

Table 2 Summary of stage 1, stage 2 and overall meta-analyses for SNPs reaching genome-wide significance after stages 1 and 2

SNP ^a	Chr.	Position ^b	Closest gene ^c	Major/minor alleles	MAF ^d	Stage 1		Stage 2		Overall		
						OR (95% CI) ^e	Meta <i>P</i> value	OR (95% CI) ^e	Meta <i>P</i> value	OR (95% CI) ^e	Meta <i>P</i> value	<i>I</i> ² (%), <i>P</i> value ^f
Known GWAS-defined associated genes												
rs6656401	1	207692049	<i>CR1</i>	G/A	0.197	1.17 (1.12–1.22)	7.7×10^{-15}	1.21 (1.14–1.28)	7.9×10^{-11}	1.18 (1.14–1.22)	5.7×10^{-24}	0, 7.8×10^{-1}
rs6733839	2	127892810	<i>BIN1</i>	C/T	0.409	1.21 (1.17–1.25)	1.7×10^{-26}	1.24 (1.18–1.29)	3.4×10^{-19}	1.22 (1.18–1.25)	6.9×10^{-44}	28, 6.1×10^{-2}
rs10948363	6	47487762	<i>CD2AP</i>	A/G	0.266	1.10 (1.07–1.14)	3.1×10^{-8}	1.09 (1.04–1.15)	4.1×10^{-4}	1.10 (1.07–1.13)	5.2×10^{-11}	0, 9×10^{-1}
rs11771145	7	143110762	<i>EPHA1</i>	G/A	0.338	0.90 (0.87–0.93)	8.8×10^{-10}	0.90 (0.86–0.95)	2.8×10^{-5}	0.90 (0.88–0.93)	1.1×10^{-13}	14, 2.4×10^{-1}
rs9331896	8	27467686	<i>CLU</i>	T/C	0.379	0.86 (0.84–0.89)	9.6×10^{-17}	0.86 (0.82–0.90)	4.5×10^{-10}	0.86 (0.84–0.89)	2.8×10^{-25}	0, 4.9×10^{-1}
rs983392	11	59923508	<i>MS4A6A</i>	A/G	0.403	0.90 (0.87–0.93)	2.8×10^{-11}	0.90 (0.86–0.94)	4.5×10^{-6}	0.90 (0.87–0.92)	6.1×10^{-16}	1, 4.5×10^{-1}
rs10792832	11	85867875	<i>PICALM</i>	G/A	0.358	0.88 (0.85–0.91)	6.5×10^{-16}	0.85 (0.81–0.89)	1.1×10^{-11}	0.87 (0.85–0.89)	9.3×10^{-26}	0, 9.8×10^{-1}
rs4147929	19	1063443	<i>ABCA7</i>	G/A	0.190	1.14 (1.10–1.20)	1.7×10^{-9}	1.17 (1.10–1.24)	9.9×10^{-8}	1.15 (1.11–1.19)	1.1×10^{-15}	0, 9.4×10^{-1}
rs3865444 ^g	19	51727962	<i>CD33</i>	C/A	0.307	0.91 (0.88–0.94)	5.1×10^{-8}	0.99 (0.94–1.04)	6.9×10^{-1}	0.94 (0.91–0.96)	3.0×10^{-6}	0, 6.9×10^{-1}
New loci reaching genome-wide significance in the discovery analysis												
rs9271192	6	32578530	<i>HLA-DRB5– HLA-DRB1</i>	A/C	0.276	1.11 (1.07–1.16)	1.6×10^{-8}	1.12 (1.06–1.18)	4.2×10^{-5}	1.11 (1.08–1.15)	2.9×10^{-12}	0, 5.4×10^{-1}
rs28834970	8	27195121	<i>PTK2B</i>	T/C	0.366	1.10 (1.07–1.14)	3.3×10^{-9}	1.11 (1.06–1.17)	4.3×10^{-6}	1.10 (1.08–1.13)	7.4×10^{-14}	10, 3.0×10^{-1}
rs11218343	11	121435587	<i>SORL1</i>	T/C	0.039	0.76 (0.70–0.83)	5.0×10^{-11}	0.78 (0.70–0.88)	4.0×10^{-5}	0.77 (0.72–0.82)	9.7×10^{-15}	0, 8.3×10^{-1}
rs10498633	14	92926952	<i>SLC24A4– RIN3</i>	G/T	0.217	0.90 (0.87–0.94)	1.5×10^{-7}	0.93 (0.88–0.98)	7.8×10^{-3}	0.91 (0.88–0.94)	5.5×10^{-9}	0, 6.3×10^{-1}
rs8093731 ^g	18	29088958	<i>DSG2</i>	C/T	0.017	0.54 (0.43–0.67)	4.6×10^{-8}	1.01 (0.80–1.28)	9.0×10^{-1}	0.73 (0.62–0.86)	1.0×10^{-4}	38, 3.9×10^{-2}
New loci reaching genome-wide significance in the combined discovery and replication analysis												
rs35349669	2	234068476	<i>INPP5D</i>	C/T	0.488	1.07 (1.03–1.10)	9.6×10^{-5}	1.10 (1.05–1.15)	5.7×10^{-5}	1.08 (1.05–1.11)	3.2×10^{-8}	0, 8.0×10^{-1}
rs190982	5	88223420	<i>MEF2C</i>	A/G	0.408	0.92 (0.89–0.95)	2.5×10^{-6}	0.93 (0.89–0.98)	3.4×10^{-3}	0.93 (0.90–0.95)	3.2×10^{-8}	0, 6.4×10^{-1}
rs2718058	7	37841534	<i>NME8</i>	A/G	0.373	0.93 (0.90–0.96)	1.3×10^{-5}	0.91 (0.87–0.95)	6.3×10^{-5}	0.93 (0.90–0.95)	4.8×10^{-9}	0, 9.2×10^{-1}
rs1476679	7	100004446	<i>ZCWPW1</i>	T/C	0.287	0.92 (0.89–0.96)	7.4×10^{-6}	0.89 (0.85–0.94)	9.7×10^{-6}	0.91 (0.89–0.94)	5.6×10^{-10}	0, 7.0×10^{-1}
rs10838725	11	47557871	<i>CELF1</i>	T/C	0.316	1.08 (1.04–1.11)	6.7×10^{-6}	1.09 (1.04–1.14)	4.1×10^{-4}	1.08 (1.05–1.11)	1.1×10^{-8}	0, 7.6×10^{-1}
rs17125944	14	53400629	<i>FERMT2</i>	T/C	0.092	1.13 (1.07–1.19)	1.0×10^{-5}	1.17 (1.08–1.26)	1.6×10^{-4}	1.14 (1.09–1.19)	7.9×10^{-9}	10, 3.0×10^{-1}
rs7274581	20	55018260	<i>CASS4</i>	T/C	0.083	0.87 (0.82–0.92)	1.6×10^{-6}	0.89 (0.82–0.96)	4.1×10^{-3}	0.88 (0.84–0.92)	2.5×10^{-8}	0, 9.9×10^{-1}

Chr., chromosome.

^aSNPs showing the best level of association after meta-analysis of stages 1 and 2. ^bBuild 37, assembly hg19. ^cGenes located ± 100 kb of the top SNP. ^dAverage in the discovery sample.^eCalculated with respect to the minor allele. ^fCochran's *Q* test. ^gNot replicated in stage 2.

signals regulating neuronal activity such as mitogen-activated protein kinase (MAPK) signaling¹⁶. *PTK2B* is involved in the induction of long-term potentiation in the hippocampal CA1 (cornu ammonis 1) region, a central process in the formation of memory¹⁷. We cannot, however, exclude the possibility that there are multiple signals in the *PTK2B-CLU* region that are functionally connected to a single gene. For instance, two SNPs associated with genome-wide significance in the *PTK2B-CLU* region are eQTLs for the gene *DPYSL2* that has been implicated in Alzheimer's disease¹⁸ (**Supplementary Table 3**).

The fourth locus was *SLC24A4* (encoding solute carrier family 24 (sodium/potassium/calcium exchanger), member 4). The *SLC24A4* gene encodes a protein involved in iris development and hair and

skin color variation in humans in addition to being associated with the risk of developing hypertension^{19,20}. *SLC24A4* is also expressed in the brain and may be involved in neural development²¹. Of note, in the vicinity of the most strongly associated SNP is another gene called *RIN3* (encoding Ras and Rab interactor 3), and its gene product directly interacts with the *BIN1* gene product²², a protein that may be connected to tau-mediated pathology²³.

In addition to these four loci reaching genome-wide significance in stage 1, seven new loci reached genome-wide significance in the combined analysis.

The strongest association at one of these new loci was intronic in the *ZCWPW1* gene (encoding zinc finger, CW type with PWWP