drug target as being either druggable or potentially druggable fails to account for brain penetration, dose-responsiveness and safety over the long term. Lastly, all of the above work is computational in nature, the concepts generated should be looked at in terms of providing a framework for prioritization, one which needs to be further validated using cellular, animal as well as appropriate clinical experiments before any of the identified genes may be taken seriously as drug targets in PD.

## Conclusion

While genome-wide association studies have revealed a large number of PD risk loci, their relationship to coherent biological pathways and therapeutic drug targets still remains unclear. Through the identification of 122 PD-related genes, including the integration of disease associations, pathway enrichment and tractability, it is demonstrated that risk loci for PD converge into a small number of recurring pathways and also overlaps with many other diseases. This provides further support for the concept of PD as a systemic disorder rather than a disease of discrete loci. Taken together, such observations represent progress towards the goal of linking genetic discoveries to drugs by turning a plain catalogue of GWAS associations into a biological and druggability roadmap. By considering pathways and positions in the druggable genome rather than single loci, the research characterizes PD risk genes not only from the point of view of how well they fit into established drug-target patterns but also as means of determining where entirely novel target validation is required. Such a strategy can be further refined by incorporating new GWAS, functional genomics and pharmacology data as they become available, leading to smarter prioritization of disease-modifying therapeutic targets in PD.

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## Appendices

**Appendix 1** : Table displaying the chromosome number, starting and ending position of each of the mapped genes for PD in Genome Reference Consortium Human Build 38 assembly.

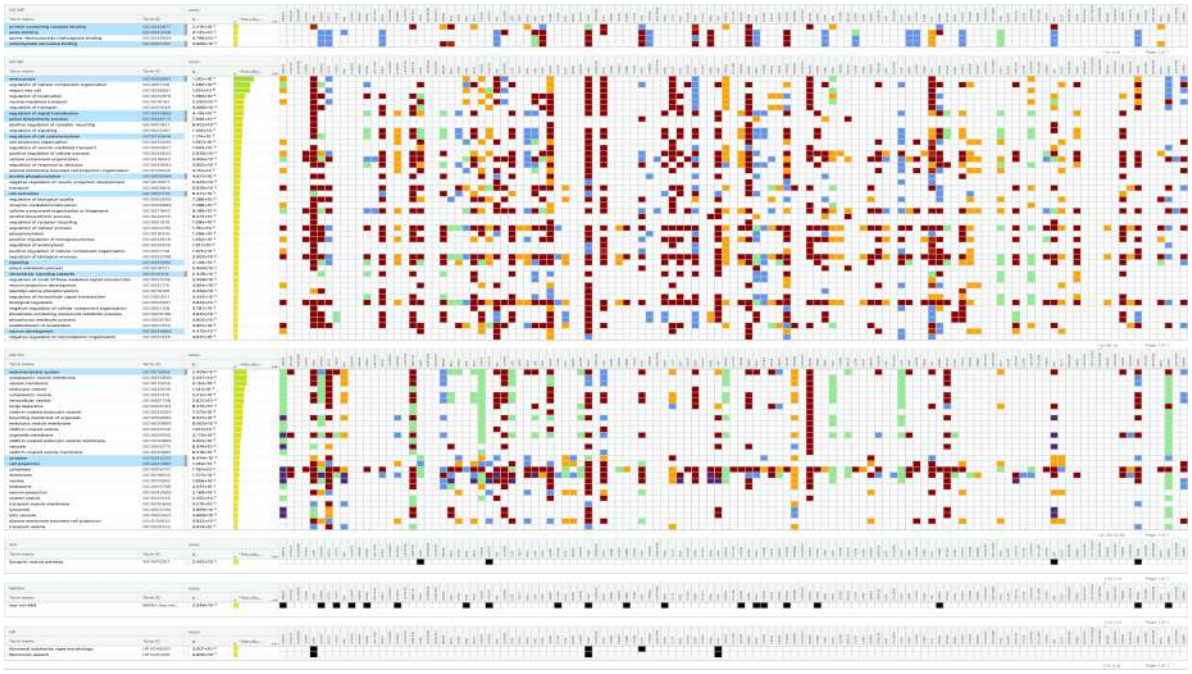
| ***Serial. No.*** | **Genes** | ***Chromosome number*** | ***Starting position*** | ***Ending position*** |
|---|---|---|---|---|
| | | | | |
| 1 | *GAK* | 4 | 849275 | 932411 |
| 2 | *TMEM175* | 4 | 932168 | 958741 |
| 3 | *SPPL2B* | 19 | 2328613 | 2355095 |
| 4 | *LZTS3* | 20 | 3162617 | 3174504 |
| 5 | *DDRGK1* | 20 | 3188734 | 3204700 |
| 6 | *CRLS1* | 20 | 6006052 | 6040053 |
| 7 | *CHRNB1* | 17 | 7445061 | 7457710 |
| 8 | *RNF141* | 11 | 10511673 | 10541334 |
| 9 | *CTSB* | 8 | 11842524 | 11869533 |
| 10 | *ITGA8* | 10 | 15513954 | 15719936 |
| 11 | *BST1* | 4 | 15703000 | 15775614 |
| 12 | *MSR1* | 8 | 16107878 | 16567490 |
| 13 | *RN7SL474P* | 8 | 16863196 | 16863496 |
| 14 | *TBC1D5* | 3 | 17157162 | 18444817 |
| 15 | *SH3GL2* | 9 | 17579066 | 17797129 |
| 16 | *LCORL* | 4 | 17841187 | 18021993 |
| 17 | *KCNS3* | 2 | 17877847 | 18361616 |
| 18 | *SYT17* | 16 | 19167971 | 19268332 |
| 19 | *BIN3* | 8 | 22620418 | 22669148 |
| 20 | *GPNMB* | 7 | 23235967 | 23275108 |
| 21 | *GPR89P* | 6 | 27737000 | 27738494 |
| 22 | *RSL24D1P1* | 6 | 27780619 | 27781111 |
| 23 | *RBMS3* | 3 | 28574791 | 30010391 |
| 24 | *RABEP2* | 16 | 28904420 | 28936526 |
| 25 | *CD19* | 16 | 28931965 | 28939342 |
| 26 | *TRIM40* | 6 | 30136028 | 30151592 |
| 27 | *SETD1A* | 16 | 30957294 | 30984664 |
| 28 | *SLC44A4* | 6 | 31863192 | 31879198 |
| 29 | *EHMT2-AS1* | 6 | 31877808 | 31884204 |

| | | | | |
|---|---|---|---|---|
| 30 | *FGD4* | 12 | 32399558 | 32646050 |
| 31 | *HLA-DRB1* | 6 | 32577902 | 32589848 |
| 32 | *HLA-DQA1* | 6 | 32628179 | 32647062 |
| 33 | *DNM1L* | 12 | 32679200 | 32745650 |
| 34 | *ASXL3* | 18 | 33578219 | 33751195 |
| 35 | *UBAP2* | 9 | 33921691 | 34049420 |
| 36 | *MIPOL1* | 14 | 37197891 | 37579125 |
| 37 | *DYRK1A* | 21 | 37365573 | 37526358 |
| 38 | *LRRK2* | 12 | 40196744 | 40369285 |
| 39 | *MUC19* | 12 | 40393395 | 40570832 |
| 40 | *LINC02400* | 12 | 41764125 | 41774671 |
| 41 | *GXYLT1* | 12 | 42081845 | 42144874 |
| 42 | *RETREG3* | 17 | 42579513 | 42610623 |
| 43 | *RIT2* | 18 | 42743218 | 43115719 |
| 44 | *ATXN7L3-AS1* | 17 | 44198520 | 44234868 |
| 45 | *UBTF* | 17 | 44205033 | 44221626 |
| 46 | *FAM171A2* | 17 | 44353215 | 44363868 |
| 47 | *RNA5SP443* | 17 | 45327366 | 45327497 |
| 48 | *ARHGAP27* | 17 | 45393898 | 45434421 |
| 49 | *LINC02210-CRHR1* | 17 | 45620344 | 45835826 |
| 50 | *MAPT-AS1* | 17 | 45799390 | 45895704 |
| 51 | *RPL13AP21* | 12 | 46004038 | 46004685 |
| 52 | *KANSL1* | 17 | 46029916 | 46225389 |
| 53 | *SLC38A1* | 12 | 46183054 | 46270070 |
| 54 | *NSF* | 17 | 46590669 | 46757679 |
| 55 | *WNT3* | 17 | 46762506 | 46833154 |
| 56 | *IP6K2* | 3 | 48688003 | 48740353 |
| 57 | *CAB39L* | 13 | 49308629 | 49444342 |
| 58 | *NOD2* | 16 | 50693217 | 50733348 |
| 59 | *SMAD4* | 18 | 51025828 | 51085045 |
| 60 | *SRSF10P1* | 18 | 51158282 | 51159383 |
| 61 | *CASC16* | 16 | 52552055 | 52652132 |
| 62 | *GCH1* | 14 | 54842008 | 54903280 |
| 63 | *RORA* | 15 | 60488284 | 61229308 |
| 64 | *ELOVL7* | 5 | 60751791 | 60844274 |
| 65 | *BRIP1* | 17 | 61679139 | 61863561 |
| 66 | *LINC02349* | 15 | 61713005 | 61731389 |

| | | | | |
|---|---|---|---|---|
| 67 | *RABGEF1P1* | 7 | 66554588 | 66576923 |
| 68 | *RNU4-66P* | 6 | 71652474 | 71652611 |
| 69 | *RIMS1* | 6 | 71886550 | 72403150 |
| 70 | *RPS6KL1* | 14 | 74903951 | 74923302 |
| 71 | *SCARB2* | 4 | 76158737 | 76234536 |
| 72 | *FAM47E* | 4 | 76214040 | 76284294 |
| 73 | *DNAH17* | 17 | 78423697 | 78577396 |
| 74 | *DLG2* | 11 | 83455012 | 85628335 |
| 75 | *RNU6-835P* | 14 | 87996345 | 87996448 |
| 76 | *GPR65* | 14 | 88005135 | 88014811 |
| 77 | *GPRIN3* | 4 | 89236383 | 89307937 |
| 78 | *SNCA* | 4 | 89700345 | 89838315 |
| 79 | *KCNIP3* | 2 | 95297327 | 95386081 |
| 80 | *LINC00456* | 13 | 97117149 | 97187578 |
| 81 | *MBNL2* | 13 | 97221434 | 97394121 |
| 82 | *MAP4K4* | 2 | 101696850 | 101894690 |
| 83 | *GBF1* | 10 | 102245371 | 102382899 |
| 84 | *PAM* | 5 | 102753981 | 103031149 |
| 85 | *LINC02527* | 6 | 111900305 | 111909420 |
| 86 | *CCN6* | 6 | 112054075 | 112069686 |
| 87 | *CAMK2D* | 4 | 113418054 | 113761927 |
| 88 | *BAG3* | 10 | 119650879 | 119677913 |
| 89 | *INPP5F* | 10 | 119726035 | 119829151 |
| 90 | *KPNA1* | 3 | 122421902 | 122514947 |
| 91 | *HIP1R* | 12 | 122834453 | 122862961 |
| 92 | *ZNF608* | 5 | 124636913 | 124748807 |
| 93 | *LINC02240* | 5 | 124808887 | 125602227 |
| 94 | *CYRIB* | 8 | 129839593 | 130017504 |
| 95 | *GALNT9* | 12 | 132196372 | 132329598 |
| 96 | *FBRSL1* | 12 | 132489551 | 132585188 |
| 97 | *HMGB1P13* | 6 | 132868218 | 132868859 |
| 98 | *LINC00326* | 6 | 132908105 | 133107410 |
| 99 | *IGSF9B* | 11 | 133896438 | 133956968 |
| 100 | *TMEM163* | 2 | 134455759 | 134719100 |
| 101 | *C5orf24* | 5 | 134845680 | 134859735 |
| 102 | *TXNDC15* | 5 | 134874318 | 134901635 |
| 103 | *MED12L* | 3 | 151085286 | 151437072 |
| 104 | *PMVK* | 1 | 154924732 | 154937008 |

| | | | | |
|---|---|---|---|---|
| 105 | *HMGN2P18* | 1 | 155148544 | 155148813 |
| 106 | *KRTCAP2* | 1 | 155169408 | 155173475 |
| 107 | *GBA1* | 1 | 155234447 | 155245178 |
| 108 | *SEMA4A* | 1 | 156147366 | 156178869 |
| 109 | *SLC25A44* | 1 | 156193932 | 156212796 |
| 110 | *SPTSSB* | 3 | 161344798 | 161372880 |
| 111 | *RNU6-481P* | 1 | 161401289 | 161401395 |
| 112 | *FCGR2A* | 1 | 161505415 | 161524013 |
| 113 | *STK39* | 2 | 167949900 | 168247739 |
| 114 | *RN7SL813P* | 2 | 168451324 | 168451606 |
| 115 | *CLCN3* | 4 | 169612438 | 169723673 |
| 116 | *VAMP4* | 1 | 171700160 | 171743206 |
| 117 | *METTL13* | 1 | 171781660 | 171814023 |
| 118 | *MCCC1* | 3 | 183015218 | 183116075 |
| 119 | *NUCKS1* | 1 | 205712822 | 205750270 |
| 120 | *RAB29* | 1 | 205767986 | 205775482 |
| 121 | *ITPKB* | 1 | 226631688 | 226739323 |
| 122 | *SIPA1L2* | 1 | 232397622 | 232631404 |

**Appendix 2**: Detailed analysis of functional enrichment of GWAS-analysed mapped genes from g: Profiler.



**Appendix 3:** 21 specific mapped genes associated with PD taking part in the 7 main shared biological pathways

| Sr no. | GENES ASSOCIATED WITH PARKINSON'S | CHROMOSOME NUMBER | MECHANISM IN BRIEF |
|---|---|---|---|
| 1 | *SCARB2* | 4 | lysosome biosynthesis, immune regulation and transport for cholesterol. |
| 2 | *CTSB* | 8 | Lysosomal protease, α-synuclein degradation degrades intracellular proteins |
| 3 | *TMEM175* | 4 | Lysosomal potassium channel, pH regulation and membrane potential |
| 4 | *BST1* | 4 | Calcium signaling, neuroinflammation modulation |
| 5 | *LRRK2* | 12 | Kinase activity, vesicle trafficking dysfunction |
| 6 | *GCH1* | 14 | Dopamine synthesis via BH4 production |
| 7 | *KANSL1* | 17 | Chromatin remodeling, neuronal gene regulation |
| 8 | *RIT2* | 18 | Dopaminergic neuron signaling, vesicle trafficking |
| 9 | *WNT3* | 17 | WNT signaling, neuronal development regulation |
| 10 | *MAPT-AS1* | 17 | Tau protein expression regulation, antisense RNA |
| 11 | *DNM1L* | 12 | Mitochondrial fission, dynamics imbalance |
| 12 | *VAMP4* | 1 | Vesicle fusion, synaptic trafficking defects |
| 13 | *SIPA1L2* | 1 | Cytoskeletal organization, synaptic maintenance |
| 14 | *SH3GL2* | 9 | Endocytosis, synaptic vesicle recycling |
| 15 | *TMEM163* | 2 | Zinc transport, synaptic vesicle function |
| 16 | *MAP4K4* | 2 | Stress signaling, neuronal apoptosis pathways |
| 17 | *LCORL* | 4 | Transcription regulation, unclear PD mechanism |
| 18 | *CAMK2D* | 4 | Calcium signaling, synaptic plasticity regulation |
| 19 | *STK39* | 2 | Ion transport regulation, cellular stress response |

| | | | |
|---|---|---|---|
| 20 | *BAG3* | 10 | Autophagy regulation, protein quality control |
| 21 | *RAB29* | 1 | Vesicle trafficking, LRRK2 activation pathway |

**Appendix 4:** Table representing the genes and drugs to their corresponding clinical phase trials.

| Sr. NO | PHASE | GENES | DRUGS |
|---|---|---|---|
| 1 | Unknown | CHRNB1 | TUBOCURARINE CHLORIDE, PIPECURONIUM BROMIDE |
| 2 | Early phase I | CHRNB1 | ATRACURIUM BESYLATE |
| 3 | Phase I | SLC44A4 | ASG-5ME |
| 4 | Phase I/II | GPNMB | GLEMBATUMUMAB, GLEMBATUMUMAB VEDOTIN |
| 5 | Phase II | SNCA, HLA-DRB1, CD19, GBA1, KCNS3, CHRNB1 | CINPANEMAB, APOLIZUMAB, PLOVAMER ACETATE, MDX-1342, ONCOLYSIN B, COLTUXIMAB RAVTANSINE, DENINTUZUMAB MAFODOTIN, AFEGOSTAT, AFEGOSTAT TARTRATE, NERISPIRDINE, MIVACURIUM CHLORIDE |
| 6 | Phase III | SNCA, CD19, KCNS3, CHRNB1 | PRASINEZUMAB, OBEXELIMAB, GUANIDINE, ROCURONIUM BROMIDE, CISATRACURIUM BESYLATE |
| 7 | Approval | GPNMB, CD19, NOD2, KCNS3, CHRNB1 | GLEMBATUMUMAB VEDOTIN, TISAGENLECLEUCEL, BLINATUMOMAB, LONCASTUXIMAB TESIRINE, TAFASITAMAB, AXICABTAGENE CILOLEUCEL, INEBILIZUMAB, BREXUCABTAGENE AUTOLEUCEL, LISOCABTAGENE MARALEUCEL, MIFAMURTIDE, GUANIDINE HYDROCHLORIDE, AMIFAMPRIDINE PHOSPHATE, AMIFAMPRIDINE, DALFAMPRIDINE, SUXAMETHONIUM, ROCURONIUM, CISATRACURIUM, MIVACURIUM, ATRACURIUM, VECURONIUM, VECURONIUM BROMIDE, SUCCINYLCHOLINE CHLORIDE, RAPACURONIUM BROMIDE, TUBOCURARINE, PIPECURONIUM, DECAMETHONIUM, METOCURINE IODIDE, GALLAMINE THRIETHIODIDE, DOXACURIUM, PANCURONIUM |

**Appendix 5:** 11 specified functional genes that can potentially be druggable.

| Sr. No | POTENIALLY DRUGGABLE GENES | FUNCTIONS |
|---|---|---|
| 1 | *SCARB2* | Common variants near SCARB2 are associated with Parkinson's disease and intracranial aneurysm, implicating lysosomal dysfunction in disease risk. |
| 2 | *CTSB* | CTSB variants are GWAS hits in Parkinson's disease, again pointing to lysosomal biology in PD susceptibility. |
| 3 | *TMEM175* | Locus at TMEM175 is a robust PD GWAS hit linked to lysosomal and autophagy pathways. |
| 4 | *LRRK2* | Multiple GWAS have confirmed LRRK2 as a major PD risk locus across ancestries. |
| 5 | *GCH1* | GCH1 variants are associated with PD and with levels of biomarker traits related to dopamine synthesis. |
| 6 | *FCGR2A* | FCGR2A locus is associated with autoimmune and inflammatory diseases, including inflammatory bowel disease and systemic lupus erythematosus. |
| 7 | *WNT3* | Variants near WNT3 are associated with cognitive performance and intelligence in large meta-analysis GWAS. |
| 8 | *RIT2* | RIT2 region harbors GWAS signals for PD and related dopaminergic traits. |
| 9 | *MAPT-AS1* | Variants in the MAPT–KANSL1 region are associated with PD, other tauopathies and some cognitive traits |
| 10 | *KANSL1* | Variants in the MAPT–KANSL1 region are associated with PD, other tauopathies and some cognitive traits |
| 11 | *NSF* | NSF lies in a GWAS locus for PD and synaptic function traits. |