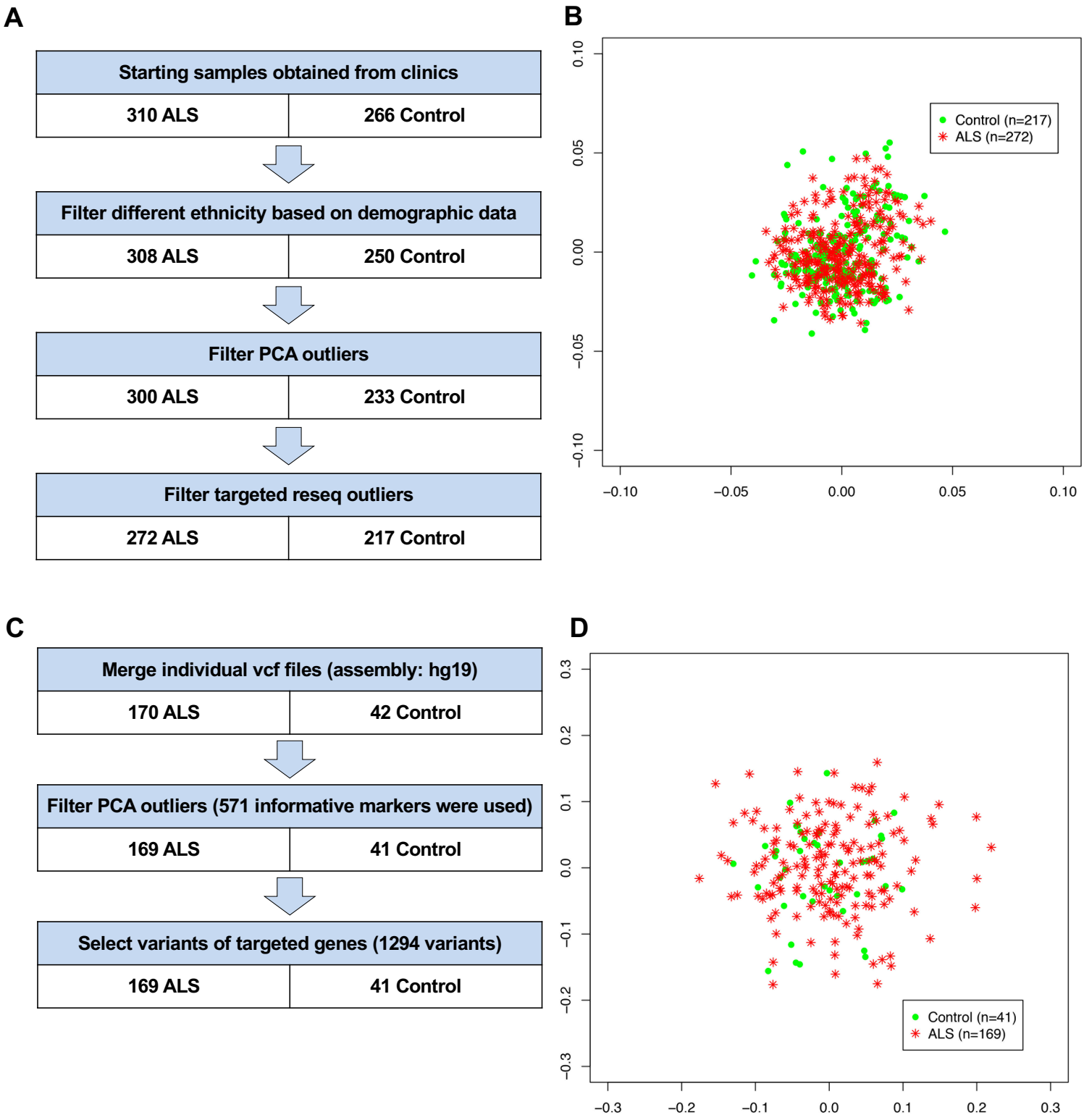
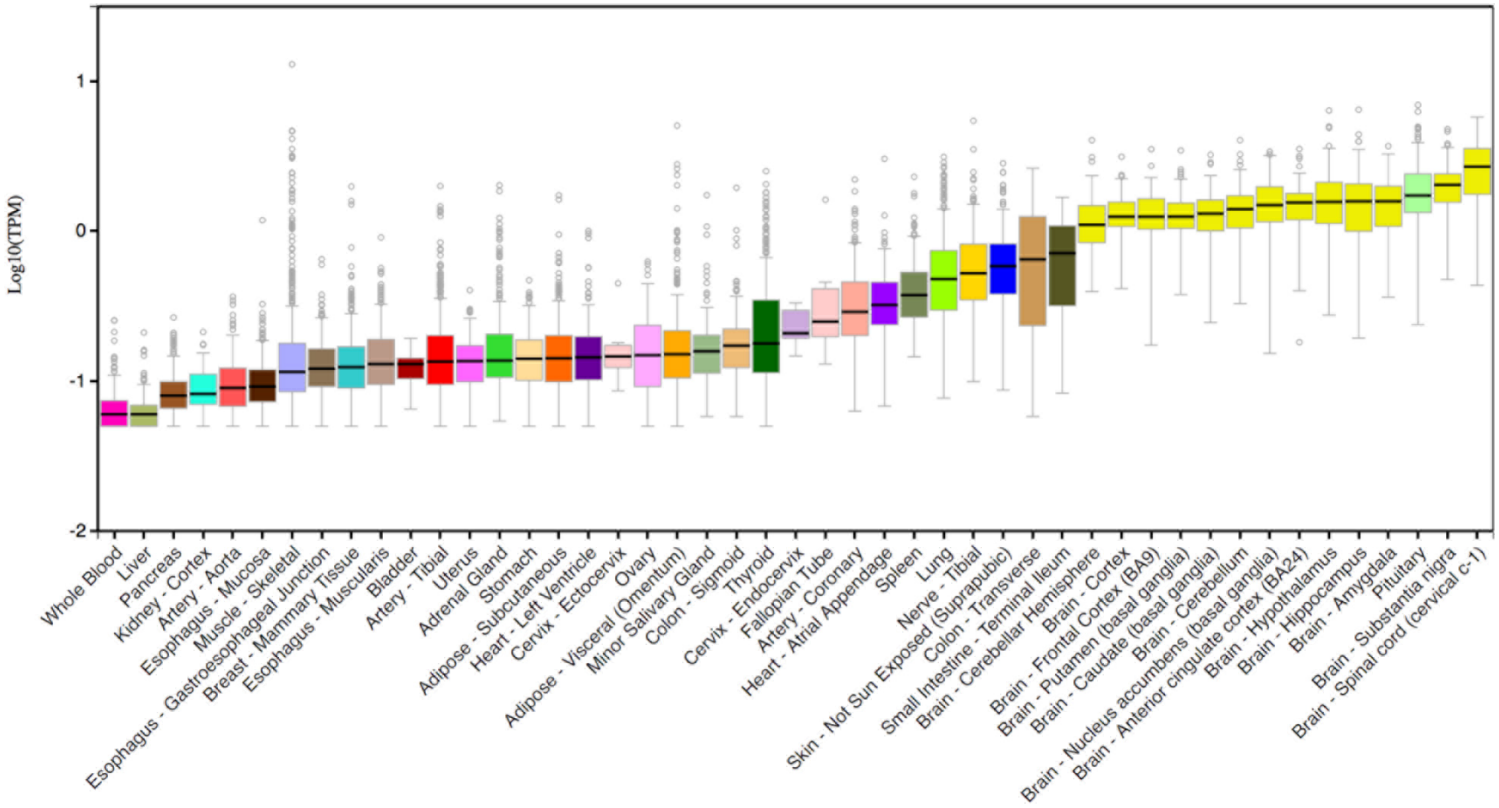


Supplementary Figure 1 Quality control of samples used for statistical testing using targeted resequencing and a validation Project MinE dataset. (A) 38 ALS cases and 49 controls were filtered out during each quality control step, and final 272 ALS cases and 217 controls were passed after quality control. Additional 2 ALS cases that have known ALS genes, SOD1 and TARDBP, were excluded for SKAT analysis. (B) Principal component analysis (PCA) plot of samples that were passed after quality control. (C) 169 ALS cases and 41 controls were passed after PCA. Additional 2 ALS cases that have mutations in SOD1 were excluded for further analysis. (D) Principal component analysis (PCA) plot of ALS cases and controls passed after quality control.



Supplementary Figure 2 Gene expression for MYH15 in 47 tissues obtained from GTEx Analysis Release V7 (dbGaP Accession phs000424.v7.p2). Expression values are shown in TPM (Transcripts Per Million).a

Supplementary Table 1: Clinical information of four C9ALS patients included in whole-genc

Sample Group	Sample ID	Sex	Age of onset
YALS	SL119751	F	34.33
	SL119752	F	41.65
OALS	SL119753	F	72.37
	SL119754	M	72.86

Supplementary Table 2: List of genic variants exclusively found in either YALS or OALS in whole-genome sequencing

Patient type	chr	pos	snp id	ref	alt	maf	gene symbol	annotation type	aa change	strand	cadd	phastCons	phyloP	heterozygotes ids	homozygote ids
YALS	chr1	15445709	rs515726210	T	A	NA	CTRC	Replacement	V251D	+	26.772	0.543	0.472	SL119751;SL119752	NA
YALS	chr1	15445753	NA	G	A	NA	CTRC	Non-Coding (Splice Donor)		+	12.382	0.74	0.709	SL119751;SL119752	NA
YALS	chr1	47794752	NA	G	C	NA	TRABD2B	Replacement	N274K	-	23.425	0.996	0.945	SL119751;SL119752	NA
YALS	chr1	67412777	NA	A	C	NA	SERBP1	Non-Coding (3UTR)		-	13.386	0.949	0.945	SL119751;SL119752	NA
YALS	chr1	67412839	NA	A	T	NA	SERBP1	Non-Coding (3UTR)		-	14.39	1	0.945	SL119751;SL119752	NA
YALS	chr1	67412861	NA	G	A	NA	SERBP1	Non-Coding (3UTR)		-	14.724	1	0.945	SL119751;SL119752	NA
YALS	chr1	92483381	rs34631763	C	T	0.009684505	GFI1	Replacement	S36N	-	18.406	0.201	0	SL119751;SL119752	NA
YALS	chr1	112600798	rs116580400	T	C	0.009784345	ST7L	Replacement	R168G	-	22.087	0.996	0.945	SL119751;SL119752	NA
YALS	chr1	115925198	rs10923803	G	T	0.002196486	RP11-12L8.1	Non-Coding		+	13.051	0.984	0.945	SL119751;SL119752	NA
YALS	chr1	155795096	NA	T	G	NA	GON4L	Replacement	E567D	-	17.067	1	0.945	SL119751;SL119752	NA
YALS	chr1	155795125	NA	C	A	NA	GON4L	Replacement	E558*	-	21.083	1	0.945	SL119752	NA
YALS	chr1	180114558	rs142500573	C	T	0.00778754	CEP350	Non-Coding (3UTR)		+	14.055	0.996	0.945	SL119751;SL119752	NA
YALS	chr1	247155424	NA	A	T	NA	ZNF124	Non-Coding (3UTR)		-	12.717	0.917	0.709	SL119751;SL119752	NA
YALS	chr1	247155432	NA	G	T	NA	ZNF124	Non-Coding (3UTR)		-	14.055	0.913	0.709	SL119751;SL119752	NA
YALS	chr1	247155436	NA	A	T	NA	ZNF124	Non-Coding (3UTR)		-	13.386	0.858	0.709	SL119751;SL119752	NA
YALS	chr1	247155444	NA	C	T	NA	ZNF124	Non-Coding (3UTR)		-	15.059	0.713	0.709	SL119751;SL119752	NA
YALS	chr1	247155445	NA	A	T	NA	ZNF124	Non-Coding (3UTR)		-	12.382	0.709	0.709	SL119751;SL119752	NA
YALS	chr1	248488874	rs199519459	G	A	NA	OR2T5	Replacement	V96I	+	17.736	0.024	0	SL119751;SL119752	NA
YALS	chr1	248489049	rs200959275	T	C	NA	OR2T5	Replacement	F154S	+	13.051	0	0	SL119751;SL119752	NA
YALS	chr1	248558785	NA	T	G	NA	OR2T29	Replacement	E236A	-	10.039	0.063	0	SL119751;SL119752	NA
YALS	chr2	96848428	NA	T	G	NA	ANKRD39	Replacement	H142P	-	18.74	0.937	0.709	SL119751;SL119752	NA
YALS	chr2	107892532	NA	A	G	NA	RGPD4	Non-Coding (3UTR)		+	13.72	0.988	0.945	SL119751;SL119752	NA
YALS	chr2	189873653	NA	A	C	NA	PMS1	Replacement	L715F	+	24.094	0.996	0.945	SL119751;SL119752	NA
YALS	chr2	203296493	NA	G	A	NA	CYP20A1	Replacement	D390N	+	22.756	0.965	0.945	SL119751;SL119752	NA
YALS	chr2	218459828	rs563821163	T	C	0.000199681	USP37	Replacement	T869A	-	21.417	1	0.945	SL119751;SL119752	NA
YALS	chr2	218459832	NA	C	A	NA	USP37	Replacement	E867D	-	20.748	0.996	0.945	SL119751;SL119752	NA
YALS	chr2	218459858	NA	C	T	NA	USP37	Replacement	G859R	-	32.795	0.996	0.945	SL119751;SL119752	NA
YALS	chr2	218459908	NA	G	A	NA	USP37	Non-Coding (Splice Acceptor)		-	14.724	0.98	0.945	SL119751;SL119752	NA
YALS	chr3	50256215	NA	T	C	NA	GNAI2	Replacement	I111T	+	22.087	0.965	0.945	SL119751;SL119752	NA
YALS	chr3	108493131	NA	G	T	NA	MYH15	Replacement	S273Y	-	22.087	0.039	0	SL119751;SL119752	NA
YALS	chr3	170038072	rs187596124	C	G	NA	GPR160	Non-Coding (5UTR)		+	13.051	0.15	0	SL119751;SL119752	NA
YALS	chr3	195292453	NA	C	T	NA	ACAP2	Non-Coding (Splice Acceptor)		-	26.102	0.996	0.945	SL119751;SL119752	NA
YALS	chr3	195297212	NA	T	A	NA	ACAP2	Replacement	K489*	-	22.421	1	0.945	SL119752	NA
YALS	chr4	86453	NA	T	G	NA	ZNF595	Replacement	C134G	+	15.394	0.906	0.709	SL119751;SL119752	NA
YALS	chr4	39823037	rs62307873	C	T	0.001797125	PDS5A	Non-Coding (3UTR)		-	15.059	1	0.945	SL119751;SL119752	NA
YALS	chr4	70824318	NA	C	A	NA	GRSF1	Non-Coding (3UTR)		-	13.72	0.437	0.236	SL119751;SL119752	NA
YALS	chr4	78499716	rs386676424;rs7695038	C	G	0.001397764	FRAS1	Non-Coding (Splice Acceptor)		+	10.374	0.98	0.945	NA	SL119751;SL119752
YALS	chr4	145138188	NA	A	G	NA	OTUD4	Replacement	Y798H	-	27.106	1	0.945	SL119751;SL119752	NA
YALS	chr4	145152617	NA	C	A	NA	OTUD4	Replacement	G233*	-	22.421	0.996	0.945	SL119751	NA
YALS	chr4	176151924	NA	G	T	NA	WDR17	Replacement	G830V	+	28.78	1	0.945	SL119751;SL119752	NA
YALS	chr5	132604931	NA	C	A	NA	RAD50	Replacement	R884S	+	25.433	0.996	0.945	SL119751;SL119752	NA
YALS	chr5	132604946	NA	G	A	NA	RAD50	Replacement	E889K	+	23.091	1	0.945	SL119751;SL119752	NA
YALS	chr5	132604949	NA	C	A	NA	RAD50	Replacement	Q890K	+	22.756	1	0.945	SL119751;SL119752	NA
YALS	chr5	132604956	NA	T	A	NA	RAD50	Replacement	V892E	+	22.756	0.996	0.945	SL119751;SL119752	NA
YALS	chr5	132604957	NA	G	A	NA	RAD50	Silent	V892V	+	10.709	0.996	0.945	SL119751;SL119752	NA
YALS	chr5	132604987	NA	C	A	NA	RAD50	Replacement	Y902*	+	35.807	0.862	0.709	SL119751;SL119752	NA
YALS	chr5	134360096	NA	T	G	NA	CDKL3	Non-Coding (Splice Acceptor)		-	18.74	0.996	0.945	SL119751;SL119752	NA
YALS	chr5	176881302	rs145827614	C	T	0.00778754	HK3	Replacement	R876H	-	16.063	0.925	0.709	SL119751;SL119752	NA
YALS	chr6	34876038	rs17703221	T	C	0.004193291	UHRF1BP1	Non-Coding (3UTR)		+	10.374	0.76	0.709	SL119751;SL119752	NA
YALS	chr6	35342634	rs11571502	G	C	0.00399361	PPARD	Non-Coding (5UTR)		+	15.059	0.043	0	SL119751;SL119752	NA
YALS	chr6	35411220	rs9658135	G	A	0.006988818	PPARD	Non-Coding (Splice Donor)		+	16.398	0.878	0.709	SL119751;SL119752	NA
YALS	chr6	35426727	rs9658170	G	A	0.006988818	PPARD	Non-Coding (3UTR)		+	10.709	0	0	SL119751;SL119752	NA
YALS	chr6	38906260	NA	C	G	NA	DNAH8	Replacement	Y3067*	+	43.839	0.988	0.945	SL119752	NA
YALS	chr6	38906299	NA	C	A	NA	DNAH8	Replacement	Y3080*	+	43.839	0.98	0.945	SL119752	NA
YALS	chr6	38906325	NA	G	A	NA	DNAH8	Replacement	G3089D	+	31.791	0.996	0.945	SL119751;SL119752	NA
YALS	chr6	75891294	NA	A	C	NA	MYO6	Replacement	E978D	+	15.059	0.693	0.472	SL119751;SL119752	NA
YALS	chr6	116431127	rs34994230	A	G	0.006888978	DSE	Replacement	I282V	+	23.425	0.996	0.945	SL119751;SL119752	NA
YALS	chr6	121449716	NA	A	G	NA	GJA1	Non-Coding (3UTR)		+	15.059	0.996	0.945	SL119751;SL119752	NA
YALS	chr6	138339851	NA	C	A	NA	KIAA1244	Non-Coding (3UTR)		+	11.043	0.039	0	SL119751;SL119752	NA
YALS	chr6	157208928	NA	C	T	NA	ARID1B	Non-Coding (3UTR)		+	14.055	0.996	0.945	SL119751;SL119752	NA
YALS	chr6	157208934	NA	C	T	NA	ARID1B	Non-Coding (3UTR)		+	12.717	0.992	0.945	SL119751;SL119752	NA
YALS	chr6	157208941	NA	G	T	NA	ARID1B	Non-Coding (3UTR)		+	13.051	0.996	0.945	SL119751;SL119752	NA
YALS	chr7	5943927	NA	A	C	NA	RSPH10B2	Replacement	N531K	-	23.091	0.024	0	SL119751;SL119752	NA
YALS	chr7	5943938	NA	T	G	NA	RSPH10B2	Replacement	I528L	-	24.429	0.449	0.236	SL119751;SL119752	NA
YALS	chr7	87904377	NA	A	C	NA	DBF4	Replacement	D337A	+	26.102	0.996	0.945	SL119751;SL119752	NA
YALS	chr7	87904378	NA	C	T	NA	DBF4	Silent	D337D	+	13.051	0.996	0.945	SL119751;SL119752	NA
YALS	chr7	87904409	NA	A	T	NA	DBF4	Replacement	K348*	+	40.827	0.972	0.945	SL119751	NA
YALS	chr7	92519028	NA	C	A	NA	PEX1	Silent	V108V	-	15.059	0.996	0.945	SL119751;SL119752	NA
YALS	chr7	107657564	NA	A	G	NA	SLC26A4-AS1	Non-Coding		-	10.039	0.008	0	SL119751;SL119752	NA
YALS	chr7	139561645	NA	A	T	NA	HIPK2	Non-Coding (3UTR)		-	15.394	1	0.945	SL119751;SL119752	NA
YALS	chr8	22693189	NA	T	C	NA	EGR3	Non-Coding (5UTR)		-	13.051	0.815	0.709	SL119751;SL119752	NA
YALS	chr8	41931283	rs117665105	T	C	0.006988818	KAT6A	Non-Coding (3UTR)		-	10.039	0.902	0.709	SL119751;SL119752	NA
YALS	chr8	93804878	rs201791586	G	A	0.000199681	TMEM67	Silent	A732A	+	14.39	0.992	0.945	SL119751;SL119752	NA
YALS	chr8	93804884	NA	A	G	NA	TMEM67	Non-Coding (Splice Donor)		+	10.374	0.791	0.709	SL119751;SL119752	NA
YALS	chr9	66918360	rs531820325	C	A	0.0000998	ZNF658	Replacement	T265K	+	14.39	0.004	0	SL119751;SL119752	NA
YALS	chr9	85677459	NA	A	T	NA	AGTPBP1	Replacement	I138N	-	26.772	0.984	0.945	SL119751;SL119752	NA
YALS	chr9	110429999	rs142508835	A	T	0.009185304	SVEP1	Replacement	S1846T	-	22.421	0.748	0.709	SL119751;SL119752	NA
YALS	chr9	137171651	rs72763276	G	A	0.003194888	TMEM210	Replacement	R72W	-	10.374	0.551	0.472	SL119751;SL119752	NA
YALS	chr9	137452391	NA	T	G	NA	NSMF	Replacement	I374L	-	23.76	1	0.945	SL119751;SL119752	NA
YALS	chr9	137452394	NA	T	G	NA	NSMF	Replacement	K373Q	-	23.425	0.996	0.945	SL119751;SL119752	NA
YALS	chr10	27195886	NA	T	G	NA	ACBD5	Non-Coding (3UTR)		-	10.374	0.094	0	SL119751;SL119752	NA
YALS	chr10	47001445	NA	C	T	NA	PTPN20A	Non-Coding (3UTR)		+	10.039	0.028	0	SL119752	SL119751
YALS	chr10	47523418	NA	C	T	NA	AGAP10	Replacement	E37K	-	12.717	0.008	0	SL119751;SL119752	NA
YALS	chr10	99794460	NA	G	A	NA	ABCC2	Replacement	W208*	+	37.815	0.996	0.945	SL119751;SL119752	NA
YALS	chr10	133289836	NA	T	C	NA	TUBGCP2	Replacement	I320V	-	17.067	0.996	0.945	SL119751;SL119752	NA
YALS	chr11	2138714	NA	G	C	NA	IGF2	Non-Coding (5UTR)		-	15.728	0.972	0.945	SL119751;SL119752	NA
YALS	chr11	47261271	NA	A	G	NA	NR1H3	Replacement	K177R	+	27.106	0.996	0.945	SL119751;SL119752	NA
YALS	chr11	62702462	NA	A	C	NA	BSCL2	Non-Coding (Splice Donor)		-	15.394	0.976	0.945	SL119751;SL119752	NA
YALS	chr11	84923413	rs146213168	C	T	0.009784345	DLG2	Non-Coding (5UTR)		-	19.075	0.988	0.945	SL119751;SL119752	NA
YALS	chr12	56586866	NA	T	A	NA	RBMS2	Silent	S297S	+	21.083	0.996	0.945	SL119751;SL119752	NA
YALS	chr12	56586893	NA	G	C	NA	RBMS2	Replacement	W306C	+	22.087	0.992	0.945	SL119751;SL119752	NA
YALS	chr12	68841234	NA	T	G	NA	MDM2	Non-Coding (3UTR)		+	11.043	0.433	0.236	SL119751;SL119752	NA
YALS	chr12	69820897	NA	A	T	NA	RAB3IP	Non-Coding (3UTR)		+	13.386	0.142	0	SL119751;SL119752	NA
YALS	chr12	101352119	NA	C	A	NA	UTP20	Replacement	S1650*	+	39.823	0.988	0.945	SL119752	NA
YALS	chr12	101352135	NA	C	A	NA	UTP20	Replacement	Y1655*	+	37.815	1	0.945	SL119752	NA
YALS	chr12	101352149	NA	T	A	NA	UTP20	Replacement	I1660N	+	31.791	1	0.945	SL119751;SL119752	NA
YALS	chr12	109188118	NA	T	G	NA	ACACB	Replacement	F700L	+	22.756	0.996	0.945	SL119751;SL119752	NA
YALS	chr13	101722800	rs149661933	C	T	0.004992013	FGF14	Non-Coding (3UTR)		-	11.043	0.555	0.472	SL119751;SL119752	NA
YALS	chr14	49895956	rs1064615	T	G	0.008985623	ARF6	Non-Coding (3UTR)		+	14.39	0.075	0	SL119751;SL119752	NA
YALS	chr14	52756579	NA	C	A	NA	STYX	Replacement	P91T	+	20.748	1	0.945	SL119751;SL119752	NA
YALS	chr14	52756605	NA	C	A	NA	STYX	Replacement	F99L	+	17.402	0.996	0.945	SL119751;SL119752	NA
YALS	chr14	55067260	NA	C	A	NA	MAPK1IP1L	Non-Coding (3UTR)		+	11.043	0.201	0	SL119751;SL119752	NA
YALS	chr15	38484265	NA	G	C	NA	FAM98B	Replacement	G303A	+	20.748	0.996	0.945	SL119751;SL119752	NA
YALS	chr15	43154830	NA	A	T	NA	TMEM62	Replacement	Q394L	+	18.406	0.992	0.945	SL119751;SL119752	NA
YALS	chr15	89195615	rs146738558	G	A	0.002995208	ABHD2	Non-Coding (3UTR)		+	15.059	1	0.945	SL119751;SL119752	NA

YALS	chr16	10747281	NA	G	A	NA	NUBP1	Non-Coding (Splice Donor)		+	10.374	0.276	0.236	SL119751;SL119752	NA
YALS	chr16	23562624	NA	G	A	NA	UBFD1	Non-Coding (Splice Acceptor)		+	21.752	0.925	0.709	SL119751;SL119752	NA
YALS	chr16	77284045	NA	T	A	NA	ADAMTS18	Replacement	N1193Y	-	16.732	0.996	0.945	SL119751;SL119752	NA
YALS	chr16	87419785	NA	G	A	NA	ZCCHC14	Replacement	P211L	-	22.421	1	0.945	SL119751;SL119752	NA
YALS	chr16	87419794	NA	A	G	NA	ZCCHC14	Replacement	L208P	-	25.433	1	0.945	SL119751;SL119752	NA
YALS	chr16	87419831	NA	T	A	NA	ZCCHC14	Replacement	R196W	-	26.102	0.945	0.945	SL119751;SL119752	NA
YALS	chr16	89919683	rs11547464	G	A	0.002795527	MC1R	Replacement	R142H	+	22.087	1	0.945	SL119751;SL119752	NA
YALS	chr17	6695727	NA	T	A	NA	SLC13A5	Replacement	K352*	-	33.799	0.012	0	SL119751;SL119752	NA
YALS	chr17	7602906	NA	C	T	NA	FXR2	Non-Coding (Splice Donor)		-	16.063	0.866	0.709	SL119751;SL119752	NA
YALS	chr17	18805539	rs2589696	A	G	NA	TVP23B	Non-Coding (Splice Acceptor)		+	11.378	0.839	0.709	SL119751;SL119752	NA
YALS	chr17	39066886	NA	G	C	NA	PLXDC1	Non-Coding (3UTR)		-	11.713	0.039	0	SL119751;SL119752	NA
YALS	chr17	40701933	NA	T	A	NA	KRT24	Replacement	I206F	-	29.783	0.5	0.472	SL119751;SL119752	NA
YALS	chr17	50135246	NA	A	G	NA	PPP1R9B	Non-Coding (3UTR)		-	13.72	0.992	0.945	SL119751;SL119752	NA
YALS	chr17	65225096	rs34797451	G	A	0.00399361	RGS9	Replacement	R498H	+	22.756	0.555	0.472	SL119751;SL119752	NA
YALS	chr18	11854252	NA	T	C	NA	CHMP1B	Non-Coding (3UTR)		+	19.744	0.409	0.236	SL119751;SL119752	NA
YALS	chr18	11854300	NA	C	T	NA	CHMP1B	Non-Coding (3UTR)		+	12.717	0.067	0	SL119751;SL119752	NA
YALS	chr18	79342309	NA	C	A	NA	ATP9B	Replacement	C775*	+	12.047	0.992	0.945	SL119751	NA
YALS	chr19	111016	rs200336441	T	G	NA	OR4F17	Replacement	F113C	+	10.709	0.913	0.709	SL119751;SL119752	NA
YALS	chr19	3275972	NA	G	C	NA	CELF5	Replacement	G171R	+	18.74	0.953	0.945	SL119751;SL119752	NA
YALS	chr19	3275973	NA	G	C	NA	CELF5	Replacement	G171A	+	18.74	0.961	0.945	SL119751;SL119752	NA
YALS	chr19	3275975	NA	A	C	NA	CELF5	Replacement	S172R	+	17.402	0.972	0.945	SL119751;SL119752	NA
YALS	chr19	3275976	NA	G	C	NA	CELF5	Replacement	S172T	+	17.067	0.972	0.945	SL119751;SL119752	NA
YALS	chr19	5744446	NA	T	A	NA	CATSPERD	Replacement	L198*	+	33.799	0.008	0	SL119751;SL119752	NA
YALS	chr19	5744449	NA	G	A	NA	CATSPERD	Replacement	G199D	+	15.728	0.012	0	SL119751;SL119752	NA
YALS	chr19	5768223	NA	T	A	NA	CATSPERD	Replacement	Y539N	+	23.425	0.028	0	SL119751;SL119752	NA
YALS	chr19	6667118	NA	A	T	NA	TNFSF14	Replacement	L62H	-	12.047	0.992	0.945	SL119751;SL119752	NA
YALS	chr19	6667130	NA	G	T	NA	TNFSF14	Replacement	P58Q	-	10.039	0.921	0.709	SL119751;SL119752	NA
YALS	chr19	10173904	NA	T	A	NA	DNMT1	Replacement	D217V	-	18.071	0.819	0.709	SL119751;SL119752	NA
YALS	chr19	16552144	NA	A	G	NA	SLC35E1	Non-Coding (3UTR)		-	10.374	0.165	0	SL119751;SL119752	NA
YALS	chr19	19933957	NA	T	A	NA	ZNF93	Silent	I334I	+	16.732	0.858	0.709	SL119751;SL119752	NA
YALS	chr19	19933962	NA	C	T	NA	ZNF93	Replacement	T336I	+	16.398	0.78	0.709	SL119751;SL119752	NA
YALS	chr19	19933969	NA	G	T	NA	ZNF93	Replacement	E338D	+	15.059	0.602	0.472	SL119751;SL119752	NA
YALS	chr19	19933971	NA	A	T	NA	ZNF93	Replacement	K339I	+	15.728	0.591	0.472	SL119751;SL119752	NA
YALS	chr19	21808503	NA	A	G	NA	ZNF43	Replacement	C512R	-	24.094	0.933	0.709	SL119751;SL119752	NA
YALS	chr19	39422251	NA	T	A	NA	PLEKHG2	Replacement	L547Q	+	17.402	0.969	0.945	SL119751;SL119752	NA
YALS	chr19	47874750	NA	T	C	NA	SULT2A1	Replacement	S218G	-	19.409	0.748	0.709	SL119751;SL119752	NA
YALS	chr19	47874755	NA	T	C	NA	SULT2A1	Replacement	K216R	-	22.087	0.795	0.709	SL119751;SL119752	NA
YALS	chr19	49625977	NA	T	G	NA	PRR12	Non-Coding (3UTR)		+	13.051	0.098	0	SL119751;SL119752	NA
YALS	chr19	49959773	rs201740168	C	A	NA	SIGLEC11	Replacement	A265S	-	12.717	0.354	0.236	SL119751;SL119752	NA
YALS	chr19	50422933	NA	G	C	NA	SPIB	Replacement	E79Q	+	12.717	0.016	0	SL119751;SL119752	NA
YALS	chr19	50422935	NA	A	C	NA	SPIB	Replacement	E79D	+	11.713	0.016	0	SL119751;SL119752	NA
YALS	chr19	53914590	NA	A	C	NA	CACNG7	Non-Coding (Splice Donor)		+	14.724	0.988	0.945	SL119751;SL119752	NA
YALS	chr19	54927666	NA	T	G	NA	NLRP7	Replacement	S946R	-	22.087	0.055	0	SL119751;SL119752	NA
YALS	chr20	45078818	NA	C	T	NA	STK4	Non-Coding (3UTR)		+	10.374	0.382	0.236	SL119751;SL119752	NA
YALS	chr21	26841068	NA	G	T	NA	ADAMTS1	Replacement	N436K	-	12.047	0.917	0.709	SL119751;SL119752	NA
YALS	chr21	26841073	NA	A	C	NA	ADAMTS1	Replacement	S435A	-	16.063	0.992	0.945	SL119751;SL119752	NA
YALS	chr21	26841076	NA	G	C	NA	ADAMTS1	Replacement	L434V	-	17.067	0.996	0.945	SL119751;SL119752	NA
YALS	chr21	26841089	NA	C	A	NA	ADAMTS1	Replacement	M429I	-	21.752	0.984	0.945	SL119751;SL119752	NA
YALS	chr21	26841093	NA	T	A	NA	ADAMTS1	Replacement	H428L	-	20.079	0.972	0.945	SL119751;SL119752	NA
YALS	chr21	26841094	NA	G	C	NA	ADAMTS1	Replacement	H428D	-	19.075	0.969	0.945	SL119751;SL119752	NA
YALS	chr21	26841097	NA	A	G	NA	ADAMTS1	Replacement	S427P	-	17.736	0.925	0.709	SL119751;SL119752	NA
YALS	chrX	13816977	rs3747420	T	C	0.000455789	GPM6B	Non-Coding (5UTR)		-	10.039	0.992	0.945	SL119752	SL119751
YALS	chrX	24550436	rs1055186	A	C	0.01	PDK3	Non-Coding (3UTR)		+	12.047	0.063	0	SL119751	SL119752
YALS	chrX	40680755	NA	T	C	NA	MED14	Non-Coding (Splice Donor)		-	15.394	0.984	0.945	SL119751;SL119752	NA
OALS	chr1	1722769	NA	A	G	NA	CDK11A	Replacement	L17P	-	21.752	1	0.945	SL119753;SL119754	NA
OALS	chr1	166939574	rs41269698	G	A	0.007587859	ILDR2	Non-Coding (Splice Acceptor)		-	15.394	0.996	0.945	SL119753;SL119754	NA
OALS	chr1	167126528	rs6668826	G	A	0.000798722	DUSP27	Replacement	R466H	+	12.047	0.083	0	SL119753	SL119754
OALS	chr2	110543432	NA	T	C	NA	RGPD8	Replacement	E798G	-	18.071	0.976	0.945	SL119753;SL119754	NA
OALS	chr3	10505548	rs111408739	T	C	NA	ATP2B2	Non-Coding (5UTR)		-	16.732	0.909	0.709	SL119753;SL119754	NA
OALS	chr3	113396696	rs77501585	C	G	0.009984026	CFAP44	Replacement	G534A	-	29.783	0.909	0.709	SL119753;SL119754	NA
OALS	chr5	1240642	rs7447815	C	G	0.000599042	SLC6A18	Replacement	Y319*	+	26.102	0.063	0	SL119753;SL119754	NA
OALS	chr5	140552044	rs202193903;rs368142622	C	G	NA	SRA1	Non-Coding		-	19.744	0.382	0.236	SL119753	SL119754
OALS	chr5	160259745	rs139134014	C	T	0.004592652	CCNJL	Replacement	V151I	-	13.72	0.417	0.236	SL119753;SL119754	NA
OALS	chr6	149572573	NA	G	A	NA	GINM1	Replacement	V83I	+	22.087	1	0.945	SL119753;SL119754	NA
OALS	chr6	160707780	rs143079629	G	A	0.001797125	PLG	Replacement	R89K	+	15.059	0.823	0.709	SL119753;SL119754	NA
OALS	chr7	99434936	rs150504114	G	A	0.007188498	PTCD1	Replacement	R103C	-	15.728	0.228	0	SL119753;SL119754	NA
OALS	chr7	100107269	rs146348021	C	T	0.001397764	TAF6	Replacement	G671S	-	14.39	0.161	0	SL119753;SL119754	NA
OALS	chr7	100127910	rs201045178	A	C	0.000399361	MBLAC1	Replacement	Q172P	+	21.752	0.413	0.236	SL119753;SL119754	NA
OALS	chr8	38393827	NA	A	T	NA	LETM2	Non-Coding (3UTR)		+	14.055	0.508	0.472	SL119753;SL119754	NA
OALS	chr9	83880361	rs200952027	C	T	0.001500001	KIF27	Replacement	R860Q	-	22.756	0.953	0.945	SL119754	SL119753
OALS	chr10	45773308	NA	G	C	NA	FAM21C	Replacement	G674R	+	23.091	0.98	0.945	SL119753;SL119754	NA
OALS	chr10	45826107	NA	G	C	NA	AGAP6	Replacement	D515E	-	16.398	0.807	0.709	SL119753;SL119754	NA
OALS	chr10	50129923	NA	C	A	NA	FAM21A	Replacement	P1177T	+	20.748	0.921	0.709	SL119753;SL119754	NA
OALS	chr10	73763876	rs35528438	A	G	0.00798722	SEC24C	Replacement	I374V	+	21.752	0.996	0.945	SL119753;SL119754	NA
OALS	chr11	67253595	rs34925153	A	G	0.006389776	KDM2A	Silent	P1025P	+	14.39	0.988	0.945	SL119753;SL119754	NA
OALS	chr12	133080312	rs116668890	G	A	NA	ZNF140	Non-Coding (5UTR)		+	11.043	0	0	SL119753;SL119754	NA
OALS	chr19	7613156	NA	T	C	NA	CAMSAP3	Replacement	F915S	+	23.091	0.98	0.945	SL119753;SL119754	NA
OALS	chr19	7613161	NA	A	C	NA	CAMSAP3	Replacement	K917Q	+	23.425	0.992	0.945	SL119753;SL119754	NA
OALS	chr19	32973495	rs531017428	T	C	NA	C19orf40	Replacement	L59P	+	21.417	0.98	0.945	SL119753;SL119754	NA
OALS	chr19	49782063	NA	T	C	NA	AP2A1	Replacement	S85P	+	25.768	0.996	0.945	SL119753;SL119754	NA
OALS	chr21	36387733	NA	G	A	NA	CHAF1B	Non-Coding (Splice Donor)		+	18.74	0.988	0.945	SL119753;SL119754	NA
OALS	chr22	15528700	NA	T	A	NA	OR11H1	Replacement	M181K	+	23.76	0.917	0.709	SL119753;SL119754	NA
OALS	chr22	32194461	rs3986037	C	T	0.003194888	RFPL2	Replacement	R50H	-	12.382	0.087	0	SL119753;SL119754	NA
OALS	chr22	37655664	NA	C	G	NA	SH3BP1	Replacement	L696V	+	15.394	0.984	0.945	SL119753;SL119754	NA
OALS	chrX	88753806	rs5984611	G	A	0.00375	CPXCR1	Replacement	R131H	+	15.059	0	0	SL119753	SL119754

SupplementaryTable 3: fly ortholog of human genes

patient type	human symbol	fly symbol	Fly GeneID	FlyBaseID	DIOPT Score	Weighted Score	Rank	Best Score	Best Score Reverse	Prediction Derived From
YALS	ST7L	CG3634	40301	FBgn0037026	8	7.706	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	CTRC	CG32260	317943	FBgn0052260	2	1.933	high	Yes	Yes	Compara, RoundUp
YALS	GON4L	mute	2768848	FBgn0085444	6	5.908	high	Yes	Yes	Compara, Inparanoid, Panther, Phylome, RoundUp, TreeFam
YALS	SERBP1	vig2	43016	FBgn0046214	8	7.708	high	Yes	Yes	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	SERBP1	vig	34885	FBgn0024183	8	7.708	high	Yes	Yes	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	GFI1	sens-2	33957	FBgn0051632	6	5.803	moderate	Yes	No	Compara, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	ANKRD39	CG44001	326173	FBgn0264743	8	7.813	high	Yes	Yes	Compara, Homologene, OMA, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	PMS1	Pms2	36705	FBgn0011660	2	1.903	moderate	Yes	No	eggNOG, RoundUp
YALS	RGPD4	Nup358	43041	FBgn0039302	8	7.706	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	GNAI2	Galphai	38765	FBgn0001104	10	9.719	moderate	Yes	No	Compara, eggNOG, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	ACAP2	CenB1A	42735	FBgn0039056	11	10.719	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	MYH15	Mhc	35007	FBgn0264695	8	7.706	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	FRAS1	kon	35104	FBgn0032683	3	2.74	moderate	Yes	No	Compara, eggNOG, Phylome
YALS	PDS5A	pds5	36286	FBgn0260012	9	8.716	moderate	Yes	No	Compara, eggNOG, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	GRSF1	glo	41431	FBgn0259139	4	3.941	moderate	Yes	No	Compara, OrthoDB, Panther, Phylome
YALS	OTUD4	otu	31789	FBgn0003023	4	3.943	moderate	Yes	No	Compara, Panther, Phylome, RoundUp
YALS	RAD50	rad50	37564	FBgn0034728	9	8.818	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OMA, Panther, Phylome, RoundUp, TreeFam
YALS	HK3	Hex-A	45875	FBgn0001186	7	6.744	moderate	Yes	No	Compara, eggNOG, OrthoDB, orthoMCL, Panther, Phylome, RoundUp
YALS	CDKL3	CG7236	33798	FBgn0031730	2	1.901	moderate	Yes	No	eggNOG, OrthoDB
YALS	PPARD	Hr96	42993	FBgn0015240	3	2.96	moderate	Yes	No	eggNOG, Panther, TreeFam
YALS	PPARD	Eip75B	39999	FBgn0000568	3	2.95	moderate	Yes	No	eggNOG, Isobase, Panther
YALS	KIAA1244	CG5937	31537	FBgn0029834	10	9.568	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, orthoMCL, Phylome, RoundUp, TreeFam
YALS	ARID1B	osa	42130	FBgn0261885	8	7.749	high	Yes	Yes	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, RoundUp
YALS	MYO6	jar	42889	FBgn0011225	10	9.768	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, Panther, Phylome, RoundUp, TreeFam
YALS	UHRF1BP1	CG34126	318872	FBgn0083962	9	8.709	high	Yes	Yes	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	DNAH8	CG9492	41171	FBgn0037726	7	6.705	moderate	Yes	No	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, TreeFam
YALS	DBF4	chif	34974	FBgn0000307	4	3.773	moderate	Yes	No	eggNOG, Phylome, RoundUp, TreeFam
YALS	HIPK2	Hipk	38070	FBgn0035142	9	8.729	high	Yes	Yes	eggNOG, Inparanoid, Isobase, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	PEX1	Pex1	45460	FBgn0013563	8	7.708	high	Yes	Yes	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	TMEM67	CG15923	42443	FBgn0038814	10	9.718	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OMA, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	KAT6A	enok	37859	FBgn0034975	7	6.608	high	Yes	Yes	Compara, eggNOG, Inparanoid, orthoMCL, Phylome, RoundUp, TreeFam
YALS	EGR3	sr	42162	FBgn0003499	3	2.893	moderate	Yes	No	Compara, RoundUp, TreeFam
YALS	SVEP1	uif	33983	FBgn0031879	2	1.905	high	Yes	Yes	eggNOG, Inparanoid
YALS	AGTPBP1	CG31019	318558	FBgn0051019	2	1.903	moderate	Yes	No	eggNOG, RoundUp
YALS	AGTPBP1	NnaD	32329	FBgn0265726	2	1.8	moderate	Yes	No	eggNOG, orthoMCL
YALS	AGAP10	CenG1A	34803	FBgn0028509	2	1.81	moderate	Yes	No	orthoMCL, Phylome
YALS	ABCC2	MRP	34686	FBgn0032456	6	5.601	moderate	Yes	No	Compara, eggNOG, OrthoDB, orthoMCL, Phylome, TreeFam
YALS	ACBD5	CG8814	33492	FBgn0031478	8	7.706	high	Yes	Yes	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	TUBGCP2	Grip84	32946	FBgn0026430	12	11.669	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	NR1H3	EcR	35540	FBgn0000546	6	5.783	high	Yes	Yes	Compara, eggNOG, Isobase, orthoMCL, Panther, RoundUp
YALS	DLG2	dlg1	32083	FBgn0001624	8	7.609	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Phylome, RoundUp, TreeFam
YALS	BSCL2	Seipin	31245	FBgn0040336	8	7.708	high	Yes	Yes	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	RBMS2	shep	38605	FBgn0052423	7	6.709	high	Yes	Yes	Compara, eggNOG, Inparanoid, OrthoDB, Phylome, RoundUp, TreeFam
YALS	ACACB	ACC	35761	FBgn0033246	8	7.708	moderate	Yes	No	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	UTP20	CG4554	37570	FBgn0034734	10	9.718	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OMA, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	FGF14	bnl	42356	FBgn0014135	3	2.96	moderate	Yes	No	eggNOG, Panther, TreeFam
YALS	STYX	Mkp	4379907	FBgn0083992	4	3.804	moderate	Yes	No	eggNOG, OrthoDB, orthoMCL, RoundUp
YALS	ARF6	Arf51F	36699	FBgn0013750	12	11.669	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam

YALS	ABHD2	Hydr2	33532	FBgn0014906	11	10.719	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	FAM98B	CG5913	43132	FBgn0039385	8	7.909	moderate	Yes	No	Compara, eggNOG, Inparanoid, OMA, OrthoDB, Panther, RoundUp, TreeFam
YALS	NUBP1	CG17904	35000	FBgn0032597	10	9.768	high	Yes	Yes	Compara, Homologene, Inparanoid, Isobase, OMA, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	ADAMTS18	CG4096	31490	FBgn0029791	4	3.931	moderate	Yes	No	Compara, eggNOG, OrthoDB, Panther
YALS	TVP23B	CG5021	39025	FBgn0035944	10	9.719	high	Yes	Yes	Compara, eggNOG, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	PPP1R9B	Spn	46194	FBgn0010905	5	4.948	moderate	Yes	No	Compara, Inparanoid, Panther, Phylome, RoundUp
YALS	FXR2	Fmr1	37528	FBgn0028734	8	7.706	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	SLC13A5	Indy	40049	FBgn0036816	9	8.759	high	Yes	Yes	Compara, eggNOG, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp
YALS	RGS9	CG42450	32874	FBgn0259927	5	4.77	high	Yes	Yes	eggNOG, orthoMCL, Panther, Phylome, TreeFam
YALS	PLXDC1	l(1)G0289	31964	FBgn0028331	7	6.808	moderate	Yes	No	Compara, eggNOG, Inparanoid, Panther, Phylome, RoundUp, TreeFam
YALS	CHMP1B	Chmp1	40036	FBgn0036805	9	8.819	high	Yes	Yes	Compara, eggNOG, Inparanoid, OMA, OrthoDB, Panther, Phylome, RoundUp, TreeFam
YALS	ATP9B	CG31729	34736	FBgn0051729	10	9.665	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, orthoMCL, Panther, Phylome, TreeFam
YALS	CACNG7	stg1	318064	FBgn0064123	4	3.86	high	Yes	Yes	eggNOG, orthoMCL, Panther, TreeFam
YALS	CELF5	bru-3	39527	FBgn0264001	8	7.606	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OrthoDB, orthoMCL, Phylome, TreeFam
YALS	SLC35E1	CG14621	33128	FBgn0031183	10	9.656	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
YALS	PLEKHG2	GEFmeso	37134	FBgn0050115	7	6.844	high	Yes	Yes	Compara, eggNOG, Isobase, OrthoDB, Panther, RoundUp, TreeFam
YALS	SULT2A1	St2	41098	FBgn0037665	6	5.749	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, Phylome, RoundUp
YALS	STK4	hpo	37247	FBgn0261456	7	6.808	moderate	Yes	No	Compara, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	ADAMTS1	AdamTS-A	41887	FBgn0038341	7	6.744	moderate	Yes	No	Compara, eggNOG, OrthoDB, orthoMCL, Panther, Phylome, RoundUp
YALS	GPM6B	M6	40383	FBgn0037092	5	4.875	moderate	Yes	No	eggNOG, Inparanoid, Panther, Phylome, TreeFam
YALS	PDK3	Pdk	35970	FBgn0017558	12	11.669	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
YALS	MED14	MED14	38073	FBgn0035145	11	10.719	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	DUSP27	CG7378	32888	FBgn0030976	3	2.831	moderate	Yes	No	Compara, eggNOG, OrthoDB
OALS	CDK11A	Pitslre	40292	FBgn0016696	7	6.919	moderate	Yes	No	eggNOG, Inparanoid, Isobase, OrthoDB, Panther, RoundUp, TreeFam
OALS	RGPD8	Nup358	43041	FBgn0039302	8	7.706	moderate	Yes	No	Compara, eggNOG, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, TreeFam
OALS	CFAP44	CG34124	4379887	FBgn0083960	9	8.713	high	Yes	Yes	Compara, eggNOG, Homologene, OMA, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	ATP2B2	PMCA	43787	FBgn0259214	8	7.708	moderate	Yes	No	Compara, eggNOG, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	SLC6A18	CG43066	37129	FBgn0262476	7	6.774	high	Yes	Yes	eggNOG, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	CCNJL	CycJ	38428	FBgn0010317	4	3.795	moderate	Yes	No	Compara, eggNOG, Inparanoid, TreeFam
OALS	MBLAC1	CG9117	33846	FBgn0031766	10	9.709	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	PTCD1	CG4611	38601	FBgn0035591	7	6.679	high	Yes	Yes	eggNOG, Inparanoid, OrthoDB, orthoMCL, Phylome, RoundUp, TreeFam
OALS	TAF6	Taf6	40134	FBgn0010417	9	8.708	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	LETM2	Letm1	37912	FBgn0019886	6	5.803	moderate	Yes	No	Compara, eggNOG, Panther, Phylome, RoundUp, TreeFam
OALS	KIF27	cos	35653	FBgn0000352	3	3.02	moderate	Yes	No	OMA, Panther, Phylome
OALS	FAM21C	FAM21	37331	FBgn0034529	6	5.728	high	Yes	Yes	eggNOG, Inparanoid, OMA, orthoMCL, Phylome, RoundUp
OALS	SEC24C	Sec24CD	33409	FBgn0262126	9	8.758	high	Yes	Yes	Compara, Homologene, Inparanoid, Isobase, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	FAM21A	FAM21	37331	FBgn0034529	6	5.728	high	Yes	Yes	eggNOG, Inparanoid, OMA, orthoMCL, Phylome, RoundUp
OALS	AGAP6	CenG1A	34803	FBgn0028509	4	3.67	moderate	Yes	No	eggNOG, orthoMCL, Phylome, TreeFam
OALS	KDM2A	Kdm2	41090	FBgn0037659	10	9.768	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, Isobase, OMA, Panther, Phylome, RoundUp, TreeFam
OALS	C19orf40	Ercc1	36654	FBgn0028434	2	1.81	moderate	Yes	No	eggNOG, Phylome
OALS	AP2A1	AP-2alpha	33211	FBgn0264855	10	9.719	moderate	Yes	No	Compara, eggNOG, Inparanoid, OMA, OrthoDB, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	CAMSAP3	Patronin	36978	FBgn0263197	7	6.703	moderate	Yes	No	Compara, eggNOG, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	CHAF1B	Caf1-105	36107	FBgn0033526	9	8.708	high	Yes	Yes	Compara, eggNOG, Homologene, Inparanoid, orthoMCL, Panther, Phylome, RoundUp, TreeFam
OALS	SH3BP1	RhoGAP92B	42371	FBgn0038747	6	5.885	moderate	Yes	No	eggNOG, Inparanoid, OMA, Panther, Phylome, TreeFam

Supplementary Table 4: RNAi lines used in this study

patient type	gene symbol	fly ortholog	stock source	Reagent ID
YALS	ABCC2	MRP	TRiP Short Hairpin	38316
YALS	ABCC2	MRP	VDRC KK	105419
YALS	ACACB	ACC	TRiP Short Hairpin	34885
YALS	ADAMTS18	CG4096	TRiP Short Hairpin	44522
YALS	AGTPBP1	NnaD	TRiP Short Hairpin	33549
YALS	AGTPBP1	NnaD	TRiP Short Hairpin	44036
YALS	ARF6	Arf51F	TRiP Short Hairpin	51417
YALS	ARF6	Arf51F	TRiP Short Hairpin	27261
YALS	ARID1B	osa	TRiP Short Hairpin	35447
YALS	ARID1B	osa	TRiP Short Hairpin	31266
YALS	ATP9B	CG31729	TRiP Short Hairpin	51819
YALS	BSCL2	Seipin	TRiP Short Hairpin	37501
YALS	CELF5	bru-3	TRiP Short Hairpin	50734
YALS	CELF5	bru-3	TRiP Short Hairpin	43318
YALS	CELF5	bru-3	VDRC KK	109946
YALS	CHMP1B	Chmp1	TRiP Short Hairpin	33928
YALS	CHMP1B	Chmp1	TRiP Short Hairpin	28906
YALS	DBF4	chif	TRiP Short Hairpin	33365
YALS	DLG2	dlg1	TRiP Short Hairpin	31521
YALS	DLG2	dlg1	TRiP Short Hairpin	35286
YALS	DLG2	dlg1	VDRC KK	109274
YALS	DNAH8	CG9492	TRiP Short Hairpin	51725
YALS	EGR3	sr	TRiP Short Hairpin	27701
YALS	FAM98B	CG5913	TRiP Short Hairpin	53965
YALS	FAM98B	CG5913	VDRC GD	40336
YALS	FGF14	bnl	TRiP Short Hairpin	34572
YALS	FXR2	Fmr1	TRiP Short Hairpin	35200
YALS	FXR2	Fmr1	TRiP Short Hairpin	27484
YALS	GFI1	sens-2	TRiP Short Hairpin	34984
YALS	GPM6B	M6	TRiP Short Hairpin	37503
YALS	GPM6B	M6	TRiP Short Hairpin	54032
YALS	GRSF1	glo	TRiP Short Hairpin	36066
YALS	GRSF1	glo	TRiP Short Hairpin	33668
YALS	HIPK2	Hipk	TRiP Short Hairpin	35363
YALS	HIPK2	Hipk	TRiP Short Hairpin	56458
YALS	HIPK2	Hipk	TRiP Short Hairpin	20760
YALS	HIPK2	Hipk	VDRC KK	108254
YALS	HK3	Hex-A	TRiP Short Hairpin	35155
YALS	HK3	Hex-A	VDRC KK	103536
YALS	KAT6A	enok	TRiP Short Hairpin	42941
YALS	KAT6A	enok	TRiP Short Hairpin	29518
YALS	MED14	MED14	TRiP Short Hairpin	34575

YALS	MYH15	Mhc	TRiP Short Hairpin	35729
YALS	MYH15	Mhc	TRiP Short Hairpin	26299
YALS	MYH15	Mhc	VDRC KK	105355
YALS	NR1H3	EcR	TRiP Short Hairpin	58286
YALS	NR1H3	EcR	TRiP Short Hairpin	29374
YALS	OTUD4	otu	TRiP Short Hairpin	34065
YALS	PDK3	Pdk	TRiP Short Hairpin	28635
YALS	PDK3	Pdk	TRiP Short Hairpin	35142
YALS	PDK3	Pdk	VDRC KK	106641
YALS	PDS5A	pds5	TRiP Short Hairpin	35632
YALS	PEX1	Pex1	TRiP Short Hairpin	51497
YALS	PEX1	Pex1	TRiP Short Hairpin	28979
YALS	PLEKHG2	GEFmeso	TRiP Short Hairpin	42545
YALS	PLEKHG2	GEFmeso	VDRC GD	39952
YALS	PLXDC1	l(1)G0289	TRiP Short Hairpin	33690
YALS	PLXDC1	l(1)G0289	TRiP Short Hairpin	32910
YALS	PMS1	Pms2	TRiP Short Hairpin	55614
YALS	PPARD	Eip75B	TRiP Short Hairpin	43231
YALS	PPARD	Eip75B	TRiP Short Hairpin	26717
YALS	PPARD	Eip75B	VDRC KK	108399
YALS	RBMS2	shep	TRiP Short Hairpin	43545
YALS	RBMS2	shep	TRiP Short Hairpin	38218
YALS	RGPD4	Nup358	TRiP Short Hairpin	34967
YALS	RGPD4	Nup358	TRiP Short Hairpin	33003
YALS	SERBP1	vig	TRiP Short Hairpin	35183
YALS	SERBP1	vig	TRiP Short Hairpin	35184
YALS	STK4	hpo	TRiP Short Hairpin	35176
YALS	STK4	hpo	TRiP Short Hairpin	27661
YALS	SVEP1	uif	TRiP Short Hairpin	38354
YALS	SVEP1	uif	TRiP Short Hairpin	38365
YALS	SVEP1	uif	VDRC KK	101153
YALS	TMEM67	CG15923	TRiP Short Hairpin	53289
YALS	TUBGCP2	Grip84	TRiP Short Hairpin	33548
YALS	UTP20	CG4554	TRiP Short Hairpin	53270
YALS	UTP20	CG4554	VDRC GD	103706
YALS	UTP20	CG4554	VDRC KK	103706
YALS	UTP20	CG4554	VDRC GD	21620
OALS	CAMSAP3	Patronin	TRiP Short Hairpin	36659
OALS	CCNJL	CycJ	TRiP Short Hairpin	37521
OALS	CDK11A	Pitslre	TRiP Short Hairpin	35157
OALS	CDK11A	Pitslre	VDRC KK	107303
OALS	KDM2A	Kdm2	TRiP Short Hairpin	33699
OALS	KDM2A	Kdm2	TRiP Short Hairpin	31360
OALS	KDM2A	Kdm2	VDRC KK	109295
OALS	KIF27	cos	TRiP Short Hairpin	44472

OALS	KIF27	cos	VDRC KK	108914
OALS	LETM2	Letm1	TRiP Short Hairpin	37502
OALS	SH3BP1	RhoGAP92B	TRiP Short Hairpin	33391

Supplementary Table 5: Summary of clinical information on ALS cases and controls included in targeted resequencing

		ALS	Unaffected control
Gender	Female	120 (38.7%)	141 (53.0%)
	Male	190 (61.3%)	125 (47.0%)
Average of age-at-onset		56.8	N/A
Average of age-at-recruitment		N/A	75.4

Supplementary Table 6: Gene-based analysis of rare variants for targeted resequencing

Group	Genes	Targeted Resequencing		
		variant number	SKAT p-value	SKAT-O p-value
Suppressors	CELF5	2	0.8699	0.8699
	DLG2	10	**0.0418**	0.09971
	FAM98B	3	0.48711	0.62493
	HK3	19	0.885	0.97769
	PDK3	1	0.86912	0.86912
	KDM2A	5	0.69728	0.87765
	KIF27	19	0.64552	0.88058
Enhancers	ABCC2	12	0.65511	0.60758
	MYH15	16	**0.0195**	**0.03697**
	PLEKHG2	12	0.7032	0.87329
	PPARD	3	0.3854	0.62406
	SVEP1	39	0.82087	0.89962
	UTP20	27	0.48725	0.7171
	CDK11A	15	0.8892	0.41197

Supplementary Table 7: Gene-based analysis of rare variants for WGS dataset

Group	Genes	WGS		
		variant number	SKAT p-value	SKAT-O p-value
Suppressors	CELF5	0	-	-
	DLG2	2	0.30207097	0.30207097
	FAM98B	6	0.87353369	0.31996341
	HK3	19	0.43986132	0.67842778
	PDK3	1	0.60350993	0.60350993
	KDM2A	1	0.59609034	0.59609034
	KIF27	7	0.33940203	0.42108945
Enhancers	ABCC2	16	0.96040603	0.34382896
	MYH15	6	0.01232624	0.01707692
	PLEKHG2	12	0.8085755	0.36646429
	PPARD	0	-	-
	SVEP1	23	0.71040196	0.74890023
	UTP20	18	0.72497056	0.96158609
	CDK11A	3	0.23908214	0.23908214

Supplementary Table 8: List of variants with a statistical significance found in targeted resequencing and WGS

Gene	chr	position	ID	Ref	Alt	aa change	Function	Cadd	Targeted resequencing				Replication (WGS)			
									Heterozygotes in ALS	Homozygotes in ALS	Heterozygotes in Control	Homozygotes in Control	Heterozygotes in ALS	Homozygotes in ALS	Heterozygotes in Control	Homozygotes in Control
MYH15	chr3	108394107	rs56118396	C	T	R1748Q	nonSynonymous	2	1		7					
MYH15	chr3	108398706		G	G	E1708D	nonSynonymous	3.5	1							
MYH15	chr3	108398765	rs76478083	G	A	R1689C	nonSynonymous	24	5	1	2					
MYH15	chr3	108398829		G	+A	M1667NA	nonSynonymous	NA		1						
MYH15	chr3	108410709	rs377336538	C	G	A1477P	nonSynonymous	22.5	1							
MYH15	chr3	108410805	rs368421301	C	T	G1445R	nonSynonymous	23.5			1					
MYH15	chr3	108410826	rs368538771	C	T	G1438R	nonSynonymous	26	1							
MYH15	chr3	108410882		C	C	A1419G	nonSynonymous	21	1							
MYH15	chr3	108410906		A	-A	E1411NA	nonSynonymous	NA			1					
MYH15	chr3	108428833	rs61744539	G	A	R1141*	nonSynonymous	37	4		2		1			
MYH15	chr3	108430899	rs534599773	A	G	M1102T	nonSynonymous	13.2							1	
MYH15	chr3	108437581	rs148843085	T	G	Q1085P	nonSynonymous	23.4					1			
MYH15	chr3	108441178	rs368092347	T	G	E933A	nonSynonymous	14.6					1			
MYH15	chr3	108444779		T	C	E859G	nonSynonymous	15.1					1			
MYH15	chr3	108444826		G	A	R843S	nonSynonymous	21.5	1							
MYH15	chr3	108454106	rs199678295	C	T	A787T	nonSynonymous	23.5			1					
MYH15	chr3	108476492		A	C	M400V	nonSynonymous	11.5			1					
MYH15	chr3	108499455	rs202126707	G	A	T195I	nonSynonymous	24.5	1		1				2	
MYH15	chr3	108501734		G	T	R126H	nonSynonymous	25.5			1					
MYH15	chr3	108501756	rs200749942	C	T	V119M	nonSynonymous	23.5			2					
DLG2	chr11	83462065		C	A	Q815*	StopGain	40			1					
DLG2	chr11	83786749		C	A	A484V	nonSynonymous	32			1					
DLG2	chr11	83930478	rs185568966	G	A	P344L	nonSynonymous	34	1		1					
DLG2	chr11	83965464	rs373325643	T	C	N249S	nonSynonymous	23	1							
DLG2	chr11	84163487		G	T	E95K	nonSynonymous	26.5	1							
DLG2	chr11	84316847	rs373138134	T	G	H100P	nonSynonymous	16.5			1					
DLG2	chr11	84316958	rs557645711	C	G	R63T	nonSynonymous	10.5			1					
DLG2	chr11	84317123		A	C	Q8R	nonSynonymous	11	1							
DLG2	chr11	85111692		C	T	A109D	nonSynonymous	18			1					
DLG2	chr11	85285273	rs373336609	C	T	E45K	nonSynonymous	25			1					