

Figure. S1 Distribution of CADD scores.

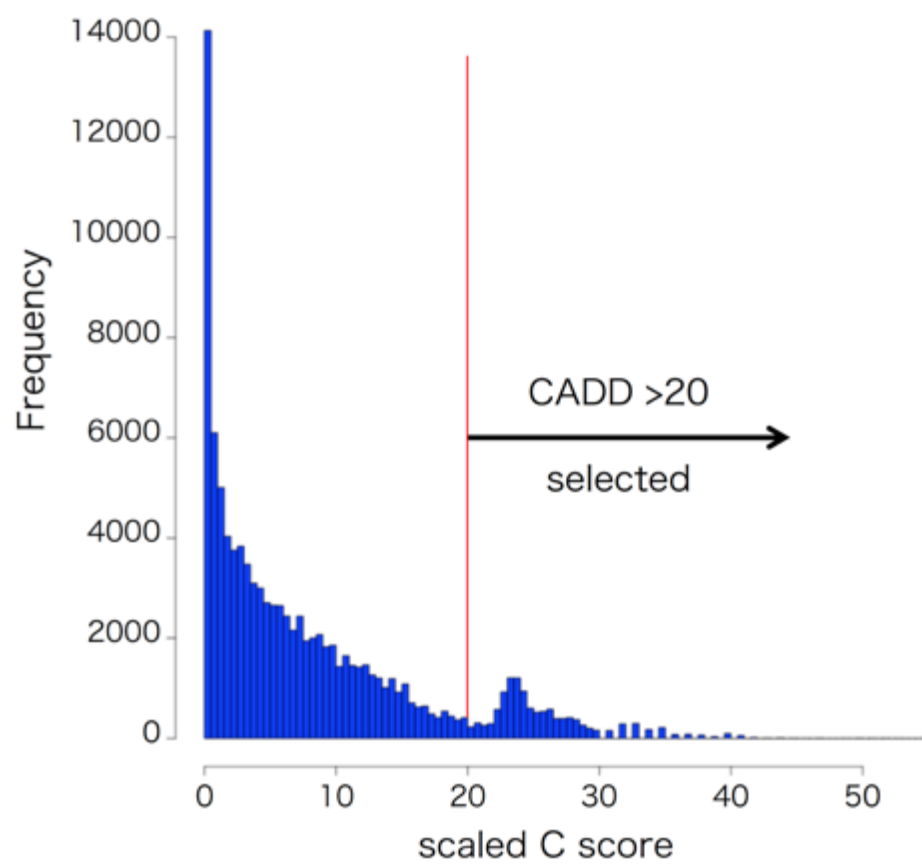


Figure. S2 Gene expression in the brain.

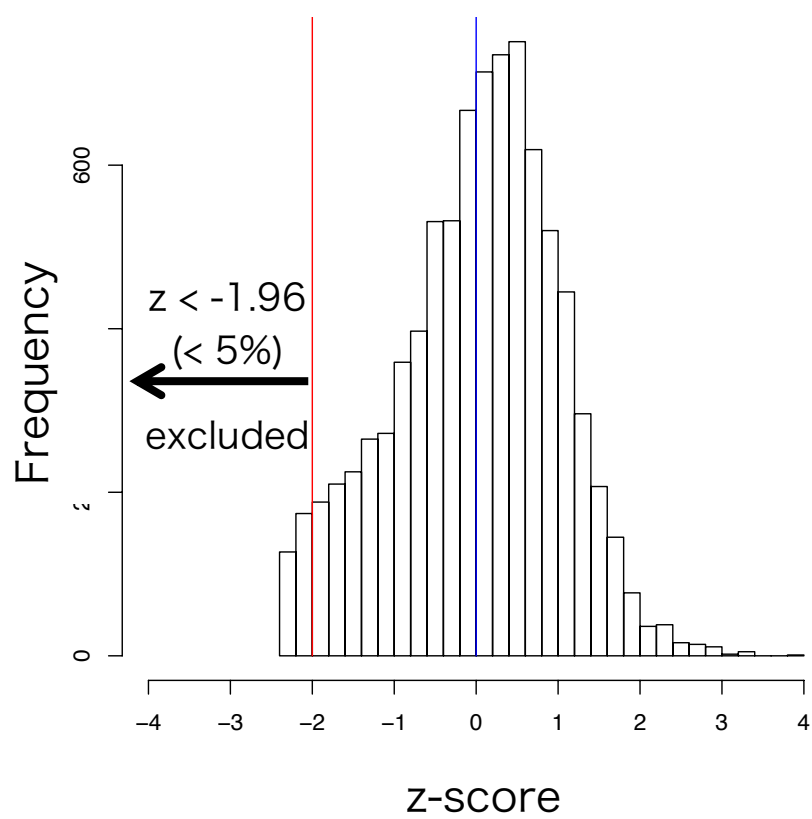


Figure. S3 Distribution of the number of variants in genes.

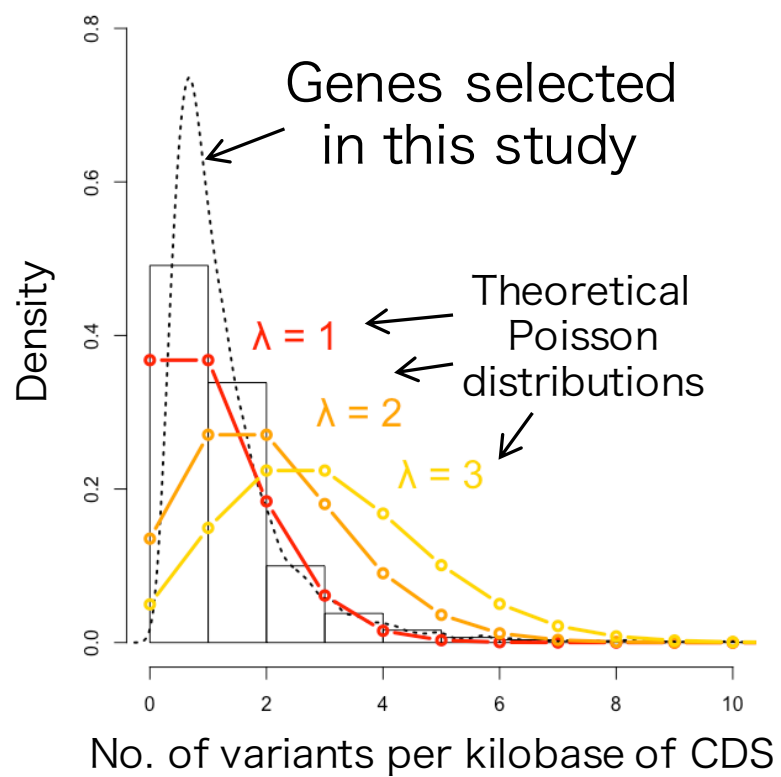


Figure. S4 Detailed images of the immunocytochemistry shown in Fig. 2b.

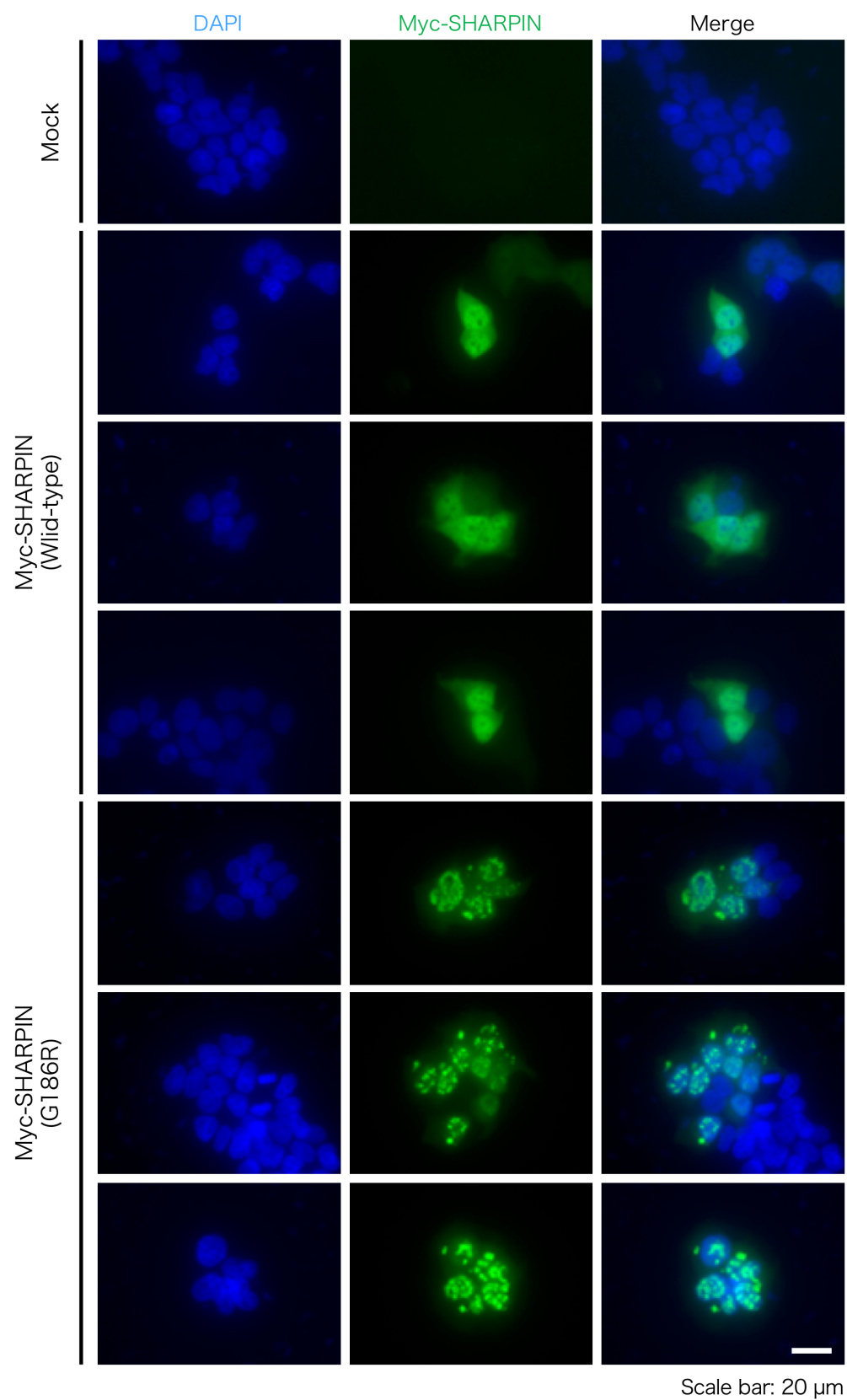


Figure. S5 G186 of SHARPIN is highly conserved among species. Protein sequences of SHARPIN for each species were obtained from UniProt and the region near G186 was compared.

Species	UniProt_ID		G186	Ubiquitin-like domain
Human	SHRPN_HUMAN	167	GNLTEREELAGSLARAIAGGDEKGAAQVAAVLAQHRVALSVQLQEACFP	226
Mouse	SHRPN_MOUSE	165	GNF-KKEELATRLSQAIAAGGDEKAAAQVAAVLAQHHLVALNVQLMEAWFP	223
Rat	SHRPN_RAT	165	GNL-KKEELATHLAQAIAGGDEKAAAQVAAILAQHHLVALNVQLLEAWFP	223
Bovine	SHRPN_BOVIN	165	GDLMEKEELAGRLTRAVEGGDEKGAAQAAAILAQHRVALRVQLQEAYFP	224
Pig	F1RSNO_PIG	162	GDLLKEELAGRLAQAIESGDEKRAEAAATLAQHHAALRIQLQEACFP	221
Dog	J9NZD2_CANLF	156	GDSPEKEELVGRLLARAIEDGDEKGAAQAAALLAQHHLVALSVRLREACFP	215
Cat	M3WFA6_FELCA	162	GDLTEKEELVGRLLAQAIEGDEKGAAQAAATLARHHLVALSVQLQEACFP	221
Horse	F6VDB9_HORSE	165	GDLMEKEELVGRLLARAIEGDKKGAAQTAAILAQHHLVALRVQLQEACFP	224
Sheep	W5Q004_SHEEP	165	GDLMEKEELAGRLTQAVEGGDEKGAQAQAAAILAQHRVALRVQLQEAYFP	224
Bat	G1P7Y4_MYOLU	162	GDLMEKEELAGRLAQAIEDGDKGAQAQAAALLAQHHLVALSVQLQESCF	221
Alligator	AOA1U8DPC8_ALLSI	44	LELSKTEDLALRLSLAIEVGNQAASQCAMVLARQQASLRIQPKESSHTN	103
Chameleon	H9GC14_ANOCA	163	SQLARKEELALRLSAAIDLGDEVEAVRSATALSQQAAPLRIVLKESCYPT	222
Zebrafish	X1WDE8_DANRE	135	LLSLMKEELCVLSRAIEAGDAQAAARYATDLAQQMTLSIQAPRDTDDKD	194

Table S1 Samples used for exome sequencing.

		LOAD patients	NC subjects
n		202	176
Sex	Male	62	99
	Female	140	77
Age : mean (min-max)		77.6 (52-94)	73.2 (65-91)
MMSE ^a : mean (min-max)		18.5 (0-27)	29.4 (28-30)

^a MMSE: Score of Mini Mental State Examination (MMSE), which is a questionnaire to measure cognitive impairment.

Table S2 Demographic features of the NCGG samples genotyped.

		AD	NC	Total
n		2,183	919	3,102
Sex	M	746	453	1,199
	F	1,437	466	1,903
Age		78.7 ± 6.9	75.2 ± 6.4	77.7 ± 6.9
MMSE		18.9 ± 5.4	27.6 ± 2.0	20.8 ± 6.0
APOE	ε3/3	1040	582	1622
	ε4/3	690	130	820
	ε4/4	124	13	137
	ε3/2	90	50	140
	ε4/2	19	3	22
	ε2/2	3	3	6
	NA	217	138	355

Table S3 Samples used in the first association study of candidate AD risk variants.

Source of Samples		No. of Samples	
		Case	Control
	WES	202	176 ^a
NCGG	Genotyping (NCGG hospital)	2,183	919 ^a
	Genotyping (Elderly cohort)	—	2,001 ^a
RIKEN	WGS	—	1,764
	Genotyping	—	5,580
TMM	WGS (3.5KJPN)	—	3,554
Total		2,385	13,994

^a All individuals were ≥ 65 y/o

Table S4 Demographic features of the second cohort set used in the association study.

		Case	Control	Total
n		2,180	2,486	4,666
Sex	M	651	1,363	2,014
	F	1,529	1,123	2,652
Age		78.3 ± 6.1	76.3 ± 6.6	77.2 ± 6.4
APOE	ε3/3	974	1,881	2,855
	ε4/3	921	365	1,286
	ε4/4	194	13	207
	ε3/2	63	201	264
	ε4/2	27	20	47
	ε2/2	1	6	7

Table S5 Ten genes with significantly accumulated variants.

Gene Name	Actual No. of variants ^a	Expected No. of variants ^b	<i>q</i> -value (FDR)
<i>MEF2B</i>	11	1.53	0.0017
<i>ZNF740</i>	8	0.8	0.0027
<i>TYK2</i>	18	4.93	0.003
<i>ZNF14</i>	13	2.67	0.003
<i>DGAT2</i>	10	1.61	0.0033
<i>SHARPIN</i>	10	1.61	0.0033
<i>TEKT3</i>	11	2.04	0.0036
<i>PXN</i>	12	2.51	0.0043
<i>ROGDI</i>	8	1.19	0.0093
<i>ZNF786</i>	13	3.25	0.0093

^a Number of filtered-variants in 202 patients

^b (Total filtered-variants in 202 patients / Total CDS-length of all genes) × CDS-length

Table S6 Accumulation of variants in LOAD patients compared with NC controls.

Genes	Carrier in AD	Carrier in NC	Non-carrier in AD	Non-carrier in NC	<i>q</i> -value (FDR)
<i>SHARPIN</i>	13	1	189	175	0.025
<i>ZNF786</i>	13	1	189	175	0.025
<i>TKY2</i>	26	8	176	168	0.025
<i>PXN</i>	12	1	190	175	0.025
<i>DGAT2</i>	10	1	192	175	0.053
<i>ROGDI</i>	14	5	188	171	0.17
<i>TEKT3</i>	23	11	179	165	0.17
<i>MEF2B</i>	7	2	195	174	0.32
<i>ZNF740</i>	5	1	197	175	0.32
<i>ZNF14</i>	15	9	187	167	0.48