

Integrating Genetic Biomarkers to Improve Diagnosis in Young-Onset Dementia: Insights from the MiND Study

Bhalala OG¹⁻⁴, Wang L^{2,3}, Gerring Z^{2,3}, Han J^{2,3}, Kang M^{5,6}, Trounson B⁴, Loi S^{5,6}, Velakoulis D^{5,6}, Eratne D^{5,6} and Bahlo M^{2,3}, The MiND Study Group



Introduction

Young-onset dementia, with symptom onset before 65 years, presents diagnostic challenges due to atypical neuropsychiatric features and clinical overlap between Alzheimer's disease (AD), frontotemporal dementia (FTD) and Lewy body dementia (LBD) and primary psychiatric disorders (PPD) such as schizophrenia and bipolar disorder. Misdiagnosis is common, delaying access to appropriate care. Blood-based biomarkers including neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and P-tau217 distinguish AD from FTD or PPD with over 90% accuracy, but performance is substantially lower for non-AD neurodegeneration versus PPD.¹ The genetic architecture of neurodegeneration, encompassing polygenic risk, repeat expansions and mitochondrial biology, offers complementary diagnostic precision. We examined the relationship between genetic and protein biomarkers within the MiND cohort of individuals assessed for young-onset dementia.

Methods

Participants with young-onset neurocognitive and psychiatric symptoms were prospectively recruited from a tertiary referral centre. Following consensus-based diagnostic review after more than one year of follow-up, 297 were diagnosed with PPD, 57 with AD, 162 with non-AD neurodegenerative disorders (oNDG), and 213 community-matched participants served as healthy controls (HC). The study was approved by the Melbourne Health HREC.

Microarray genotyping was performed for 589 participants using the Illumina Global Screening Array-24 v3.0 (GSA) with PsychArray and Multi-Disease Booster panels. 140 participants underwent Illumina short-read whole genome sequencing (WGS) with GATK variant calling. Overlapping SNPs underwent TOPMed imputation (hg38) and QC. 729 participants were retained with 8.1 million SNPs.

Plasma NfL and GFAP were measured by Simoa HD-X, and p-tau217 by the UGOT in-house assay¹, in 398 participants. Downstream analyses included PRS calculation (PRS-CS)², repeat expansion detection (ExpansionHunter v5, 74 loci), and mitochondrial DNA copy number estimation (mitoCN).³ R (4.5.2) was used for statistical analyses.

Table 1 | MiND Study Demographics.

	HC N = 213	PPD N = 297	AD N = 57	oNDG N = 162
Sex (Female)	167 (78%)	170 (57%)	28 (49%)	75 (46%)
Age	61.5 (49.3, 68.4)	53.5 (40.5, 62.6)	61.8 (58.6, 67.5)	60.5 (47.6, 67.5)
APOE E4 Carrier	64 (30%)	86 (29%)	32 (56%)	58 (36%)
Ancestry				
AFR	0 (0%)	0 (0%)	1 (1.8%)	0 (0%)
EAS	7 (3.3%)	7 (2.4%)	1 (1.8%)	4 (2.5%)
EUR	200 (94%)	284 (96%)	55 (96%)	154 (95%)
SAS	4 (1.9%)	5 (1.7%)	0 (0%)	3 (1.9%)
Other	2 (0.9%)	1 (0.3%)	0 (0%)	1 (0.6%)

n (%); Median (Q1, Q3)

HC, healthy control; PPD, primary psychiatric disorder; AD, Alzheimer's disease; oNDG, non-AD neurodegenerative disorders; AFR, African; EAS, East Asian; EUR, European; SAS, South Asian; Other, Admixed ancestry.

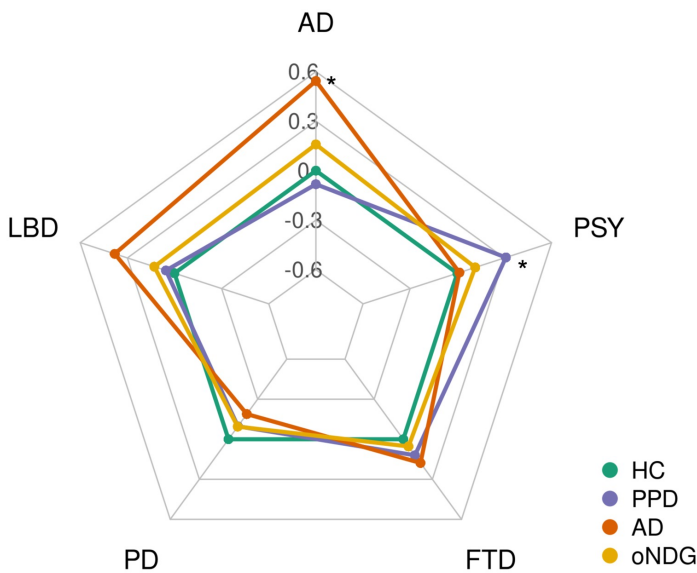


Figure 1 | Radar Plot of Disease-Specific Polygenic Risk Scores. Residual polygenic risk scores, accounting for the first ten principal components, were derived using PRS-CS from five disease-specific GWAS. Scores were scaled to the HC group, with a mean of 0 and a standard deviation of 1, for each disease-specific PRS.⁴⁻⁸ HC, healthy control (green); PPD, primary psychiatric disorder (purple); AD, Alzheimer's disease (orange); oNDG, non-AD neurodegenerative disorders (yellow); PSY, cross-disorder psychiatric PRS.⁵ *, Bonferroni-corrected *p*-value < 0.05 for AD PRS: AD vs HC cases and PSY PRS: PPD vs HC.

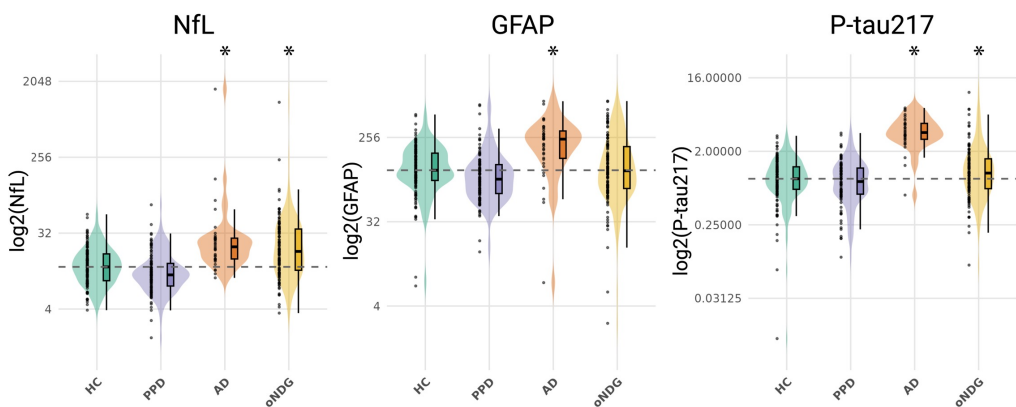


Figure 2 | Protein Biomarker Distribution by Diagnostic Categories. Log2-transformed values of protein biomarkers NfL, GFAP and P-tau217 demonstrate differential distribution. NfL levels were significantly higher for AD and oNDG. GFAP levels were significantly elevated in AD only. P-tau217 levels were the highest in AD, but significantly increased in oNDG, compared to HC. *, Bonferroni-corrected *p*-value < 0.05 compared to HC.

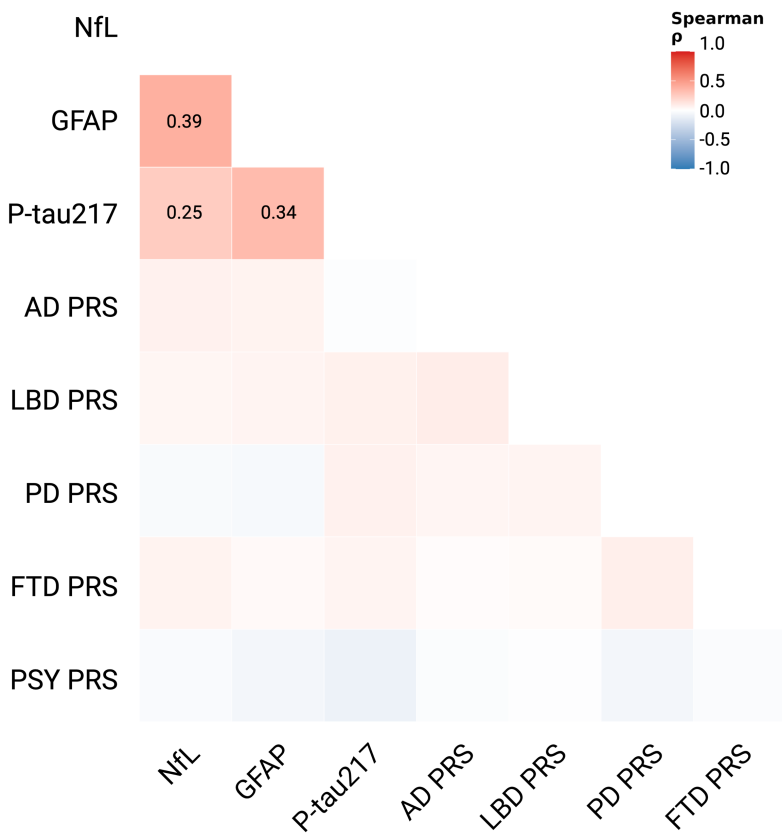


Figure 3 | Correlation of Protein and PRS Biomarkers. Spearman correlation analyses (adjusted for Age, Sex, Diagnosis and APOE) demonstrate moderate correlation amongst the protein biomarkers NfL, GFAP and P-tau217, but not with PRS biomarkers.

Table 2 | Identification of Known Pathogenic Repeat Expansions.

Locus	Chromosome	Age Range	Expansion Lengths	Clinical Diagnosis
C9ORF72	9	61-70	2,117	bvFTD
C9ORF72	9	51-60	2,36	FTD-MND
FGF14	13	31-40	46,107	SCA
RFC1 (AAGGG)	4	61-70	52,52	DLB

74 known pathogenic repeat expansions were screened in WGS data using ExpansionHunter v5. Four pathogenic repeat expansion candidates were identified after downstream QC analyses. bvFTD, behavioural-variant FTD; FTD-MND, FTD-motor neuron disease; SCA, spinocerebellar ataxia; DLB, Dementia with Lewy bodies.

mtDNA copy number vs Diagnosis

$F_{\text{trimmed-means}}(3, 20.31) = 3.92, p = 0.02, \hat{\xi} = 0.48, \text{CI}_{95\%} [0.18, 0.74], n_{\text{obs}} = 131$

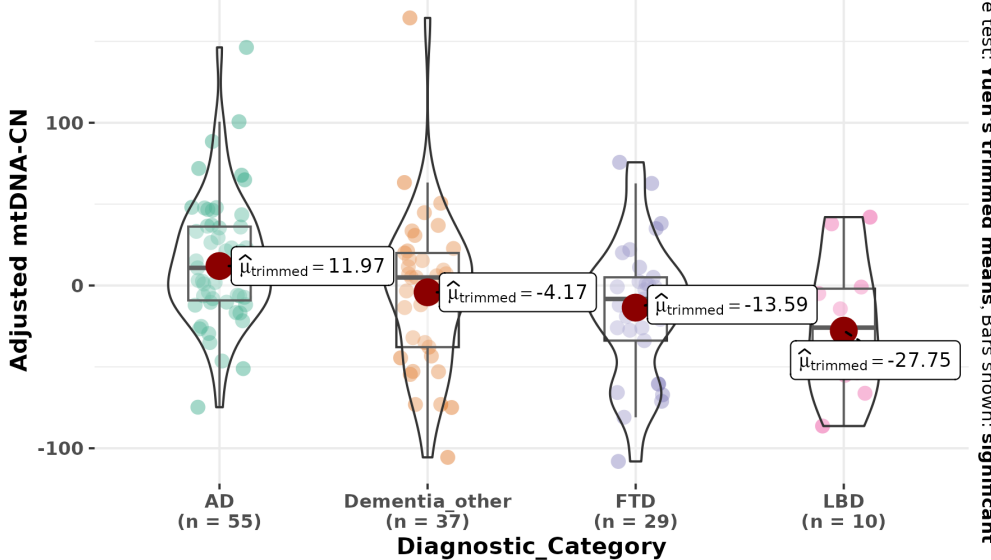


Figure 4 | Mitochondrial Copy Number Across Diagnoses. Mitochondrial copy number (mtDNA-CN) was calculated from WGS data (n=140), adjusted for age and sex, using mitoCN.³ Participants with AD had the highest adjusted mtDNA-CN, compared to other diagnostic categories.

Conclusions

We demonstrate the impact of genomic data in the MiND study. In particular, the Alzheimer's and Psychiatric PRS values are higher in AD and PPD, compared to HC, respectively. Importantly, protein and PRS biomarkers are not correlated, suggesting they identify orthogonal signals. WGS analyses reveal novel insights into detection of pathogenic repeat expansions and the associations of mitochondrial copy number with diagnoses. Our findings motivate further integration of genetic and proteomic data for young-onset dementia diagnosis.

¹Royal Melbourne Hospital, Department of Medicine, Parkville, Australia, ²The University of Melbourne, Department of Medical Biology, Parkville, Australia, ³WEHI, Genetics and Gene Regulation, Parkville, Australia, ⁴Florey Institute of Neuroscience and Mental Health, Parkville, Australia, ⁵Royal Melbourne Hospital, Neuropsychiatry Centre, Parkville, Australia, ⁶The University of Melbourne, Department of Psychiatry, Parkville, Australia



¹Eratne et al, Alzheimer's & Dementia, 2025.

²Ge et al, Nature Communications, 2019.

³Wang et al, npj Parkinson's Disease, 2024.

⁴Bellenguez et al, Nature Genetics, 2022.

⁵Grotzinger et al, Nature, 2025.

⁶Leonard, GP2 et al, medRxiv 2025.

⁷Chia et al, Nature Genetics, 2021.

⁸Mazoni et al, AJHG, 2024.

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