Polygenic Risk Score in Parkinson's Tied to Cortical Thinning

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The study covered in this summary was published in medRxiv.org as a preprint and has not yet been peer reviewed.

Key Takeaways

- Higher genetic risk of Parkinson's disease (PD) was associated with lower brain cortical thickness in posterior areas and greater cortical surface area.
- Genome-wide association studies have identified 90 gene variants that contribute to PD risk, yet the causative mechanisms are largely unknown.
- Polygenic risk scores (PRS) for PD in healthy adults, consisting of genetic, neuroimaging, and behavioral data from the UK Biobank constructed from genome-wide association studies, were analyzed to determine neural and clinical correlates.
- A positive genetic correlation was found between total cortical surface area and three phenotypes: PD, educational attainment, and cognitive ability.

Why This Matters

- The cortical thickness and surface area associations found in this study may represent different mechanisms of genetic vulnerability to PD.
- These findings may help researchers understand and interpret the prodromal symptoms of PD, leading to earlier and more targeted interventions.

Study Design

- The study involved data from a subset of 42,488 participants (31,386 after exclusions) of the UK Biobank with brain-imaging measures including thickness and surface area.
- Data analysis was performed using standard software (FreeSurfer, FSL, Plink, MATLAB, and Python), and gene expression maps were generated using abagen.
    - The following metrics were analyzed: association of PD-PRS with cortical thickness and surface area, comparison with PD atrophy distribution, role of connectivity, comparison with genetic effects on cortical structure, comparison with gene expression maps, virtual histology, gene ontology analysis, and behavioral correlates of genetic risk for PD.

Key Results

- Genetically determined cortical thinning corresponds to the progressive neural tissue loss seen in PD. Areas of lower cortical thickness in subjects with higher genetic risk are the same areas that tend to atrophy faster in PD.
- PD-PRS–related cortical thinning was observed in occipital and parietal lobes, less so in the medial and orbital prefrontal areas, similar to the cortical thinning distribution seen in PD in other cohorts.
- Analysis suggests that PD genetic risk may result from accumulation of toxic proteins, lysosomal dysfunction, and synaptic damage, all of which may be present in patients without overt PD.

Limitations

- The PD-PRS accounts for only 16% to 36% of the heritability of PD; other unstudied genetic effects may also contribute to PD risk.
- No causal relationship between brain patterns and PD development was proven; findings are correlative.
- The authors assert that future studies should investigate MRI measures of basal ganglia and white matter integrity, also available in the UK Biobank.

Study Disclosures

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This is a summary of a preprint research study,"Neuroanatomical Correlates of Polygenic RIsk for Parkinson's Disease," by Nooshin Abbasi and colleagues from Montreal Neurologic Institute, McGill University, on medRxiv provided to you by Medscape. This study has not yet been peer reviewed. The full text of the study can be found on medRxiv.org.

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