

1 **Table S1:** Characteristics of the 29 genome-wide significant genetic variants associated with Alzheimer's disease.

Chr	Pos	A0	A1	rs ID	Gene	AF	Locus discovered in	Effect estimate from	log OR _I ^k	Type	Rsq
1	207692049	A	G	rs6656401	CR1	0.803	Lambert <i>et al.</i> (2009)	Lambert <i>et al.</i> (2013)	-0.17	Genotyped	-
2	127892810	C	T	rs6733839	BIN1	0.409	Seshadri <i>et al.</i> (2010)	Lambert <i>et al.</i> (2013)	0.20	Genotyped	-
2	234068476	C	T	rs35349669	INPP5D	0.512	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	0.08	Genotyped	-
4	11711232	T	G	rs13113697	HS3ST1	0.282	Desikan <i>et al.</i> (2015)	Desikan <i>et al.</i> (2015)	-0.07	Imputed	0.96
5	88223420	G	A	rs190982	MEF2C	0.408	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	0.08	Genotyped	-
6	32578530	C	A	rs9271192	HLA-DRB1	0.724	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	-0.11	Genotyped	-
6	41129207	C	T	rs143332484	TREM2 R62H	0.007	Sims <i>et al.</i> (2017)	Sims <i>et al.</i> (2017)	0.50	Genotyped	-
6	41129252	C	T	rs75932628	TREM2 R47H	0.001	Guerreiro <i>et al.</i> (2013), Jonsson <i>et al.</i> (2013)	Sims <i>et al.</i> (2017)	0.89	Imputed	0.68
6	47487762	A	G	rs10948363	CD2AP	0.266	Hollingworth <i>et al.</i> (2011), Naj <i>et al.</i> (2011)	Lambert <i>et al.</i> (2013)	0.10	Genotyped	-
7	37841534	A	G	rs2718058	NME8	0.373	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	-0.08	Genotyped	-
7	100004446	C	T	rs1476679	ZCWPW1	0.713	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	0.09	Genotyped	-
7	143110762	G	A	rs11771145	EPHA1	0.338	Hollingworth <i>et al.</i> (2011), Naj <i>et al.</i> (2011)	Lambert <i>et al.</i> (2013)	-0.10	Genotyped	-
8	27195121	T	C	rs28834970	PTK2B	0.366	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	0.10	Genotyped	-
8	27467686	C	T	rs9331896	CLU	0.379	Harold <i>et al.</i> (2009), Lambert <i>et al.</i> (2009)	Lambert <i>et al.</i> (2013)	0.15	Genotyped	-
10	11720308	A	G	rs7920721	ECHDC3	0.387	Desikan <i>et al.</i> (2015)	Desikan <i>et al.</i> (2015)	0.07	Imputed	0.98
11	47557871	T	C	rs10838725	CELF1	0.316	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	0.08	Genotyped	-
11	59923508	A	G	rs983392	MS4A6A	0.403	Hollingworth <i>et al.</i> (2011), Naj <i>et al.</i> (2011)	Lambert <i>et al.</i> (2013)	-0.10	Genotyped	-
11	85867875	A	G	rs10792832	PICALM	0.642	Harold <i>et al.</i> (2009)	Lambert <i>et al.</i> (2013)	0.14	Genotyped	-
11	121435587	T	C	rs11218343	SORL1	0.039	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	-0.26	Genotyped	-
14	53400629	T	C	rs17125944	FERMT2	0.092	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	0.13	Genotyped	-
14	92926952	G	T	rs10498633	SLC24A4-RIN3	0.217	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	-0.09	Genotyped	-
16	81942028	C	G	rs72824905	PLCG2	0.015	Sims <i>et al.</i> (2017)	Sims <i>et al.</i> (2017)	-0.39	Imputed	0.88
17	44353222	T	G	rs2732703	KANSL1	0.127	Jun <i>et al.</i> (2016)	Lambert <i>et al.</i> (2013)	-0.14	Imputed	0.81
17	47297297	T	C	rs616338	ABI3	0.006	Sims <i>et al.</i> (2017)	Sims <i>et al.</i> (2017)	-0.36	Imputed	0.71
19	1061892	G	C	rs200538373	ABCA7 G>C	0.001	Steinberg <i>et al.</i> (2015)	Steinberg <i>et al.</i> (2015)	-0.65	Imputed	0.76
19	1063443	A	G	rs4147929	ABCA7 A>G	0.810	Hollingworth <i>et al.</i> (2011), Naj <i>et al.</i> (2011)	Lambert <i>et al.</i> (2013)	-0.14	Imputed	0.99
19	45411941	T	C	rs429358	ApoE E4	0.148	Saunders <i>et al.</i> (1993), Strittmatter <i>et al.</i> (1993)	Sims <i>et al.</i> (2017)	1.05	Imputed	0.99
19	45412079	C	T	rs7412	ApoE E2	0.072	Corder <i>et al.</i> (1994)	Sims <i>et al.</i> (2017)	-0.79	Genotyped	-
20	55018260	T	C	rs7274581	CASS4	0.083	Lambert <i>et al.</i> (2013)	Lambert <i>et al.</i> (2013)	-0.13	Genotyped	-

2 Abbreviations: *Chr*, chromosome; *Pos*, chromosomal position (GRCh37, hg19); *A0*, reference allele in HRC reference panel; *A1*, tested allele (alternative allele in HRC
3 reference panel); *rs ID*, variant ID; *Gene*, gene associated with the variant; *AF*, frequency of A1 in HRC reference panel; $\log OR_i^k$, published log(odds ratio) and relative
4 standard errors, *i.e* the first or largest case-control study that reported the variant association with AD; *Type*, whether the variant was genotyped or imputed in our datasets;
5 *Rsq*, imputation quality for imputed variants. References to the papers reported in this table are: ⁴⁻¹⁷.

6 **Table S2:** Human Genome Variation Society (HGVS) codes for the tested
7 variants

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Genomic position	Rs ID	Ref HRC	Alt HRC	HGVS nomenclature
1:207692049	rs6656401	A	G	NC_000001.10:g.207692049A>G
2:127892810	rs6733839	C	T	NC_000002.11:g.127892810C>T
2:234068476	rs35349669	C	T	NC_000002.11:g.234068476C>T
4:11711232	rs13113697	T	G	NC_000004.11:g.11711232T>G
5:88223420	rs190982	G	A	NC_000005.9:g.88223420G>A
6:32578530	rs9271192	C	A	NT_113891.2:g.4029235A>C
6:41129207	rs143332484	C	T	NC_000006.11:g.41129207C>T
6:41129252	rs75932628	C	T	NC_000006.11:g.41129252C>T
6:47487762	rs10948363	A	G	NC_000006.11:g.47487762A>G
7:37841534	rs2718058	A	G	NC_000007.13:g.37841534A>G
7:100004446	rs1476679	C	T	NC_000007.13:g.100004446C>T
7:143110762	rs11771145	G	A	NC_000007.13:g.143110762G>A
8:27195121	rs28834970	T	C	NC_000008.10:g.27195121T>C
8:27467686	rs9331896	C	T	NC_000008.10:g.27467686C>T
10:11720308	rs7920721	A	G	NC_000010.10:g.11720308A>G
11:47557871	rs10838725	T	C	NC_000011.9:g.47557871T>C
11:59923508	rs983392	A	G	NC_000011.9:g.59923508A>G
11:85867875	rs10792832	A	G	NC_000011.9:g.85867875A>G
11:121435587	rs11218343	T	C	NC_000011.9:g.121435587T>C
14:53400629	rs17125944	T	C	NC_000014.8:g.53400629T>C
14:92926952	rs10498633	G	T	NC_000014.8:g.92926952G>T
16:81942028	rs72824905	C	G	NC_000016.9:g.81942028C>G
17:44353222	rs2732703	T	G	NC_000017.10:g.44353222T>G
17:47297297	rs616338	T	C	NC_000017.10:g.47297297T>C
19:1061892	rs200538373	G	C	NC_000019.9:g.1061892G>C
19:1063443	rs4147929	A	G	NC_000019.9:g.1063443A>G
19:45411941	rs429358	T	C	NC_000019.9:g.45411941T>C
19:45412079	rs7412	C	T	NC_000019.9:g.45412079C>T
20:55018260	rs7274581	T	C	NC_000020.10:g.55018260T>C

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10 Abbreviations: Genomic position, chromosome and position an GRCh37 (hq19); Rs ID, variant identifier; Ref
11 HRC, reference allele in Human Reference Consortium (HRC) panel; Alt HRC, alternative allele in HRC
12 panel; HGVS nomenclature, official nomenclature according to Human Genome Variation Society (HGVS)
13 and link to dbSNP database.

14

15 **Table S3:** Comparison between using extreme AD cases compared to using extreme controls in association analyses

Rs ID	Gene	Extreme AD cases vs. Normal Controls (EA vs. NC)				Normal AD cases vs. Extreme Controls (NA vs. EC)			
		log OR_l^k (SE)	log OR_{EA-NC}^k (SE)	P -value _{EA-NC}	E_{EA-NC}^k (95% CI, p)	log OR_{NA-EC}^k (SE)	P -value _{NC-EC} [#]	E_{NA-EC}^k (95% CI, p)	
rs75932628	TREM2 (R47H)	0.89 (0.09)	1.56 (0.66)	1.86x10 ⁻² *	1.76 (0.28 - 3.34, 3.2x10 ⁻¹)	3.04 (2.75)	5.11x10 ⁻¹	3.42 (-3.85 - 10.92, 5.0x10 ⁻¹)	
rs7920721	ECHDC3	0.07 (0.01)	0.17 (0.05)	2.61x10 ⁻³ *	2.54 (0.84 - 4.96, 7.8x10 ⁻²)	0.21 (0.08)	1.51x10 ⁻¹	3.14 (0.26 - 6.60, 1.5x10 ⁻¹)	
rs10498633	SLC24A4-RIN3	-0.09 (0.01)	-0.18 (0.07)	8.95x10 ⁻³ *	1.85 (0.46 - 3.79, 2.4x10 ⁻¹)	-0.38 (0.46)	8.59x10⁻³*	3.93 (1.67 - 6.81, 9.2x10⁻³)	
rs2718058	NME8	-0.08 (0.01)	-0.03 (0.06)	6.45x10 ⁻¹	0.35 (-1.16 - 1.91, 3.8x10 ⁻¹)	-0.34 (0.08)	5.99x10⁻³*	4.46 (1.87 - 7.90, 7.6x10⁻³)	
rs72824905	PLCG2	-0.39 (0.06)	-0.47 (0.30)	1.23x10 ⁻¹	1.21 (-0.33 - 3.00, 7.7x10 ⁻¹)	-1.13 (0.29)	3.47x10⁻²*	2.89 (1.14 - 5.07, 3.4x10⁻²)	
rs9271192	HLA-DRB1	-0.11 (0.01)	-0.13 (0.09)	1.40x10 ⁻¹	1.19 (-0.42 - 3.01, 8.0x10 ⁻¹)	-0.34 (0.13)	1.33x10 ⁻¹	3.18 (0.38 - 6.49, 1.4x10 ⁻¹)	
rs1476679	ZCWPW1	0.09 (0.01)	0.14 (0.06)	1.94x10 ⁻² *	1.59 (0.23 - 3.25, 3.9x10 ⁻¹)	0.20 (0.08)	2.45x10 ⁻¹	2.30 (0.10 - 4.86, 2.4x10 ⁻¹)	
rs4147929	ABCA7 (A>G)	-0.14 (0.02)	-0.17 (0.07)	2.13x10 ⁻² *	1.18 (0.18 - 2.35, 7.4x10 ⁻¹)	-0.31 (0.11)	2.20x10 ⁻¹	2.16 (0.27 - 4.13, 2.2x10 ⁻¹)	
rs7412	APOE (ε2)	-0.79 (0.03)	-1.09 (0.14)	2.36x10⁻¹⁵*	1.38 (1.02 - 1.76, 3.7x10⁻²)	-1.37 (0.12)	3.46x10⁻⁵*	1.75 (1.39 - 2.11, 1.5x10⁻⁴)	
rs13113697	HS3ST1	-0.07 (0.01)	0.00 (0.06)	9.70x10 ⁻¹	0.04 (-1.97 - 2.04, 3.1x10 ⁻¹)	-0.18 (0.09)	3.12x10 ⁻¹	2.70 (-0.60 - 6.53, 3.0x10 ⁻¹)	
rs616338	ABI3	-0.36 (0.05)	-0.70 (0.28)	1.23x10 ⁻² *	1.92 (0.41 - 3.79, 2.4x10 ⁻¹)	-0.37 (0.47)	9.87x10 ⁻¹	1.03 (-2.10 - 4.19, 9.7x10 ⁻¹)	
rs10948363	CD2AP	0.10 (0.01)	0.07 (0.06)	2.79x10 ⁻¹	0.70 (-0.54 - 2.11, 6.5x10 ⁻¹)	0.22 (0.09)	2.78x10 ⁻¹	2.28 (-0.01 - 4.83, 2.7x10 ⁻¹)	
rs429358	APOE (ε4)	1.05 (0.03)	1.36 (0.07)	1.19x10⁻⁸⁴*	1.30 (1.16 - 1.45, 1.4x10⁻⁵)	1.84 (0.14)	4.22x10⁻⁶*	1.75 (1.43 - 2.07, 1.8x10⁻⁵)	
rs11771145	EPHA1	-0.10 (0.01)	-0.09 (0.06)	1.12x10 ⁻¹	0.93 (-0.21 - 2.18, 8.9x10 ⁻¹)	-0.23 (0.08)	2.06x10 ⁻¹	2.24 (0.26 - 4.32, 2.1x10 ⁻¹)	
rs10838725	CELF1	0.08 (0.01)	0.07 (0.06)	2.49x10 ⁻¹	0.87 (-0.61 - 2.58, 8.5x10 ⁻¹)	0.13 (0.09)	5.92x10 ⁻¹	1.71 (-1.01 - 4.60, 5.9x10 ⁻¹)	
rs28834970	PTK2B	0.10 (0.01)	0.08 (0.06)	1.44x10 ⁻¹	0.84 (-0.27 - 2.08, 7.9x10 ⁻¹)	0.20 (0.08)	3.04x10 ⁻¹	2.03 (0.08 - 4.12, 3.0x10 ⁻¹)	
rs983392	MS4A6A	-0.11 (0.01)	-0.02 (0.06)	7.08x10 ⁻¹	0.20 (-0.89 - 1.27, 1.4x10 ⁻¹)	-0.26 (0.08)	1.16x10 ⁻¹	2.40 (0.66 - 4.33, 1.1x10 ⁻¹)	
rs11218343	SORL1	-0.26 (0.03)	-0.21 (0.15)	1.55x10 ⁻¹	0.82 (-0.30 - 2.03, 7.3x10 ⁻¹)	-0.42 (0.19)	4.71x10 ⁻¹	1.63 (-0.09 - 3.42, 4.6x10 ⁻¹)	
rs6733839	BIN1	0.20 (0.01)	0.17 (0.06)	3.04x10 ⁻³ *	0.84 (0.27 - 1.42, 5.8x10 ⁻¹)	0.29 (0.08)	3.22x10 ⁻¹	1.49 (0.55 - 2.48, 3.1x10 ⁻¹)	
rs10792832	PICALM	0.14 (0.01)	0.17 (0.06)	3.25x10 ⁻³ *	1.20 (0.40 - 2.07, 6.3x10 ⁻¹)	0.15 (0.08)	8.81x10 ⁻¹	1.10 (-0.28 - 2.49, 8.8x10 ⁻¹)	
rs7274581	CASS4	-0.13 (0.02)	-0.16 (0.10)	1.08x10 ⁻¹	1.24 (-0.24 - 3.10, 7.5x10 ⁻¹)	-0.09 (0.14)	8.18x10 ⁻¹	0.70 (-1.96 - 3.33, 8.2x10 ⁻¹)	
rs143332484	TREM2 (R62H)	0.50 (0.07)	0.09 (0.22)	6.76x10 ⁻¹	0.19 (-0.71 - 1.10, 7.8x10 ⁻²)	0.95 (0.39)	3.40x10 ⁻¹	1.92 (0.05 - 3.95, 3.4x10 ⁻¹)	
rs118172952	KANSL1	-0.14 (0.03)	-0.08 (0.08)	3.32x10 ⁻¹	0.56 (-0.65 - 2.11, 5.0x10 ⁻¹)	-0.20 (0.11)	6.52x10 ⁻¹	1.44 (-0.65 - 3.74, 6.8x10 ⁻¹)	
rs6656401	CR1	-0.17 (0.01)	-0.12 (0.07)	7.04x10 ⁻²	0.73 (-0.05 - 1.58, 5.1x10 ⁻¹)	-0.18 (0.10)	8.97x10 ⁻¹	1.09 (-0.32 - 2.52, 9.0x10 ⁻¹)	
rs200538373	ABCA7 (G>C)	-0.65 (0.14)	0.13 (0.51)	7.94x10 ⁻¹	-0.21 (-1.93 - 1.49, 1.4x10 ⁻¹)	-0.99 (0.64)	6.43x10 ⁻¹	1.54 (-0.85 - 4.15, 6.3x10 ⁻¹)	
rs9331896	CLU	0.15 (0.01)	0.17 (0.06)	3.73x10 ⁻³ *	1.14 (0.36 - 2.00, 7.1x10 ⁻¹)	0.06 (0.08)	3.96x10 ⁻¹	0.43 (-0.92 - 1.73, 3.9x10 ⁻¹)	
rs35349669	INPP5D	0.08 (0.01)	0.09 (0.05)	1.23x10 ⁻¹	1.15 (-0.06 - 2.53)	0.04 (0.08)	6.98x10 ⁻¹	0.51 (-2.23 - 3.08, 7.1x10 ⁻¹)	

rs17125944	<i>FERMT2</i>	0.13 (0.02)	-0.01 (0.09)	8.75x10 ⁻¹	-0.11 (-1.30 - 1.07)	0.03 (0.13)	5.20x10 ⁻¹	0.26 (-2.21 - 2.60, 7.1x10 ⁻¹)
rs190982	<i>MEF2C</i>	0.08 (0.01)	0.00 (0.05)	9.94x10 ⁻¹	0.01 (-1.25 - 1.27)	-0.06 (0.08)	1.48x10 ⁻¹	-0.84 (-3.81 - 1.61, 1.4x10 ⁻¹)
AVERAGE		0.94 ± 0.12, p = 6.8x10⁻¹			1.88 ± 0.24, p = 1.0x10⁻⁴			

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17 Abbreviations: *Rs ID*, variant identifier; *Gene*, gene associated with the variant; $\log OR_I^k$ (*SE*), published log(odds ratio) and relative standard error; $\log OR_{EA-NC}^k$ (*SE*),
18 log(odds ratio) and relative standard error for comparison of extreme cases with normal controls; E_{EA-NC}^k (*95% CI, p*), increased effect-size relative to published effect-size,
19 95% confidence interval and p-value of difference relative to published effect sizes; $\log OR_{NA-EC}^k$ (*SE*), log(odds ratio) and relative standard error for comparison of normal
20 AD cases with centenarian controls; E_{NA-EC}^k (*95% CI, p*), increased effect-size, 95% confidence intervals and p-value of difference relative to published effect-size; Bold
21 type: variants with significant E_{1-2}^k ; Stars*: p-value significant at nominal threshold ($p < 0.05$); Asterisk#: p-value of association of Normal Controls (*NC*) and Extreme Controls
22 (*EC*).
23

24 **Table S4:** Comparison between using younger early-onset cases (AAO <60 years) early-onset cases (AAO <65 years) and
25 using late-onset AD cases (AAO >65 years) relative to normal controls

Rs ID	Gene	log OR _I ^k (SE)	Younger early-onset AD cases (AAO < 60 y.o) vs. Normal Controls (yEA vs. NC)			Early-onset cases (AAO < 65 y.o) vs. Normal Controls (eEA vs. NC)			Late-onset cases (AAO > 65 y.o) vs. Normal Controls (IEA vs. NC)		
			log OR _{yEA-NC} ^k (SE)	P-value _{yEA-NC}	E _{yEA-NC} ^k (95% CI, p)	log OR _{eEA-NC} ^k (SE)	P-value _{eEA-NC}	E _{eEA-NC} ^k (95% CI, p)	log OR _{IEA-NC} ^k (SE)	P-value _{IEA-NC}	E _{IEA-NC} ^k (95% CI, p)
rs75932628	TREM2 (R47H)	0.89 (0.09)	0.48 (1.24)	6.97x10 ⁻¹	0.54 (-2.25 - 3.29, 7.4x10 ⁻¹)	1.41 (0.83)	9.02x10 ⁻²	1.58 (-0.25 - 3.58, 5.5x10 ⁻¹)	1.57 (0.68)	2.16x10 ⁻² *	1.78 (0.28 - 3.41, 3.2x10 ⁻¹)
rs7920721	ECHDC3	0.07 (0.01)	0.16 (0.09)	9.11x10 ⁻²	2.44 (-0.41 - 5.31, 3.2x10 ⁻¹)	0.16 (0.07)	3.64x10 ⁻² *	2.38 (0.12 - 5.32, 2.3x10 ⁻¹)	0.18 (0.07)	7.66x10 ⁻³ *	2.70 (0.69 - 5.44, 9.9x10 ⁻²)
rs10498633	SLC24A4-RIN3	-0.09 (0.02)	-0.27 (0.12)	2.26x10 ⁻²	2.88 (0.39 - 5.38, 1.4x10 ⁻¹)	-0.16 (0.09)	8.34x10 ⁻²	1.66 (-0.19 - 3.94, 5.1x10 ⁻¹)	-0.19 (0.08)	1.96x10 ⁻² *	2.01 (0.35 - 4.18, 2.5x10 ⁻¹)
rs2718058	NME8	-0.08 (0.01)	0.11 (0.10)	2.68x10 ⁻¹	-1.40 (-3.90 - 1.08, 5.9x10 ⁻²)	-0.01 (0.08)	9.40x10 ⁻¹	0.08 (-1.95 - 2.16, 3.7x10 ⁻¹)	-0.05 (0.07)	4.98x10 ⁻¹	0.61 (-1.23 - 2.53, 6.7x10 ⁻¹)
rs72824905	PLCG2	-0.39 (0.06)	-0.56 (0.57)	3.28x10 ⁻¹	1.45 (-1.42 - 4.31, 7.5x10 ⁻¹)	-0.38 (0.41)	3.63x10 ⁻¹	0.97 (-1.19 - 3.24, 9.7x10 ⁻¹)	-0.54 (0.39)	1.63x10 ⁻¹	1.40 (-0.61 - 3.69, 7.0x10 ⁻¹)
rs9271192	HLA-DRB1	-0.11 (0.01)	-0.07 (0.10)	5.22x10 ⁻¹	0.61 (-1.28 - 2.54, 6.8x10 ⁻¹)	-0.21 (0.12)	6.50x10 ⁻²	1.98 (-0.11 - 4.43, 3.6x10 ⁻¹)	-0.07 (0.11)	5.11x10 ⁻¹	0.65 (-1.34 - 2.72, 7.1x10 ⁻¹)
rs1476679	ZCWPW1	0.09 (0.01)	-0.01 (0.10)	8.79x10 ⁻¹	-0.20 (-2.43 - 1.99, 2.8x10 ⁻¹)	0.01 (0.08)	9.13x10⁻¹	0.10 (-1.73 - 1.98, 3.1x10⁻¹)	0.24 (0.07)	1.15x10⁻³*	2.73 (1.04 - 4.96, 4.3x10⁻²)
rs4147929	ABCA7 (A>G)	-0.14 (0.02)	-0.27 (0.12)	2.50x10 ⁻²	1.88 (0.23 - 3.51, 2.9x10 ⁻¹)	-0.19 (0.10)	5.35x10 ⁻²	1.30 (-0.01 - 2.81, 6.4x10 ⁻¹)	-0.16 (0.09)	7.30x10 ⁻²	1.10 (-0.12 - 2.43, 8.8x10 ⁻¹)
rs7412	APOE (ε2)	-0.79 (0.03)	-1.61 (0.32)	7.26x10 ⁻⁷	2.05 (1.22 - 2.87, 1.3x10 ⁻²)	-1.41 (0.22)	3.77x10⁻¹⁰*	1.80 (1.21 - 2.40, 8.6x10⁻³)	-0.89 (0.16)	2.52x10⁻⁸*	1.13 (0.72 - 1.56, 5.1x10⁻¹)
rs13113697	HS3ST1	-0.07 (0.01)	0.13 (0.11)	2.41x10 ⁻¹	-1.93 (-5.15 - 1.28, 7.5x10 ⁻²)	0.03 (0.08)	7.16x10 ⁻¹	-0.46 (-3.29 - 2.12, 2.5x10 ⁻¹)	-0.03 (0.08)	7.37x10 ⁻¹	0.38 (-1.94 - 2.86, 5.9x10 ⁻¹)
rs616338	ABI3	-0.36 (0.05)	-0.75 (0.42)	7.37x10 ⁻²	2.06 (-0.19 - 4.39, 3.6x10 ⁻¹)	-0.49 (0.37)	1.90x10 ⁻¹	1.35 (-0.68 - 3.60, 7.4x10 ⁻¹)	-0.82 (0.31)	8.01x10 ⁻³ *	2.27 (0.61 - 4.43, 1.3x10 ⁻¹)
rs10948363	CD2AP	0.10 (0.01)	-0.00 (0.11)	9.79x10 ⁻¹	-0.01 (-2.20 - 2.18, 3.7x10 ⁻¹)	0.06 (0.08)	4.89x10 ⁻¹	0.60 (-1.11 - 2.47, 6.4x10 ⁻¹)	0.07 (0.07)	3.23x10 ⁻¹	0.77 (-0.77 - 2.45, 7.7x10 ⁻¹)
rs429358	APOE (ε4)	1.05 (0.03)	1.27 (0.11)	8.69x10 ⁻³¹	1.21 (1.01 - 1.42, 3.6x10 ⁻²)	1.32 (0.09)	3.76x10 ⁻⁵⁰ *	1.26 (1.08 - 1.44, 3.4x10⁻³)	1.42 (0.08)	1.86x10 ⁻⁶⁶ *	1.36 (1.19 - 1.53, 4.5x10 ⁻⁴)
rs11771145	EPHA1	-0.10 (0.01)	-0.04 (0.10)	7.06x10 ⁻¹	0.37 (-1.61 - 2.29, 5.1x10 ⁻¹)	0.00 (0.08)	9.76x10 ⁻¹	-0.02 (-1.55 - 1.57, 2.1x10 ⁻¹)	-0.17 (0.07)	1.63x10 ⁻² *	1.70 (0.32 - 3.36, 3.2x10 ⁻¹)
rs10838725	CELF1	0.08 (0.01)	0.25 (0.10)	1.17x10 ⁻²	3.15 (0.70 - 5.60, 8.5x10 ⁻²)	0.13 (0.08)	9.61x10 ⁻²	1.66 (-0.30 - 4.04, 5.1x10 ⁻¹)	0.02 (0.07)	7.94x10 ⁻¹	0.24 (-1.65 - 2.17, 4.2x10 ⁻¹)
rs28834970	PTK2B	0.10 (0.01)	0.25 (0.09)	9.04x10 ⁻³	2.50 (0.60 - 4.42, 1.2x10 ⁻¹)	0.12 (0.07)	1.06x10 ⁻¹	1.23 (-0.27 - 2.92, 7.7x10 ⁻¹)	0.05 (0.07)	4.59x10 ⁻¹	0.52 (-0.87 - 2.01, 5.1x10 ⁻¹)
rs983392	MS4A6A	-0.11 (0.01)	0.09 (0.09)	3.20x10 ⁻¹	-0.87 (-2.62 - 0.89, 6.8x10 ⁻²)	0.12 (0.07)	1.16x10⁻¹	-1.11 (2.62 - 0.24, 2.8x10⁻³)	-0.13 (0.07)	6.31x10⁻²	1.19 (-0.04 - 2.63, 7.6x10 ⁻¹)
rs11218343	SORL1	-0.26 (0.03)	0.04 (0.24)	8.73x10 ⁻¹	-0.13 (-1.92 - 1.66, 2.0x10 ⁻¹)	-0.14 (0.20)	4.78x10 ⁻¹	0.54 (-0.92 - 2.11, 5.4x10 ⁻¹)	-0.27 (0.19)	1.54x10 ⁻¹	1.02 (-0.39 - 2.55, 9.8x10 ⁻¹)
rs6733839	BIN1	0.20 (0.01)	0.21 (0.09)	2.49x10 ⁻²	1.07 (0.12 - 2.01, 8.7x10 ⁻¹)	0.19 (0.07)	1.16x10 ⁻² *	0.95 (0.23 - 1.73, 9.1x10 ⁻¹)	0.15 (0.07)	2.36x10 ⁻² *	0.78 (0.10 - 1.48, 5.2x10 ⁻¹)
rs10792832	PICALM	0.14 (0.01)	0.16 (0.10)	1.13x10 ⁻¹	1.11 (-0.30 - 2.51, 8.8x10 ⁻¹)	0.18 (0.08)	2.10x10 ⁻² *	1.28 (0.20 - 2.43, 6.1x10 ⁻¹)	0.16 (0.07)	2.33x10 ⁻² *	1.12 (0.16 - 2.18, 8.1x10 ⁻¹)
rs7274581	CASS4	-0.13 (0.02)	-0.26 (0.18)	1.54x10 ⁻¹	1.98 (-0.75 - 4.71, 4.8x10 ⁻¹)	-0.34 (0.15)	2.31x10 ⁻² *	2.53 (0.39 - 5.43, 1.6x10 ⁻¹)	-0.04 (0.12)	7.18x10 ⁻¹	0.33 (-1.60 - 2.24, 4.6x10 ⁻¹)
rs143332484	TREM2 (R62H)	0.50 (0.07)	0.17 (0.37)	6.52x10 ⁻¹	0.34 (-1.10 - 1.80, 3.7x10 ⁻¹)	0.25 (0.28)	3.73x10 ⁻¹	0.51 (-0.62 - 1.67, 3.9x10 ⁻¹)	-0.03 (0.28)	9.19x10 ⁻¹	-0.06 (-1.22 - 1.09, 6.9x10 ⁻²)
rs118172952	KANSL1	-0.14 (0.03)	-0.17 (0.14)	2.22x10 ⁻¹	1.25 (-0.74 - 3.27, 8.0x10 ⁻¹)	0.01 (0.10)	8.95x10 ⁻¹	-0.10 (-1.86 - 1.57, 1.8x10 ⁻¹)	-0.15 (0.10)	1.26x10 ⁻¹	1.09 (-0.33 - 3.20, 9.1x10 ⁻¹)
rs6656401	CR1	-0.17 (0.01)	-0.31 (0.11)	4.39x10 ⁻³	1.87 (0.58 - 3.15, 1.9x10 ⁻¹)	-0.17 (0.09)	5.43x10 ⁻²	1.02 (0.01 - 2.14, 9.6x10 ⁻¹)	-0.08 (0.08)	3.04x10 ⁻¹	0.50 (-0.46 - 1.49, 3.0x10 ⁻¹)
rs200538373	ABCA7 (G>C)	-0.65 (0.14)	0.00 (0.90)	9.97x10 ⁻¹	-0.02 (-2.79 - 2.74, 4.7x10 ⁻¹)	0.29 (0.62)	6.39x10 ⁻¹	-0.45 (-2.63 - 1.52, 1.3x10 ⁻¹)	-0.03 (0.64)	9.57x10 ⁻¹	0.05 (-2.10 - 2.21, 3.6x10 ⁻¹)
rs9331896	CLU	0.15 (0.01)	0.28 (0.10)	5.39x10 ⁻³	1.92 (0.59 - 3.23, 1.8x10 ⁻¹)	0.13 (0.08)	1.03x10 ⁻¹	0.86 (-0.16 - 1.93, 7.9x10 ⁻¹)	0.20 (0.07)	4.89x10 ⁻³ *	1.34 (0.41 - 2.37, 4.6x10 ⁻¹)
rs35349669	INPP5D	0.08 (0.01)	0.14 (0.10)	1.52x10 ⁻¹	1.82 (-0.68 - 4.35, 5.2x10 ⁻¹)	0.15 (0.07)	4.23x10 ⁻² *	2.04 (0.04 - 4.59, 3.1x10 ⁻¹)	0.04 (0.07)	5.59x10 ⁻¹	0.52 (-1.33 - 2.43, 6.0x10 ⁻¹)

rs17125944	<i>FERMT2</i>	0.13 (0.02)	-0.15 (0.16)	3.44×10^{-1}	-1.17 (-3.63 - 1.24, 7.7×10^{-2})	0.01 (0.12)	9.25×10^{-1}	0.08 (-1.83 - 2.01, 3.2×10^{-1})	-0.04 (0.11)	7.47×10^{-1}	-0.27 (-2.12 - 1.45, 1.3×10^{-1})
rs190982	<i>MEF2C</i>	0.08 (0.01)	-0.11 (0.09)	2.52×10^{-1}	-1.43 (-3.91 - 1.03, 5.3×10^{-2})	-0.05 (0.07)	4.98×10^{-1}	-0.67 (-2.85 - 1.33, 9.7×10^{-2})	0.03 (0.07)	6.12×10^{-1}	0.45 (-1.32 - 2.41, 5.6×10^{-1})
AVERAGE			0.87 ± 0.20, $p = 7.3 \times 10^{-1}$			0.86 ± 0.16, $p = 7.9 \times 10^{-1}$			1.01 ± 0.14, $p = 4.6 \times 10^{-1}$		

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28 Abbreviations: *Rs ID*, variant ID; *Gene*, gene associated with the variant according to paper in which was first associated; $\log OR_I^k$, published log(odds ratio) and relative
29 standard error, *i.e* the first or largest case-control study that reported the variant association with AD; $\log OR_{yEA-NC}^k$, Effect-size and relative standard error of AD association
30 of 255 young AD cases (age at onset <60 years of age) vs. 1,664 normal controls; E_{yEA-NC}^k (95% CI, p), change in effect size when using young AD cases (age at onset <
31 60 years of age), 95% confidence intervals and p-value of difference relative to published effect sizes; $\log OR_{eEA-NC}^k$, Effect-size and relative standard error of AD association
32 of 464 early-onset AD cases vs. normal controls; E_{eEA-NC}^k (95% CI, p), increased effect size when using extreme AD early-onset, 95% confidence intervals and p-value of
33 difference relative to published effect sizes; $\log OR_{lEA-NC}^k$, Effect-size and relative standard error of association of 609 late-onset AD cases vs. normal controls; E_{lEA-NC}^k
34 (95% CI, p), increased effect size when using extreme AD late-onset, 95% confidence intervals and p-value of difference relative to published effect sizes; Bold type:
35 variants with a significant difference between the effect-sizes of 464 early-onset cases (age at onset <65) and 609 late-onset cases (age at onset >65) relative to 1,664
36 normal controls; Stars*: p-value significant at nominal threshold ($p < 0.05$).

37 **Table S5:** Functional implication of all the tested variants

<i>Locus</i>	<i>Gene</i>	<i>Variant</i>	<i>GO</i>	<i>Literature</i>	E_{EA-EC}^k
6:41129252	<i>TREM2 R47H</i>	rs75932628	positive regulation of antigen processing and presentation of peptide antigen via MHC class II (GO:0002588); phagocytosis (GO:0006911); humoral immune response (GO:0006569)	-	6.46
10:11720308	<i>ECHDC3</i>	rs7920721	metabolic process (GO:0008152)	-	4.56
14:92926952	<i>SLC24A4</i>	rs10498633	transport (GO:0006810); ion transport (GO:0006811); sodium ion transport (GO:0006814)	Neural development and regulation of blood pressure and hypertension	4.50
7:37841534	<i>NME8</i>	rs2718058	nucleoside diphosphate phosphorylation (GO:0006165); multicellular organism development (GO:0007275); cell differentiation (GO:0030154)	Cytoskeletal function and axonal transport	3.80
16:81942028	<i>PLCG2</i>	rs72824905	positive regulation of receptor internalization (GO:0002092); follicular B cell differentiation (GO:0002316); lipid metabolic process (GO:0006629)	-	3.28
6:32578530	<i>HLA-DRB1</i>	rs111418223	immune system process (GO:0002376); immunoglobulin production involved in immunoglobulin mediated immune response (GO:0002381); inflammatory response to antigenic stimulus (GO:0002437)	Immune response	3.20
7:100004446	<i>ZCWPW1</i>	rs1476679	-	Epistasis regulation and Neural development	2.97
19:1063443	<i>ABCA7 A>G</i>	rs4147929	transport (GO:0006810); phagocytosis (GO:0006909); positive regulation of cholesterol efflux (GO:0010875)	Lipid metabolism and Immune system	2.26
19:45412079	<i>APOE ε2</i>	rs7412	response to reactive oxygen species (GO:0000302); retinoid metabolic process (GO:0001523); negative regulation of endothelial cell proliferation (GO:0001937)	Lipid metabolism and cholesterol transport	2.24
17:47297297	<i>ABI3</i>	rs616338	movement of cell or subcellular component (GO:0006928); regulation of cell migration (GO:0030334)	-	2.06
4:11711232	<i>HS3ST1</i>	rs13113697	glycosaminoglycan biosynthetic process (GO:0006024)	-	2.06
6:47487762	<i>CD2AP</i>	rs10948363	protein complex assembly (GO:0006461); substrate-dependent cell migration, cell extension (GO:0006930); cell cycle (GO:0007049)	Endosomal vesicle cycling	2.00

19:45411941	<i>APOE ε4</i>	rs429358	response to reactive oxygen species (GO:0000302); retinoid metabolic process (GO:0001523); negative regulation of endothelial cell proliferation (GO:0001937)	Lipid metabolism and cholesterol transport	1.99
7:143110762	<i>EPHA1</i>	rs11771145	angiogenesis (GO:0001525); positive regulation of cell-matrix adhesion (GO:0001954); protein phosphorylation (GO:0006468)	Endosomal vesicle cycling and Immune system	1.94
11:47557871	<i>CELF1</i>	rs10838725	mRNA processing (GO:0006376); germ cell development (GO:0007281); mRNA splice site selection (GO:0006376)	Cytoskeletal function and axonal transport	1.78
8:27195121	<i>PTK2B</i>	rs28834970	MAPK cascade (GO:0000165); response to reactive oxygen species (GO:0000302); angiogenesis (GO:0001525)	Cell migration and synaptic function	1.76
11:59923508	<i>MS4A6A</i>	rs983392	-	Immune response	1.56
11:121435587	<i>SORL1</i>	rs11218343	protein targeting (GO:0006605); lipid metabolic process (GO:0006629); transport (GO:0006810)	Endosomal vesicle cycling	1.48
2:127892810	<i>BIN1</i>	rs6733839	endocytosis (GO:0006897); nucleus organization (GO:0006997); multicellular organism development (GO:0007275)	Endosomal vesicle cycling	1.28
11:85867875	<i>PICALM</i>	rs10792832	protein complex assembly (GO:0006461); endocytosis (GO:0006897); axonogenesis (GO:0007409)	Endosomal vesicle cycling	1.09
20:55018260	<i>CASS4</i>	rs7274581	cell adhesion (GO:0007155)	Cytoskeletal function and axonal transport	1.06
17:44353222	<i>KANSL1</i>	rs118172952	covalent chromatin modification (GO:0016569); histone H4-K5 acetylation (GO:0043981); histone H4-K8 acetylation (GO:0043982)	-	0.97
6:41129207	<i>TREM2 R62H</i>	rs143332484	positive regulation of antigen processing and presentation of peptide antigen via MHC class II (GO:0002588); phagocytosis (GO:0006911); humoral immune response (GO:0006569)	-	0.97
1:207692049	<i>CR1</i>	rs6656401	immune system process (GO:0002376); complement receptor mediated signaling pathway (GO:0002430); complement activation (GO:0006958)	Immune response	0.75
19:1061892	<i>ABCA7 G>C</i>	rs200538373	transport (GO:0006810); phagocytosis (GO:0006909); positive regulation of cholesterol efflux (GO:0010875)	Lipid metabolism and Immune system	0.68
8:27467686	<i>CLU</i>	rs9331896	cell morphogenesis (GO:0000902); microglial cell activation (GO:0001774); immune system process (GO:0002376)	Cholesterol and Lipid metabolism and Immune system	0.60
2:234068476	<i>INPP5D</i>	rs35349669	phosphatidylinositol biosynthetic process (GO:0006661); phosphate-containing compound metabolic process (GO:0006796); apoptotic process (GO:0006915)	Immune response	0.36

14:53400629	<i>FERMT2</i>	rs17125944	cell adhesion (GO:0007155); cell-matrix adhesion (GO:0007160); regulation of cell shape (GO:0008360)	Cytoskeletal function and axonal transport	-0.82
5:88223420	<i>MEF2C</i>	rs190982	negative regulation of transcription by RNA polymerase II (GO:0000122); MAPK cascade (GO:0000165); blood vessel development (GO:0001568)	Immune response, Neural development and synaptic functions	-1.86

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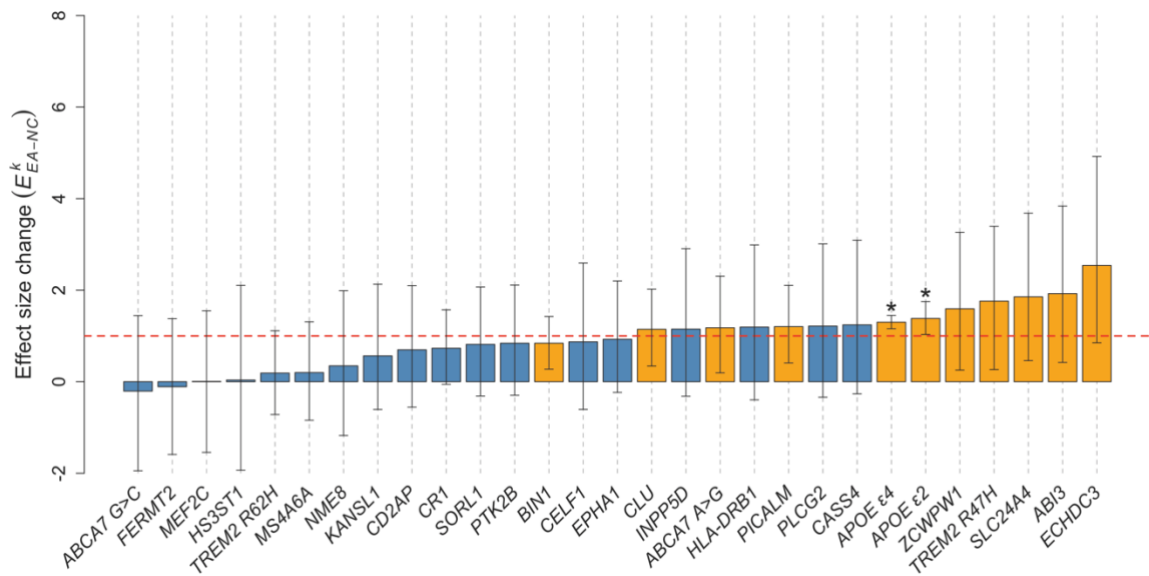
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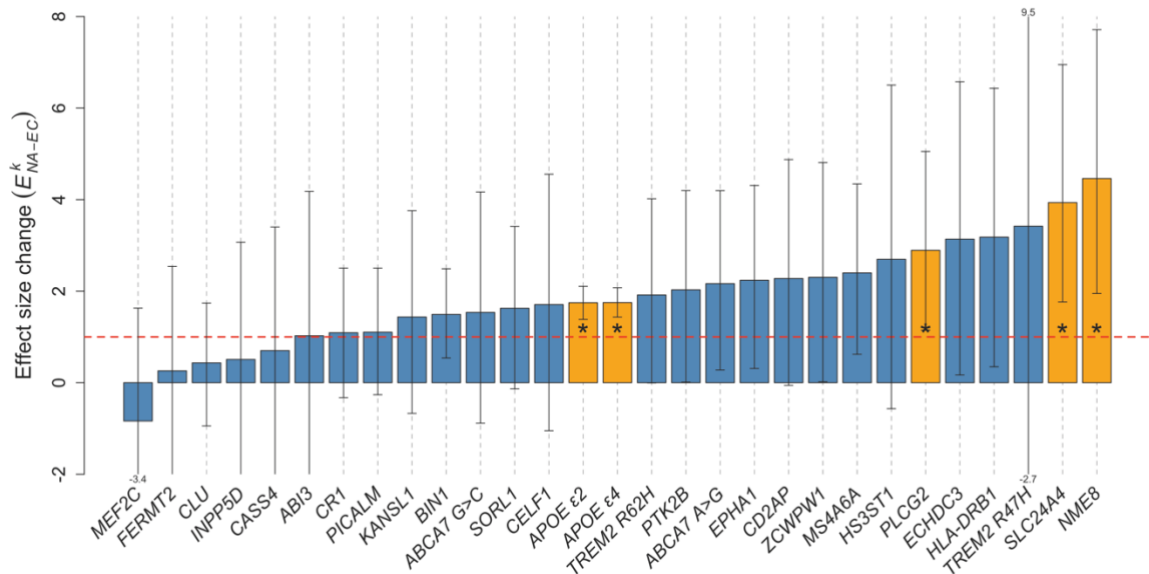
Abbreviations: Locus, genomic location of the variant; Gene, the nearest gene associated with the variant in the paper that first associated the variant with AD; RsID, variant identifier, GO annotation, first three Gene Ontology (GO) biological processes associated with gene; Literature annotation, pathway(s) associated with each gene according to a recent review regarding the genetic landscape of Alzheimer's disease⁴³; E_{EA-EC}^k , effect-size change when using extreme phenotypes relative to published effect size. Orange cells indicate variants with a decreased effect-size as compared to published effect-size. Green cells correspond to variants with an increased effect-size as compared to published effect-size.



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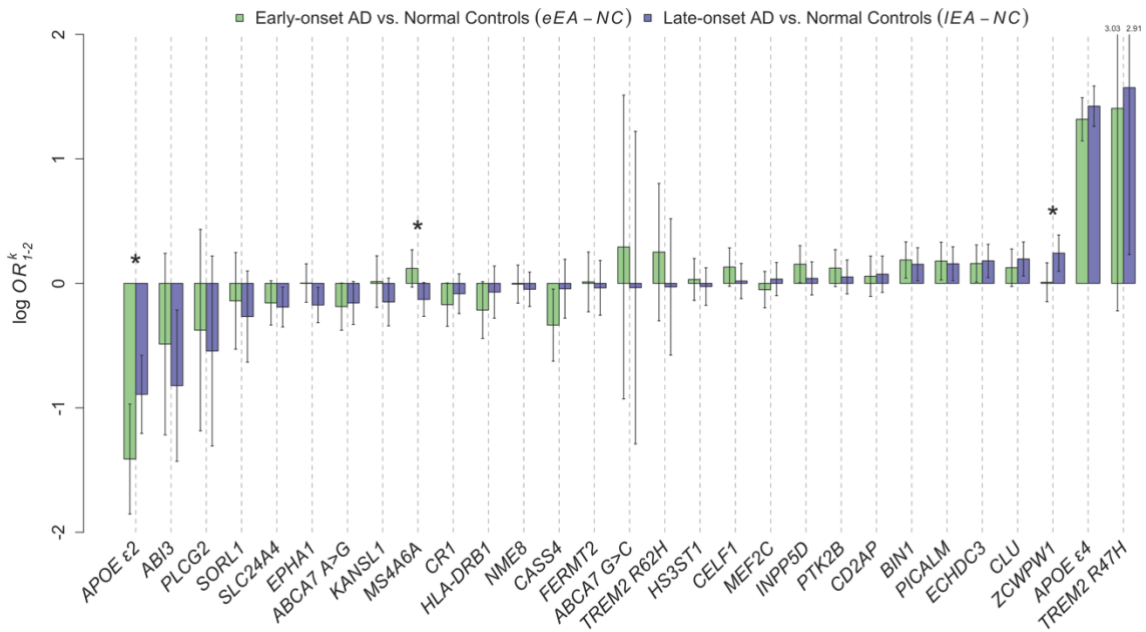
47 **Figure S1: Extreme AD cases vs. normal controls: E^k_{EA-NC} .** The effect-size change was
 48 significant for 4 variants ($p < 0.05$, two-sample z-test; bars annotated with a star [*]). Orange bars
 49 indicate nominal statistical significance for the association with AD ($p < 0.05$). Dashed red line
 50 ($E^k_{EA-NC} = 1$) indicates same effect-size as reported in literature.

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53 **Figure S2: Normal ADs vs. Extreme (centenarian) controls: E^k_{NA-EC} .** Effect-size change
 54 (E^k_{NA-EC}) was significant for 5 variants ($p < 0.05$, two-sample z-test; bars annotated with a star [*]).
 55 Orange bars indicate nominal statistical significance for the association with AD ($p < 0.05$). Dashed
 56 red line indicates same effect-size as reported in literature.

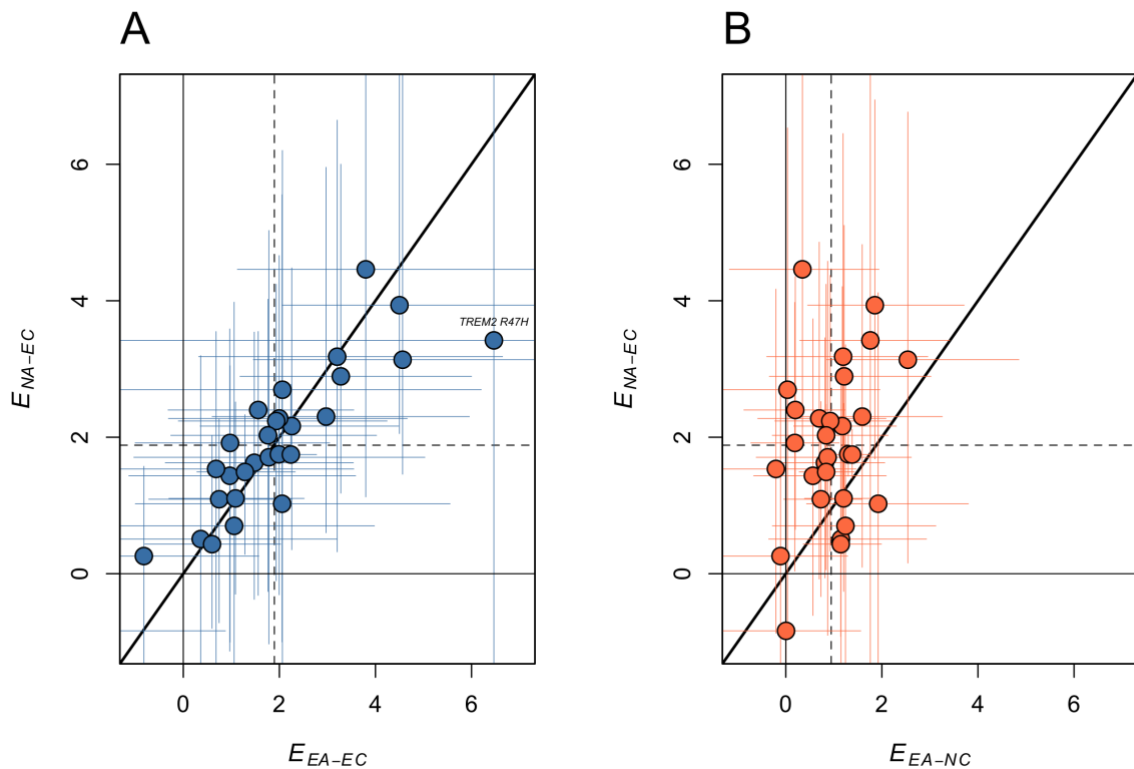


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59 **Figure S3: Early onset AD vs normal controls and late onset AD vs normal controls.** Effect-
 60 sizes and 95% confidence intervals of a comparison of early onset AD cases ($\log OR_{eEA-NC}^k$, age
 61 at onset ≤ 65 years) and late-onset AD ($\log OR_{IEA-NC}^k$, age at onset > 65 years) with normal
 62 controls. For all the variants, the 95% confidence intervals overlapped. [*]: difference between
 63 $\log OR_{eEA-NC}^k$ and $\log OR_{IEA-NC}^k$ was significant ($p < 0.05$, two-sample z-test).

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67 **Figure S4: Comparison of effect size changes at the variant level**

68 **A: Effect of using extreme AD cases vs normal AD cases:** X-axis: E^k_{EA-EC} : Effect size changes

69 from a comparison of the extreme cases and extreme (centenarian) controls relative to published

70 effect sizes. Dashed line x-axis average effect-size increase E^k_{EA-EC} at 1.90 ± 0.29 : Y-axis: E^k_{NA-EC}

71 E^k_{NA-EC} : effect size changes from a comparison normal AD cases with extreme (centenarian) controls

72 relative to published effect sizes. Dashed line y-axis: average effect-size increase E^k_{NA-EC} at 1.88

73 ± 0.24 . See Table 2 for E^k_{EA-EC} and Table S3 for E^k_{NA-EC} values

74 **B. Effect of using extreme cases vs using extreme controls:** X-axis: effect-size changes of extreme AD cases vs. normal controls

75 relative to published effect-sizes. Dashed line x-axis: average effect-size increase E^k_{EA-NC} at 0.94

76 ± 0.12 . Y-axis: Variant effect-size change of normal AD cases vs. extreme controls relative to

77 published effect-sizes. Dashed line y-axis: average effect-size increase E^k_{NA-EC} at 1.88 ± 0.24 .

78 See Table S3 for E^k_{EA-NC} and E^k_{NA-EC} values.

79