The Association Between Parkinson's Disease Brain Imaging Phenotypes and Common Genetic Variants: A Polygenic Risk Score Approach

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Introduction

Parkinson's Disease (PD) is the second most prevalent neurodegenerative disorder following Alzheimer's disease.[1] By the time motor symptoms manifest, a significant proportion of nigrostriatal neurons has been lost due to degeneration.[2] Better ways of early detection of high-risk individuals are needed, as these individuals can be targeted for PD clinical trials and future disease-modifying therapies.

Polygenic risk score (PRS) models sum the contribution of multiple genetic risk variants of variable effect sizes to represent an individual's genetic risk score for a disease.[3] In PD, PRS has shown potential in predicting PD risk,[4] age at onset,[5] and progression of cognitive and motor symptoms.[6] The association between PD PRS and other disease-specific subclinical traits, such as neuroimaging phenotypes, remains to be explored.

Methods

Data source: We included 104 PD patients and 85 controls from the Parkinson's Progression Markers Initiative (PPMI) dataset with available genotype and MRI Brain data. Demographics data of study participants are shown in Table 1.

PRS Calculation: PRS was calculated using PRSice-2 software. Genetic variants were included based on their contribution to the risk of PD.[7] The best p-value threshold was chosen based on comparing our PD patients to the healthy controls (see Figure 1).

MRI Data: T1-weighted MRI brains acquired on 3T scanners were processed using a fully-automated image analysis software, FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). Volumetric measures of key brain regions were extracted, including the basal ganglia structures, thalamus, hippocampus, and amygdala (see Figure 2). Structure volumes were divided into contralateral and ipsilateral based on the patient's motor symptoms dominance.

Analysis: Multiple linear regression models applied to examine the association between PD PRS and MRI-based brain structural volumes, while controlling for relevant covariates (e.g. age, gender, intracranial volume, and Hoehn and Yahr stage).

Results

Table 1: Baseline Characteristics

Characteristic	PD	Controls
Number of participants	104	85
Age, years	61 (38- 82)	61 (31- 81)
Male sex, %	68 (65.4)	62 (72.9)
Age at PD onset, years	59.65 (35- 81.4)	-----
Tremor, %	69 (66.3)	-----
Tremor Dominance, right side	55 (52.9)	-----

*Values are expressed as median (minimum - maximum) unless otherwise indicated

Table 2: Effect of PRS on Brain Structure Volumes

Brain Structure	Beta Coefficient (B)	Standard Error (SE)	Adjusted R-squared	P-value
Caudate				
Ipsilateral	-7.939×10^2	4.358×10^3	0.2605	0.8558
Contralateral	-2.523×10^3	4.974×10^3	-0.0120	0.6130
Putamen				
Ipsilateral	-7.423×10^3	4.457×10^3	0.5471	0.0988*
Contralateral	-1.048×10^4	4.791×10^3	0.5591	0.0312**
Globus Pallidum				
Ipsilateral	-2.804×10^3	2.244×10^3	0.2910	0.2140
Contralateral	-2.940×10^3	2.042×10^3	0.3274	0.1530
Thalamus				
Ipsilateral	-2.820×10^3	5.684×10^3	0.6140	0.6209
Contralateral	-2.484×10^3	5.091×10^3	0.6684	0.6270
Hippocampus				
Ipsilateral	-2.338×10^3	3.874×10^3	0.4492	0.5475
Contralateral	2.328×10^2	3.853×10^3	0.4275	0.9520
Amygdala				
Ipsilateral	-1.051×10^3	2.055×10^3	0.3923	0.6103
Contralateral	-4.046×10^2	1.971×10^3	0.3814	0.8378
White Matter				
Ipsilateral	1.012×10^3	1.643×10^5	0.6941	0.5394
Contralateral	1.198×10^5	1.665×10^5	0.7034	0.4733
Cortex				
Ipsilateral	1.013×10^5	1.139×10^5	0.8056	0.3760
Contralateral	1.254×10^5	1.178×10^5	0.8065	0.2894

* = significance at α = 0.1 ** = significance at α = 0.05

Figure 1: PRS P-value Threshold

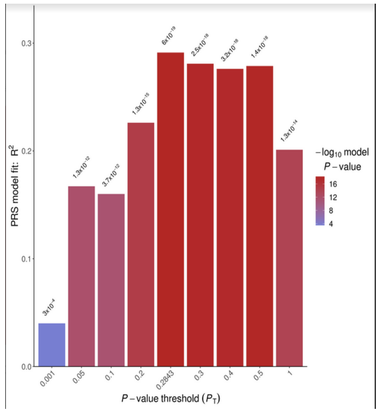


Figure 2: Brain Anatomy

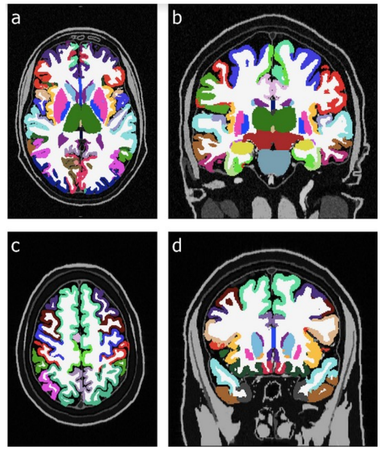
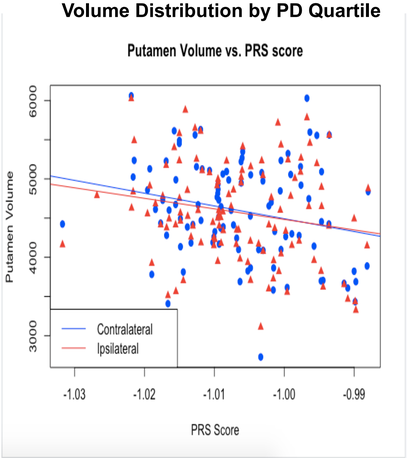


*Image from FreeSurfer

Figure 3: Contralateral Putamen Volume Distribution by PD Quartile



Contralateral Putamen Volume Distribution by Quartile

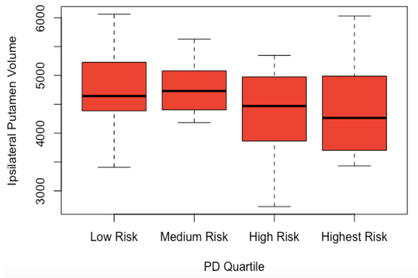
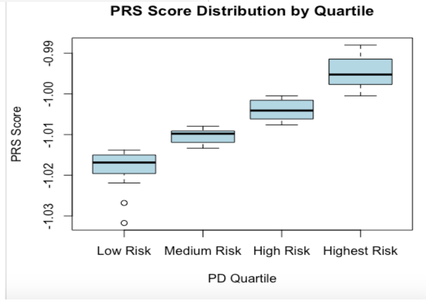


Figure 4: MRI Putamen Volume vs. PRS Score

Figure 5: PRS Quartiles Descriptive Statistics



Conclusion

In *de novo* PD, PD PRS is associated with a smaller contralateral putamen volume (p=0.03). This finding highlights the relevant relationship between PD genetic risk variants and the putamen, a key brain structure associated with PD pathological mechanisms. This study was limited by a small sample and thus replication of our findings in a larger PD sample is warranted.

References

1. *Parkinson's Statistics*. Parkinson's Foundation. (n.d.). From https://www.parkinson.org/understanding-parkinsons/statistics

2. Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell and tissue research*, *318*(1), 121–134. https://doi.org/10.1007/s00441-004-0956-9

3. Choi, S. W. & O'Reilly (2019). P. F. PRSice-2: Polygenic Risk Score software for biobank-scale data. *GigaScience 8*, giz082

4. Ibanez, L. *et al.* (2017). Parkinson disease polygenic risk score is associated with Parkinson disease status and age at onset but not with alpha-synuclein cerebrospinal fluid lev els. *BMC Neurol. 17*, 198

5. Escott-Price, V. *et al.* (2015). Polygenic risk of Parkinson disease is correlated with disease age at onset. *Ann. Neurol. 77*, 582–591

6. Paul, K. C., Schulz, J., Bronstein, J. M. *et. al.* (2018). Association of Polygenic Risk Score With Cognitive Decline and Motor Progression in Parkinson Disease. *JAMA Neurol. 75*, 360

7. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, Bras J, Young E, von Coelln R, Simón-Sánchez J, Schulte C, Sharma M, Krohn L, Pihlstrøm L, Siitonen A, Iwaki H, Leonard H, Faghri F, Gibbs JR, Hernandez DG, Scholz SW, Botia JA, Martinez M, Corvol JC, Lesage S, Jankovic J, Shulman LM, Sutherland M, Tienari P, Majamaa K, Toft M, Andreassen OA, Bangale T, Brice A, Yang J, Gan-Or Z, Gasser T, Heutink P, Shulman JM, Wood NW, Hinds DA, Hardy JA, Morris HR, Gratten J, Visscher PM, Graham RR, Singleton AB; 23andMe Research Team; System Genomics of Parkinson's Disease Consortium; International Parkinson's Disease Genomics Consortium. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol. 2019 Dec;18(12):1091-1102. doi: 10.1016/S1474-4422(19)30320-5. PMID: 31701892; PMCID: PMC8422160.