BRIEF REPORT

Lysosomal Polygenic Burden Drives Cognitive Decline in Parkinson's Disease with Low Alzheimer Risk

Jon-Anders Tunold, MD,[1,2] Manuela M.X. Tan, PhD,[1] Mathias Toft, MD, PhD,[1,2] Owen Ross, PhD,[3] Wilma D.J. van de Berg, MD, PhD,[4,5] and Lasse Pihlstrøm, MD, PhD[1*]

[1]*Department of Neurology, Oslo University Hospital, Oslo, Norway* [2]*Institute of Clinical Medicine, University of Oslo, Oslo, Norway* [3]*Mayo Clinic, Department of Neuroscience, Jacksonville, Florida, USA* [4]*Department of Anatomy and Neurosciences, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands* [5]*Amsterdam Neuroscience, Program Neurodegeneration, Amsterdam, The Netherlands*

ABSTRACT: Background: Genetics influence cognitive progression in Parkinson's disease, possibly through mechanisms related to Lewy and Alzheimer's disease pathology. Lysosomal polygenic burden has recently been linked to more severe Lewy pathology post mortem.

Objectives: To assess the influence of lysosomal polygenic burden on cognitive progression in Parkinson's disease patients with low Alzheimer's disease risk.

Methods: Using Cox regression we assessed association between lysosomal polygenic scores and time to Montreal Cognitive Assessment score ≤ 21 in the Parkinson's Progression Markers Initiative cohort (n = 374), with replication in data from the Parkinson's Disease Biomarker Program (n = 777). Patients were stratified by Alzheimer's disease polygenic risk.

Results: The lysosomal polygenic score was associated with faster progression of cognitive decline in patients with low Alzheimer's disease risk in both datasets ($P = 0.0032$ and $P = 0.0054$, respectively).

Conclusion: Our study supports complex interplay between genetics and neuropathology in Parkinson's disease-related cognitive impairment, emphasizing the role of lysosomal polygenic burden. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; polygenic risk score; lysosomal pathway; cognition; neuropathology

*__Correspondence to:__ Dr. Lasse Pihlstrøm, Department of Neurology, Oslo University Hospital, P.O. Box 4950 Nydalen, 0424 Oslo, Norway; E-mail: lasse.pihlstrom@medisin.uio.no

Jon-Anders Tunold and Manuela M. X. Tan contributed equally to this study.

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Cognitive impairment is a highly disabling non-motor manifestation of Parkinson's disease (PD) with heterogeneous onset and severity.[1-3] Understanding the risk factors and molecular mechanisms contributing to cognitive decline in PD is essential to improve prognostics and develop targeted treatment.

Advanced limbic and neocortical Lewy pathology is the most consistent neuropathological feature of Parkinson's disease dementia (PDD). However, Alzheimer's disease (AD)-related amyloid-β and tau co-pathologies are also common and independently associated with cognitive impairment in PD.[4] In line with this duality of neuropathology, established genetic risk loci for cognitive progression in PD include both *GBA1*,[5-7] which is implicated in PD risk and Lewy pathology, and *APOE*,[7,8] the major common AD susceptibility locus.

In dementia with Lewy bodies (DLB), two recent studies have found evidence of distinct genetic architectures depending on the extent of concomitant AD-pathology.[9,10] Using either neuropathology[9] or cerebrospinal fluid (CSF) biomarkers[10] to stratify DLB patients into subgroups with or without significant AD co-pathology, *APOE* was specifically associated with the former, AD-positive group, and *GBA1* with the latter, "pure" DLB group. Similarly, we recently showed that the severity of Lewy pathology is associated with lysosomal polygenic burden specifically in the subset of PD and DLB donors without AD co-pathology.[11]

We aimed to investigate if these findings can be extended to cognitive progression in the early phase of PD, hypothesizing that stratification of PD patients based on the vulnerability to AD pathology may be important for genetic studies of cognitive progression.

Methods

Sample Description

We used clinical and genetic data from two longitudinal PD cohorts; the Parkinson's Progression Markers Initiative (PPMI) and the Parkinson's Disease Biomarker Program (PDBP) (Supplementary Data S1). PPMI included PD patients within 2 years of diagnosis and without symptomatic therapy at baseline (n = 423), PDBP recruited patients at various stages of disease (n = 884). Detailed descriptions of the cohorts have been published elsewhere.[12,13] Samples of Non-European genetic ancestry were removed (Supplementary Data S1). Cognition was assessed using the Montreal Cognitive Assessment (MoCA)[14] adjusted for education. We defined MoCA ≤21/30 as indicative of PD dementia, a cut-point that has been validated and recommended in previous work.[15] The PPMI data included CSF biomarkers of AD pathology at baseline.

To determine the optimal threshold for AD polygenic risk score (PRS) to discriminate between samples with and without significant AD co-pathology, we analyzed data from 217 neuropathologically characterized Lewy body disease (LBD) samples from the Netherland's Brain Bank (NBB) as previously described.[11]

Calculation of Polygenic Risk Scores

A PRS is calculated as the weighted sum of risk alleles carried by an individual, using published genome-wide association study (GWAS) results as reference to determine the weight of each independent variant passing a defined significant threshold. Pathway-specific PRS can be generated by limiting the algorithm to include only variants annotated to a specific gene set or cell type. For all PPMI and PDBP individuals we calculated individual PD-PRS, lysosomal PD-PRS with and without *GBA1* and AD-PRS using the PRSice2 software package with default parameters and summary statistics from recent PD[16] and AD[17] GWAS meta-analyzes, respectively. PRSs were standardized to have a mean of 0 and standard deviation (SD) of 1 (Supplementary Data S1: Supplementary Methods and Supplementary Tables S1–S4).

Statistical Analyzes

All statistical analyzes were performed in R version 4.3.1 (www.r-project.org). To stratify PD patients for low or high vulnerability to AD co-pathology we first applied CSF biomarker cutoffs previously determined in AD (Supplementary Data S1).[18,19] CSF measures were log-transformed to normalize the distribution and compared between groups using *t* tests. Next, we explored stratification based on AD-PRS, taking advantage of NBB data from LBD donor brains to identify the optimal cut-point (Supplementary Data S1).[11]

TABLE 1 *Demographic table for the PPMI and PDBP cohorts*

	PPMI (n = 374)	PDBP (n = 777)
Sex, No. (%)		
Male	244 (65.2)	498 (64.1)
Female	130 (34.8)	279 (35.9)
Age at diagnosis (y), mean (SD)	61.4 (9.5)	58.8 (10.2)
Age at inclusion (y), mean (SD)	61.9 (9.5)	64.5 (9.0)
Disease duration (y) at baseline, mean (SD)	0.5 (0.5)	5.8 (5.6)
Years of education, mean (SD)	15.5 (3.0)	-
Years of education <12, No. (%)	–	21 (2.7)
Years of education 12–16, No. (%)	–	502 (64.6)
Years of education >16, No. (%)	–	252 (32.4)
Baseline UPDRS 1 score, mean (SD)	5.6 (4.2)	9.5 (6.0)
Baseline UPDRS 2 score, mean (SD)	5.8 (4.2)	10.8 (7.8)
Baseline UPDRS 3 score, mean (SD)	20.7 (8.8)	25.6 (13.5)
Baseline UPDRS 4 score, mean (SD)	NA	2.1 (3.5)
Baseline UPDRS total score, mean (SD)	32.1 (13.1)	47.8 (23.8)
Baseline MoCA, mean (SD)[a]	26.5 (3.4)	25.4 (3.5)
Number of MoCA evaluations, mean (SD)	5.2 (1.4)	2.3 (1.6)
Follow-up time (months), mean (SD)	52.7 (16.4)	16.5 (19.2)
APOE E4 alleles, No. (%)		
0	285 (76.2)	581 (74.8)
1 or 2	89 (23.8)	196 (25.2)
$A\beta_{1-42}$ > 683 pg/mL, No. (%)[b]	246 (67.7)	–
pTau <24 pg/mL, No. (%)[c]	153 (45.2)	–
tTau <266 pg/mL, No. (%)[d]	168 (45.6)	–
AD-PRS <0.29 , No. (%)[e]	248 (66.3)	518 (66.6)

[a]Patients with MoCA ≤21 at baseline were not excluded from the analysis.
[b]Samples with CSF $A\beta_{1-42}$ >683 pg/mL[19] (Elecsys units) were classified as having a low AD risk. CSF measure of $A\beta_{1-42}$ were available for 363 PPMI subjects.
[c]Samples with CSF pTau <24 pg/mL[18] (Elecsys units) were classified as having low AD risk. CSF measures of pTau were available for 338 PPMI subjects.
[d]Samples with CSF tTau <266 pg/mL[18] (Elecsys units) were classified as having low AD risk. CSF measures of tTau were available for 368 PPMI subjects.
[e]Samples with AD-PRS <0.29 SD were classified as having low AD risk. The cutoff was determined in the Netherlands Brain Bank (NBB) samples as described in Supplementary Data S1.
Abbreviations: PPMI, progression markers initiative; PDBP, Parkinson's disease biomarker program; SD, standard deviation; UPDRS, Unified Parkinson's disease rating scale; MoCA, Montreal Cognitive Assessment; AD, Alzheimer's disease; AD-PRS, Alzheimer's disease polygenic risk score; CSF, cerebrospinal fluid.

Cox proportional hazard models were used to determine the association between the PRS and time from diagnosis to MoCA ≤ 21 adjusting for age at diagnosis, sex, education, and first five genetic principal components, using the R package "survival" (Supplementary Data S1). We applied a two-stage design with discovery in the PPMI cohort and replication in the PDBP cohort, using two-sided $P < 0.05$ as significance threshold.

Results

A total of 374 individuals from PPMI and 777 from PDBP passing quality checks and with available demographic variables were included in the study (Supplementary Data S1). Demographic variables are displayed in Table 1.

When considering all PPMI subjects, the lysosomal PD-PRS was not significantly associated with time to dementia (Table 2). Next, we selectively analyzed the subset of PPMI subjects with negative AD CSF biomarkers (Table 2). CSF $A\beta_{1\text{-}42}$-based stratification classified ~70% of samples as low AD risk, and in these cases, the lysosomal PD-PRS was associated with a faster cognitive decline ($P = 0.039$). Stratifying by CSF t-tau or p-tau yielded ~50% of samples below the cut-point, where the lysosomal PD-PRS association was not significant. Among AD CSF biomarkers, the strongest association with cognitive decline in PD is found for low CSF $A\beta_{1\text{-}42}$ levels,[20-22] and this stratification also provided the best statistical power for analyzes in the low AD risk group in our data. We, therefore, interpret the CSF $A\beta_{1\text{-}42}$-stratified result as suggestive evidence of an association.

As the availability of CSF biomarker data is limited in larger sample series, we next investigated whether stratification based on polygenic AD risk could also capture the relevant subgroup with sufficient accuracy. Splitting the PPMI samples based on AD-PRS, patients with a high vulnerability to AD co-pathology (n = 126 [34%]) exhibited a significantly lower mean baseline CSF $A\beta_{1\text{-}42}$ ($P = 0.0025$). In the samples with a low vulnerability to AD co-pathology (n = 248 [66%]), the lysosomal PD-PRS was significantly associated with a shorter time to dementia (Table 2). We next aimed to follow-up this result in PDBP data using an identical approach with AD-PRS stratification and Cox regression. We replicated the association between the lysosomal PD-PRS and time to dementia in samples with a low AD risk (Table 2).

As we expected *GBA1* to be a strong driver of the lysosomal PD-PRS signal, we repeated the analysis with the lysosomal PD-PRS excluding *GBA1*. The lysosomal PD-PRS remained significantly associated with a shorter time to dementia in PPMI subjects with a normal baseline CSF $A\beta_{1\text{-}42}$ (hazard ratio [HR], 1.45; 95% confidence interval [CI], 1.0–2.1; $P = 0.0475$) and in the PDBP subjects with a low vulnerability to AD co-pathology (HR, 1.33; 95% CI, 1.05–1.67; $P = 0.0162$) (Supplementary Table S5). There were no associations between the full PD-PRS and time to cognitive impairment using CSF nor PRS measures to determine vulnerability to AD co-pathology (Supplementary Data S1: Supplementary Table S5).

Discussion

Using data from two longitudinal PD cohorts we have shown that the cumulative burden of PD susceptibility variants converging on the lysosomal pathway is associated with an earlier progression to MoCA ≤21 in subjects with a low vulnerability to AD co-pathology, extending on our recently published results in neuropathologically confirmed LBD samples.[11]

TABLE 2 *Results from Cox proportional hazards regression*

Cohort	Determination of AD risk	HR	95% CI	*P*-value	Total (n) with low AD risk	Events (n)
PPMI	–	1.15	0.87–1.53	0.32	–	59
PPMI	$A\beta_{1-42}$[a]	1.42	1.02–1.99	0.039★	246	31
PPMI	pTau[b]	0.99	0.61–1.59	0.96	153	20
PPMI	tTau[c]	0.97	0.60–1.56	0.89	168	24
PPMI	AD-PRS[d]	1.89	1.24–2.88	0.0032★	248	33
PDBP	AD-PRS[d]	1.31	1.08–1.58	0.0054★	517	93

Note: Associations between the lysosomal PD polygenic risk score and time to Montreal Cognitive Assessment ≤21 in Cox regression models, including age at diagnosis, sex, education, and first five genetic principal components as covariates. ★ Significant a two-sided $P < 0.05$.
[a]Samples with CSF $A\beta_{1-42} > 683$ pg/mL[19] (Elecsys units) were classified as having a low AD risk.
[b]Samples with CSF pTau <24 pg/mL[18] (Elecsys units) were classified as having low AD risk.
[c]Samples with CSF tTau <266 pg/mL[18] (Elecsys units) were classified as having low AD risk.
[d]Samples with AD-PRS <0.29 standard deviations (SD) were classified as having low AD risk.
Abbreviations: AD, Alzheimer's disease; HR, hazard ratio; CI, confidence interval; PPMI, Parkinson's progression markers initiative; PDBP, Parkinson's disease biomarker program; PRS, polygenic risk score; PD, Parkinson's disease; CSF, cerebrospinal fluid.

Genetic studies have highlighted a broad contribution of genes linked to lysosomal functions in PD,[23,24] and a functional association between lysosomal impairment and α-synuclein aggregation has been demonstrated for several of these.[25-27] *GBA1* is a major lysosomal risk locus for both PD[28] and DLB.[29] Variants in *GBA1* have been linked to more rapid cognitive decline and increased risk of dementia in PD.[5-7,30,31] Additionally, our results suggest lysosomal variants beyond *GBA1* contribute to cognitive decline, as the association between the lysosomal PD-PRS excluding *GBA1* and time to dementia remained significant in PPMI and PDBP subjects with a low CSF and genetic vulnerability to AD co-pathology, respectively.

Neuropathological changes in limbic and cortical brain regions are believed to be the substrate of cognitive symptoms in PD.[4] An abundance of evidence supports a role of both *APOE* E4 and *GBA1* in cognitive progression in PD.[6,8] *APOE* E4 is strongly linked to more severe AD co-pathology,[32-34] whereas *GBA1* is associated with cortical Lewy pathology, with some reports suggesting *GBA1* carriers have a "purer" LBD with less advanced AD co-pathology.[9,35,36] The present study extends on these findings, supporting that the cumulative lysosomal genetic burden is part of an overlapping genetic architecture of vulnerability to both more widespread Lewy pathology and earlier cognitive progression in PD.

We acknowledge that our study has some limitations. The sample size is limited, yet our results were replicated across both cohorts. The study was not well-powered to explore multiple different algorithm parameters for the PRS calculation such as *P*-value and clumping thresholds, which should ideally be optimized empirically in larger datasets.

We are mindful that our attempts to stratify patients based on the susceptibility to AD co-pathology are not gold standard. CSF $A\beta_{1-42}$ may distinguish between individuals with and without AD co-pathology, although the optimal cut-point in PD remains to be determined and may differ from established AD cut-points.[37,38] Additionally, our data suggests that the AD-PRS can serve as a proxy for AD co-pathology on a group level. Although clearly not as accurate as stratifying by neuropatholgocally verified AD pathology,[11] the AD-PRS provided meaningful stratification of clinical samples into subgroups in the present association study. Supporting the validity of this proxy, PPMI patients with AD-PRS above the cut-point had lower $A\beta_{1-42}$, likely reflecting a higher level of AD co-pathology.

The temporal sequence of protein pathology in PD is not known. Several investigations have documented that reduced CSF $A\beta_{1-42}$ at baseline is associated with cognitive decline,[20,22] yet the optimal threshold remains to be established. $A\beta_{1-42}$ continues to decrease over the course of disease,[39] possibly mirroring increase in AD co-pathology.[37,40] Therefore, early prediction of patients who will develop AD co-pathology using CSF measures alone remains elusive, and PRSs may offer an advantage over other biomarkers by providing risk assessment at an earlier disease stage.

In conclusion, we highlight the burden of lysosomal variants for cognitive progression in PD patients with a low vulnerability to AD co-pathology. Further, our results provide novel evidence for stratification by the polygenic burden of AD risk alleles, which may enable a more precise understanding of the genetic influence of cognitive decline in PD. Additional research with larger cohorts and more comprehensive assessment of cognition is needed to validate and expand on these findings. With further improvement, we hope that the PRSs may inform individual prognosis and facilitate detection of therapeutic targets within a precision medicine framework.

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Data Availability Statement

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (https://www.ppmi-info.org/access-data-specimens/download-data), and the Accelerating

Medicine Partnership® (AMP®) Parkinson's Disease (AMP PD) Knowledge Platform. For up-to-date information on these studies, visit https://www.ppmi-info.org and https://www.amp-pd.org.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

J.A.T.: (1) A, B, C. (2) A, B, C. (3) A, B. M.M.X.T.: (1) B, C. (2) A, B, C, (3) B. M.T.: (1) B. (3) B. O.R.: (1) B. (3) B. W.B.: (1) B. (3) B. L.P.: (1) A, B ,C. (2) A, C. (3) A, B.

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