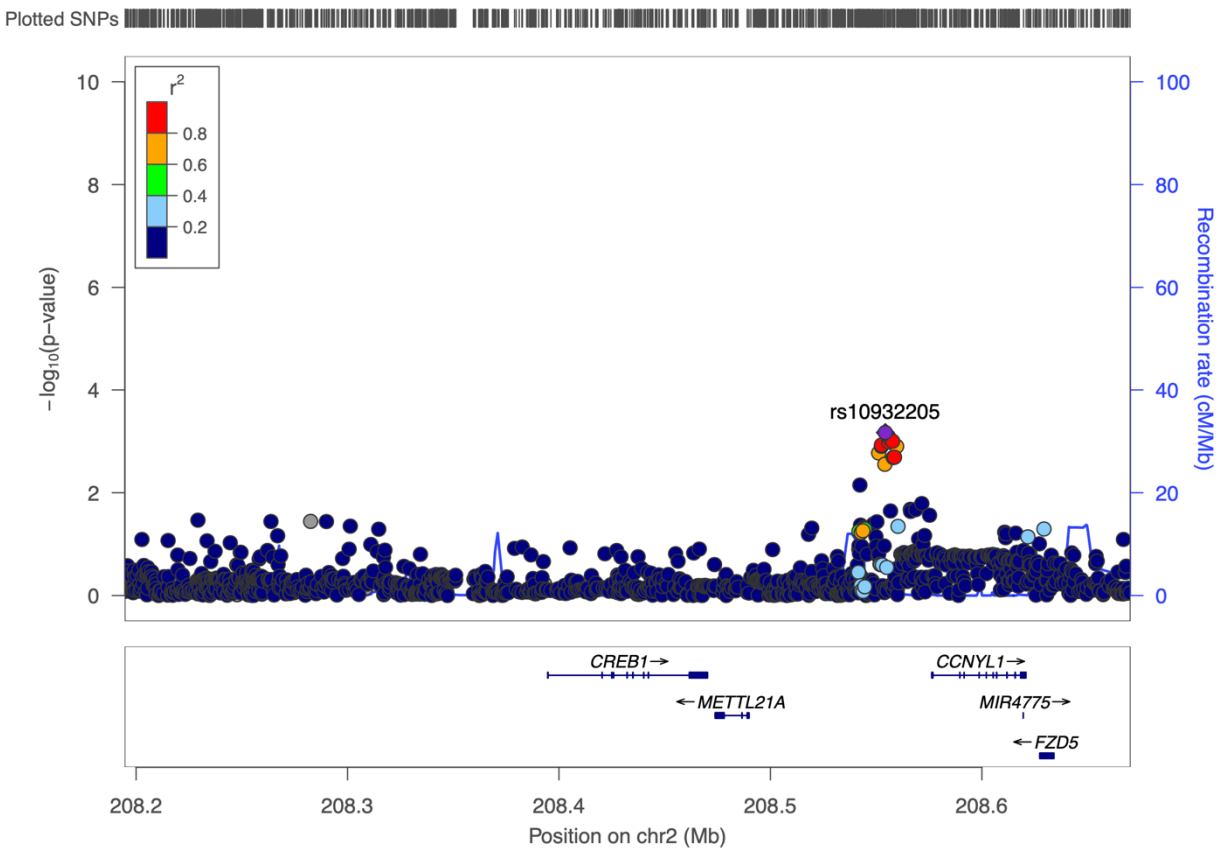

Fig.S1. The regional AD GWAS association plot for the CREB1 locus. The x-axis represents the position at chr2: 208194615-208670284 (hg19). The y-axis shows -$\log_{10}$(p-value). Each dot represents a genetic variant within this region, with the minimum P-value SNP rs10932205 ($P = 6.75\times10^{-4}$) highlighted in purple.

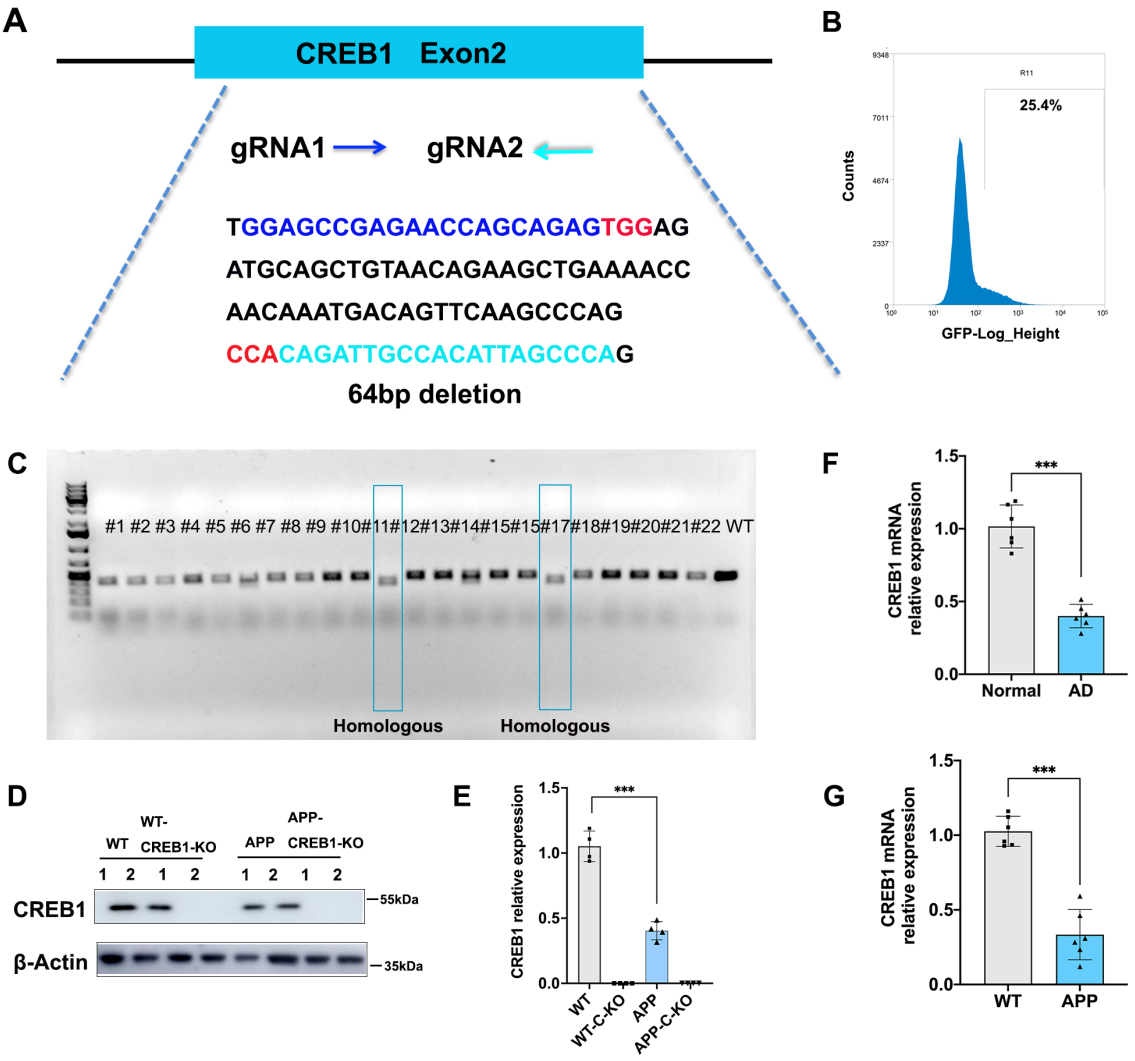

Fig.S2. (A). Guide RNA design for the generation of CREB1-KO iPSC line. **(B).** Fluorescence-activated cell sorting (FACS) to isolate GFP-positive (transfected) cells. **(C).** Agarose gel electrophoresis shows the homozygous CREB1 KO clones in WT (clone1-11), and APP iPSC lines (clone12-22). **(D).** Western blot shows undetectable levels of CREB1 protein expression in the WT-CREB1-KO and APP-CREB1-KO iPSC lines. **(E).** RT-qPCR quantification of CREB1 mRNA relative expression in the prefrontal cortex of normal individuals and AD patients (n=6). **(F).** RT-qPCR quantification of CREB1 mRNA relative expression in WT or APP iPSC-derived human cortical neurons (n=6). Data are presented as the mean ± SEM, p values were determined by one-way ANOVA followed by Tukey's post-hoc analysis, and two-tailed unpaired Student's t-test, ***$p < 0.001$. The number of samples for each group is indicated individually on each graph.

No.	FDX	CERAD	BRAAK	AGE	SEX	PMD
2259	Ctrl	0	2	78	F	21
2267	Ctrl	0	1	84	F	31
2314	Ctrl	0	2	85	M	24
2527	Ctrl	0	2	91	F	15
2543	Ctrl	0	1	87	M	18
2562	Ctrl	0	2	80	M	11
2734	AD	B	5	82	F	56
2752	AD	C	6	76	F	36
2776	AD	C	6	92	M	42
2831	AD	B	6	83	M	47
2844	AD	C	5	85	F	34
2861	AD	B	5	77	F	43

Table S1 Human postmortem AD brain tissue information. Formalin-fixed paraffin-embedded (FFPE) tissue sections from 12 human brains were analyzed, including 6 controls, 6 AD cases, and 10 μm thickness. Brain research number (No.), Final Diagnosis (FDX), Consortium to Establish a Registry for Alzheimer's Disease score (CERAD), Braak neurofibrillary tangle stage (BRAAK), Age at death (AGE), Sex (SEX), and Postmortem Delay (PMD).

Method	OR	95% CI	*P*-value
SMR	1.145	1.006-1.303	0.040
IVW	1.141	1.018-1.278	0.022

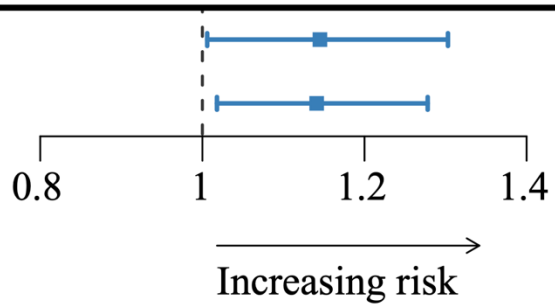

Table S2 The forest plot for the Mendelian randomization association between genetically predicted *PED4A* gene expression and AD risk.