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**eTable 1. Scoring designed for prioritizing candidate CpGs.**

GENE	CpG Candidates	cg HC (beta-difference >0,05) 1 point	cg HC (beta-difference >0.10) 1 point	cg Brain 1 point	Gene candidate Brain 1 point	cg Blood 1 point	Gene candidate Blood 1 point	DEG in Blood 0.5 point	CpGs-SNPs in Blood 0,05 point	cg DS 0,5 point	HC & Brain & Blood: *same cg 2 points *different cg 1 point	HC & Reference & Primers 0.5 point	List project FIS 0.5 point	Points
<i>ABCA7</i>	cg06169110	0	0	1	1	0	0	0,5	0	0,5	0	0	0,5	<b>3,5</b>
<i>ADAM10</i>	cg02625641	1	0	1	0	1	0	0	0	0,5	1	0	0	<b>4,5</b>
<i>ANK1</i>	cg19997384	1	0	1	0	0	0	0	0	0,5	1	0,5	0,5	<b>4,5</b>
<i>APOE</i>	cg05501958	0	0	1	1	0	1	0	0,5	0	0	0	0,5	<b>4</b>
<i>BDNF</i>	cg16257091	0	0	1	1	1	1	0	0	0	0	0	0,5	<b>4,5</b>
<i>BIN1 (GYPC)</i>	cg22883290	1	1	1	1	1	1	0,5	0,5	0,5	2	0,5	0,5	<b>10,5</b>
<i>GP1BB (SEPT5)</i>	cg11414921	1	1	1	0	1	0	0	0	0,5	1	0	0	<b>5,5</b>
<i>HAND2 (SCRG1)</i>	cg01566965	1	1	1	0	1	0	0	0	0	1	0	0	<b>5</b>
<i>HIST1H3E</i>	cg13836098; cg26092675	1	1	1	0	1	0	0	0	0,5	2	0,5	0	<b>7</b>
<i>HOXA3 (HOXA2)</i>	cg22962123; cg01301319	1	1	1	0	0	0	0	0	0	0	0,5	0,5	<b>4</b>
<i>HOXB6 (LOC404266)</i>	cg02566861	1	1	1	0	1	0	0	0	0,5	1	0	0	<b>5,5</b>
<i>IRS2</i>	cg05404236	0	1	1	0	1	0	0	0	0	1	0	0,5	<b>4,5</b>
<i>KCNN4 (SMG9)</i>	cg22904711	0	1	1	0	1	0	0	0	0,5	2	0	0,5	<b>6</b>
<i>MAP4K1</i>	cg02798280	1	1	1	0	1	0	0	0	0	2	0	0	<b>6</b>
<i>NXN (GLOD4)</i>	cg02273477	0	1	1	0	1	0	0	0	0,5	1	0	0	<b>4,5</b>
<i>PAX3 (EPHA4)</i>	cg23077820	1	1	1	0	0	0	0	0	0,5	1	0	0	<b>4,5</b>
<i>RHBDF2</i>	cg06491139	0	0	1	0	1	0	0	0	0	1	0	0	<b>3</b>
<i>RHOB (HS1BP3)</i>	cg16258854	0	1	0	0	1	0	0	0	0,5	1	0,5	0,5	<b>4,5</b>
<i>SIX3 (SIX2)</i>	cg04797742	1	1	1	0	1	0	0	0	0,5	1	0	0	<b>5,5</b>
<i>TREML2</i>	cg03526776	0	0	0	1	1	1	0	0	0	0	0	0,5	<b>3,5</b>
<i>TREM2</i>	Chr6:41129686-41129751													

The table shows the candidate CpGs according to the generated score. Abbreviations: cg: CpG dinucleotide; DEG: Differentially Expressed Genes; FIS:

“Proyectos de Investigación en Salud”, project support by the Spanish Government through grants from the Institute of Health Carlos III; HC: Hippocampus;;

SNP: single nucleotide polymorphism; DS: Down syndrome.

**eTable 2. Bisulfite PCR pyrosequencing primers.**

Gene ID	Amplicon size (bp)	Tm1	Forward Primer	Tm2	Reverse Primer
<i>ABCA7</i> pyro	196	59.1	AGTTTTGGTTTTAGGTATTAGTGTAG	59.4	ATAAACCCAACTCTATTAACCTTC
<i>ABCA7</i> seq		45.2	AGTGTAGTTTAGGTTGTT		
<i>ADAM10</i> pyro	211	58.6	ATTTAGGTTGGTGGTTGTATTTT	60.5	CCCAACTACAAACAACACAACCTT
<i>ADAM10</i> seq				46.3	ACAACACAACCTCCC
<i>ANK1</i> pyro	140	57.4	AGAGGAAGTTTTATTGTTTGAATT	58.6	CTCCATCATTTTAATTCCAACCTAATAC
<i>ANK1</i> seq		44.4	ATTAAGATTATTTAGGGTTTAGT		
<i>APOE</i> pyro	190	57.7	TGTTTTGGTAGAGTATGGTTTGTATTT	56.9	ACCATAAAAAAATTAAAAACCTACAAATC
<i>APOE</i> seq		40.0	GTTTGTAGTTTTTTGGATA		
<i>BDNF</i> seq	87	58.9	GGGAAGATAGTTGGGAATTTGT	58.6	CCCCTCCCTACTACCCTTTTCTAATATTAT
<i>BDNF</i> seq		44.9	GGGGAATTTGTTGTTTAT		
<i>BIN1</i> pyro	179	57.2	TGGTTTTTAGGTGTTAGTTTTTTAAT	58	ACATCATAAAAATATAATTCCTACCCATAA
<i>BIN1</i> seq				39.8	ACCACAACCATATATCTAAATAAT
<i>GP1BB</i> pyro	162	53.7	GTTTTGGGTTGTTGTAGT	54.9	AAAACCCCTCCAACAAAATCCT
<i>GP1BB</i> seq		39.9	AGAGAATAGGAGTTGGGTAATA		
<i>HAND2</i> pyro	147	57.9	TTGAGGTATTAGTTATTAAGATTAAGGT	59.9	CCAACAACCACTTATTTTATACACTT
<i>HAND2</i> seq		42.3	ATTAAATTTTATTTAGTTTATAGAGG		
<i>HIST</i> pyro	176	57.2	GGAAAAAGATTGTTTGAAAGAGTTAGTT	57.8	CCCCTCTATATAAAAAACAAAATCACT
<i>HIST</i> seq				35.9	ATTAATAATCCATTACTAAATTCC
<i>HOXA3</i> pyro	92	53.8	TTTGTTTTTTAGAGGGTAGTAGT	57.3	ATACCCAAATCCATACCACTAACCC
<i>HOXA3</i> seq				44.5	CTAACCCAAACAAAACC
<i>HOXB6</i> pyro	140	58.7	AGGAGGGGATAGGTATTTATTTGTAG	56.3	CAAAAAACAAACCAATCTATATTCTCCT
<i>HOXB6</i> seq		41.1	TGTAGATATTAATAGTTTTTAGAAA		
<i>IRS2</i> pyro	66	58.7	AGGGAGTAGGGGTGGTG	58.8	ACACAACCCCTCCATATCCATACC
<i>IRS2</i> seq				47.9	ACCCCTCCATATCCATACCC
<i>KCNN4</i> pyro	221	57.2	TAGGGATAGTAGAGTTTTTTTTGGTTTAG	57.8	ACCCCTACCCACAACCTATTCATA
<i>KCNN4</i> seq		44.9	GGTTGAGGGGAGGTT		
<i>MAP4K1</i> pyro	163	56.2	GGTAGTGGGAATAGTATTTGTT	58.1	AACCTTATCCCCTAACATTTCT
<i>MAP4K1</i> seq		45.1	GTGGGAATAGTATTTGTTG		
<i>NXN</i> pyro	229	58.3	AGAGAGTTGTTTTGGTAATAGAATT	57.7	ACAACAAACCTAAAAAAACTAACTTAA
<i>NXN</i> seq		44.3	GTAGATTAGAAGATGTTAAATGG		
<i>PAX3</i> pyro	252	59.8	GGGTATTTAAAAGTTTTAGGGTTGAG	58.8	ACTTTTCATTTTCATTAACCATCTACTT
<i>PAX3</i> seq		45.1	GGTGAGGAGGAATTAGTTAG		
<i>RHBDF2</i> pyro	177	58.6	GTTAGTTAATGGGGTAGATGTATAGT	58.3	CCCACATCTTCCACTTCCTCAATAAC
<i>RHBDF2</i> seq		46.6	ATGGGGTAGATGTATAGTT		
<i>RHOB</i> pyro	229	58.3	AGAGTAGGGTTTTAGAGTGTGTG	60.0	ATATAACATCCCCCATCCTC
<i>RHOB</i> seq		46.3	ATTGGAGAGGGAGTGTGG		
<i>SIX3</i> pyro	185	60.2	GGGAGTAGGATTTTAGTTGTTGATAG	58.7	CTCTCCACAAAAAACCTTAACCTTA
<i>SIX3</i> seq		45.7	GTTTGATGAGGGGAG		
<i>TREM2</i> pyro	179	59.8	AAGGGGAATAAAGTTATAGAAATAGGG	58.7	CCTCCAATTCTATTCTACACATCT
<i>TREM2</i> seq		45.5	GGAAGTTAAAGGTTAGGAA		
<i>TREML2</i> pyro	105	59.1	AATAGTGATTAAAAGTTGGGGATTATAG	61.7	CAACCCCAATCAAAACAAACCATC
<i>TREML2</i> seq		47.8	GAGGGGTTGGTAGTT		

The table shows the primer pairs used in the study. Abbreviations: ID: identification; bp: base pair; Tm: Melting Temperature.

**eTable 3. Baseline characteristics of the iBEAS study participants.**

Demographic & clinical characteristics		AD (n=80)	CONTROLS (n=100)	P value
	Age, median (IQR), years	79.00 (11)	77.00 (10)	0.086
	Sex, female/male, (% female)	47/33 (58.8)	58/42 (58.0)	0.919
	APOE ε4 carrier, pos/neg (%pos)	43/37 (53.8)	10/89 (10.1)	<0.001
	MMSE score, median (IQR)	22.50 (6.25)	30.00 (1.00)	<0.001
AD Biomarkers	GDS score, median (IQR)	4.00 (1.00)	1.00 (0.00)	<0.001
	Plasma biomarkers	AD (n=70)	CONTROLS (n=70)	P value
	Plasma pTau181, median (IQR), pg/ml	2.69 (1.56)	1.52 (0.91)	<0.001
	CSF biomarkers	AD (n=26)		
	CSF Aβ42, media ± SD, pg/ml	363.19 ± 90.71		
	CSF Aβ40, media ± SD, pg/ml	8039.89 ± 2258.10		
	CSF Aβ42 /Aβ40, media ± SD	0.047 ± 0.010		
	CSF tTau, median (IQR), pg/ml	703.00 (339.00)		
Clinical variables	CSF pTau, median (IQR), pg/ml	111.80 (61.43)		
		AD (n=80)	CONTROLS (n=100)	P value
	High blood pressure, pos/neg (%pos)	45/32 (56.3)	51/49 (51.0)	0.092
	Diabetes, pos/neg (%pos)	16/61 (20.0)	11/89 (11.0)	< 0.05
	Hyperlipidemia, pos/neg (%pos)	37/40 (46.3)	44/56 (44.0)	0.129
	Smoking, pos/neg (%pos)	21/56 (26.3)	21/79 (21.0)	0.093
	Alcohol consumption, pos/neg (%pos)	10/65 (12.5)	17/82 (17.0)	0.118
	Vitamin B12 deficiency, pos/neg (%pos)	8/67 (10.0)	8/91 (8.0)	0.139
	Serum folate deficiency, pos/neg (%pos)	5/70 (6.3)	5/93 (5.0)	0.143

Abbreviations: AD, Alzheimer's disease; APOE ε4, apolipoprotein ε4; ;MMSE, Mini-Mental State Examination; GDS, Global/Geriatric Deterioration Scale de Reisberg; IQR, Interquartile Range; SD, standard deviation; CSF, Cerebrospinal fluid

**eTable 4. Bootstrapping approach.**

value: OR		
Model	coef_auc	95%CI
Model1	(Intercept)	0 (0 to 0)
Model1	Age	1.09 (1.01 to 1.2)
Model1	Sex	1.54 (0.59 to 4.1)
Model1	<i>APOE</i> ε4 carrier	18.22 (5.92 to 79.2)
Model1	<i>NXN</i> methylation level	1.19 (1.04 to 1.38)
Model1	<i>TREML2</i> methylation level	0.92 (0.86 to 0.99)
Model1	<i>ABCA7</i> methylation level	0.68 (0.48 to 0.93)
Model1	<i>HOXA3</i> methylation level	2.05 (1.36 to 3.35)
Model1	<b>C (ROC)</b>	<b>0.89 (0.83 to 0.93)</b>
Model2	(Intercept)	0.01 (0 to 21.21)
Model2	Age	1.01 (0.92 to 1.09)
Model2	Sex	1.4 (0.54 to 4.69)
Model2	<i>APOE</i> ε4 carrier	10.52 (3.89 to 42.83)
Model2	Plasma pTau181	2.88 (1.74 to 5.53)
Model2	<b>C (ROC)</b>	<b>0.86 (0.78 to 0.92)</b>
Model3	(Intercept)	0 (0 to 0)
Model3	Age	0.99 (0.86 to 1.16)
Model3	Sex	3.72 (0.93 to 24.87)
Model3	<i>APOE</i> ε4 carrier	15.53 (2.94 to 188.67)
Model3	Plasma pTau181	5.09 (2.5 to 16.45)
Model3	<i>NXN</i> methylation level	1.35 (1.13 to 1.73)
Model3	<i>ABCA7</i> methylation level	0.59 (0.35 to 0.94)
Model3	<i>HOXA3</i> methylation level	2.79 (1.61 to 6.17)
Model3	<b>C (ROC)</b>	<b>0.94 (0.9 to 0.98)</b>

The table shows the variables included in the different multivariable logistic regression models adjusted by age and *APOE* ε4 genotype with p-value and OR for each variable after internal validation by bootstrapping approach. Abbreviations: AUC= area under the curve; ROC= receiver operating characteristic; 95%CI=95% Confidence interval; OR=Odds ratio.

**eTable 5. Analysis stratified by sex.**

<b>Female (N=89)</b>				
<b>ID</b>	<b>Genomic coordinates GRCh37/Hg19</b>	<b>AD (n=47)</b>	<b>CONTROLS (n=42)</b>	<b>P value</b>
Age, median (IQR), years		80.00 (9)	77.00 (7)	0.265
APOE ε4 carrier, pos/neg (%pos)		24/23 (51.1)	5/37 (11.9)	<0.001
ABCA7, median (IQR), % Meth	19 1046617	98.38 (3.25)	99.65 (2.32)	<0.05
ADAM10, median (IQR), % Meth	15 59041183	0.00 (3.89)	3.72 (4.90)	<0.01
APOE, median (IQR), % Meth	19 45411874	91.43 (1.04)	90.87 (2.05)	<0.01
BDNF, mean ± SD, % Meth	11 27743580	5.76 ± 1.54	6.91 ± 2.16	<0.01
BDNF, median (IQR), % Meth	11 27743583	5.90 (2.39)	6.51 (2.75)	<0.05
HOXA3, median (IQR), % Meth	7 27153577	91.50 (2.24)	90.76 (1.06)	<0.05
RHBDF2, median (IQR), % Meth	17 74467837	92.88 (6.00)	90.29 (6.15)	<0.05
TREM2, mean ± SD, % Meth	6 41129736	26.56 ± 6.29	29.73 ± 6.46	<0.05
TREM2, mean ± SD, % Meth	6 41129712	31.03 ± 6.54	34.64 ± 6.21	<0.05
TREML2, median (IQR), % Meth	6 41159608	27.06 (10.53)	32.65 (10.66)	<0.05
pTau181, median (IQR), pg/ml		2.90 (2.08)	1.41 (0.57)	<0.001
<b>Male (N=75)</b>				
<b>ID</b>	<b>Genomic coordinates GRCh37/Hg19</b>	<b>AD (n=33)</b>	<b>CONTROLS (n=42)</b>	<b>P value</b>
Age, mean ± SD, years		78.06 ± 6.50	79.76 ± 6.25	0.254
APOE ε4 carrier, pos/neg (%pos)		19/14 (57.6)	4/37 (9.8)	<0.001
ADAM10, median (IQR), % Meth	15 59041183	3.06 (4.08)	4.04 (5.25)	<0.05
ADAM10, mean ± SD, % Meth	15 59041185	1.44 ± 1.69	0.44 ± 1.10	<0.05
HOXA3, median (IQR), % Meth	7 27153577	92.25 (2.01)	90.57 (1.86)	<0.001
NXN, mean ± SD, % Meth	17 800086	79.68 ± 3.22	76.65 ± 3.47	<0.001
PAX3, media ± SD, % Meth	2 223154176	46.37 ± 7.81	43.11 ± 5.80	<0.05
RHBDF2, median (IQR), % Meth	17 74467829	92.07 (1.14)	92.94 (3.68)	<0.001
RHBDF2, median (IQR), % Meth	17 74467837	90.29 (0.66)	92.88 (6.22)	<0.01
pTau181, median (IQR), pg/ml		2.59 (1.35)	1.73 (1.37)	<0.01

The table shows the variables with significant differences after stratifying by sex. Abbreviations: ID=identification; AD, Alzheimer's disease; APOE ε4, apolipoprotein ε4; IQR, Interquartile Range; SD, standard deviation; % Meth, % Methylation.

**eTable 6. Multivariate regression logistic analysis.**

Female							
HOXA3	ID	P value	OR (95%CI)	AUC (95%CI)	Sensitivity	Specificity	Hosmer-Lemeshow test
	Age	0.083	1.07 (0.99-1.16)	0.785 (0.689 - 0.880)	66.00%	72.50%	0.878
	APOE ε4 carrier	<0.001	8.15 (2.57-25.82)				
	HOXA3 methylation level	<0.05	1.59 (1.07-2.34)				
pTau181	ID	P value	OR (95%CI)	AUC (95%CI)	Sensitivity	Specificity	Hosmer-Lemeshow test
	Age	0.339	1.06 (0.94-1.19)	0.908 (0.841 - 0.975)	81.60%	78.80%	0.756
	APOE ε4 carrier	<0.05	7.93 (1.62-38.83)				
	Plasma pTau181	<0.001	5.18 (2.04-13.14)				
Model HOXA3 + pTau181	ID	P value	OR (95%CI)	AUC (95%CI)	Sensitivity	Specificity	Hosmer-Lemeshow test
	Age	0.390	1.06 (0.93-1.20)	0.932 (0.877 - 0.986)	89.50%	84.40%	0.877
	APOE ε4 carrier	0.014	9.24 (1.58-54.13)				
	Plasma pTau181	<0.01	6.03 (1.96-18.60)				
	HOXA3 methylation level	<0.05	2.17 (1.20-3.92)				
Male							
HOXA3	ID	P value	OR (95%CI)	AUC (95%CI)	Sensitivity	Specificity	Hosmer-Lemeshow test
	Age	0.975	0.99 (0.91-1.10)	0.832 (0.731 - 0.933)	65.60%	86.50%	0.138
	APOE ε4 carrier	<0.001	10.03 (2.66-37.80)				
	HOXA3 methylation level	<0.05	1.76 (1.11-2.80)				
pTau181	ID	P value	OR (95%CI)	AUC (95%CI)	Sensitivity	Specificity	Hosmer-Lemeshow test
	Age	0.352	0.95 (0.84-1.06)	0.839 (0.738-0.939)	61.30%	87.10%	0.562
	APOE ε4 carrier	<0.01	9.81 (2.34-41.08)				
	Plasma pTau181	.114	1.65 (0.89-3.08)				
Model HOXA3 + pTau181	ID	P value	OR (95%CI)	AUC (95%CI)	Sensitivity	Specificity	Hosmer-Lemeshow test
	Age	0.262	0.92 (0.81-1.06)	0.876 (0.785 - 0.968)	83.30%	82.10%	0.658
	APOE ε4 carrier	<0.01	7.92 (1.65-37.90)				
	Plasma pTau181	0.080	1.84 (0.93-3.65)				
	HOXA3 methylation level	<0.01	2.06 (1.19-3.55)				

The table shows the variables included in the different multivariate logistic regression models adjusted by age and APOE ε4 genotype with p-value and OR for each variable after stratified by sex. Abbreviations: ID=identification; AUC= area under the curve; 95%CI=95% Confidence interval; OR=Odds ratio.

**eTable 7. PCR Amplification reaction conditions of *APOE* gene genotyping.**

Step	Temperature	Time (minutes)
Denaturation	95	0:05:00
Denaturation	95	0:01:00
Annealing	60	0:01:00
Elongation	70	0:02:00
<b>35 cycles</b>		
Elongation	72	0:05:00
	4	$\infty$

The table shows the different steps of PCR amplification used for *APOE* genotyping.