Supplementary Online Content

Fogh I, Lin K, Tiloca C, et al. Association of a locus in the *CAMTA1* gene with survival in patients with sporadic amyotrophic lateral sclerosis. *JAMA Neurol.* Published online May 31, 2016. doi:10.1001/jamaneurol.2016.1114.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Participants, GWAS Quality Control and Imputation Analyses, Statistical Analyses, and Software

1. Participating individuals

SLAGEN data collection

The SLAGEN collection included sporadic cases and healthy controls collected by the SLAGEN Consortium created through the collaboration of six appointed Neurological Hospitals in Italy including the IRCCS Istituto Auxologico Italiano in Milan, IRCCS Istituto Neurologico "Carlo Besta" in Milan, IRCCS "C. Mondino" in Pavia, "A. Avogadro" University in Novara, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico in Milan, University of Padua. Further tertiary neurological institutions across Italy jointed the SLAGEN Consortium contributing with additional sporadic cases DNA reported in Fogh I, et al.[1] Blood samples were collected after ethically approved written consent and DNA was extracted according to standard methods, DNA collection, preparation, quantification and genotype on the Illumina Human 660W Quad BeadChip array are fully described in Fogh I, et al.[1] (eTable1). Patients with family history of ALS or carrying known Mendelian risk genes were excluded from this study, with the exception of *C9orf72* mutational screening that was not extended for all the individuals included in our international data collection.

ALSGEN data collection

The international ALS GWAS data collected by the ALSGEN consortium included sporadic cases and controls from several European Countries and US is described in eTable1. The University Medical Center Utrecht collection included genotype data of individuals from the Nederland, Sweden and Belgium[2-4]; the Massachusetts General Hospital study comprised case-control collected in Boston, Atlanta, King's College London (UK) and Evry (France)[5]; the UK cohort consisted of sporadic cases from the National MND DNA and Biobank study[6], GWAS data from Irish individuals were collected by Beaumont Hospital in Dublin[7], one additional Italian study from Piedmont was genotyped at the National Institute of Health (USA)[8]. Sample selection, DNA

preparation and genotype arrays are fully reported in the original publications and summarized in eTable1.

2. GWAS quality control and imputation analyses

Genotyping and quality control

Genotyping of seven previously published ALS-GWA studies[1] was performed on different Illumina DNA platforms (eTable 1) and included raw data of 12425 individuals (6389 cases and 6037 controls). GWAS raw data were processed through stringent quality control (QC) using the PLINK 1.9 toolset [9].

First SNPs with A/T or G/C alleles were removed and genotyped SNPs data of each platform were aligned to the hg19 genome build using strand files for the Illumina common chips downloaded from the www.well.ox.ac.uk/~wrayner/strand/ database.

In each GWAS data set SNPs were removed if non-autosomal, call rate < 99%, minor allele frequency (MAF) present in less than 20 heterozygous individuals, deviated from Hardy Weinberg equilibrium (HWE) in controls (threshold of $P < 1 \times 10^{-7}$) or in cases (~35 SNPs) when in strong HW disequilibrium that led to a distorted quantile-quantile (QQ) distribution; if call rate was significantly different in cases and controls and non-randomly distributed along haplotypes ($P < 1 \times 10^{-5}$). On average 59600 SNPs were excluded per data set (eTable 2).

Per cohort individuals were excluded if sample call rate < 98%, phenotype-genotype gender information discordant; with excessive/insufficient number of heterozygous SNPs estimated by the inbreeding coefficient F ($0.02 <$ heterozygosity > 0.05). Duplicated and related individuals were identified by identical-by-descent (IBD) estimation and removed (pi-hat > 0.05). Cases and controls population structure of the individual cohorts was studied by principal components analysis (PCA) on a subset of linkage disequilibrium (LD) free SNPs using EIGENSTRAT software.[10, 11] Population outliers were identified by the first 4 principal components (PCs) variables and excluded from the analysis. After QC, an average of 10.37% of individuals was excluded across the seven cohorts (eTable 2). Next, cleaned genotype data were tested for genomic inflation and lambda estimates resulted to be minimal ($\lambda_{(gc)} < 1.02$) across data sets.

In total 11136 individuals, 5846 cases and 5290 controls passed stringent QC (eTable 2). The number of SNPs and individuals failing each QC step across the seven data sets were previously described in Supplementary Table 2, Fogh I et al.[1]

Imputation procedure

In each cohort post QC genotype data were tested for SNPs alignment between GWAS data and the 1000 Genomes Project, Phase I version 3 (NCBI build 37, hg19 coordinates, August 2012) reference panel using SHAPEIT v2.r727 toolset.[13] Variants not present in the reference panel or with strand mismatch were excluded from the analysis. Next, genotypes data were phased by inferring haplotypes structure to the equivalent heterozygous sequence reads present in the reference panel (SHAPEIT v2.r727). Finally, aligned and phased original genotypes were imputed genome wide separately in each cohort using IMPUTE version 2.3.0 program[12] and the 1000 Genomes Project, Phase I version 3 (**eTable 2).**

After imputation procedure, only genotyped SNPs data of cases were extracted from the pipeline; of these a subset of 4256 patients had complete clinical information and therefore included in the Cox proportional hazard regression analysis. There was an average of more than 30 million of original and imputed SNPs per data set (eTable2) that were filtered for uncertainty of inferred genotypes according to posterior probability (APP) > 0.9 and IMPUTE2 information metric (Info) > 0.4. Applied MAF threshold was defined by the presence of at least 20 heterozygous individuals per cohort (eTable3). On average 52.3 % of original/imputed SNPs were removed across the 7 GWAS data sets (eTable2). Finally, cleaned genetic data with coverage of 7174392 overlapping SNPs were analysed for association with ALS survival by Cox proportional hazards regression separately per cohort.

3. Statistical analysis

Cox proportional hazard regression analysis

Post-QC imputed GWAS data of each platform were imported to GenABEL-package[14] (http://www.genabel.org) on R.2.14.0[15] environment and converted into MACH format.

Hazard ratios (HRs) were estimated for each SNP genome wide and variants genetic effect on survival were evaluated using multivariate Cox proportional hazards regression analysis adjusted for age at onset, gender and the top four principal components for population stratification correction. In a subset of patients with site at onset information (81%) Cox proportional hazards model was performed including the dichotomous variable bulbar versus spinal as additional covariate.

Cox proportional hazards regression analyses under a log-additive genetic model was performed using *pacoxph* program available in ProbABEL toolset.[14] Statistical output tables of each strata were combined in METAL software[16] (http://www.sph.umich.edu/csg/abecasis/metal/) and meta-analysis was performed under the standard error scheme that weights β-coefficients and the inverse of the corresponding standard errors. Summary Cox proportional hazard scores for 7174392 overlapping SNPs showed absence of genomic inflation ($\lambda_{(gc)}$ = 1·05) (eFigure.1).

Heterogeneity of allele frequencies between studies was estimated in the combined Cox proportional hazard analysis by Cochran's Q test (Q) using METAL program. Allelic heterogeneity was calculated as I^2 ratios that range from 0 to 100%, 0% indicates no observed heterogeneity, degrees of freedom (*df*) were included as N-1 with N equal to the number of studies[17] (eTable5). The total variation across studies due to heterogeneity was calculated as:

I^2 = 100% x (Q-*df*) / Q

4. Software

All the statistical analyses presented in this study were performed on the UNIX operator system using the National Institutes for Health Research Biomedical Research Centre for Mental Health at the South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry,Psychology and Neuroscience King's College London Linux Cluster.

R.2.14.0

Plink (pngu.mgh.harvard.edu/~purcell/plink)

EIGENSTRAT (genepath.med.harvard.edu/~reich/)

Liftover (www.well.ox.ac.uk/~wrayner/strand/)

IMPUTE version 2.3.0 (mathgen.stats.ox.ac.uk/impute/)

SHAPEIT version2.r727 (mathgen.stats.ox.ac.uk/genetics_software/shapeit/)

GTOOL version 0.7.5 (www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html)

QCTOOL version 1.2 (www.well.ox.ac.uk/~gav/qctool/)

GenABEL (http://www.genabel.org)

METAL (csg.sph.umich.edu//abecasis/metal/)

SPSS version 22, IBM Corporation, Chicago, IL, USA.

eReferences

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eTable 1. Samples and Original Commercial Genotype Arrays

	Data Collection	Samples Source	Original Sample (N)	Cases (N)	Controls (N)	Illumina Arrays
1	SLAGEN Consortium	Italy	3959	1982	1977	Human 660W Q
2	UMC Utrecht	The Netherlands	911	461	450	HumanHap300
3	UMC Utrecht, Umeå , Leuven	The Netherlands, Sweden, Belgium	2806	1364	1442	HumanCNV370
4	MGH, KCL, Evry	United States, Great Britain, France	2907	1198	1710	HumanCNV370
5	Beaumont Hospital, Dublin	Ireland	432	221	211	HumanHap 550K
6	UK National MND DNA and Biobank study	Great Britain	663	663	NA	Human610-Quad
7	National Institute of Health (US)	ITALGEN Italy	747	500	247	HumanHap 550K

Description of the original published case-controls GWAS studies from where we selected only case genotypes data to be analysed in the Cox proportional hazard analyses and combined meta-analysis. The recently published SLAGEN Consortium study was collected by several appointed Neurological Hospitals in Italy. Dutch, Swedish, French, Belgian, Irish and North American, and Italian GWAS data were collected by the International Consortium on Amyotrophic Lateral Sclerosis Genetics (ALSGEN). British cases were collected by UK National MND DNA and Biobank study.
UMC, University Medical Center Utrecht, The Netherlands
MGH, Massachusetts General Hospita, Boston,USA
KCL, King's College London, London,UK.

eTable 2. Summary of Quality Control and Imputation Analysis

Study	Individuals after QC			Directly genotyped SNPs		Imputation analysis		
	Sample	Cases	Controls	Before QC	Removed	Unfiltered SNPs	Removed SNPs	Filtered SNPs
	N	N	N	N	%	N	%	N
SLAGEN	3536	1839	1697	657366	23.1	30021255	40.6	17836637
UTRECHT-1	852	432	420	317503	9.1	30019265	57.4	12799890
UTRECHT-2	2599	1300	1299	317503	6.8	30019250	50.9	14743300
IRELAND	420	213	207	561466	16.1	30022148	61.5	11547392
MND-UK	627	627	NA	471994	5.4	30021493	54.3	13722235
MGH	2449	1009	1440	307790	18.4	29994944	47.4	15769989
NIH-IT	653	426	227	500002	8.5	30021493	54.3	13722235
Total	11136	5846	5290				Mean 52.3	Shared 7174392

For each study included in the Cox proportional hazard regression analysis the table reports the number of individuals that passed stingent quality control (QC) and the proportion of markers filtered out before imputation procedure. Post QC genotyped SNPs of cases and controls were then imputed genome wide using the 1000GP, hg19 coordinates. Original and imputed data of only cases were extracted from the pipeline and filtered by average posterior probability (APP) > 0.9 and statistical information of allele frequency (Info) > 0.4. After QCs the average number of markers filtered out was 52.3% across the seven data sets (eMethods).

eTable 3. Minor Allele Frequency Filter

	Study	Sample size	MAF filter
1	SLAGEN	3536	0.003
2	UTRECHT 1	854	0.011
3	UTRECHT 2	2601	0.004
4	MGH US	2449	0.004
5	UK MND	663	0.015
6	NIH ITALY	654	0.015
7	IRELAND	422	0.02

Minor allele frequency (MAF) threshold applied to statistical output tables in Cox proportional hazard regression analyses.

eTable 4. Cox Proportional Hazards Regression Baseline Analysis

Baseline Cox Multivariate Model		
Factors	**hazard ratio (95%CI)**	***P***
Age at onset	1.030 (1.02-1.03)	< .0001
Gender	0.964 (0.89-1.03)	.37
Site at onset	1.420 (1.30-1.54)	< .0001

eTable 5. Allelic Heterogeneity

Marker	Chromosome	A1	A2	Freq1	FreqSE	Effect (β)	StdErr (β)	*P*	Direction	I^2	Q	DF	Het P
rs139550538	10	A	T	0.0292	0.0036	0.4807	0.08	1.87E-09	+++++++	0	2.908	6	0.8203
rs2412208	1	T	G	0.7394	0.0164	-0.1617	0.0293	3.53E-08	-------	57.2	14.007	6	0.02956
rs4584415	1	T	C	0.7128	0.0198	-0.1567	0.0285	3.68E-08	-------	46.5	11.22	6	0.08181
rs35447019	1	A	T	0.2602	0.0165	0.1611	0.0293	3.86E-08	+++++++	56.3	13.746	6	0.03261
rs4409676	1	T	C	0.2602	0.0162	0.1601	0.0293	4.48E-08	+++++++	57.2	14.006	6	0.02957
rs2412214	1	T	C	0.2469	0.0147	0.1642	0.0301	5.18E-08	+++++++	56	13.622	6	0.03416
rs2412210	1	T	C	0.2577	0.0168	0.1593	0.0295	6.83E-08	+++++++	59.1	14.66	6	0.02308
rs11120817	1	A	T	0.7517	0.015	-0.1582	0.0299	1.21E-07	-------	57.2	14.029	6	0.02931
rs4287204	1	A	G	0.2473	0.0149	0.1562	0.0299	1.78E-07	+++++++	55.6	13.525	6	0.03542
rs3986512	1	T	C	0.754	0.0146	-0.1569	0.0301	1.87E-07	-------	56.8	13.897	6	0.03081
rs4500344	1	T	G	0.2461	0.0145	0.1562	0.0301	2.05E-07	+++++++	56.9	13.925	6	0.03048
rs6690584	1	T	G	0.7044	0.0122	-0.1468	0.0285	2.53E-07	-------	14.5	7.014	6	0.3195
rs4436414	1	A	G	0.3927	0.0231	0.1352	0.0264	3.15E-07	+++++++	27.6	8.287	6	0.2178
rs969599	1	A	G	0.9462	0.0043	-0.3112	0.061	3.37E-07	-------	0	4.503	6	0.609
rs7414485	1	A	G	0.3935	0.0232	0.1341	0.0264	3.65E-07	+++++++	22.3	7.718	6	0.2595
rs10864263	1	T	C	0.2909	0.0111	0.1435	0.0284	4.46E-07	+++++++	33	8.954	6	0.1762
rs72911847	1	A	G	0.9702	0.0048	-0.4722	0.0938	4.76E-07	--+----	47	11.32	6	0.07897
rs2186090	1	T	C	0.2887	0.011	0.1427	0.0285	5.52E-07	+++++++	28.6	8.408	6	0.2097
rs7525119	1	T	C	0.2883	0.0114	0.1425	0.0285	5.81E-07	+++++++	28.4	8.375	6	0.2119
rs115134572	1	A	G	0.9757	0.0036	-0.4727	0.0948	6.21E-07	-------	35.8	9.341	6	0.1553
rs11120822	1	C	G	0.372	0.027	0.1337	0.0268	6.23E-07	+++++++	14.3	7.003	6	0.3205
rs11120824	1	A	G	0.3732	0.0273	0.1333	0.0268	6.58E-07	+++++++	14.6	7.022	6	0.3188
rs7546792	1	T	C	0.389	0.0235	0.1315	0.0266	7.93E-07	+++++++	26.7	8.18	6	0.2252
rs7543531	1	T	C	0.3147	0.0095	0.1371	0.028	9.68E-07	+++++++	0	4.463	6	0.6143

Allelic heterogeneity values estimated in the top rank SNPs from the combined Cox hazard regression analysis. Allelic heterogeneity was calculated as I^2 ratios ranging from 0 to 100%, where 0% indicates no observed heterogeneity. Degrees of freedom (DF) were defined by N-1 (N= number of studies); Q indicates the summary statistic of Cochran's Q test.

eTable 6. Demographic Table Describing the Sample Size, After QCs, Included in the Cox Proportional Hazards Regression Analyses Combined in Meta-analyses

Study	Information	Males	Females	Dead	Censored		AAO	Survival dead/censored		Survival dead	
	N	N	N	N	N	Freq	Mean (years)	Median (months)	Quantiles (25%-75%)	Median (months)	Quantiles (25%-75%)
SLAGEN	959	617	342	584	375	0.4	57.8 (±12.0)	36.9	20.0-71.9	40.0	24.7-65.8
UTRECHT 1	426	253	173	252	173	0.4	60.2 (±11.1)	27.0	18.7-39.1	28.0	19.8-38.5
UTRECHT 2	1065	629	436	762	303	0.3	60.7 (±12.0)	27.6	19.2-44.3	27.6	19.2-40.7
IRELAND	148	80	68	146	4	0.0	57.7 (±12.4)	32.0	21.8-54.8	30.9	21.2-53.3
MND-UK	619	394	225	545	74	0.1	60.7 (±11.1)	32.1	23.0-47.1	33.7	24.2-48.9
MGH	686	425	261	552	134	0.2	54.9 (±12.9)	39.3	26.9-59.4	37.0	26.2-53.2
NIH-IT	353	191	162	286	67	0.2	62.0 (±11.1)	40.7	24.4-57.2	32.4	22.0-49.4
TOTAL	4256	2589	1667	3125	1130	0.3	59.1 (±12.1)	32.9	21.5-53.2	32.8	22.2-49.2

AAO, *Age at symtom onset*

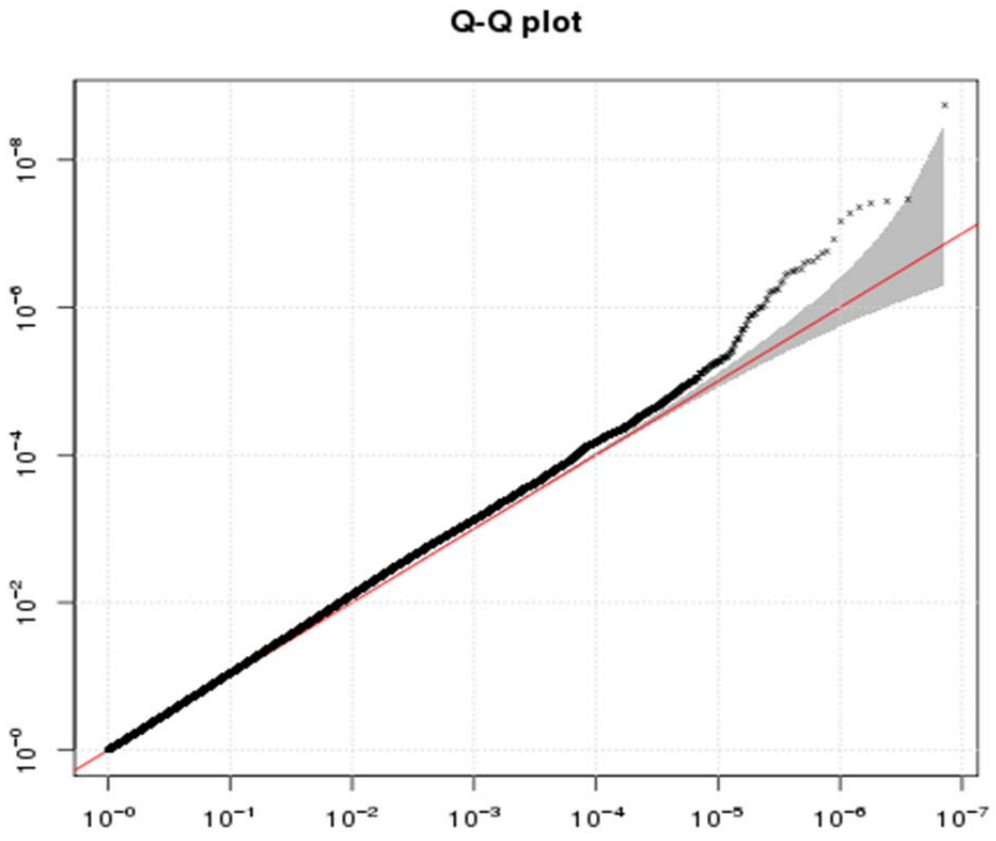
eTable 7. Demographic Table of a Subset of Patients (n=3438) With Survival and Site at Onset Information

Study	Cases	Bulbar	Bulbar Age at Onset	Spinal Age at Onset	Bulbar Female Ratio	Survival (months)
	N	%	Mean (SD)	Mean (SD)	%	Median (Quantiles 25%-75%)
SLAGEN	223	30.8	53.0 (±10.2)	56.0 (±12.9)	27.8	44.0 (18.8-39.0)
UTRECHT 1	416	30.8	62.9 (±10.2)	58.8 (±11.8)	55.5	27.0 (18.8-39.0)
UTRECHT 2	1056	32.2	64.2 (±10.7)	58.9 (±12.2)	53.4	27.6 (19.0-44.3)
IRELAND	149	28.4	62.2 (±10)	57.3 (±13.6)	65	31.9 (21.6-54.6)
MND-UK	589	31.5	63.8 (±9.8)	59.2 (±11.2)	53	32.3 (23.0-47.4)
MGH	654	30.6	59.9 (±12.9)	54.7 (±13.4)	45.8	39.7 (26.9-60.8)
NIH-IT	353	28.3	65.8 (±10.2)	60.5 (±11.2)	58	40.7 (24.4-57.0)
TOTAL	3438	29.8	62.4 (±11.4)	57.7 (±12.5)	51.8	31.0 (20.4-49.0)

eTable 8. Top-Rank SNPs From the Summary Cox Proportional Hazards Regression Model Adjusted by Sex, Age at Onset, Site of Onset, and Principal Components Covariates

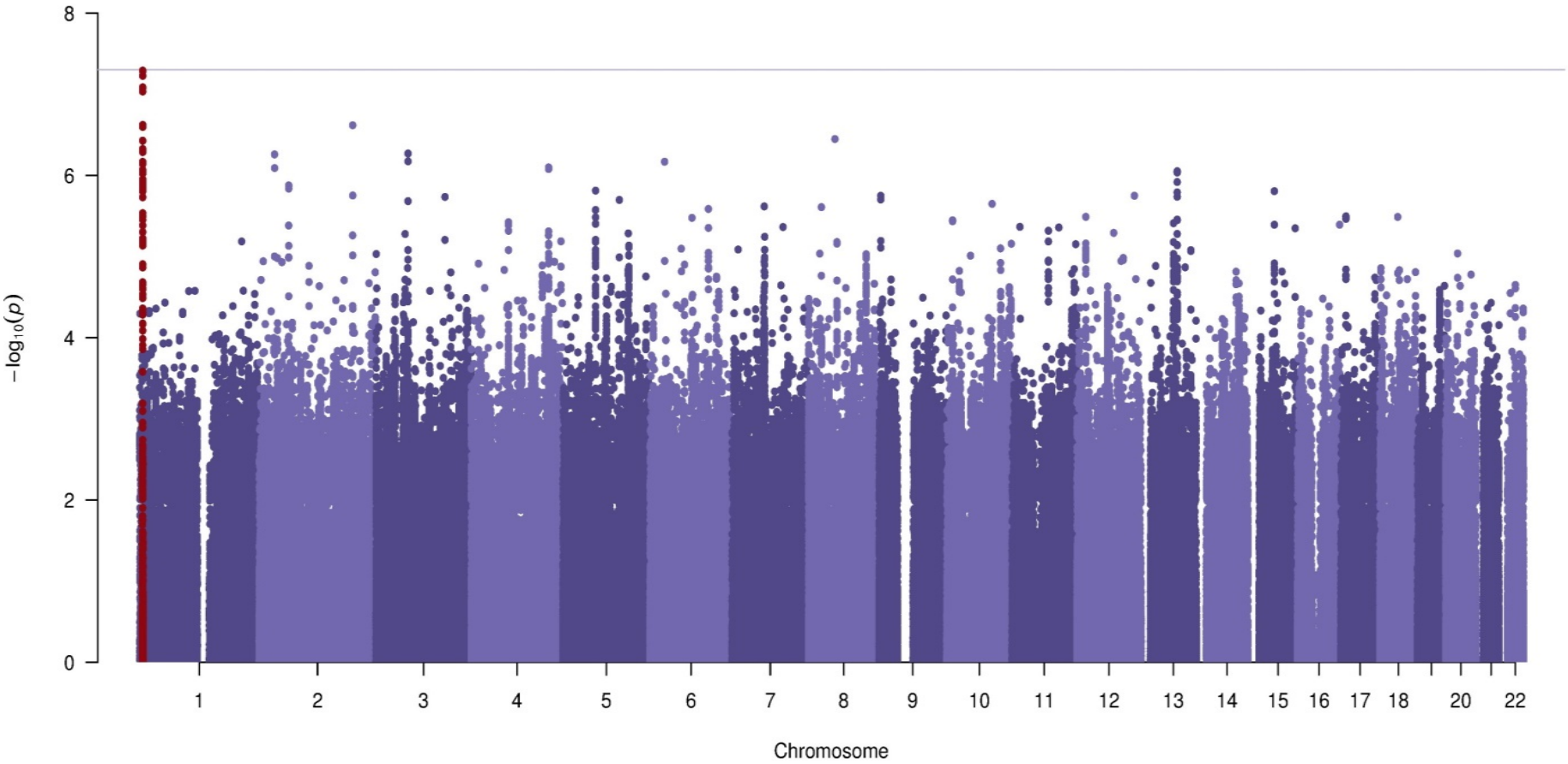
Marker	Chromosome	Position	A1	A2	Freq1	FreqSE	MinFreq	MaxFreq	Effect	StdErr	*P*	Direction
rs2412208	1	7092782	T	G	0.735	0.0147	0.718	0.761	-0.1787	0.0328	5.11E-08	-------
rs2412210	1	7092549	T	C	0.2623	0.0147	0.234	0.279	0.1795	0.033	5.19E-08	+++++++
rs35447019	1	7093158	A	T	0.2647	0.0147	0.238	0.282	0.1777	0.0328	5.92E-08	+++++++
rs6690584	1	7078434	T	G	0.7008	0.0106	0.687	0.721	-0.171	0.0319	8.23E-08	-------
rs4409676	1	7094465	T	C	0.2645	0.0146	0.239	0.282	0.1753	0.0327	8.40E-08	+++++++
rs2412214	1	7089674	T	C	0.2505	0.0136	0.228	0.268	0.1804	0.0338	9.26E-08	+++++++
rs4584415	1	7094278	T	C	0.7078	0.0187	0.685	0.742	-0.1653	0.032	2.39E-07	-------
rs72911847	2	194578775	A	G	0.9691	0.0037	0.964	0.98	-0.5203	0.1007	2.41E-07	--+----
rs11120817	1	7081233	A	T	0.748	0.0138	0.731	0.771	-0.1728	0.0335	2.53E-07	-------
chr8:54739195:I	8	54739195	G	GA	0.9788	0.0024	0.973	0.981	-0.6346	0.1247	3.57E-07	-------
rs4287204	1	7076184	A	G	0.251	0.0137	0.228	0.265	0.1704	0.0335	3.74E-07	+++++++
rs11588097	1	7071415	A	G	0.7493	0.0138	0.735	0.773	-0.169	0.0335	4.72E-07	-------
chr1:7073102:D	1	7073102	CCT	C	0.7494	0.0138	0.735	0.773	-0.169	0.0336	4.91E-07	-------
rs3986512	1	7090699	T	C	0.7503	0.0135	0.734	0.772	-0.1692	0.0337	5.16E-07	-------

eFigure 1. Quantile-Quantile (Q-Q) Plot of the Combined Cox Proportional Hazards Regression Analysis

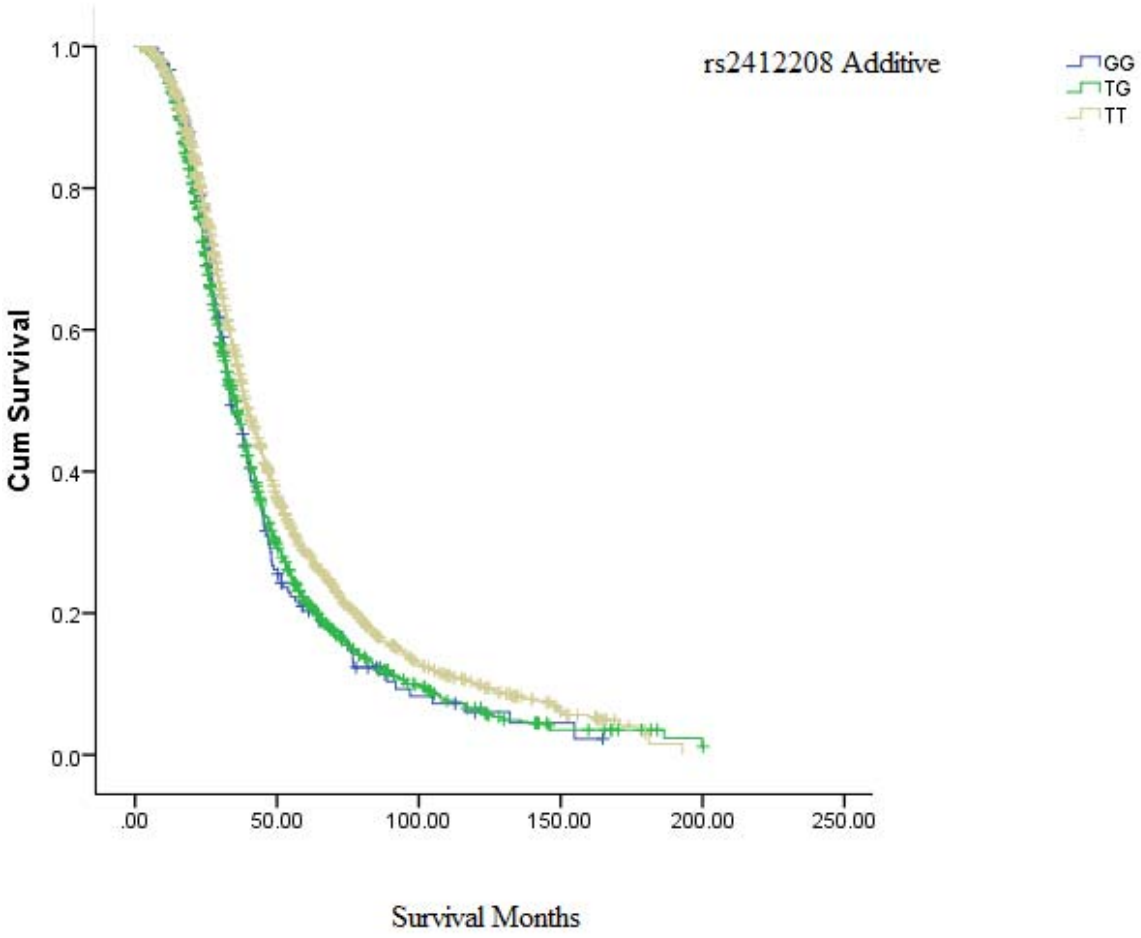


Q-Q plot measured in the summary statistic of the combined Cox proportional analysis. The observed quantilies were plotted against the expected under the null hypothesis of no association.

eFigure 2. Manhattan Plot Reports the Cox Proportional Hazards Regression Summary Statistics Adjusted by Principal Components, Sex, Age, and Site of Onset



eFigure 3. Kaplan-Meier Curves for the Top-Ranked SNP in the Summary Cox Proportional Hazards Regression Adjusted by Sex, Principal Components, Age, and Site at Onset



Summary Cox proportional hazard adjusted by site at onset							
		Patients				Survival (Months)	
rs2412208_Additive		Patient N	Events N	Censored N	Censored %	Median	(95% CI)
	GG	214	164	50	23·4	33·6	(29·6-37·5)
	GT	1365	1065	300	22	35·8	(34-37·5)
	TT	1859	1372	487	26·2	39·1	(36·5-38·6)

eFigure 4. Forest Plot of Previous Candidate Variants for ALS Survival