

Epigenetic signatures of blood-based neurodegenerative biomarkers in older adults from India

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Blood-based neurodegenerative biomarkers in older Indian adults have both individual and shared epigenetic signatures. These may be leveraged to inform biological mechanisms and improve clinical prevention and treatment of dementia in India.

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS																																																																																																																																	
South Asia is the most populous region in the world, representing 25% of the global population Prevalence of dementia in India among adults ≥ 60 is 7.4% Epigenegenetic differences in cerebrospinal fluid (CSF) and plasma can distinguish dementia cases from controls Most epigenetic studies to date: - Conducted in European ancestry - Conducted in case/control rather than population-based samples - Small/moderate samples (N$<$900) - Conducted on CSF biomarkers rather than plasma Understanding the epigenetic signatures of more easily-measured blood-based neurodegenerative biomarkers may provide insight for prevention and treatment in India, an understudied demographic in a low-resource setting	N=1,139 Indians from the Harmonized Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India (LASI-DAD),¹ mean age = 70y Neurodegenerative biomarkers measured from plasma (log transformed, Winsorized): Beta-amyloid 42/40 (Aβ42/40) Total tau (t-tau) Phosphorylated tau181 (p-tau181) Glial fibrillary acidic protein (GFAP) Neurofilament light (NFL) DNA methylation for >900K CpGs sites on Illumina Epic v2 Epigenome-wide association study (EWAS) for each biomarker using a gamma generalized mixed effects model, corrected for genomic control Genomic feature, pathway, and trait enrichment with EWAS Atlas² and EWAS Catalog³	<u>Pearson correlations among log-transformed biomarkers</u> <u>Number of significant CpGs</u> in each EWAS ranged from 31 (tTau) to 5178 (Aβ42/40) <u>Pathway enrichment for Aβ42/40</u> KEGG pathways: - Protein export, amyotrophic lateral sclerosis, Parkinson disease (FDR$<$0.1) - Prion disease, Alzheimer disease, Huntington’s disease, cerebrospinal ataxia, neurodegeneration, neutrophin signalling pathway (p$<$0.01) - No notable GO or KEGG for other biomarkers <u>Trait enrichment for all biomarkers</u> Comorbidities (metabolic syndrome, myocardial infarction) Lifestyle factors (BMI, exercise, fruit consumption, phthalate exposure, folic acid supplementation)	<u>Genomic feature enrichment for Aβ42/40</u> <table><tr><th>Feature</th><th>OR</th><th>pval</th><th>prop_top</th><th>prop_bottom</th></tr><tr><td>S_Shelf</td><td>0.93</td><td>2.40e-01</td><td>0.056</td><td>0.06</td></tr><tr><td>S_Shore</td><td>1.26</td><td>1.21e-07</td><td>0.121</td><td>0.098</td></tr><tr><td>Island</td><td>7.29</td><td>0.00e+00</td><td>0.577</td><td>0.158</td></tr><tr><td>N_Shore</td><td>1.16</td><td>8.87e-04</td><td>0.116</td><td>0.101</td></tr><tr><td>N_Shelf</td><td>0.85</td><td>1.07e-02</td><td>0.052</td><td>0.06</td></tr><tr><td>OpenSea</td><td>0.19</td><td>0.00e+00</td><td>0.225</td><td>0.608</td></tr><tr><td>PC_intron</td><td>0.74</td><td>1.25e-25</td><td>0.407</td><td>0.479</td></tr><tr><td>RNA_intron</td><td>0.81</td><td>1.29e-09</td><td>0.202</td><td>0.237</td></tr><tr><td>CDS</td><td>0.5</td><td>2.76e-20</td><td>0.029</td><td>0.056</td></tr><tr><td>exon1_CDS</td><td>2.77</td><td>5.86e-35</td><td>0.04</td><td>0.015</td></tr><tr><td>RNA_exon</td><td>1.79</td><td>7.10e-37</td><td>0.121</td><td>0.072</td></tr><tr><td>5'UTR</td><td>2.47</td><td>3.86e-10</td><td>0.012</td><td>0.005</td></tr><tr><td>3'UTR</td><td>0.75</td><td>4.17e-04</td><td>0.028</td><td>0.037</td></tr><tr><td>Promoter</td><td>1.85</td><td>1.10e-100</td><td>0.425</td><td>0.285</td></tr><tr><td>Enhancer</td><td>0.37</td><td>4.54e-89</td><td>0.062</td><td>0.152</td></tr></table> Features important for gene expression were generally more enriched for associated CpGs (e.g., CpG islands, shores, and shelves, first coding exons (Exon1_CDS), 5'UTR, promoters, and RNA exons). Features typically not important for gene expression (e.g., open sea, introns, 3'UTR) and enhancer regions were depleted. Other biomarkers showed similar, though weaker, trends. <u>Overlapping CpGs in Aβ42/40 and tTau EWAS (n_{CpG} = 28) associate with gene expression in brain</u> <table><tr><th>Probe</th><th>Gene Symbol</th><th>Location</th><th>Pearson r</th><th>p Value</th><th>Tissue</th><th>Gene function or association</th></tr><tr><td>cg17572572</td><td>GPN2</td><td>body</td><td>0.257</td><td>5.26e-10</td><td>brain</td><td></td></tr><tr><td>cg04945388</td><td>PTMA</td><td>body</td><td>0.123</td><td>3.18e-3</td><td>brain</td><td>Prothymosin Alpha, up-regulated in entorhinal cortex of AD brains</td></tr><tr><td>cg21588307</td><td>MBNL1</td><td>body</td><td>-0.114</td><td>6.28e-3</td><td>brain</td><td>Muscleblind-like 1, RNA-binding protein involved in alternative splicing regulation, links to neurodegeneratin AD</td></tr><tr><td>cg14722509</td><td>NPM1</td><td>body</td><td>-0.123</td><td>3.28e-3</td><td>brain</td><td>Nucleophosmin 1, vital for ribosomal biogenesis and neuronal survival, potential dysregulation in AD</td></tr><tr><td>cg12821632</td><td>C11orf71</td><td>promoter</td><td>-0.18</td><td>1.60e-5</td><td>brain</td><td>Potentially associated with microglia; differential methylation in AD</td></tr><tr><td>cg12821632</td><td>RBM7</td><td>body</td><td>-0.155</td><td>2.15e-4</td><td>brain</td><td>Retinoblastoma-Binding Protein 7, a mediator against tau pathologies in AD; decreased expression linked to higher tau plaque density and neuronal loss</td></tr></table>	Feature	OR	pval	prop_top	prop_bottom	S_Shelf	0.93	2.40e-01	0.056	0.06	S_Shore	1.26	1.21e-07	0.121	0.098	Island	7.29	0.00e+00	0.577	0.158	N_Shore	1.16	8.87e-04	0.116	0.101	N_Shelf	0.85	1.07e-02	0.052	0.06	OpenSea	0.19	0.00e+00	0.225	0.608	PC_intron	0.74	1.25e-25	0.407	0.479	RNA_intron	0.81	1.29e-09	0.202	0.237	CDS	0.5	2.76e-20	0.029	0.056	exon1_CDS	2.77	5.86e-35	0.04	0.015	RNA_exon	1.79	7.10e-37	0.121	0.072	5'UTR	2.47	3.86e-10	0.012	0.005	3'UTR	0.75	4.17e-04	0.028	0.037	Promoter	1.85	1.10e-100	0.425	0.285	Enhancer	0.37	4.54e-89	0.062	0.152	Probe	Gene Symbol	Location	Pearson r	p Value	Tissue	Gene function or association	cg17572572	GPN2	body	0.257	5.26e-10	brain		cg04945388	PTMA	body	0.123	3.18e-3	brain	Prothymosin Alpha, up-regulated in entorhinal cortex of AD brains	cg21588307	MBNL1	body	-0.114	6.28e-3	brain	Muscleblind-like 1, RNA-binding protein involved in alternative splicing regulation , links to neurodegenerati n AD	cg14722509	NPM1	body	-0.123	3.28e-3	brain	Nucleophosmin 1, vital for ribosomal biogenesis and neuronal survival , potential dysregulation in AD	cg12821632	C11orf71	promoter	-0.18	1.60e-5	brain	Potentially associated with microglia ; differential methylation in AD	cg12821632	RBM7	body	-0.155	2.15e-4	brain	Retinoblastoma-Binding Protein 7, a mediator against tau pathologies in AD ; decreased expression linked to higher tau plaque density and neuronal loss	- Individual and shared epigenetic signatures are detectable across neurodegenerative biomarkers - Epigenetic signatures may inform underlying biological mechanisms and improve prevention/treatment efforts in India REFERENCES https://www.lasi-dad.org/ https://ngdc.cncb.ac.cn/ewas/atlas https://www.ewascatalog.org/ FUNDING The Harmonized Diagnostic Assessment for the Longitudinal Aging study in India is funded by the National Institute on Aging, National Institutes of Health (R01AG051125, U01AG064948, R01AG080473, RF1AG055273, RF1AG087965, RF1AG088003), BrightFocus Foundation, and Gates Ventures. 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