Supplementary materials

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Appendix	Acknowledgments for the International FTD-Genomics Consortium (IFGC)

Supplementary Table 1. Clinical characteristics and multivariate linear regression results of disease subtypes in unrelated *C9orf72* patients. Additive model: AA vs AG vs GG; dominant model: AA or AG vs GG; recessive model: AA vs AG or GG. P-values <0.05 are presented in bold font.

		Combined *C9orf72* patients	Disease phenotypes			ALS subtypes			FTD subtypes			
			Combined ALS	Combined FTD	Combined FTD-ALS	Bulbar ALS	Limb ALS	UALS	bvFTD	PNFA	SD	UFTD
Number of cases (%)		304 (100%)	59 (19.4%)	174 (57.2%)	71 (23.3%)	23 (7.5%)	35 (12.8%)	1 (0.3%)	157 (51.6%)	7 (2.3%)	7 (2.3%)	3 (1%)
Sex (Male, n, percentage)		167 (54.9%)	27 (45.7%)	100 (57.5%)	40 (56.3%)	8 (34.8%)	18 (51.4%)	1 (100%)	92 (58.6)	5 (71%)	3 (42.9%)	0 (0%)
AO (years, median, IQR)		58 (52-64)	58 (55-67.5)	58 (51.3-63)	57 (52-64)	60 (57-68)	57 (54-67)	NA	58 (51-63)	60 (58-62.5)	58 (50-62.5)	62 (56.5-65)
AO (years, mean, range)		59 (34-80)	59.5 (37-78)	57.4 (34-80)	57.9 (38-73)	61.4 (51-73)	58.4 (37-78)	NA	57.2 (34-77)	60.9 (56-69)	58.7 (48-80)	60.3 (51-68)
Additive Model	adjusted p*	**0.0000023**	**0.002**	**0.0008**	0.125	0.07	**0.015**	NA	**0.0043**	NA	NA	NA
	r^2	0.077	0.19	0.057	0.06	0.04	0.28	NA	0.078	NA	NA	NA
	B (SE)	3.2 (0.67)	4.97 (1.53)	2.82 (0.8)	2.63 (1.69)	3.77 (2)	5.9 (2.3)	NA	2.52 (0.87)	NA	NA	NA
Dominant Model	adjusted p*	**0.00003**	**0.0002**	**0.04**	0.14	**0.04**	**0.001**	NA	0.07	NA	NA	NA
	r^2	0.06	0.26	0.02	0.02	0.09	0.3	NA	0.03	NA	NA	NA
	B (SE)	1.44 (0.95)	8.5 (2.1)	2.6 (1.3)	3.4 (2.3)	5.9 (2.7)	11.1 (3)	NA	2.4 (1.3)	NA	NA	NA
Recessive Model	adjusted p*	**0.0005**	0.3	**0.0004**	0.4	0.47	0.6	NA	**0.001**	NA	NA	NA
	r^2	0.04	0.06	0.07	0.03	0.4	0.04	NA	0.07	NA	NA	NA
	B (SE)	4.5 (1.3)	3.3 (3.2)	5.7 (1.6)	2.6 (3.2)	3.3 (4.4)	2.5 (4.6)	NA	5.4 (1.7)	NA	NA	NA

*p-values adjusted for sex and rs1990622 genotypes; NA = not applicable, UALS = unspecified ALS; UFTD= unspecified FTD; bvFTD = behavioural frontotemporal dementia, SD = semantic dementia, PNFA = progressive nonfluent aphasia.

Supplementary Table 2. Clinical characteristics and multivariate linear regression results of disease subtypes in unrelated *C9orf72* negative patients. Additive model: AA vs AG vs GG; dominant model: AA or AG vs GG; recessive model: AA vs AG or GG. P-values <0.05 are presented in bold font.

		***C9orf72* negative patients**	**Disease phenotypes**			**FTD subtypes**			
			ALS	**FTD**	**FTD-ALS**	**bvFTD**	**PNFA**	**SD**	**UFTD**
Number of cases (%)		2634 (100%)	328 (12.5%)	2142 (81.3%)	164 (6.2%)	1364 (51.8%)	326 (12.4%)	359 (13.6%)	93 (3.5%)
Sex (Male, n, percentage)		1441 (54.7%)	196 (59.8%)	1136 (53%)	109 (66.5%)	727 (53.3%)	156 (47.9%)	205 (57.1%)	48 (51.6%)
AO (years, median, IQR)		62 (55-69)	60 (51-69)	62 (55-65)	61.5 (56-68)	62 (56-66.5)	65 (58-71)	61.5 (55-68)	64 (56-70)
AO (years, mean, range)		61.5 (23-90)	59.5 (24-87)	61.8 (23-90)	61.6 (31-89)	61.8 (41-85)	64.5 (41-86)	61.1 (23-90)	63 (31-85)
Additive Model	adjusted p*	**0.03**	0.39	**0.03**	0.47	**0.04**	0.1	0.32	0.06
	r^2	0.007	0.002	0.01	0.008	0.013	0.019	0.003	0.022
	B (SE)	0.61 (0.28)	0.85 (0.97)	0.66 (0.3)	-0.8 (1.2)	0.81 (0.4)	1.1 (0.68)	-0.62 (0.63)	3.1 (1.6)
Dominant Model	adjusted p*	0.33	0.75	0.24	0.38	0.19	0.07	**0.032**	0.1
	r^2	0.006	0.0003	0.01	0.005	0.01	0.02	0.009	0.01
	B (SE)	0.41 (0.42)	0.45 (1.4)	0.52 (0.45)	-1.3 (1.5)	0.78 (0.6)	1.83 (1)	-1.9 (0.9)	3.9 (2.3)
Recessive Model	adjusted p*	**0.007**	0.23	**0.01**	0.9	**0.035**	0.47	0.3	0.16
	r^2	0.009	0.004	0.01	0.0002	0.013	0.012	0.004	0.003
	B (SE)	1.41 (0.52)	2.2 (1.8)	1.4 (0.55)	-0.3 (2.4)	1.49 (0.7)	0.92 (1.28)	1.2 (1.2)	4.1 (2.9)

*p-values adjusted for sex.

Supplementary Table 3. Sample characteristics of the ALS cases whose frontal cortex tissues were used in the gene expression experiments.

Total number	25
Sex (number of men, %)	15 (60%)
Age of death (mean, SD) in years	64.24 (11.05)
Age of death (median, IQR) in years	65 (59-72)

IQR = interquartile range

Supplementary Table 4. PCR primers used to obtain genotypes for rs9357140, rs2143466 and rs1990622.

Primer name	Primer sequence
rs9357140 forward	5'-GGTCCTAGGTGGCTATGTGG-3'
rs9357140 reverse	5'-GAAAGCCATCTTCCAGGTGT-3'
rs2143466 forward	5'-TGAAAAGTCCATGCCCTACC-3'
rs2143466 reverse	5'-TTCACTTGCCCTATCCCAAC-3'
rs1990622 forward	5’- GCATTGTGTTTGATTGTAGGGG-3’
rs1990622 reverse	5’- ACTCCAGGACTTATGTGGCC-3’

Supplementary Table 5. The variants genotyped or imputed for the replication cohort.

FTD-GWAS Phase I (n=150)

CHR	POS	rs#	REF	ALT	Genotyped	Imputed	Imputation score
6	32282033	rs547261	G	A		yes	0.99
6	32289318	rs547077	T	C	yes		
6	32290954	rs485774	A	G		yes	0.99
6	32297337	rs9368713	T	C	yes		
6	32298372	rs9405090	A	G	yes		
6	32301514	rs9357140	G	A		yes	0.99
6	32307382	rs1033500	G	A		yes	0.99
6	32333955	rs9268368	T	C	yes		
6	32336586	rs9268384	A	G	yes		
6	32309323	rs2143466	C	T		yes	0.99
7	12283787	rs1990622	A	G		yes	0.99

FTD-GWAS Phase II (n=37)

CHR	POS	rs#	REF	ALT	Genotyped	Imputed	Imputation score
6	32282033	rs547261	G	A	yes		
6	32289318	rs547077	T	C	yes		
6	32290954	rs485774	A	G		yes	0.99
6	32297337	rs9368713	T	C		yes	0.99
6	32298372	rs9405090	A	G	yes		
6	32301514	rs9357140	G	A		yes	0.99
6	32307382	rs1033500	G	A	yes		
6	32333955	rs9268368	T	C	yes		
6	32336586	rs9268384	A	G		yes	0.99
6	32309323	rs2143466	C	T		yes	1
7	12283787	rs1990622	A	G		yes	0.43

Supplementary Table 6. Results of testing endogenous gene expression in nine frontal cortex tissues (n=3 per rs9357140 genotype) using Normfinder. Lower stability values represent less variability.

Gene name	Stability value
UBC	0.359
HPRT1	0.379
B2M	0.049
RPLP0	0.099

Supplementary Table 7. The association between DNA methylation of CpG-SNPs and age of onset in 46 *C9orf72* patients (10 top-significant CpGs are listed).

CpG ID	p-value	q-value	Rs#	Gene
cg18698799	6.0E-06	0.035	rs9357140	*C6orf10*
cg26690318	9.6E-06	0.035	rs12763379	*PYROXD2*
cg10528537	1.8E-05	0.045	rs2143466	*C6orf10*
cg04541421	0.00046	0.595	rs11647	*C2orf74*
cg01429471	0.00058	0.590	rs56142004	
cg00892703	0.00062	0.590	rs62068681	*CPNE7*
cg15102777	0.00063	0.590	rs17153581	*BCCIP*
cg08324400	0.00064	0.590	rs12652492	
cg01733958	0.00075	0.615	rs1573732	*TMEM8A*
cg27443567	0.00085	0.630	rs2297186	*PCID2*

Supplementary Table 8. The distribution of rs9357140 genotypes in *C9orf72* ALS, FTD and FTD-ALS patients.

	AA (n, %)	AG (n, %)	GG (n, %)	Total number	Trend analysis	p-value
ALS	9 (15.3%)	27 (45.8%)	23 (39%)	59	ALS vs FTD	0.98
FTD-ALS	8 (11.3%)	45 (63.3%)	18 (25.4%)	71	ALS vs FTD-ALS	0.39
FTD	32 (18.4%)	69 (39.7%)	73 (41.9%)	174	FTD vs FTD-ALS	0.33

Supplementary Table 9. eQTL analysis using the GTeX database revealed significant changes in gene expression associated with rs9357140 genotypes in different tissues (10 top-significant hits are listed).

Gencode Id	Gene Symbol	P-Value	NES	Tissue
ENSG00000225914.1	*LOC101929163*	7.6E-09	-0.66	Brain - Nucleus accumbens (basal ganglia)
ENSG00000196126.6	*HLA-DRB1*	4.1E-06	-0.42	Brain – Frontal cortex
ENSG00000196126.6	*HLA-DRB1*	2.3E-05	-0.3	Testis
ENSG00000196126.6	*HLA-DRB1*	3.4E-06	-0.19	Skin - Sun Exposed (Lower leg)
ENSG00000196126.6	*HLA-DRB1*	5.0E-05	-0.17	Adipose - Subcutaneous
ENSG00000204308.6	*RNF5*	2.6E-07	0.12	Muscle - Skeletal
ENSG00000204296.7	*C6orf10*	5.3E-08	0.13	Testis
ENSG00000213676.6	*ATF6B*	1.1E-05	0.13	Muscle - Skeletal
ENSG00000213676.6	*ATF6B*	2.4E-05	0.15	Adipose - Subcutaneous
ENSG00000204314.6	*PRRT1*	2.6E-06	0.17	Esophagus - Mucosa

Supplementary Table 10. Coding and non-coding effects of 196 variants in the *C6orf10/LOC101929163* LD-block (chr6: 32213638 – 32338386) associated with age of onset in *C9orf72* carriers. The 10 SNPs (including rs9357140) investigated in the current study are in red. NA = not applicable. See the pdf file (Supplementary Table 10.pdf).

Supplementary Table 10.Coding and non-coding effects of 196 variants in the C6orf10/LOC101929163 LD-block (chr6: 32213638 – 32338386) associated with age of onset in C9orf72 carriers

RS_Number	Position	Alleles		Minor allele frequencies	Distance	Dprime	R^2	Correlated Alleles	Function	Amino acid change	Polyphen	SIFT	CpG-SNP	DNaseI hyperactivity site	Items (total 125)	Cluster score (total 1000)	Transcriptional factor binding sites
rs9267956	32213638	A	G	0.3618	-87876	0.9738	0.9124	G=A,A=G	NA				yes	chr6:32213606-32213775	2	225	no
rs1559876	32215769	G	C	0.3588	-85745	0.9868	0.9249	G=G,A=C	NA				yes				no
rs9267996	32221934	A	G	0.3588	-79580	0.9868	0.9249	G=A,A=G	NA				no				no
rs9268000	32223531	A	C	0.34	-77983	0.9954	0.866	G=A,A=C	NA				no	chr6:32222966-32223535	114	1000	no
rs147193449	32227488	A	G	0.3718	-74026	1	0.9958	G=A,A=G	NA				no				no
rs144338179	32227912	G	-	0.3718	-73602	1	0.9958	G=G,A=-	NA				no				no
rs9268045	32229655	C	T	0.3718	-71859	1	0.9958	G=C,A=T	NA				no				no
rs4959091	32231014	G	A	0.3718	-70500	1	0.9958	G=G,A=A	NA				yes				no
rs2395114	32233547	A	G	0.3718	-67967	1	0.9958	G=A,A=G	NA				no				no
rs9268082	32234953	G	T	0.3718	-66561	1	0.9958	G=G,A=T	NA				no	chr6:32234786-32235115	3	371	no
rs9268086	32238266	C	T	0.3718	-63248	1	0.9958	G=C,A=T	NA				yes				no
rs2395115	32238802	T	C	0.3718	-62712	1	0.9958	G=T,A=C	NA				no				no
rs2022539	32239558	A	C	0.3718	-61956	1	0.9958	G=A,A=C	NA				no				no
rs9268113	32248166	G	C	0.3688	-53348	0.9829	0.9578	G=G,A=C	NA				yes				no
rs9268115	32248364	C	T	0.3748	-53150	1	0.9831	G=C,A=T	NA				yes				no
rs7454557	32252274	A	G	0.3718	-49240	1	0.9958	G=A,A=G	NA				yes				no
rs9268129	32254225	G	C	0.3658	-47289	0.9957	0.9704	G=G,A=C	NA				yes				no
rs9268141	32256132	G	A	0.3658	-45382	0.9957	0.9704	G=G,A=A	NA				yes				no
rs4713518	32257337	A	G	0.3718	-44177	1	0.9958	G=A,A=G	NA				yes				no
rs482194	32260559	A	G	0.3718	-40955	1	0.9958	G=A,A=G	NA				no				no
rs560505	32261771	A	G	0.3658	-39743	0.9957	0.9704	G=A,A=G	missense	p.Ser227Pro	benign	deleterious	no				no
rs518374	32265710	A	C	0.3718	-35804	1	0.9958	G=A,A=C	NA				no				no
rs565571	32266535	G	A	0.3658	-34979	0.9957	0.9704	G=G,A=A	NA				yes	chr6:32266401-32266970	44	560	no
rs537757	32268501	A	T	0.3718	-33013	1	0.9958	G=A,A=T	NA				no				no
rs533876	32268980	A	G	0.3718	-32534	1	0.9958	G=A,A=G	NA				no				no
rs477005	32270500	A	G	0.3658	-31014	0.9957	0.9704	G=A,A=G	NA				no				no
rs544358	32273158	G	C	0.3718	-28356	1	0.9958	G=G,A=C	NA				no				no
rs540926	32276169	A	G	0.3718	-25345	1	0.9958	G=A,A=G	NA				no				no
rs484302	32276300	G	A	0.3718	-25214	1	0.9958	G=G,A=A	NA				yes				no
rs1265776	32276502	A	G	0.3718	-25012	1	0.9958	G=A,A=G	NA				yes				no
rs502626	32278266	A	G	0.3718	-23248	1	0.9958	G=A,A=G	NA				no				no
rs547261	32282033	G	A	0.3718	-19481	1	0.9958	G=G,A=A	NA				no				no
rs143081527	32282622	ACTCTAG	-	0.3718	-18892	1	0.9958	G=TTTGACAACT	NA				no				no
rs495140	32284423	A	T	0.3718	-17091	1	0.9958	G=A,A=T	NA				no	chr6:32284261-32284475	2	200	no
rs567828	32284950	T	A	0.3718	-16564	1	0.9958	G=T,A=A	NA				no				no
rs531094	32286102	T	A	0.3718	-15412	1	0.9958	G=T,A=A	NA				no				no
rs557539	32286680	G	A	0.3787	-14834	1	0.9666	G=G,A=A	NA				no				no
rs560324	32286984	T	G	0.3787	-14530	1	0.9666	G=T,A=G	NA				no				no
rs2746115	32287329	C	T	0.3757	-14185	1	0.979	G=C,A=T	NA				no	chr6:32287266-32287415	1	177	no
rs580921	32287496	A	G	0.3509	-14018	0.9955	0.9092	G=A,A=G	NA				yes				no
rs575765	32288041	T	C	0.3718	-13473	1	0.9958	G=T,A=C	NA				no				no
rs574710	32288190	T	C	0.3787	-13324	1	0.9666	G=T,A=C	NA				yes				no
rs539703	32288462	A	C	0.3718	-13052	1	0.9958	G=A,A=C	NA				no				no
rs540639	32288564	T	G	0.3787	-12950	1	0.9666	G=T,A=G	NA				yes				no
rs542525	32288805	T	C	0.3787	-12709	1	0.9666	G=T,A=C	NA				yes				no
rs544100	32288932	T	A	0.3718	-12582	1	0.9958	G=T,A=A	NA				no				no
rs546857	32289240	C	T	0.3658	-12274	0.9957	0.9704	G=C,A=T	NA				no				no
rs547077	32289318	T	C	0.3787	-12196	1	0.9666	G=T,A=C	NA				no				no
rs572730	32289764	C	T	0.3718	-11750	1	0.9958	G=C,A=T	NA				no				no
rs55723730	32290694	-	A	0.3718	-10820	1	0.9958	G=-,A=A	NA				no				no
rs55695092	32290697	-	AA	0.3718	-10817	1	0.9958	G=-,A=AA	NA				no				no
rs487649	32290748	A	G	0.3718	-10766	1	0.9958	G=A,A=G	NA				yes				no
rs485774	32290954	A	G	0.3718	-10560	1	0.9958	G=A,A=G	NA				no				no
rs374409084	32291270	AG	-	0.3718	-10244	1	0.9958	G=AG,A=-	NA				no				no
rs523627	32291837	G	T	0.3718	-9677	1	0.9958	G=G,A=T	NA				no				no
rs525607	32292084	C	T	0.3787	-9430	1	0.9666	G=C,A=T	NA				no				no
rs74839053	32292571	T	A	0.3718	-8943	1	0.9958	G=T,A=A	NA				no				no
rs552339	32292715	G	A	0.3718	-8799	1	0.9958	G=G,A=A	NA				no				no
rs533885	32293152	A	G	0.3718	-8362	1	0.9958	G=A,A=G	NA				yes				no
rs510181	32293434	A	C	0.3787	-8080	1	0.9666	G=A,A=C	NA				no				no
rs2395143	32293578	C	G	0.334	-7936	0.9905	0.835	G=C,A=G	NA				yes				no
rs471081	32293598	A	T	0.3787	-7916	0.9957	0.9583	G=A,A=T	NA				no				no
rs471964	32293671	G	A	0.3638	-7843	0.9913	0.9537	G=G,A=A	NA				no				no
rs504703	32294017	T	C	0.3718	-7497	1	0.9958	G=T,A=C	NA				no				no
rs476584	32294192	G	A	0.3797	-7322	1	0.9626	G=G,A=A	NA				yes				no
rs501545	32294566	G	A	0.3728	-6948	1	0.9915	G=G,A=A	NA				yes				no
rs476885	32294712	A	G	0.3718	-6802	1	0.9958	G=A,A=G	NA				no				no
rs504203	32294843	T	C	0.3718	-6671	1	0.9958	G=T,A=C	NA				yes				no
rs505274	32294992	G	A	0.3718	-6522	1	0.9958	G=G,A=A	NA				no	chr6:32294941-32295190	11	196	no
rs508805	32295350	G	A	0.3708	-6164	0.9957	0.9915	G=G,A=A	NA				no				no
rs524578	32295357	G	A	0.3777	-6157	0.9957	0.9624	G=G,A=A	NA				no				no
rs4424116	32295553	G	C	0.3718	-5961	1	0.9958	G=G,A=C	NA				yes				no
rs28381583	32295575	-	T	0.4105	-5939	0.9727	0.8005	G=-,A=T	NA				no				no
rs6913605	32295694	A	G	0.3658	-5820	1	0.9789	G=A,A=G	NA				yes				no
rs77200712	32295747	T	A	0.3688	-5767	0.9957	0.983	G=T,A=A	NA				no				no
rs6457542	32295828	A	G	0.3708	-5686	0.9957	0.9915	G=A,A=G	NA				yes				no
rs6457543	32296029	T	G	0.3648	-5485	1	0.9747	G=T,A=G	NA				no				no
rs6457544	32296057	C	T	0.3648	-5457	1	0.9747	G=C,A=T	NA				yes				no
rs12528615	32296316	C	T	0.3718	-5198	1	0.9958	G=C,A=T	NA				no				no
rs10947252	32296375	G	A	0.3708	-5139	1	1	G=G,A=A	NA				no				no
rs10947253	32296555	G	C	0.3708	-4959	1	1	G=G,A=C	NA				yes				no
rs9348880	32296780	C	T	0.3777	-4734	1	0.9707	G=C,A=T	NA				no				no
rs9348881	32296842	C	G	0.3787	-4672	1	0.9666	G=C,A=G	NA				yes				no
rs9394086	32297124	A	T	0.3708	-4390	1	1	G=A,A=T	NA				no	chr6:32297041-32297210	6	170	no
rs9368711	32297156	T	C	0.3708	-4358	1	1	G=T,A=C	NA				no				no
rs9368712	32297328	G	A	0.3698	-4186	1	0.9957	G=G,A=A	NA				yes				no
rs9368713	32297337	T	C	0.3708	-4177	1	1	G=T,A=C	NA				yes				no
rs9368714	32297341	G	A	0.326	-4173	1	0.821	G=G,A=A	NA				no				no
rs9380289	32297417	G	A	0.3708	-4097	1	1	G=G,A=A	NA				yes				no
rs146253974	32297641	ATTTTAAC	-	0.3708	-3873	1	1	G=AGATTTTAAC	NA				no				no
rs75052715	32297660	C	G	0.3708	-3854	1	1	G=C,A=G	NA				no				no
rs9296021	32297690	C	T	0.3708	-3824	1	1	G=C,A=T	NA				no				no
rs372016821	32297798	TCTT	-	0.3708	-3716	1	1	G=TCTT,A=-	NA				no				no
rs9296022	32297955	G	A	0.3708	-3559	1	1	G=G,A=A	NA				no				no
rs9405090	32298372	A	G	0.3708	-3142	1	1	G=A,A=G	missense	p.Ser170Pro	benign	tolerated	no				no
rs9296023	32298648	A	G	0.3688	-2866	1	0.9915	G=A,A=G	NA				yes				no
rs28381584	32298979	-	CC	0.3708	-2535	1	1	G=-,A=CC	NA				no				no
rs742582	32299715	G	A	0.3708	-1799	1	1	G=G,A=A	NA				yes				no
rs910052	32299873	G	T	0.3708	-1641	1	1	G=G,A=T	NA				no				no
rs1076711	32300374	T	G	0.3708	-1140	1	1	G=T,A=G	NA				no				no
rs761190	32300470	T	G	0.3708	-1044	1	1	G=T,A=G	NA				yes				no
rs9394087	32300848	T	C	0.3777	-666	1	0.9707	G=T,A=C	NA				yes				no
rs9366793	32301289	T	C	0.3787	-225	1	0.9666	G=T,A=C	NA				no				no
rs9348882	32301322	C	T	0.3708	-192	1	1	G=C,A=T	NA				no				no

rs36044579	32301369	AC	-	0.3708	-145	1	1	G=AC,A=-	NA				no				no
rs9380290	32301452	C	G	0.3777	-62	1	0.9707	G=C,A=G	NA				yes				no
rs9357140	32301514	G	A	0.3708	0	1	1	G=G,A=A	NA				yes	chr6:32301426-32301575	1	147	no
rs9391777	32301804	G	C	0.3708	290	1	1	G=G,A=C	NA				no				no
rs1474729	32302045	A	C	0.3708	531	1	1	G=A,A=C	NA				no				no
rs1474728	32302067	C	T	0.3708	553	1	1	G=C,A=T	NA				no				no
rs9405091	32302539	A	G	0.3708	1025	1	1	G=A,A=G	NA				yes				no
rs9378257	32302541	T	G	0.3708	1027	1	1	G=T,A=G	NA				no				no
rs9405092	32302728	T	G	0.3708	1214	1	1	G=T,A=G	NA				yes				no
rs9405093	32302741	G	T	0.3708	1227	1	1	G=G,A=T	NA				no				no
rs9378258	32302757	G	A	0.3708	1243	1	1	G=G,A=A	NA				no				no
rs10807100	32303068	G	A	0.3708	1554	1	1	G=G,A=A	NA				no				no
rs6929776	32303511	G	A	0.3777	1997	1	0.9707	G=G,A=A	NA				no				no
rs6930681	32304031	G	A	0.3708	2517	1	1	G=G,A=A	NA				no				no
rs9366794	32304222	C	G	0.3708	2708	1	1	G=C,A=G	NA				yes				no
rs70993817	32304750	G	-	0.3708	3236	1	1	G=G,A=-	NA				no				no
rs12194915	32305029	T	A	0.3738	3515	1	0.9873	G=T,A=A	NA				no				no
rs973037	32305125	C	T	0.3757	3611	1	0.979	G=C,A=T	NA				yes	chr6:32305061-32305210	1	117	no
rs2022535	32305142	C	T	0.3777	3628	1	0.9707	G=C,A=T	NA				no				no
rs973036	32305143	C	G	0.3777	3629	1	0.9707	G=C,A=G	NA				yes				no
rs926594	32305370	T	G	0.3738	3856	1	0.9873	G=T,A=G	NA				no				no
rs926591	32305690	C	A	0.3738	4176	1	0.9873	G=C,A=A	NA				no				no
rs9368715	32306022	G	A	0.3738	4508	1	0.9873	G=G,A=A	NA				no				no
rs3817982	32306262	T	C	0.3738	4748	1	0.9873	G=T,A=C	NA				no				no
rs2022534	32307137	T	C	0.3738	5623	1	0.9873	G=T,A=C	NA				no				no
rs2022533	32307260	T	G	0.3807	5746	1	0.9585	G=T,A=G	NA				no				no
rs1033500	32307382	G	A	0.3748	5868	1	0.9831	G=G,A=A	missense	p.Pro112Leu	possibly damaging	tolerated	no				no
rs1033498	32307869	T	C	0.3738	6355	1	0.9873	G=T,A=C	NA				yes				no
rs1033497	32308062	A	G	0.3738	6548	1	0.9873	G=A,A=G	NA				no				no
rs2395144	32308345	T	G	0.3738	6831	1	0.9873	G=T,A=G	NA				no				no
rs4469285	32308642	G	A	0.3738	7128	1	0.9873	G=G,A=A	NA				yes				no
rs7453102	32308690	A	G	0.3738	7176	1	0.9873	G=A,A=G	NA				yes				no
rs2179579	32308734	A	G	0.3738	7220	1	0.9873	G=A,A=G	NA				yes				no
rs2179578	32308770	G	A	0.3738	7256	1	0.9873	G=G,A=A	NA				yes				no
rs2143468	32309003	A	T	0.3767	7489	1	0.9748	G=A,A=T	NA				no				no
rs2143467	32309296	C	G	0.3738	7782	1	0.9873	G=C,A=G	NA				yes				no
rs2143466	32309323	C	T	0.3867	7809	1	0.9346	G=C,A=T	NA				yes				no
rs2143465	32309352	T	C	0.3738	7838	1	0.9873	G=T,A=C	NA				yes				no
rs2143464	32309434	T	C	0.3738	7920	1	0.9873	G=T,A=C	NA				yes				no
rs9268256	32309864	C	T	0.3738	8350	1	0.9873	G=C,A=T	NA				no				no
rs9268257	32310103	G	A	0.3738	8589	1	0.9873	G=G,A=A	NA				yes				no
rs9268258	32310684	G	A	0.3738	9170	1	0.9873	G=G,A=A	NA				no	chr6:32310681-32310830	1	101	no
rs9268259	32310803	G	A	0.3738	9289	1	0.9873	G=G,A=A	NA				no	chr6:32310681-32310830	1	101	no
rs9268260	32310967	C	T	0.3738	9453	1	0.9873	G=C,A=T	NA				yes				no
rs9268261	32310986	C	G	0.3738	9472	1	0.9873	G=C,A=G	NA				yes				no
rs1555117	32311148	C	G	0.3738	9634	1	0.9873	G=C,A=G	NA				yes				no
rs2395145	32311871	T	A	0.3738	10357	1	0.9873	G=T,A=A	NA				no				no
rs2395146	32311875	T	A	0.3738	10361	1	0.9873	G=T,A=A	NA				no				no
rs1555116	32312740	C	A	0.3738	11226	1	0.9873	G=C,A=A	NA				no				no
rs4576282	32312796	A	G	0.3738	11282	1	0.9873	G=A,A=G	NA				no				no
rs9268271	32312883	C	T	0.3738	11369	1	0.9873	G=C,A=T	NA				yes				no
rs4959024	32313010	C	T	0.3738	11496	1	0.9873	G=C,A=T	NA				no				no
rs4959092	32313011	T	G	0.3738	11497	1	0.9873	G=T,A=G	NA				yes				no
rs4959093	32313097	T	C	0.3738	11583	1	0.9873	G=T,A=C	NA				yes				no
rs4959094	32313136	C	T	0.3738	11622	1	0.9873	G=C,A=T	NA				no				no
rs4959025	32313143	A	C	0.3738	11629	1	0.9873	G=A,A=C	NA				yes				no
rs4959026	32313461	G	T	0.3738	11947	1	0.9873	G=G,A=T	NA				no				no
rs4959096	32314676	G	A	0.3738	13162	1	0.9873	G=G,A=A	NA				no				no
rs9268283	32315173	T	C	0.3738	13659	1	0.9873	G=T,A=C	NA				yes				no
rs9268284	32315216	G	A	0.3738	13702	1	0.9873	G=G,A=A	NA				no				no
rs9268285	32315557	T	C	0.3738	14043	1	0.9873	G=T,A=C	NA				yes				no
rs9268286	32315593	C	G	0.3738	14079	1	0.9873	G=C,A=G	NA				no				no
rs2076542	32317127	G	A	0.3738	15613	1	0.9873	G=G,A=A	NA				no				no
rs2076541	32317215	T	C	0.3738	15701	1	0.9873	G=T,A=C	NA				no				no
rs2076540	32317276	T	C	0.3678	15762	0.9871	0.962	G=T,A=C	NA				no				no
rs2076538	32317471	A	C	0.3738	15957	1	0.9873	G=A,A=C	NA				no				no
rs143741085	32317922	TTTC	-	0.3738	16408	1	0.9873	G=TTTC,A=-	NA				no				no
rs761187	32318036	A	G	0.3678	16522	0.9871	0.962	G=A,A=G	NA				no				no
rs2143463	32318729	A	G	0.3738	17215	1	0.9873	G=A,A=G	NA				yes				no
rs9268301	32319637	G	A	0.327	18123	1	0.8247	G=G,A=A	NA				yes				no
rs9268307	32326531	T	C	0.3738	25017	1	0.9873	G=T,A=C	NA				no				no
rs9268326	32330153	T	C	0.3738	28639	1	0.9873	G=T,A=C	NA				yes				no
rs9268327	32330164	C	G	0.3767	28650	1	0.9748	G=C,A=G	NA				yes				no
rs9268329	32330174	A	G	0.3777	28660	1	0.9707	G=A,A=G	NA				no				no
rs9268333	32330651	C	T	0.3738	29137	1	0.9873	G=C,A=T	NA				no				no
rs6934200	32331069	T	C	0.3738	29555	1	0.9873	G=T,A=C	NA				no				no
rs6912095	32331429	C	A	0.3738	29915	1	0.9873	G=C,A=A	NA				no				no
rs9268343	32331824	A	G	0.3728	30310	0.9957	0.9831	G=A,A=G	NA				no				no
rs9268344	32331837	C	T	0.3728	30323	0.9957	0.9831	G=C,A=T	NA				no				no
rs9268345	32331841	G	A	0.3728	30327	0.9957	0.9831	G=G,A=A	NA				no				no
rs9268346	32331927	C	G	0.3738	30413	1	0.9873	G=C,A=G	NA				no				no
rs9268357	32332996	C	G	0.3738	31482	1	0.9873	G=C,A=G	NA				no				no
rs9268363	32333410	A	C	0.3738	31896	1	0.9873	G=A,A=C	NA				no				no
rs9268368	32333955	T	C	0.3748	32441	1	0.9831	G=T,A=C	missense	p.Tyr69Cys	benign	deleterious	no				no
rs9268369	32334224	C	G	0.3738	32710	1	0.9873	G=C,A=G	NA				no				no
rs9268370	32334258	G	T	0.3738	32744	1	0.9873	G=G,A=T	NA				yes				no
rs9268373	32334489	G	A	0.3738	32975	1	0.9873	G=G,A=A	NA				yes				no
rs2073046	32336074	C	T	0.3738	34560	1	0.9873	G=C,A=T	NA				no				no
rs9268384	32336586	A	G	0.3738	35072	1	0.9873	G=A,A=G	missense	p.Tyr36His	benign	deleterious	yes				no
rs9268386	32337234	G	A	0.3738	35720	1	0.9873	G=G,A=A	NA				no				no
rs9268387	32337367	T	G	0.3738	35853	1	0.9873	G=T,A=G	NA				no				no
rs9268394	32338386	G	C	0.3738	36872	1	0.9873	G=G,A=C	NA				no				no

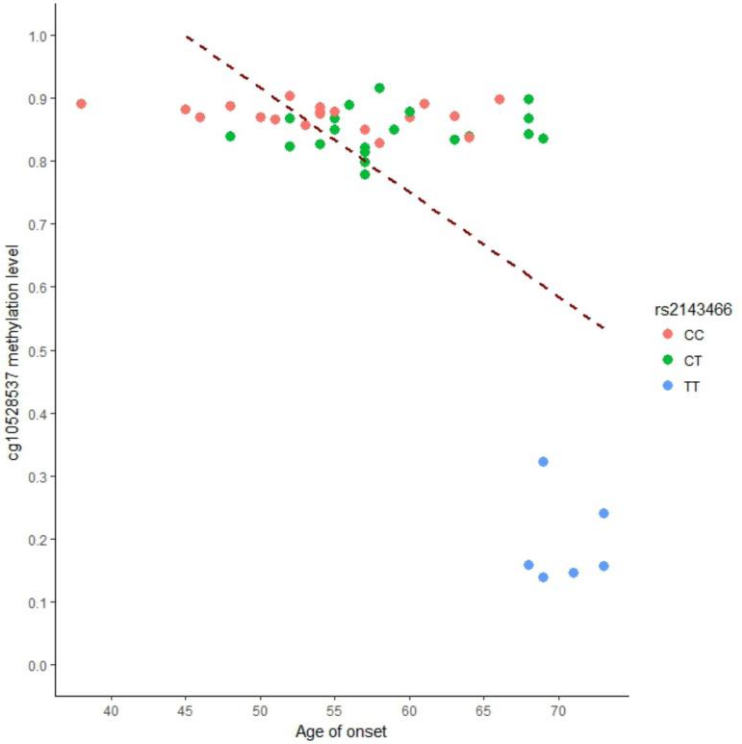
Supplementary Table 11. The SNPs located within or close to the *C6orf10/LOC101929163* locus (chr6: 32213638–32338386) reported to be associated with neurodegenerative or autoimmune diseases.

SNP	R^2 associated with rs9357140	Candidate gene	p-value	Reported odds ratio (95% CI)*	Disease	Reference
rs9268877	0	*HLA-DRA/HLA-DRB5*	1×10^{-8}	1.204(1.11-1.3)	FTD	PMID:24943344
rs9268856	0.06	*HLA-DRA/HLA-DRB5*	5.51×10^{-9}	0.8(0.76-0.86)	FTD	PMID:24943344
rs9271192	0.07	*HLA-DRB1*	0.004	2.069(1.26-3.43)	AD	PMID:29190991
rs3135388	0.06	*HLA-DRA*	8.94×10^{-81}	1.99(1.84-2.15)	Multiple Sclerosis	PMID: 17660530
rs3129871	0.27	*HLA-DRA*	5.7×10^{-15}	1.72(1.59-1.86)	Multiple Sclerosis	PMID: 23472185
rs3129882	0.03	*HLA-DRA*	1.9×10^{-10}	1.26(1.17-1.35)	Parkinson's disease	PMID: 20711177
rs3129934	0.1	*C6orf10*	9×10^{-11}	3.3(2.3-4.9)	Multiple Sclerosis	PMID: 22457343
rs2395148	0.03	*C6orf10*	2×10^{-10}	5.37(3.02-9.56)	Arthritis	PMID: 18576341
rs6910071	0.39	*C6orf10*	1×10^{-299}	2.88(2.73-3.03)	Rheumatoid arthritis	PMID: 20453842
rs9296015	0.16	*NOTCH4*	1×10^{-8}	1.85(1.49-2.27)	Systemic sclerosis	PMID: 21779181
rs443198	0.008	*NOTCH4*	9×10^{-21}	1.82(1.59-2.04)	Systemic sclerosis	PMID:21779181
rs2273017	0.45	*C6orf10*	2×10^{-22}	1.53(1.40-1.66)	Grave's disease	PMID: 21900946
rs404860	0.0005	*NOTCH4*	4×10^{-23}	1.21(1.16-1.25)	Asthma	PMID: 21804548

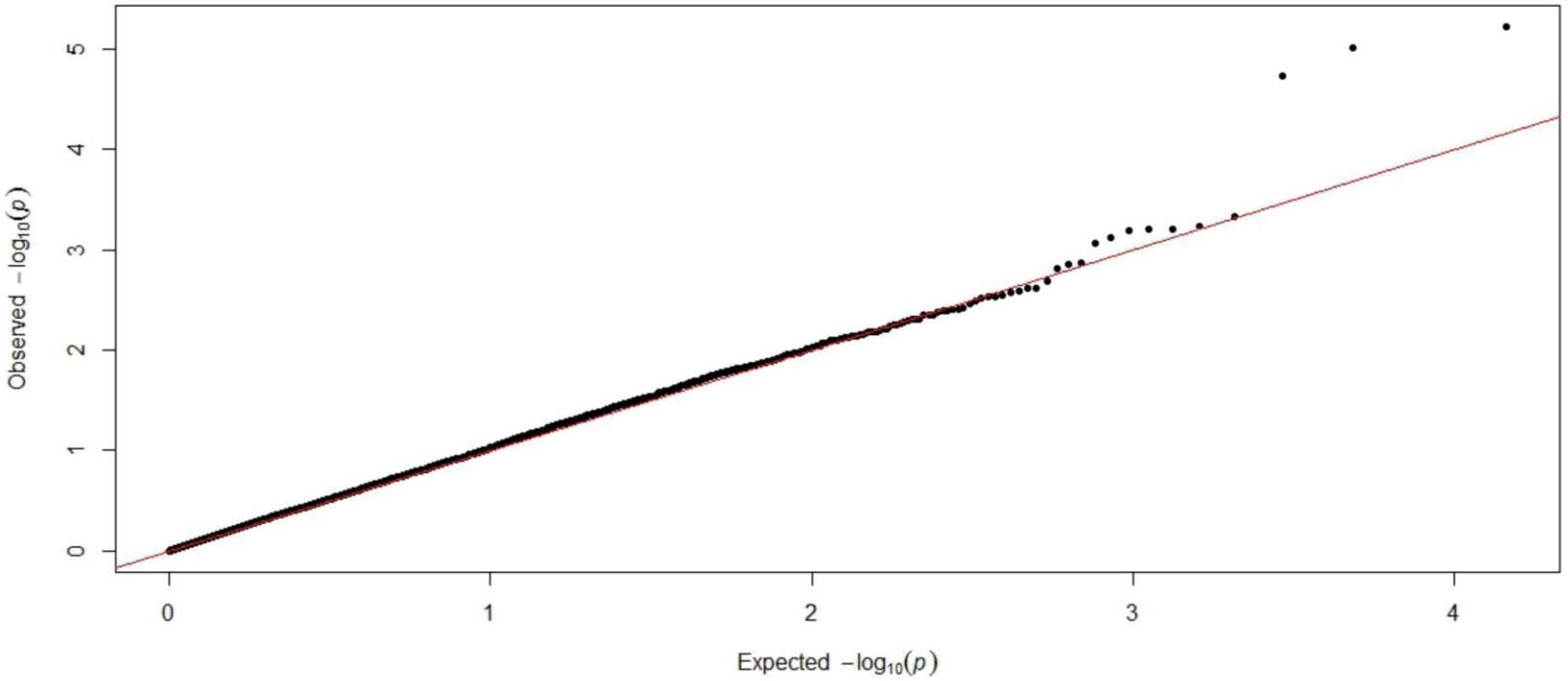
*SNPs with an OR $\geq$1.2 or $\leq$ 0.8 were included.

Supplementary Table 12. The distribution of phenotypes for *C9orf72* carriers in the discovery and replication stages.

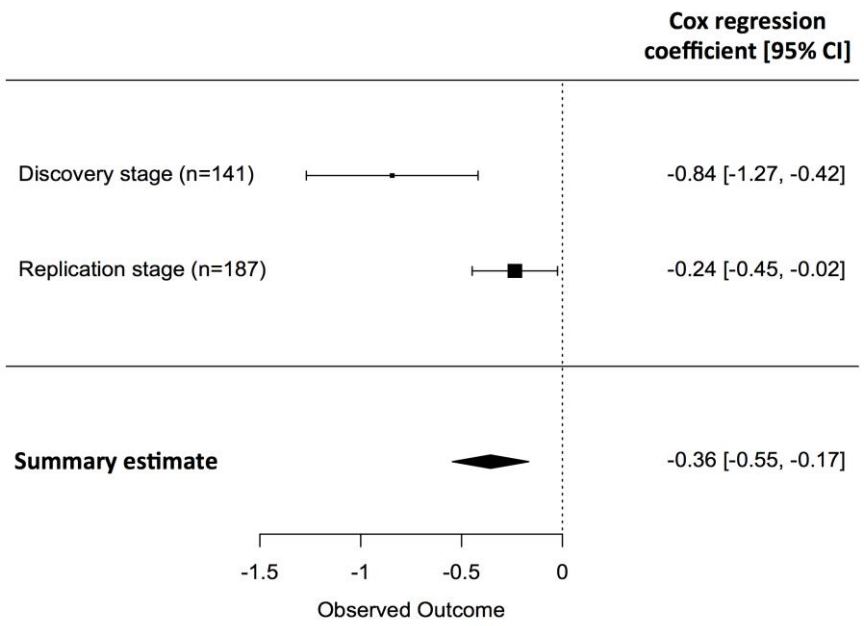
	ALS	FTD	FTD-ALS	Asymptomatic	Total number
Discovery stage	61 (42.4%)	40 (27.8%)	21 (14.5%)	22 (15.3%)	144
Replication stage	0	136 (72.7%)	51 (27.3%)	0	187



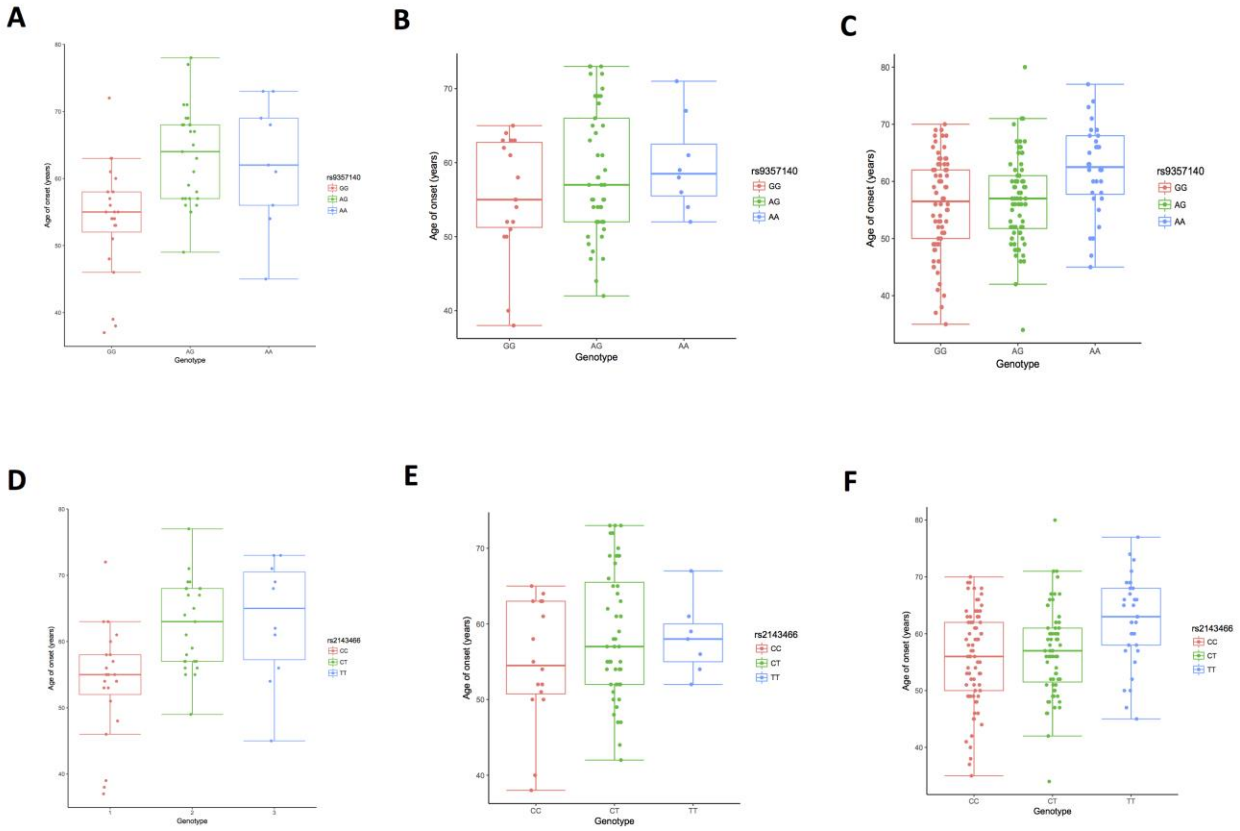
Supplementary Figure 1. Genotypes of rs2143466 in the discovery cohort are significantly associated with DNA methylation status ($p<1.0\times10^{-6}$, B=-0.25) and AO ($p=7.0\times10^{-6}$ adjusted for sex and *TMEM106B* genotypes, B=7.1).



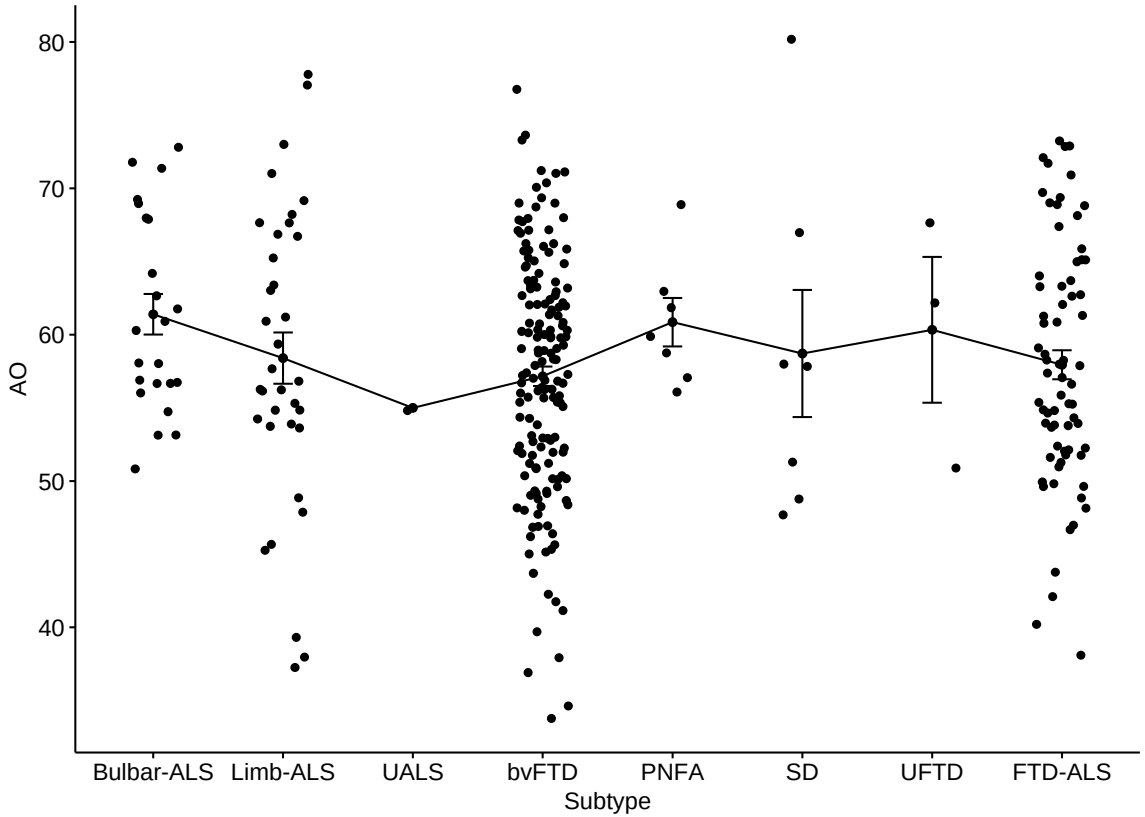
Supplementary Figure 2. A Q-Q plot of the genome-wide DNA methylation analysis of CpG-SNPs.



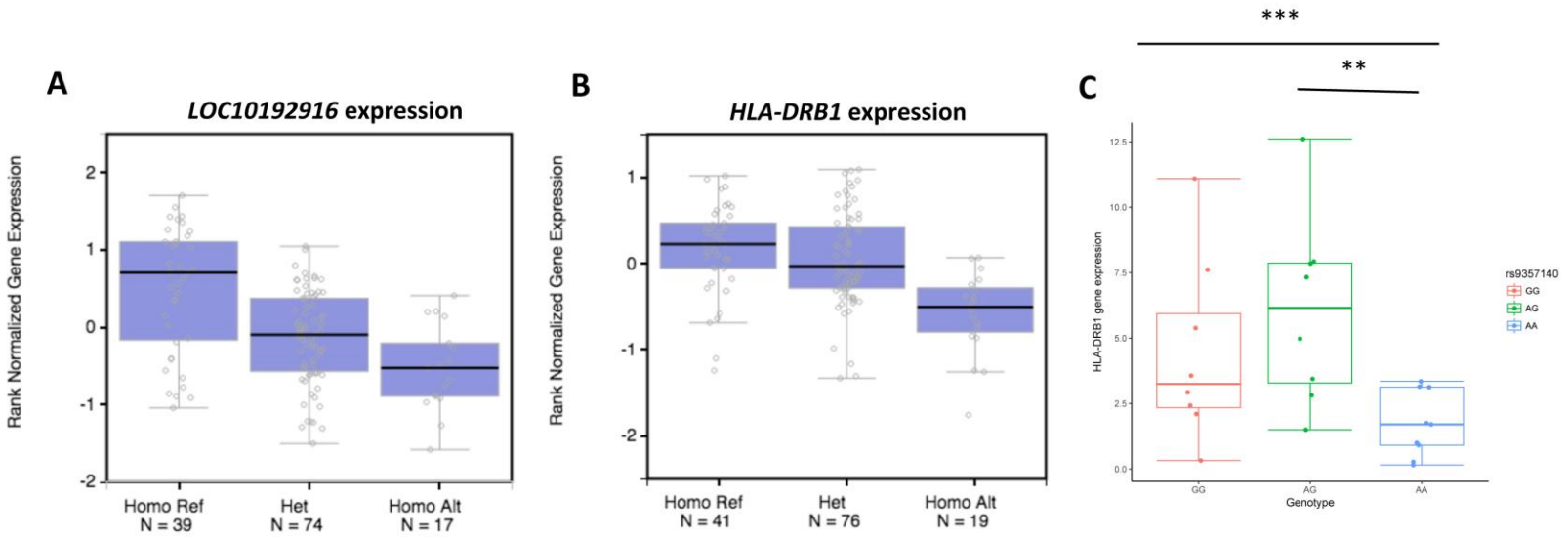
Supplementary Figure 3. The result of the Cox regression coefficient meta-analysis of rs2143466 for the discovery (n=141) and replication (n=187) cohorts; the regression coefficient equals logHR; CI = confidence interval.



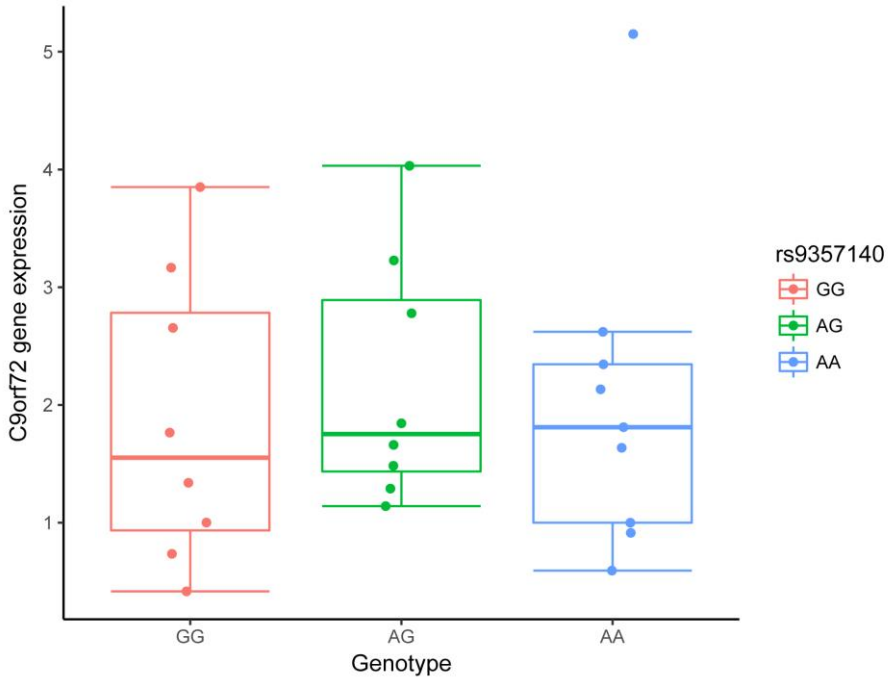
Supplementary Figure 4. (**A-C**) Box-Scatter plots representing the association between rs9357140 genotypes and age of onset in *C9orf72* patients with ALS (**A**): adjusted p=0.002, B=4.0 (SE: 1.53); FTD-ALS (**B**): adjusted p=0.125, B=2.63(SE:1.69); and FTD (**C**): adjusted p=0.0008, B=2.82 (SE: 0.83). (**D-F**) Box-Scatter plots representing the association between rs2143466 genotypes and age of onset in *C9orf72* patients with ALS (**D**): adjusted p=0.0007, B=5.1 (SE: 1.43); FTD-ALS (**E**): adjusted p=0.199, B=2.3 (SE:1.77); and FTD (**F**): adjusted p=0.0004, B=2.95 (SE: 0.82).



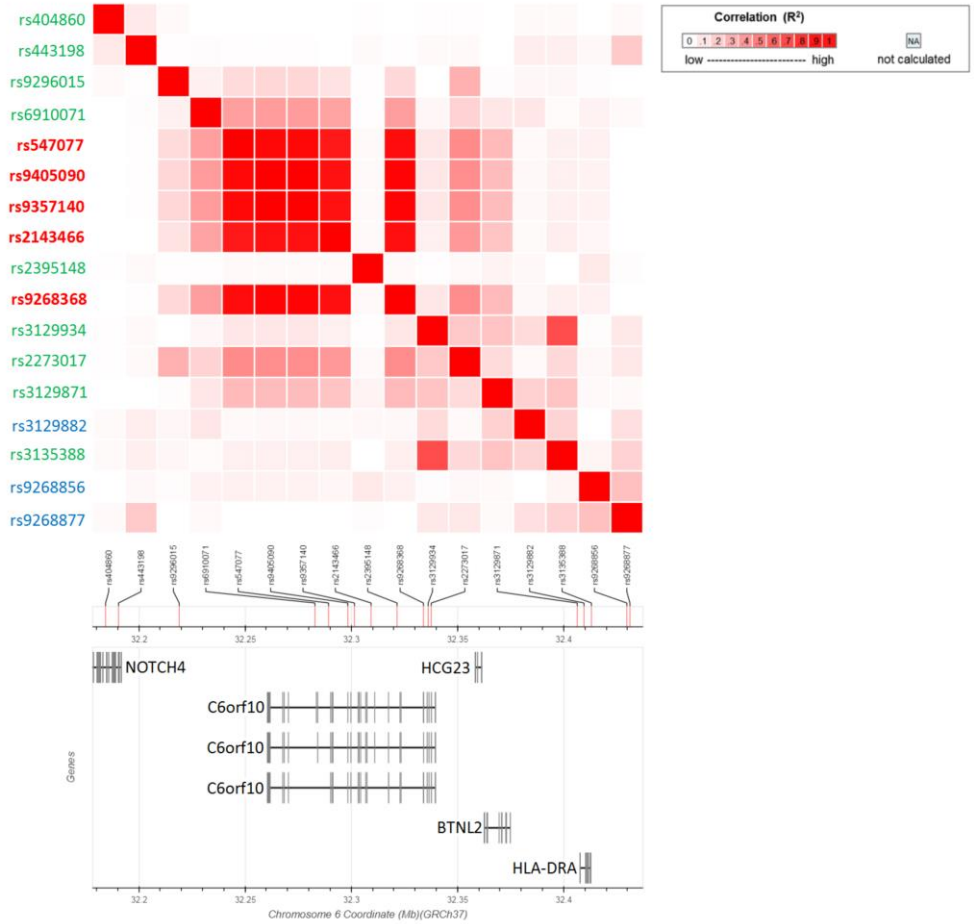
Supplementary Figure 5. Scatter plot of age of onset (AO) in disease subtypes of unrelated *C9orf72* patients (total n=304). Mean AO and standard error bar for each group are presented. We found no significant difference in AO among the ALS subtypes (bulbar ALS, limb ALS, unspecified ALS) or FTD subtypes (bvFTD, SD, PNFA, unspecified FTD): $p>0.05$, Kruskal Wallis test.



Supplementary Figure 6. Results of the association study of rs9357140 using GTEx eQTL data (Ref=G-allele, Alt=A-allele) and quantitative RT-PCR. Genotypes of rs9357140 are significantly associated with (**A**) *LOC101929163* expression in nucleus accumbens ($p=7.6\times10^{-6}$, n=130) and (**B**) *HLA-DRB1* expression in frontal cortex tissues ($p=4.1\times10^{-6}$, n=136). (**C**) In 25 ALS frontal cortex tissues, rs9357140 AA-carriers have reduced *HLA-DRB1* expression compared to AG- or GG-carriers ($^{**}p=0.001$ for AA vs AG; $^{***}p=0.000003$ for AA vs GG; Mann-Whitney U test).



Supplementary Figure 7. Genotypes of rs9357140 are not associated with *C9orf72* expression (p>0.05, Mann-Whitney U test) in frontal cortex tissues from 25 ALS cases. Expression *C9orf72* and *HLA-DRB1* are not significantly correlated with each other (p=0.23, multivariate linear regression, adjusted for sex).



Supplementary Figure 8. LD-plot with the location of the genetic variations (rs547077, rs9405090, rs9357140, rs2143466, and rs9268368) significantly associated with age of onset in *C9orf72* patients (in red font), as well as nearby top-significant variants (rs404860, rs443198, rs9296015, rs6910071, rs2395148, rs3129934, rs2273017, rs3129871, rs3129882, rs3135388, rs9268856, and rs9268877) reported to be linked to neurodegenerative (blue font) or autoimmune (green font) diseases (Supplementary Table 11).

APPENDIX

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