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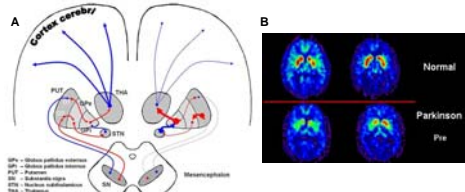
## Abstract

Parkinson's disease (PD) is a chronic, degenerative neurological disorder that is estimated to affect at least 1.5 million people in the United States and 6 million worldwide (1,2). The average age at onset is 60 (affecting 1/100 people) however approximately 5-10% of patients experience onset around age 40, and people as young as 30 can also be diagnosed with this disease (1,2). Furthermore, there is no objective test or biomarker for Parkinson's and the rate of misdiagnosis can be relatively high. Proper diagnosis, and development of successful therapies is compounded by the complexity of the brain as many PD related proteins are differentially expressed and regulated both temporally and spatially in the brain (4). Thus, PD manifestation varies greatly among individuals.

A major hurdle in the development of neuroprotective therapies for PD is due to a limited understanding of the underlying pathobiology: the death of dopaminergic neurons and subsequent loss of dopamine-regulated functions that regulate coordinated movement. This results in random events of dopamine release, a loss of the ability to control movement and manifests as tremor, bradykinesia, postural instability, gait difficulty and rigidity.

To increase the incidence of correct diagnosis a better understanding of the molecular mechanism(s) behind cell death in dopaminergic neurons and how this varies amongst different individuals, is key. In an attempt to elucidate these mechanisms and identify potential new targets, we used a pathway analysis approach to analyze data from a high-resolution, genome-wide association study (GWAS) of PD (4). We also demonstrate how PD specific GWAS data analysis can be used to identify potential therapies of other aging, neurological diseases such as Alzheimer's by discerning the common molecular signatures.

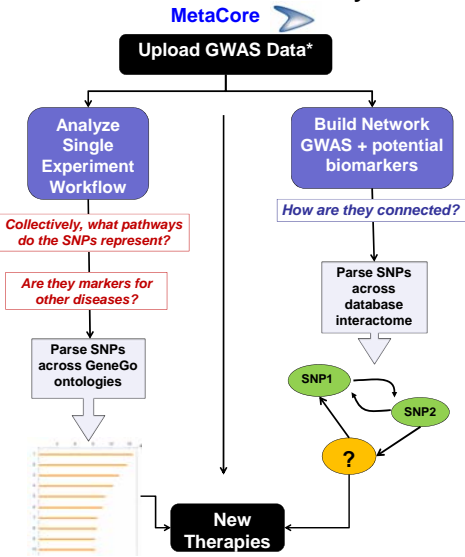
## 1. Pathogenesis of Parkinson's



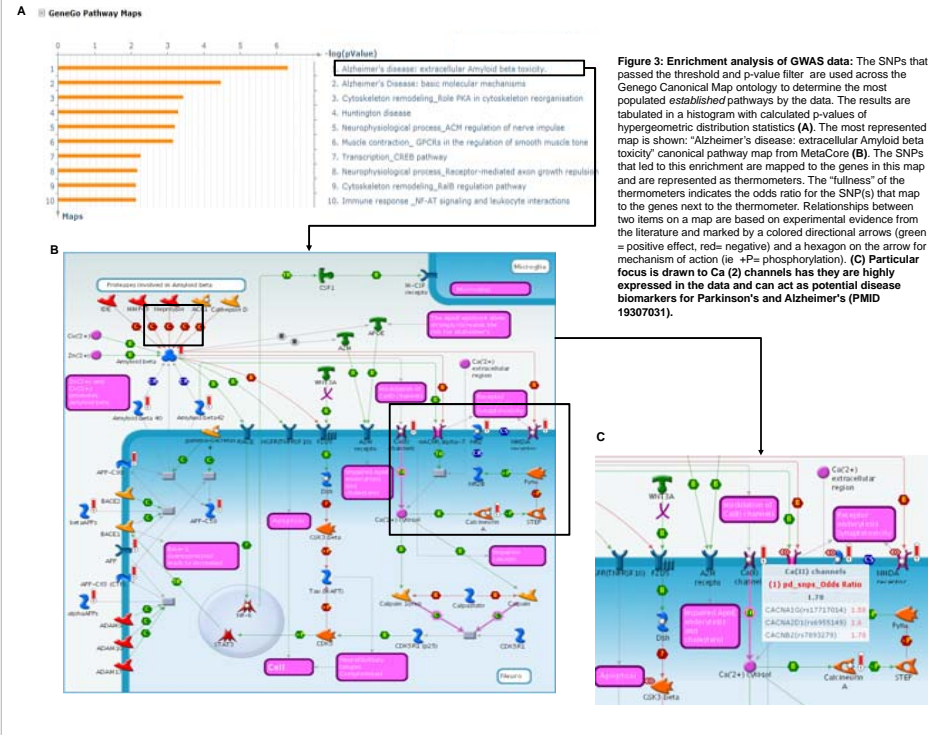
**Figure 1:** (A) A diagram of dopaminergic pathways in the human brain. In a normal brain (left), dopamine is secreted from neurons in the substantia nigra (SN) and extend into the putamen region (PUT) causing DIRECT stimulation (blue arrows) of other regions of the brain. This is followed by a sequence of suppressive events (red arrows) as a mechanism of controlled regulation. In PD, (right), the controlled regulation of dopamine activity is lost due to the loss of neurons in the SN and subsequent loss of dopamine release. Source: [http://commons.wikimedia.org/wiki/File:DA-flopps\\_in\\_PD.jpg](http://commons.wikimedia.org/wiki/File:DA-flopps_in_PD.jpg)

(B) A 18F PET scan that shows decreased dopamine activity in the basal ganglia region of the brain in a PD patient (middle left) compared to a normal individual (top left). Source: [http://rstqstc.nasa.gov/intro/Part2\\_26d.htm](http://rstqstc.nasa.gov/intro/Part2_26d.htm)

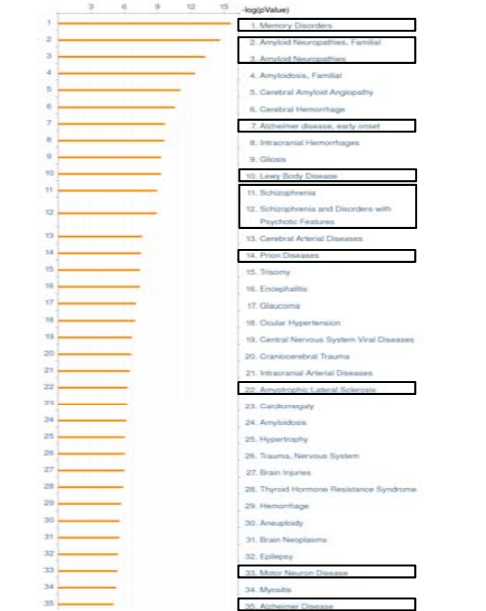
## 2. Flow Chart of Data Analysis



## 3. Most representative Pathways and Potential New Biomarkers



## 4. Top 35 Represented Diseases



**Figure 4:** Enrichment analysis of GWAS data with Disease Ontology: The SNPs that passed the threshold and p-value filter are used across the Disease ontology to determine the most represented diseases according to annotated disease markers. The results are tabulated in a histogram with calculated p-values of hypergeometric distribution statistics. Other aging neuronal diseases enriched with GWAS SNPs are marked with black boxes.

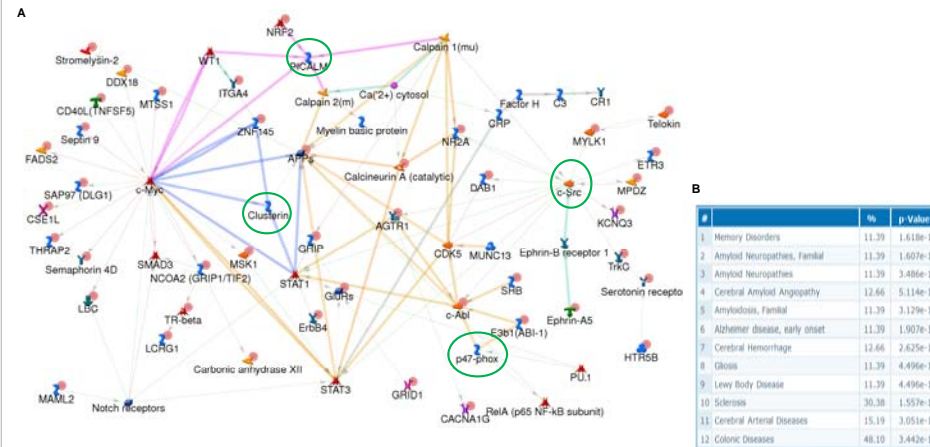
## Summary

- To better understand the molecular mechanisms that lead to PD, we analyzed data from a recent GWAS using a systemic pathway approach.
- The most affected SNPs were found to collectively represent amyloid-beta toxicity, which is also a defined mechanism of Alzheimer's pathogenesis. Key SNPs that dictate representation of amyloid toxicity include calcium channels *CACNA1*, *CACNB2* and *CACND21*, and calcineurin.
- Enrichment analysis across GeneGo Maps also indicate the role of development, the cytoskeleton and immune response as key pathways in PD pathogenesis.
- The GWAS PD data is also representative of other neurological diseases including Alzheimer's, schizophrenia and ALS. Further analysis for each disease category in GeneGo's ontology can lead to identification of specific SNPs as markers for each disease.
- The connectivity of the GWAS data was determined using network building algorithms to discern if any of the SNPs were interconnected and how. This approach highlighted the role of c-Abl, *PICALM*, and *Clusterin* in regulating altered SNPs (not expressed by the data) in PD but also Alzheimer's and ALS (further confirmed by the literature 5-6).
- Network analysis of the GWAS data also highlights key altered SNPs that may be potential targets for developing therapies. For example, *MAML2* and *MYLK1* are regulators of developing and differentiation of neurons and could potentially be targeted to enhance neuronal regeneration and synapse function (7-8).

## References

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## 5. Interaction Network of GWAS Parkinson's SNPs and Potential New Biomarkers



**Figure 5:** Interaction network of GWAS Parkinson's SNPs. (A) The shortest pathway network algorithm was used to determine all interactions within the SNPs from the GWAS data. Newly identified neurodegenerative disease markers were added (*Clusterin*, *PICALM* PMID: 19734902 and *c-Abl* PMID: 1601719) to determine possible links between Alzheimer's and PD. Upstream and downstream effectors of *PICALM* are in magenta, of *c-Abl* are in orange and of *Clusterin* are in blue. Potential new markers drawn in from the data base are marked in green circles. Potential markers from the GWAS data are marked with red circles in the upper right hand corner of the object. Relationships between two items on a map are based on experimental evidence from the literature and marked by a colored directional arrows (green = positive effect, red = negative) and a hexagon on the arrow for mechanism of action (ie +P= phosphorylation). (B) The items on this network also represent other neurological diseases.