

ORIGINAL ARTICLE

Delineating the genetic heterogeneity of ALS using targeted high-throughput sequencing

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ABSTRACT

Background Over 100 genes have been implicated in the aetiology of amyotrophic lateral sclerosis (ALS). A detailed understanding of their independent and cumulative contributions to disease burden may help guide various clinical and research efforts.

Methods Using targeted high-throughput sequencing, we characterised the variation of 10 Mendelian and 23 low penetrance/tentative ALS genes within a population-based cohort of 444 Irish ALS cases (50 fALS, 394 sALS) and 311 age-matched and geographically matched controls.

Results Known or potential high-penetrance ALS variants were identified within 17.1% of patients (38% of fALS, 14.5% of sALS). 12.8% carried variants of Mendelian disease genes (*C9orf72* 8.78%; *SETX* 2.48%; *ALS2* 1.58%; *FUS* 0.45%; *TARDBP* 0.45%; *OPTN* 0.23%; *VCP* 0.23%; *ANG*, *SOD1*, *VAPB* 0%), 4.7% carried variants of low penetrance/tentative ALS genes and 9.7% (30% of fALS, 7.1% of sALS) carried previously described ALS variants (*C9orf72* 8.78%; *FUS* 0.45%; *TARDBP* 0.45%). 1.6% of patients carried multiple known/potential disease variants, including all identified carriers of an established ALS variant ($p<0.01$); *TARDBP:c.859G>A(p.[G287S])* ($n=2/2$ sALS). Comparison of our results with those from studies of other European populations revealed significant differences in the spectrum of disease variation ($p=1.7\times10^{-4}$).

Conclusions Up to 17% of Irish ALS cases may carry high-penetrance variants within the investigated genes. However, the precise nature of genetic susceptibility differs significantly from that reported within other European populations. Certain variants may not cause disease in isolation and concomitant analysis of disease genes may prove highly important.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a terminal neurodegenerative disease characterised by the degeneration of upper and lower motor neurons. Lifetime risk is approximately 1/400¹ and in most instances an underlying cause cannot be established. Nonetheless, 22 genes have been implicated in Mendelian forms of the condition while a further 82 have been associated with disease risk (<http://alsod.iop.kcl.ac.uk>).²

A detailed understanding of disease heterogeneity is important to facilitate appropriate stratification of subcohorts for clinical research purposes.

However, the relative importance of identified ALS genes is largely unknown and to date the most comprehensive studies have analysed only six or seven disease-associated genes.^{3 4} Investigation of the cumulative effect of variation across distinct disease loci has also been limited, although a significant excess in the co-occurrence of putative disease variants among fALS patients has recently been demonstrated.⁵ There is also little known as to how the genetic aetiology of ALS varies across populations. Previous studies have suggested significant variability in the importance of specific disease genes,^{6 7} but these studies have involved comparisons of selected patient cohorts and no comparative study of population-based cohorts has yet been performed.

To establish the relative and cumulative frequencies of disease variants across 33 of the most well-established ALS-related genes, we analysed a population-based cohort of 444 Irish ALS cases and 311 age-matched and geographically matched controls by multiplexed targeted high-throughput sequencing. This represents the most extensive survey of ALS loci to date. To assess the importance of disease heterogeneity across populations, we compare our results with those reported by previous population-based studies of major disease genes. We also search for correlations in the co-occurrence of putative disease variants and investigate the importance of cumulative susceptibility across distinct disease loci.

MATERIALS AND METHODS

Study participants

All participating patients were recruited between 1999 and 2011 through the ALS Register of the Republic of Ireland or the ALS Register of Northern Ireland.⁸ All patients were of Irish ancestry and met the revised El Escorial criteria for possible, probable or definite ALS. Patients with an identifiable family history of ALS among first, second or third degree relatives were classified as 'familial', otherwise patients were classified as 'sporadic'. Controls were neurologically normal at the time of blood donation and included the spouses of attending patients and volunteers recruited at primary care offices across the country. Informed written consent was obtained from all participants and the study was approved by the research and ethics committee in Beaumont Hospital, Dublin.



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Targeted resequencing

Indexed paired-end Illumina sequencing libraries¹⁰ were prepared for 444 cases and 311 controls. Libraries were enriched for the coding exons of target genes using custom SureSelect kits (Agilent, Santa Clara, California, USA) and resequenced at either TrinSeq (Dublin, Ireland) or GATC Biotech (Konstanz, Switzerland). Generated sequencing reads were aligned to the GRCh37 build of the human genome using Burrows-Wheeler Aligner (BWA) V0.6.1.¹¹ Subsequent quality control, depth of coverage analyses, power analyses, variant calling and variant annotation were performed using SAMtools V0.1.18,¹² the GATK V2.1–2,¹³ Picard V1.60 (<http://picard.sourceforge.net/>), Variant Effect Predictor V2.7,¹⁴ Python V2.7.3 (<http://www.python.org/>) and R V2.14.1 (<http://www.r-project.org/>) along with the March 2012 release from the 1000 genomes project,¹⁵ the ESP6500 release from the NHLBI exome sequencing project (Exome Variant Server, NHLBI Exome Sequencing Project (ESP), Seattle, Washington, USA (URL: <http://evs.gs.washington.edu/EVS/>) (Accessed 18 July 2012)) and Ensembl 69.¹⁶ Further details on library preparation, target enrichment, sequencing and the analysis of sequence data are provided in the supporting materials and methods.

Statistical analyses

Unless otherwise indicated, all statistical analyses were conducted in R V2.14.1.

Evaluation of high-penetrance disease models

One-tailed binomial tests were used to assess whether the frequencies of variant carriers within a series of control cohorts were higher than could be accounted for under high-penetrance disease models.¹⁷ These control cohorts included an Irish panel (internal controls), a European panel (internal controls, the ESP6500—European American cohort, the 1000 genomes—European cohort) and a global panel (internal controls, the full ESP6500 cohort, the full 1000 genomes cohort). The expected carrier frequencies were taken as the product of patient carrier frequencies and the respective population risks for ALS (Irish 1/290; European 1/397; Global 1/397).¹ High-penetrance disease models were rejected when the p value associated with any one of the three cohorts was <0.05. Carriers were defined as individuals homozygous for the variant allele for the evaluation of recessive disease models and individuals homozygous/ heterozygous for the variant allele for the evaluation of dominant disease models.

Analysis of variant co-occurrence

One-tailed binomial tests were used to explore whether the frequencies of cases carrying multiple splice site/non-synonymous ALS gene variants exceeded chance expectation. As per van Blitterswijk *et al*,⁵ the expected frequency of this occurrence was taken as (the number of cases carrying ≥1 variant/the total number of cases)*(the number of controls carrying ≥1 variant/the total number of controls). Variants were excluded from these analyses, if the frequency of carriers among European/Global controls from the ESP6500 and 1000 genomes projects exceeded one of several potential critical values (see online supplementary tables S3 and S4 for details).

The frequency with which carriers of previously reported ALS variants also carried variants of additional Mendelian disease genes (3/43) was used to estimate the probability of observing multiple Mendelian disease gene variants among all identified carriers of a given ALS variant (ie, 33/33 C9orf72 hexanucleotide expansion carriers OR 2/2 TARDBP:c.859G>A(p.[G287S]) carriers OR 2/2 FUS:c.1574C>T(p.[P525L]) carriers).

Analysis of population heterogeneity

The burden of putative disease variants across ANG, C9orf72, FUS, OPTN, SOD1 and TARDBP within the Irish and Italian ALS populations was compared first using c-alpha tests where singleton variants were collapsed into a single per locus count¹⁸ and second using allele count-based Fisher exact tests. To avoid artificial inflation of population differences due to biases in missing genotype rates, c-alpha test permutations were performed at each variant site independently.

Single variant association testing

Variants were tested for association with case-control status using PLINK V1.07.¹⁹ Allelic, dominant and recessive disease models were tested using Fisher exact tests. Multiple testing correction was performed by the Westfall and Young permutation method. Synonymous variants were not considered in the correction of p values obtained from non-synonymous or splice site variants. Association tests were performed with and without sample filtering based on status for established disease mutations and a family history of ALS.

RESULTS

Study participants

Four hundred and forty-four Irish ALS patients (57.7% men; mean age of onset = 61.7 ± 12.0 years; 65.4% spinal onset, 31.8% bulbar onset, 2.8% generalised onset) and 311 age-matched and geographically matched controls (47.2% men; mean age of sampling = 60.3 ± 11.8 years) were included in the study. Fifty-three patients (11.9%) were recruited through the population-based Northern Irish ALS Register (Belfast, Northern Ireland) while the remaining 391 (88.1%) were recruited through the Irish ALS Register.⁸ Fifty patients (11.3%) were classified as ‘familial’ while 394 (88.7%) were classified as ‘sporadic’ according to recently published criteria.⁹ Twenty-four of the sporadic (6.1%) and 15 of the familial (30.0%) patients previously tested positive for pathogenic expansions of the C9orf72 hexanucleotide repeat.²⁰

Targeted resequencing

Study participants were screened for variants within the coding exons of 10 genes previously associated with Mendelian forms of ALS (ALS2, ANG, C9orf72, FUS, OPTN, SETX, SOD1, TARDBP, VAPB, VCP) and 23 low penetrance/tentative ALS genes (ATXN2, CHMP2B, DCTN1, DPP6, ELP3, FGGY, FIG4, GRN, HFE, IFNK, ITPR2, MAPT, MOB3B, NEFH, NIPA1, PARK7, PON1, PON2, PON3, PRPH, SIGMAR1, SPG11, UNC13A). At the time of target gene selection, the causative variant within the chromosome 9p linkage region had not been resolved and accordingly MOB3B and IFNK were included as tentative ALS genes.²¹ Given the large number of study participants and target exons involved, samples were resequenced using a multiplexed targeted high-throughput sequencing strategy.²² In total, 26.3 × 10⁶ sequencing reads mapping to target positions were generated. Ninety-nine per cent of target bases were covered by at least 1 sequencing read and on an average each target position was covered by a mean of 27.3 sequencing reads per sample (see online supplementary table S1). Power to observe any variant with a patient allele frequency ≥0.5% was estimated to range from 0% to 98.8% across target positions with a median of 98.7% (IQR: 98.3–98.8%, figure 1A). A more detailed account of the distribution of variant detection power across target genes can be found in online supplementary figure S1. Four hundred and seventy-seven potential sequence variants

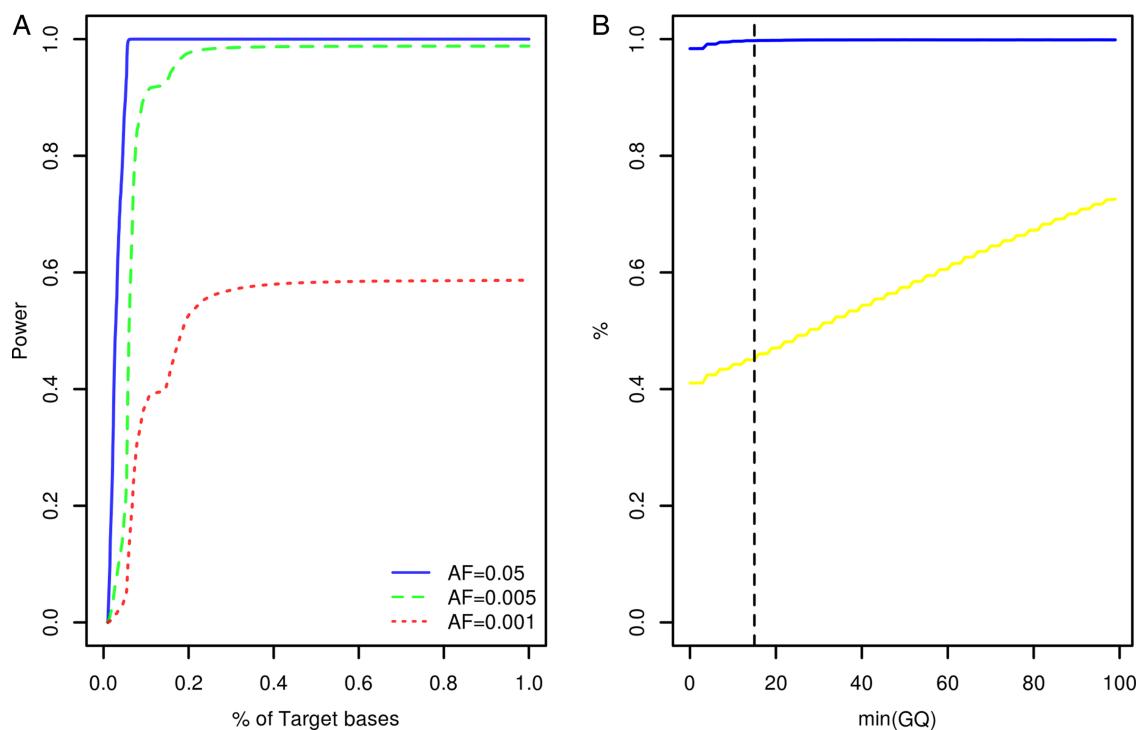


Figure 1 Target gene resequencing. (A) Cumulative density plot outlining the distribution of power to observe variants with patient allele frequencies of 0.05, 0.005 and 0.001. Power estimates were derived from the distribution of sequence coverage across target positions (see online supplementary materials and methods). (B) X-axis denotes the minimum sequencing genotype quality score (GQ) accepted for inference of sample genotypes across 85 variant sites. The blue line denotes the relationship between minimum GQ and the rate of concordance among sample genotypes ascertained by resequencing and sample genotypes ascertained using BeadChip assays. The yellow line denotes the relationship between minimum GQ and missing genotype rate among the sequencing call sets ($n=567$ samples). The vertical dotted line indicates the GQ threshold employed during this study (see online supplementary materials and methods). AF, allele frequency.

were identified across target intervals (see online supplementary table S2). Ninety-five of these were designated as possible machine errors (see online supplementary materials and methods and table S2) and are not considered further. To evaluate the accuracy of genotypes inferred across the remainder of sites, genotypes called for 567 samples across 85 variants (target intervals ± 50 bp) were compared with genotypes previously ascertained using Illumina HumanHap 550,²³ Illumina Human610-Quad (deCODE Genetics, Reykjavik, Iceland) and Illumina OmniExpressExome-8v1 (Atlas Biolabs, Berlin, Germany) single nucleotide polymorphism BeadChip assays. This comparison revealed a genotype concordance rate of 98.9% among sequencing and BeadChip calls following genotype quality control (figure 1B, see online supplementary materials and methods).

ALS-related variants

Based on the frequencies of carriers among internal controls and samples analysed by the NHLBI exome sequencing and 1000 genomes projects, all but 52 sequence variants were excluded as causing ALS with high penetrance (see the Methods section). Two of these represented previously described ALS variants; *TARDBP*: c.859G>A(p.[G287S])^{24–26}; *FUS*:c.1574C>T(p.[P525L]).²⁷ The remainder included 15 synonymous variants, 1 splice site variant (*DCTN1*:c.2887-2A>G), 20 missense variants classified as ‘deleterious’ by SIFT²⁸ or ‘possibly/ probably damaging’ by PolyPhen²⁹ and 14 missense variants classified as ‘tolerated’ by SIFT and ‘benign’ by PolyPhen. For the purpose of this study, all but the 15 synonymous variants were regarded as potentially disease causing. Seventy-six patients (38.0% of fALS, 14.5% of sALS, 17.1% of

combined) carried either one of these potential disease variants or a previously described ALS variant, with 57 (34.0% of fALS, 10.2% of sALS, 12.8% of combined) carrying variants of Mendelian disease genes (table 1. *C9orf72* 39; *SETX* 11; *ALS2* 7; *FUS* 2; *TARDBP* 2; *OPTN* 1; *VCP* 1. *ANG*, *SOD1*, *VAPB* 0), 21 (6.0% of fALS, 4.6% of sALS, 4.7% of combined) carrying variants of low penetrance/tentative ALS genes (table 2. *SPG11* 7; *ELP3* 3; *CHMP2B* 2; *DCTN1* 2; *MAPT* 2; *DPP6* 1; *FGGY* 1; *HFE* 1; *ITPR2* 1; *PON2* 1; *UNC13A* 1. *ATXN2*, *FIG4*, *GRN*, *IFNK*, *MOB3B*, *NEFH*, *NIPA1*, *PARK7*, *PON1*, *PON3*, *PRPH*, *SIGMAR1* 0) and 43 (30.0% of fALS, 7.1% of sALS, 9.7% of combined) carrying a known ALS variant (table 1. *C9orf72* 39; *FUS* 2; *TARDBP* 2).

Patient phenotypes

Both patients carrying the *TARDBP*:c.859G>A(p.[G287S]) substitution were sporadic and presented with bulbar onset disease at 66/67 years of age. One patient remains alive at 51 months from disease onset, while the other died 49 months from disease onset. Both patients were cognitively intact. Both carriers of the *FUS*:c.1574C>T(p.[P525L]) substitution were also sporadic. They exhibited an exceptionally young age of onset (13/21 years) and rapid disease progression (disease duration: 11–17 months). One patient experienced spinal onset disease while the other experienced bulbar onset. Both were cognitively intact. A detailed account of the phenotype exhibited by *C9orf72* repeat expansion carriers has been provided previously.²⁰ Further details on the phenotypes of all patients determined to carry known or possible disease variants are listed in online supplementary table S5.

Table 1 Putative disease variants of Mendelian ALS genes

Gene	Variant	SIFT	PolyPhen	Model	fALS	sALS	IRL	EUR	GLO
ALS2*	c.3094C>T(p.[Arg1032Cys])	Deleterious	Probably damaging	D	0/49	1/375	0/274	NR	NR
ALS2*	c.2606A>C(p.[Gln869Pro])	Deleterious	Probably damaging	D	0/50	1/390	0/290	NR	NR
ALS2*	c.2566A>G(p.[Thr856Ala])	Tolerated	Possibly damaging	D	0/47	1/373	0/253	NR	NR
ALS2*	c.2408A>G(p.[Lys803Arg])	Tolerated	Possibly damaging	D	0/50	1/391	0/289	NR	NR
ALS2*	c.2098A>G(p.[Thr700Ala])	Tolerated	Benign	D	0/50	2/386	0/279	NR	NR
C9orf72	Repeat expansion	—	—	D	15/45	24/367	0/188	NR	NR
FUS	c.1574C>T(p.[Pro525Leu])	Deleterious	Possibly damaging	D	0/43	2/319	0/250	NR	NR
OPTN	c.1192C>G(p.[Gln398Glu])	Tolerated	Benign	D	0/50	1/368	0/243	NR	NR
SETX	c.7682C>T(p.[Ser2561Leu])	Tolerated	Benign	D	0/50	2/358	0/253	1/4553	1/6756
SETX	c.7645G>A(p.[Val2549Ile])	Deleterious	Benign	D	0/50	2/389	0/305	0/4605	1/6808
SETX	c.5842A>G(p.[Met1948Val])	Deleterious	Probably damaging	D	0/50	1/388	0/279	NR	NR
SETX	c.5587A>G(p.[Thr1863Ala])	Deleterious	Probably damaging	D	1/50	0/391	0/278	NR	NR
SETX	c.2975A>G(p.[Lys992Arg])	Deleterious	Benign	R	1/50	0/388	0/280	NR	NR
SETX	c.2842C>A(p.[Pro948Thr])	Tolerated	Benign	D	1/50	0/387	0/282	NR	NR
SETX	c.2755G>C(p.[Val919Leu])	Tolerated	Benign	D	0/50	1/384	0/266	NR	NR
SETX	c.814C>G(p.[His272Asp])	Deleterious	Probably damaging	D	0/50	1/387	0/280	NR	NR
TARDBP	c.859G>A(p.[Gly287Ser])	Tolerated	Benign	D	0/50	2/390	0/300	NR	NR
VCP	c.2249A>G(p.[Asn750Ser])	Tolerated	Benign	D	0/50	1/389	0/306	NR	NR

Variants previously associated with ALS are shown in bold.

*Gene conventionally associated with recessively inherited ALS.

D—Variant may cause disease in a dominant fashion and carrier frequencies relate to heterozygote carriers.

R—Variants may cause disease in a recessive fashion and carrier frequencies relate to homozygous carriers.

NR—Variant not reported within either the 1000 genomes or ESP6500 datasets (samples of European ancestry=4679, total number of samples=7595).

ALS2—ENST00000264276; FUS—ENST00000254108; OPTN—ENST00000263036; SETX—ENST00000224140; TARDBP—ENST00000240185; VCP—ENST00000358901.

ALS, amyotrophic lateral sclerosis; ESP, Exome Sequencing Project.

Co-occurrences of ALS gene variants

Analysis of the number of cases carrying multiple rare or low-frequency variants revealed no detectable excesses across either

the Mendelian genes alone or the entire dataset (see online supplementary tables S3 and S4). Seven patients (4.0% of fALS, 1.3% of sALS, 1.6% of combined) carried two variants classified

Table 2 Putative disease variants of low penetrance/tentative ALS genes

Gene	Variant	SIFT	PolyPhen	Model	fALS	sALS	IRL	EUR	GLO
CHMP2B	c.118A>G(p.[Lys40Glu])	Deleterious	Possibly damaging	D	0/50	1/373	0/261	NR	NR
CHMP2B	c.123G>T(p.[Gln41His])	Deleterious	Possibly damaging	D	0/50	1/373	0/263	NR	NR
DCTN1	c.2887-2A>G(p.?)	—	—	D	0/39	2/239	0/246	NR	NR
DPP6	c.883G>A(p.[Glu295Lys])	Deleterious	Probably damaging	D	0/50	1/390	0/296	NR	NR
ELP3	c.206G>T(p.[Arg69Leu])	Deleterious	Benign	D	0/50	1/381	0/294	NR	NR
ELP3	c.326G>A(p.[Cys109Tyr])	Deleterious	Probably damaging	D	1/50	1/390	0/278	1/4578	1/6781
FGGY	c.1716G>A(p.[Met572Ile])	Tolerated	Possibly damaging	D	0/48	1/376	0/285	NR	NR
HFE	c.766G>A(p.[Val256Ile])	Tolerated	Benign	D	0/50	1/388	0/295	NR	NR
ITPR2	c.3614G>A(p.[Arg1205Gln])	Tolerated	Probably damaging	D	0/50	1/371	0/266	NR	NR
MAPT	c.284C>T(p.[Thr95Met])	Tolerated	Benign	D	0/10	1/50	0/50	1/4349	1/6549
MAPT	c.698C>T(p.[Pro233Leu])	Tolerated	Probably damaging	D	0/14	1/79	0/80	NR	NR
PON2	c.661T>G(p.[Ser221Ala])	Tolerated	Benign	D	0/49	1/381	0/257	NR	NR
SPG11*	c.7324G>C(p.[Ala2442Pro])	Deleterious	Probably damaging	D	0/50	1/391	0/282	NR	NR
SPG11*	c.4343G>A(p.[Cys1448Tyr])	Deleterious	Possibly damaging	D	0/50	1/388	0/300	NR	NR
SPG11*	c.3680A>G(p.[Lys1227Arg])	Tolerated	Benign	D	1/50	0/390	0/302	NR	NR
SPG11*	c.2577A>C(p.[Gln859His])	Tolerated	Benign	D	0/50	1/380	0/267	NR	NR
SPG11*	c.1930A>T(p.[Thr644Ser])	Tolerated	Benign	D	1/49	0/382	0/265	NR	NR
SPG11*	c.1529G>A(p.[Ser510Asn])	Tolerated	Probably damaging	D	0/50	1/389	0/282	NR	NR
SPG11*	c.394A>G(p.[Ser132Gly])	Tolerated	Benign	D	0/50	1/391	0/279	NR	NR
UNC13A	c.3098T>A(p.[Val1033Asp])	Tolerated	Benign	D	0/49	1/372	0/286	NR	NR

D—Variant may cause disease in a dominant fashion and carrier frequencies relate to heterozygote carriers.

NR—Variant not reported within either the 1000 genomes or ESP6500 datasets (samples of European ancestry=4679, total number of samples=7595).

CHMP2B—ENST00000263780; DCTN1—ENST00000361874; DPP6—ENST00000377770; ELP3—ENST00000256398; FGGY—ENST00000371218; HFE—ENST00000357618; ITPR2—ENST00000381340; MAPT—ENST00000344290; PON2—ENST00000222572; SPG11—ENST00000261866; UNC13A—ENST00000519716.

*Gene conventionally associated with recessively inherited ALS.

ALS, amyotrophic lateral sclerosis; ESP, Exome Sequencing Project.

as known or potential ALS variants in the previous analysis (online supplementary table S5). In the case of four of these individuals, both variants fell within Mendelian disease genes. Notably, these four individuals included both identified carriers of the *TARDBP:c.859G>A(p.[G287S])* variant, who were observed to also carry either an *ALS2:c.2566A>G(p.Thr856Ala)* or an *SETX:c.814C>G(p.His272Asp)* substitution. The probability of such an observation for all carriers of any previously reported ALS variant was estimated to be less than 1%, suggesting that these co-occurrences may be pathologically meaningful. Other observed co-occurrences of putative disease variants included *ALS2:c.2098A>G(p.Thr700Ala)* and *SETX:c.7682C>T(p.Ser2561Leu)*, the *C9orf72* repeat expansion and *CHMP2B:c.123G>T(p.Gln41His)*, the *C9orf72* repeat expansion and *SETX:c.2842C>A(p.Pro948Thr)*, the *C9orf72* repeat expansion and *SPG11:c.3680A>G(p.Lys1227Arg)*, the *DCTN1:c.2887-2A>G* splice acceptor site variant and *SPG11:c.1529G>A(p.Ser510Asn)*. Further details on these patients can be found in online supplementary table S5.

Variation in the frequency of ALS variants across populations

To assess the potential importance of genetic heterogeneity across populations, we compared the estimated frequencies of ANG,

C9orf72, *FUS*, *OPTN*, *SOD1* and *TARDBP* disease variants among Irish patients with those reported by population-based studies of Italian cohorts.^{3 4} The difference was statistically significant (combined $p=1.7\times 10^{-4}$, table 3), supporting a correlation between genetic susceptibility and population of origin. Of the 32 variants analysed, only the *C9orf72* repeat expansion and the *FUS:c.1574C>T(p.[P525L])* substitution were observed among both Irish and Italian patients. The *C9orf72* expansion was significantly more common among Irish patients (8.78% vs 4.39%, $p=3.95\times 10^{-4}$) while *SOD1* and *TARDBP* variants were significantly more common among Italian patients (*SOD1*: 2.00% vs 0.00%, $p=3.8\times 10^{-3}$; *TARDBP*: 2.00% vs 0.45%, $p=0.035$). The overall frequencies of *FUS* and *OPTN* variants were similar (*FUS*: 0.30% vs 0.45%, $p=0.61$; *OPTN*: 0.20% vs 0.23%, $p=1$). *ANG* variants were identified only among Italian patients but the frequency difference was not significant (0.30% vs 0.00%, $p=0.56$).

Single variant association testing

Case-control association tests were performed under additive, dominant and recessive disease models and under various sample and variant inclusion criteria; however, no significant associations with disease risk were observed.

Table 3 The frequencies of ALS variants are population specific

Gene	Variant	% Italian (n=1003)	% Irish (n=444)	p Value
<i>ANG</i>	c.232A>G(p.K54E)	0.1	0	0.56*
	c.338G>A(p.W89X)	0.1	0	
	c.433C>T(p.R121C)	0.1	0	
<i>C9orf72</i>	Repeat Expansion	4.39	8.78	$3.95\times 10^{-4}*$
<i>FUS</i>	c.1542G>C(p.R514S)	0.1	0	$0.18\ddagger, 0.61^*$
	c.1562G>T(p.R521L)	0.1	0	
	c.1574C>T(p.P525L)	0.1	0.45	
<i>OPTN</i>	c.1192C>G(p.Gln398Glu)	0	0.23	$1\ddagger, 1^*$
	c.1499T>C(p.L500P)	0.1	0	
	c.1703T>C(p.L568S)	0.1	0	
<i>SOD1</i>	c.34G>T(p.D11Y)	0.3	0	$3.7\times 10^{-3}*$
	c.59A>G(p.N19S)	0.1	0	
	c.63C>G(p.F20L)	0.1	0	
	c.115C>G(p.L38V)	0.1	0	
	c.142G>T(p.V47F)	0.1	0	
	c.203T>C(p.L67P)	0.1	0	
	c.256G>A(p.G85S)	0.1	0	
	c.271G>A(p.D90N)	0.1	0	
	c.272A>C(p.D90A)	0.3	0	
	c.281G>A(p.G93D)	0.3	0	
	c.328G>T(p.D109Y)	0.2	0	
	c.400_402delGAA(p.E133del)	0.1	0	
	c.435G>C(p.L144F)	0.1	0	
	c.800A>G(p.N267S)	0.2	0	$0.026\ddagger, 0.035^*$
<i>TARDBP</i>	c.859G>A(p.Gly287Ser)	0	0.45	
	c.881G>T(p.G294V)	0.2	0	
	c.909A>C(p.Q303H)	0.1	0	
	c.1009A>G(p.M337V)	0.1	0	
	c.1102G>A(p.G368S)	0.1	0	
	c.1144G>A(p.A382T)	0.9	0	
	c.1147A>G(p.I383V)	0.1	0	
	c.1169A>G(p.N390S)	0.3	0	
Combined	–	9.07	9.91	$1.7\times 10^{-4}\ddagger, 0.25^*$

Analysed variants include the *C9orf72* hexanucleotide repeat expansion and non-synonymous variants reported as patient specific. Analysis of *TARDBP* was restricted to exon 6 while analysis of *FUS* was restricted to exons 14 and 15 and analysis of *OPTN* was restricted to exons 5, 9, 12 and 14.³

*Comparison of combined variant frequencies using a Fisher exact test.

†Comparison of independent variant frequencies using a χ^2 -test.

ALS, amyotrophic lateral sclerosis.

DISCUSSION

We have screened a population-based cohort of 444 Irish ALS patients and 311 age-matched and geographically matched controls for variants within the coding exons of 33 previously reported ALS genes. This represents the most extensive survey of known ALS loci to date and is the first to employ a multiplexed targeted next-generation sequencing strategy to efficiently analyse multiple ALS loci simultaneously. The resulting dataset exhibited high sensitivity in terms of predicted power to identify rare patient variants and high accuracy in terms of genotype assignment.

We found that up to 17.1% of Irish ALS cases (38.0% of fALS, 14.5% of sALS) may carry high-penetrance disease variants within the investigated genes. However, only 10 of the 33 genes analysed represent well-established Mendelian disease genes, and it is anticipated that many of the possible disease variants identified will not be ALS related. Additionally, it should be noted that variants of *ALS2* and *SPG11* were observed solely in heterozygous configurations, but that these genes have previously been associated with ALS only under recessive disease models.^{30–31} It is also worth noting that as reported in previous studies,³² no disease variants could be identified within the coding sequence of the *C9orf72* gene.

A total of 9.7% of the patients (30% of fALS, 7.1% of sALS) were found to carry previously reported ALS variants, with 8.78% carrying the *C9orf72* repeat expansion, 0.45% carrying the *FUS*:c.1574C>T(p.[P525L]) substitution and 0.45% carrying the *TARDBP*:c.859G>A(p.[G287S]) substitution. The phenotype of *FUS*:c.1574C>T(p.[P525L]) carriers was consistent with that reported previously,²⁷ with both patients exhibiting an exceptionally young age of onset and rapid disease progression. Conversely, we observed that carriers of the *TARDBP*:c.859G>A(p.[G287S]) variant exhibited a disease of comparatively late onset and slow progression. Review of *TARDBP*:c.859G>A(p.[G287S]) carriers reported across this study and previous publications^{24–26} revealed that disease onset ranged from 52 to 70 years of age while disease duration ranged from 49 to ≥93 months.

Despite prior evidence to support models of high disease penetrance, 62% of *C9orf72* expansion carriers and all *FUS*:c.1574C>T(p.[P525L]) and *TARDBP*:c.859G>A(p.[G287S]) carriers were classified as sporadic. Modelling of the effects of penetrance and family size on the rate of familial disease has previously shown that inheritance of high-penetrance variants can occur in the absence of a detectable family history.³³ Conversely, the presence of a family history does not necessarily infer the presence of a common disease aetiology⁹ and it is not always the case that disease variants are inherited. For example, the *FUS*:c.1574C>T(p.[P525L]) substitution has been reported to occur as a de novo event in multiple cases.²⁷ Taken together, our results therefore support the contention that the distinction between familial and sporadic disease is of limited utility from both clinical and research perspectives.

Substantial differences have been described in the general spectrum of rare and low-frequency genetic variations across populations.^{15–34} A degree of population differentiation would therefore also be anticipated in the genetics of disease pathogenesis. Formal comparison of our results with those reported by studies of major disease genes in Italy confirmed that this is the case with ALS. We observed significant differences in the nature of genetic susceptibility across the two populations ($p=1.7\times10^{-4}$), finding that only two of the 32 variants identified among either Irish or Italian patients could be identified among both. One of these shared variants was the *FUS*:c.1574C>T(p.[P525L]) substitution, which is notable as limited population differentiation may have been predicted a priori,

given the associated age of mortality and the importance of de novo occurrence. The other was the *C9orf72* repeat expansion, which has been shown to occur with high frequency among various European populations.^{3–5–35} However, we observed that the expanded allele occurred with a significantly higher frequency in the Irish population than the Italian (Irish=8.78%, Italian=4.39%, $p=3.95\times10^{-4}$). Conversely, we observed that variants of *SOD1* and *TARDBP* were significantly more common among Italian patients than Irish (*SOD1*:Irish=0.00%, Italian=2.00%, $p=3.8\times10^{-3}$; *TARDBP*:Irish=0.45%, Italian=2.00%, $p=0.035$). The absence of *SOD1* variants in the Irish population is particularly striking, as the gene is believed to make significant contributions to disease burden across Scandinavia (9.6%),³⁶ the USA (7.5%),³⁷ Germany (12%—familial cases only),³⁸ Italy (2.1%),³ France (56%—familial cases only)³⁹ and Korea (3.9%).⁷

A recent analysis of ALS patients from the Netherlands revealed that mutations of multiple ALS-associated genes could be identified in 9/57 families ($p=1.57\times10^{-7}$),⁵ suggesting that oligogenic susceptibility may play an important role in ALS aetiology. In the current study, we searched for excesses in the co-occurrence of rare and low-frequency variations across a wider panel of disease genes. Our findings did not reveal any significant deviations from chance expectation, even when the analysis was restricted to genes analysed in the Dutch study (data not shown). However, we did observe that 1.6% of patients (4.0% of fALS, 1.3% of sALS) carried multiple variants classified as known or potential high-penetrance ALS variants and that this included all identified carriers of one previously reported ALS variant ($p<0.01$). This variant occurred within the *TARDBP* gene (*TARDBP*:c.859G>A(p.[G287S])), which is noteworthy as the strongest evidence for oligogenic-based disease in the Dutch analysis also related to a *TARDBP* variant (c.1055A>G(p.[N352S])). *TARDBP*:c.859G>A(p.[G287S]) has previously been identified among patients from Italy,²⁴ France²⁶ and the UK²⁵ but has not yet to our knowledge been reported in healthy controls. As studies that have previously reported the variant analysed the *TARDBP* gene in isolation, it is not known whether carriers identified elsewhere also carry additional disease variants. The potential relevance of oligogenic susceptibility in ALS aetiology means that the exploration of oligogenic models may become increasingly important in disease gene mapping and studies of genotype–phenotype correlations. It also means that known disease genes should be studied together rather than in isolation and that patients testing positive for disease variants at one locus should not be excluded from subsequent analysis of additional disease loci.

No associations were established between any of the identified variants and case–control status. However, power to evaluate the pathogenicity of low-frequency variants was limited and further investigation of patients and matched controls by future studies may reveal disease-relevant effects. We have therefore provided a complete account of the variation identified across both cases and controls (see online supplementary table S2).

Strong correlations have been observed between patient phenotypes and individual disease variants^{20–27} and it may be the case that other clinical features such as the frequency of cognitive impairment, the burden of disability and drug response also vary across populations. While the clinical phenotype within European populations is broadly similar, our data would suggest that general extrapolation of findings from individually characterised ancestral populations must be undertaken with caution. A deeper understanding of disease heterogeneity across populations will require further analysis of representative patient

cohorts, and is likely to be of benefit in cohort stratification for future clinical trials.

In conclusion, we have used targeted high-throughput sequencing to conduct an extensive population-based survey of ALS gene variant frequencies. We found that 17.1% of Irish cases may carry high-penetrance disease variants within the investigated genes, with previously established disease variants accounting for up to 9.7%. We have also found that the *C9orf72* hexanucleotide repeat expansion represents the most common of these variants. Our study was limited by the exclusion of more recently reported disease genes like *SQSTM1*⁴⁰ and *UBQLN2*⁴¹ and by the absence of any functional analyses of putative disease variants. However, we identified significant differences in the frequencies of disease variants between Irish and other European populations, demonstrating that distinct patient populations cannot always be treated as homogenous. Finally, we also uncovered evidence that supports the potential relevance of oligogenic susceptibility in ALS aetiology and suggests that the *TARDBP:c.859G>A(p.[G287S])* variant may not cause disease in isolation.

Contributors KPK: study design. Preparation of genomic sequencing libraries and target enrichment. Alignment of sequence data and related quality control. Variant calling and related quality control. All statistical analyses, drafting of manuscript. RLM: study design. Preparation of genomic sequencing libraries and target enrichment. Alignment of sequence data and related quality control, drafting of manuscript. SB: study design. Investigation of patient family histories. ME: cognitive testing of patients. MH: data management and retrieval from the Irish ALS Register. EMK: next-generation sequencing and related quality control at TrinSeq. PC: next-generation sequencing and related quality control at TrinSeq. DWM: next-generation sequencing and related quality control at TrinSeq. CGD: provision of DNA and clinical details relating to patients from Northern Ireland. DGB: study design and supervision, editing of manuscript. OH: principal investigator, study design and supervision, patient collection and phenotyping, director of the ALS Register, drafting and editing of manuscript.

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Competing interests None.

Ethics approval Research and Ethics committee in Beaumont Hospital, Dublin.

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Supplementary materials and methods

Targeted resequencing

RNA probes complementary in sequence to the coding exons (\pm 2bp) of target genes were designed using e-array (<https://earray.chem.agilent.com/earray/>) and manufactured as part of custom SureSelect kits (Agilent, Santa Clara, CA). A tiling frequency of 2x was selected during kit design and small target intervals were extended such that all intervals were targeted by at least 2 distinct probes. Paired end Illumina sequencing libraries were prepared for 444 cases and 311 controls using DNA extracted from venous blood (KBioscience, Herts, England). Libraries were subsequently enriched for target sequences using the custom SureSelect kits. Library preparation and target enrichment was performed as per the “SureSelect Target Enrichment System for Illumina Paired-End Sequencing Library protocol version 2.3” protocol with the following modifications. 1) Only 1 μ g of DNA was used in library preparations. 2) DNA fragmentation was performed either using a Covaris system (Covaris, Woburn, MA) as per the manufacturer's instructions, enzymatically or through sonication. Where enzymatic fragmentation was performed, 15.8 μ l of DNA (63.3 ng/ μ l) was incubated with 2 μ l NEBNext dsDNA fragmentase (New England Biolabs, Ipswich, MA) in NEBNext fragmentase reaction buffer @ 30 °C for 20 min. 5 μ l of 0.5 M EDTA was then used to stop the reaction. Where fragmentation was performed through sonication, 100 μ l of DNA (10 ng/ μ l) was subjected to 60 min of sonication (30 sec on, 30 sec off) using a Bioruptor (Diagenode, Liège, Belgium) at low power. 3) Extended Illumina adapters including 6 bp indexes were used in place of standard adapters (Metabion, Martinsried, Germany). All indexes were at least an edit distance of 2 from one another. 4) Following adapter ligation, libraries were subjected to electrophoresis through a 2% Low Range Ultra agarose gel (BioRad, Hercules, CA) stained with SYBR Green 1 nucleic acid gel stain (Sigma, Arklow, Ireland) for 90 mins @ 140 V. Fragments of 300 – 400 bp were manually

excised from gel, using a Safe Imager™ 2.0 Blue Light Transilluminator (Invitrogen, Carlsbad, CA) for visualization. DNA was extracted from gel slices using QIAquick Gel Extraction Kits (Qiagen, West Sussex, UK) as per the manufacturer's instructions. 5) 5 cycles of PCR were performed instead of 4 prior to target enrichment, and Phusion (New England Biolabs) was used for all PCR reactions. 6) Libraries labelled with distinct indexes were pooled prior to target enrichment such that the expected sequence coverage of target intervals would have a mean of ~ 30x per sample. 203 case libraries were resequenced by 80 bp paired-end resequencing on an Illumina Genome Analyzer II at TrinSeq, Institute of Molecular Medicine, Trinity College Dublin, Ireland. The remainder of libraries were resequenced by 101 bp single-end sequencing on a HiSeq 2000 at GATC Biotech AG, Konstanz, Switzerland.

Analysis of sequence data

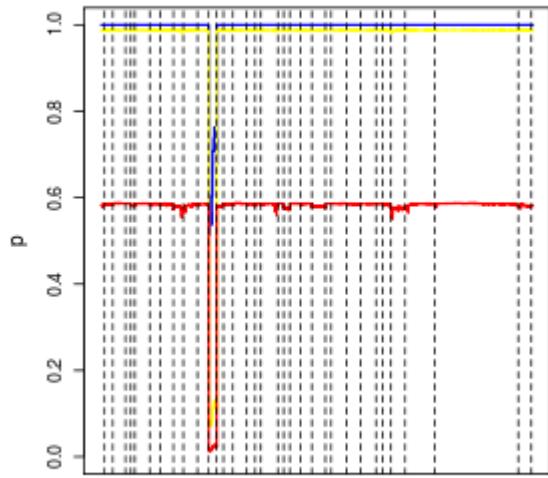
Sequencing reads were aligned using BWA to build GRCh37 of the human genome (“http://www.broadinstitute.org/gsa/wiki/index.php/GSA_FTP_Server”). Alignments were annotated with sample of origin based on detected adapter indexes. SAMtools was used to sort and index alignment files. Picard was used to merge alignment files and remove PCR duplicates. The GATK was used to perform local indel realignment, recalibrate base quality (BQ) scores, determine per sample depth of coverage across target intervals, call variants and assign sample genotypes. Base calls were only considered for depth of coverage analyses or variant calling when they were associated with BQ scores ≥ 20 and alignment mapping quality scores ≥ 20 .

Variant annotation and quality control

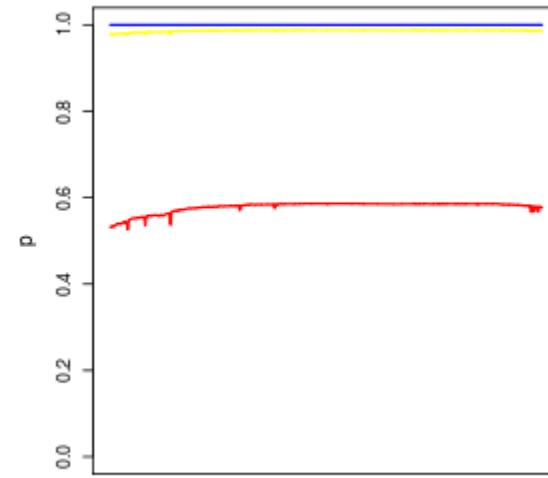
The effects of variants at the protein level were predicted using Variant Effect Predictor version 2.7 (<http://www.ensembl.org/info/docs/variation/vep/index.html>) and Ensembl 69 (<http://www.ensembl.org/>). Predictions were based only on transcripts annotated as protein coding and included PolyPhen and SIFT pathogenicity classifications. Genotype frequencies within external control cohorts were imported from the March 2012 release of the 1000 genomes project (<http://www.1000genomes.org/>) and the ESP6500 release of the NHLBI exome sequencing project (Exome Variant Server, NHLBI Exome Sequencing Project (ESP), Seattle, WA (URL: <http://evs.gs.washington.edu/EVS/>) [Accessed 2012 Jul 18]). Variants were assigned a status of either “pass” or “fail” based on whether they met a series of quality control criteria. These criteria included a minimum variant quality score of 30, a genotype call rate $\geq 10\%$, and “QD”, “FS”, “ReadPosRankSum” and “HaplotypeScore” values within the range observed for the subset of variants noted also to have been reported by the 1000 genomes or NHLBI Exome Sequencing projects. Additionally, novel case variants which were observed to occur only *in cis* with other novel case variants were interpreted as possible misalignments and assigned a status of “fail”. Variant quality score, “QD”, “FS”, “ReadPosRankSum” and “HaplotypeScore” values were calculated using the GATK. Genotype calls associated with genotype quality scores < 15 were reset to missing prior to variant quality control.

Estimation of variant detection power

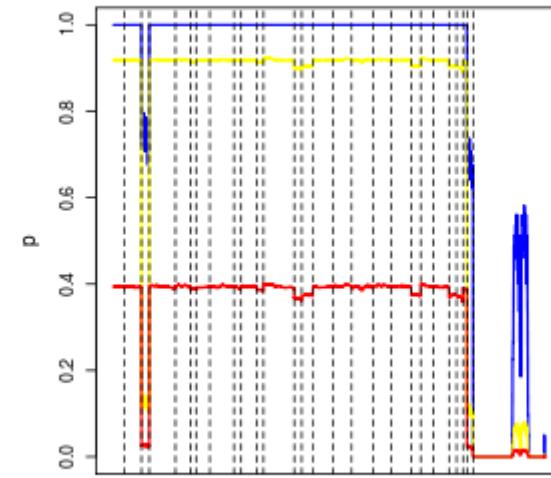
For each target position, per sample sequence coverage was used to calculate the expected total of resequenced chromosomes. The probability of including a mutated chromosome among this total was then calculated for a range of minor allele frequencies using R version 2.14.1 (<http://www.r-project.org/>). Both the sampling of patients from the Irish ALS population and the sampling of chromosomes during resequencing were assumed to follow binomial distributions.



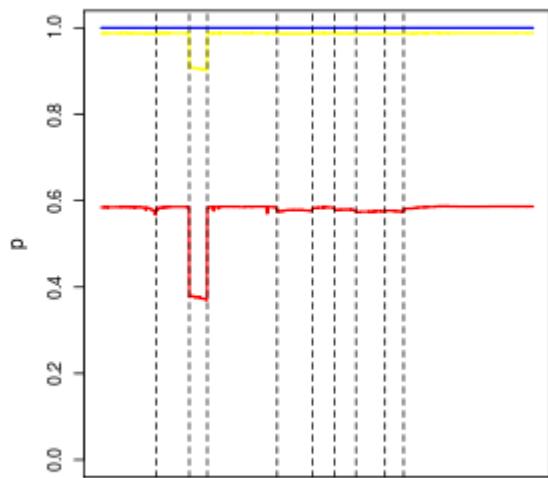
ALS2



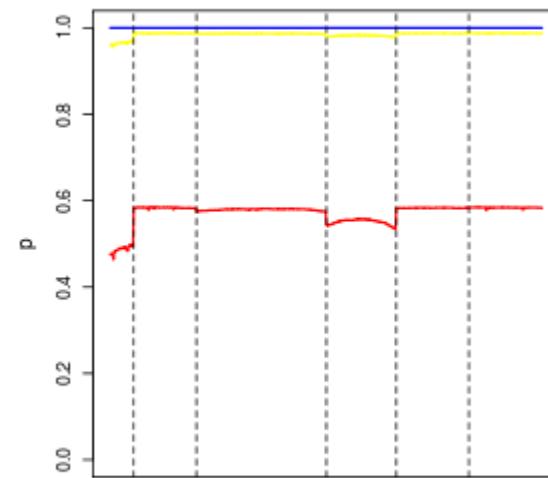
ANG



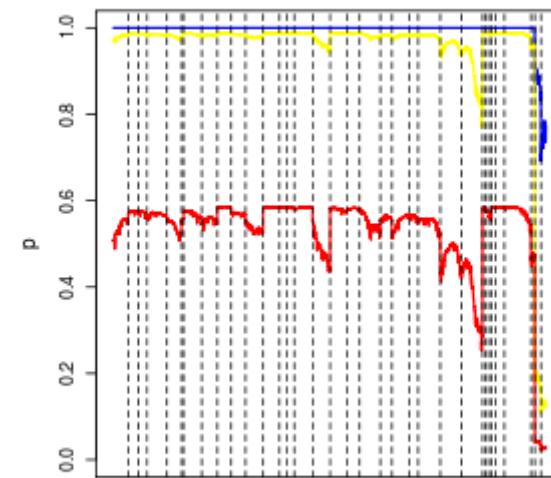
ATXN2



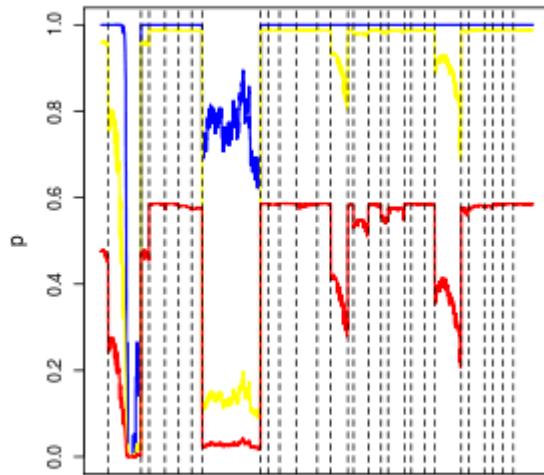
C9orf72



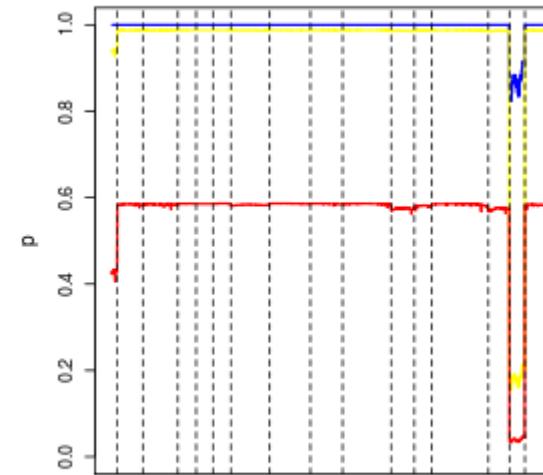
CHMP2B



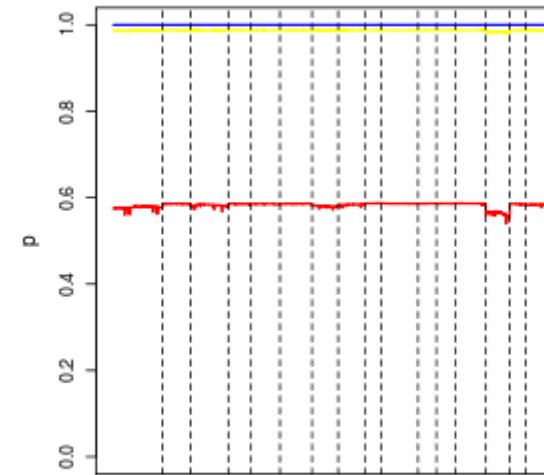
DCTN1



DPP6



ELP3



FGGY

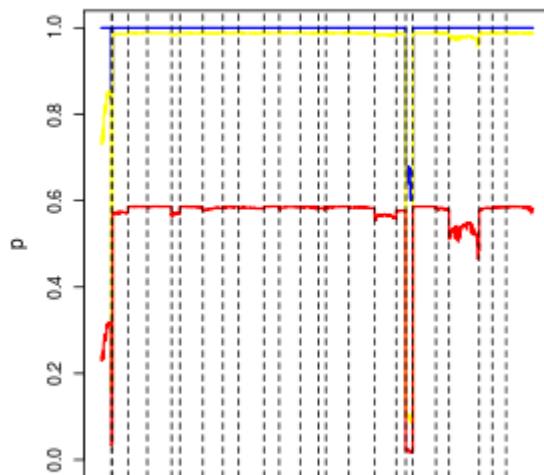
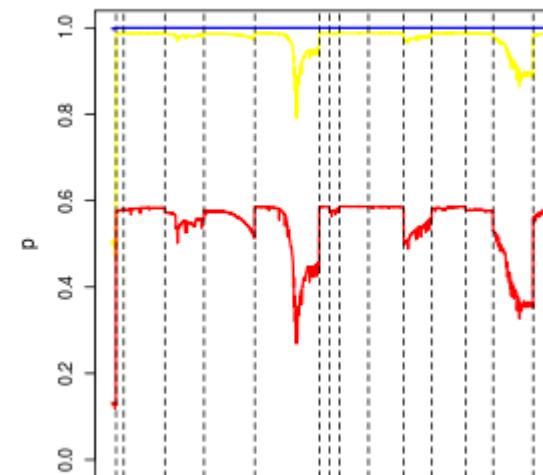
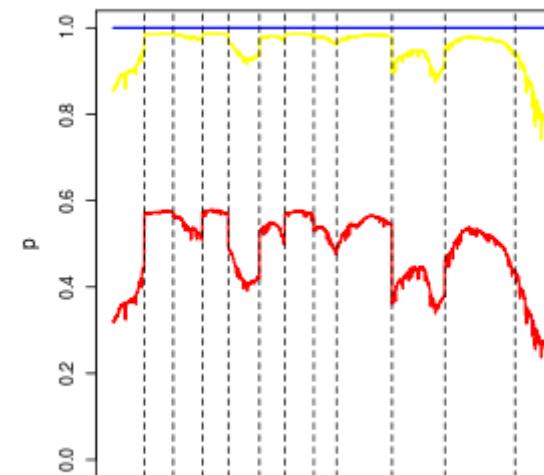


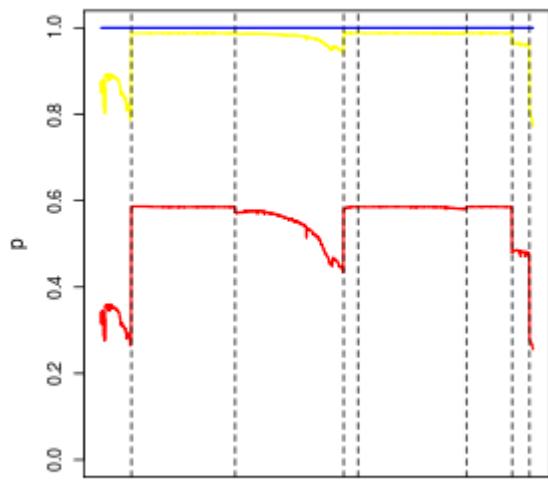
FIG4



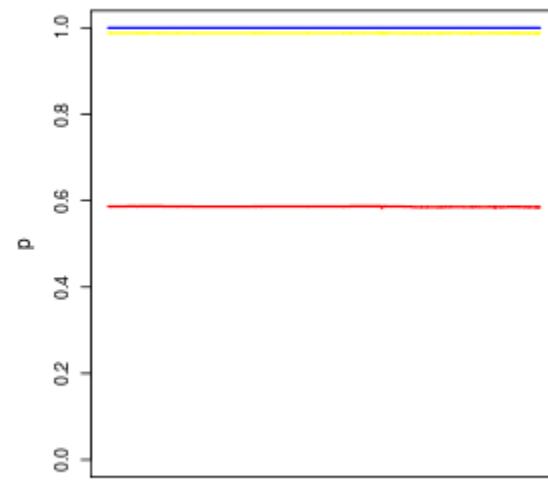
FUS



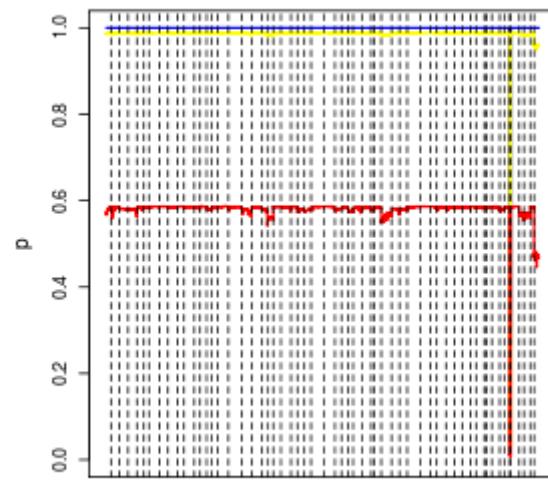
GRN



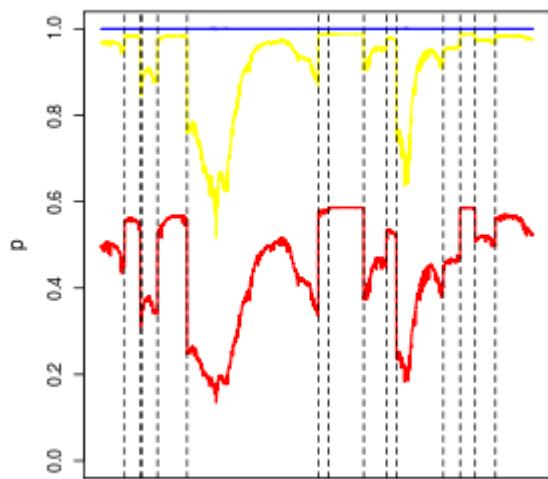
HFE



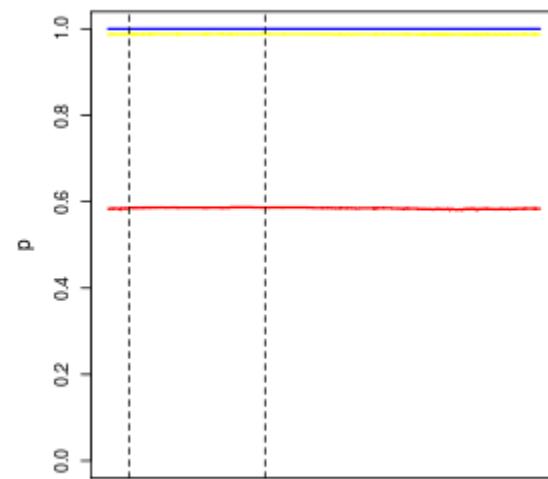
IFNK



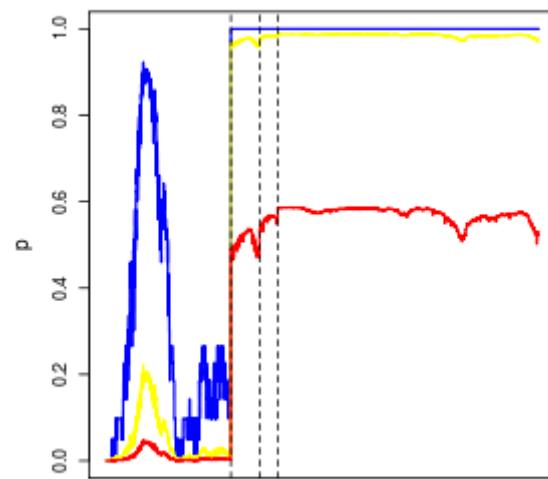
ITPR2



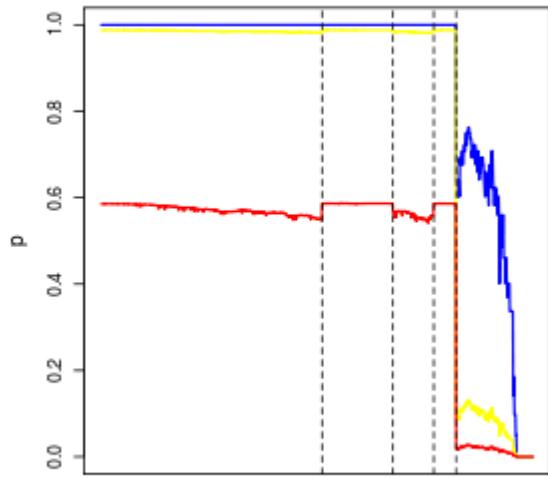
MAPT



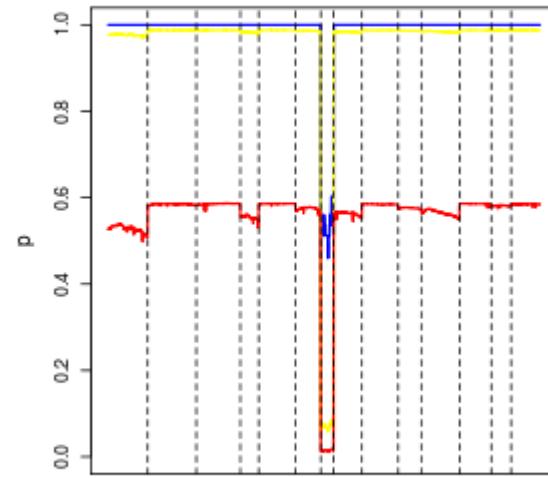
MOB3B



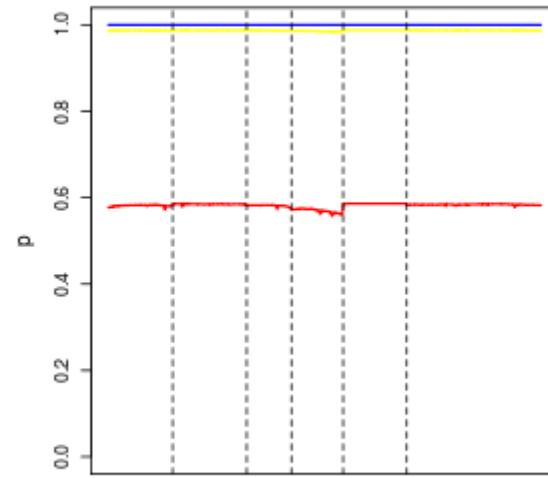
NEFH



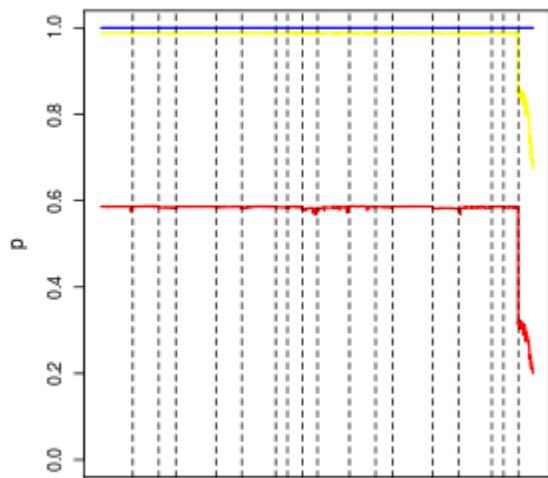
NIPA1



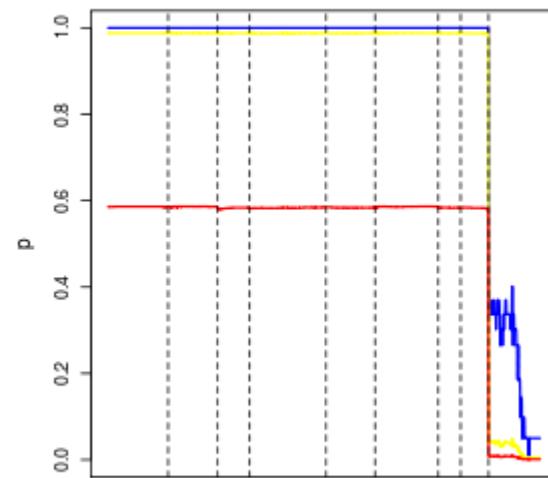
OPTN



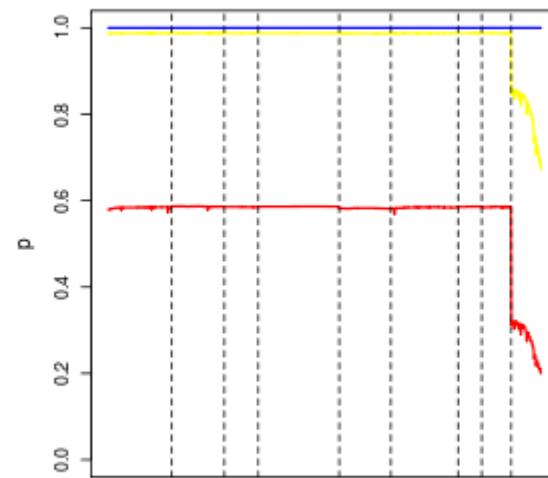
PARK7



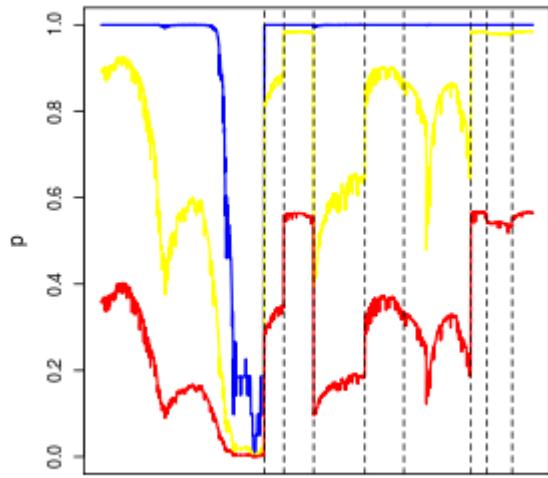
PON1



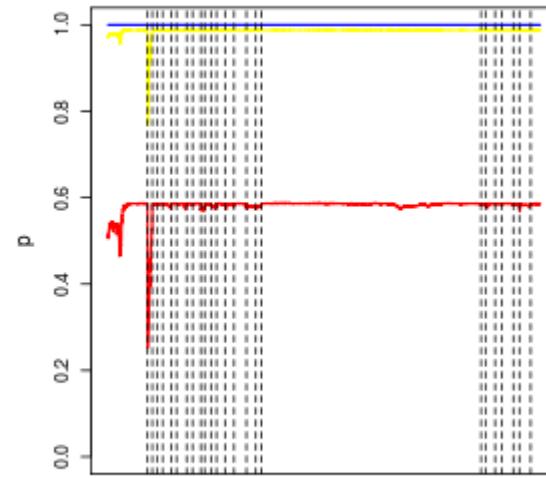
PON2



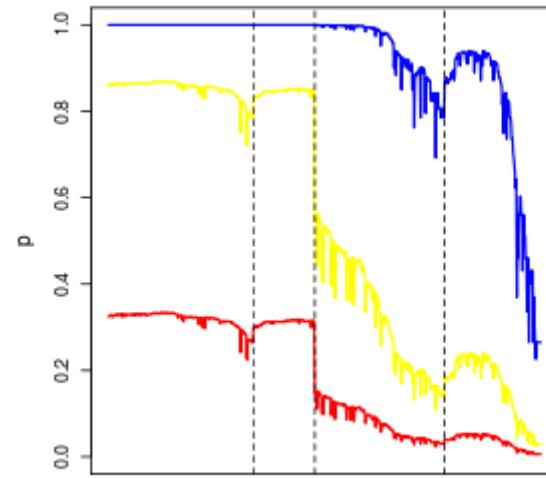
PON3



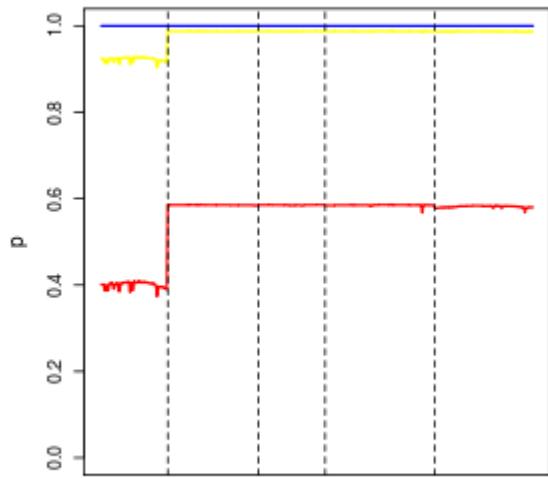
PRPH



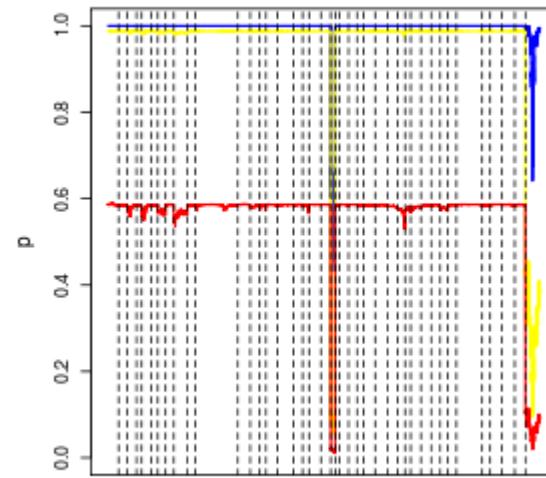
SETX



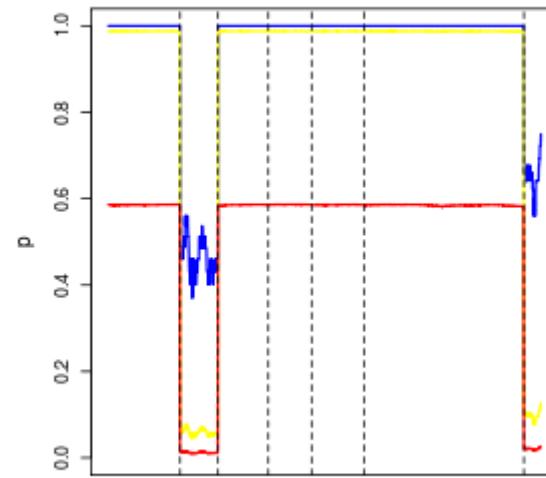
SIGMAR1



SOD1



SPG11



TARDBP

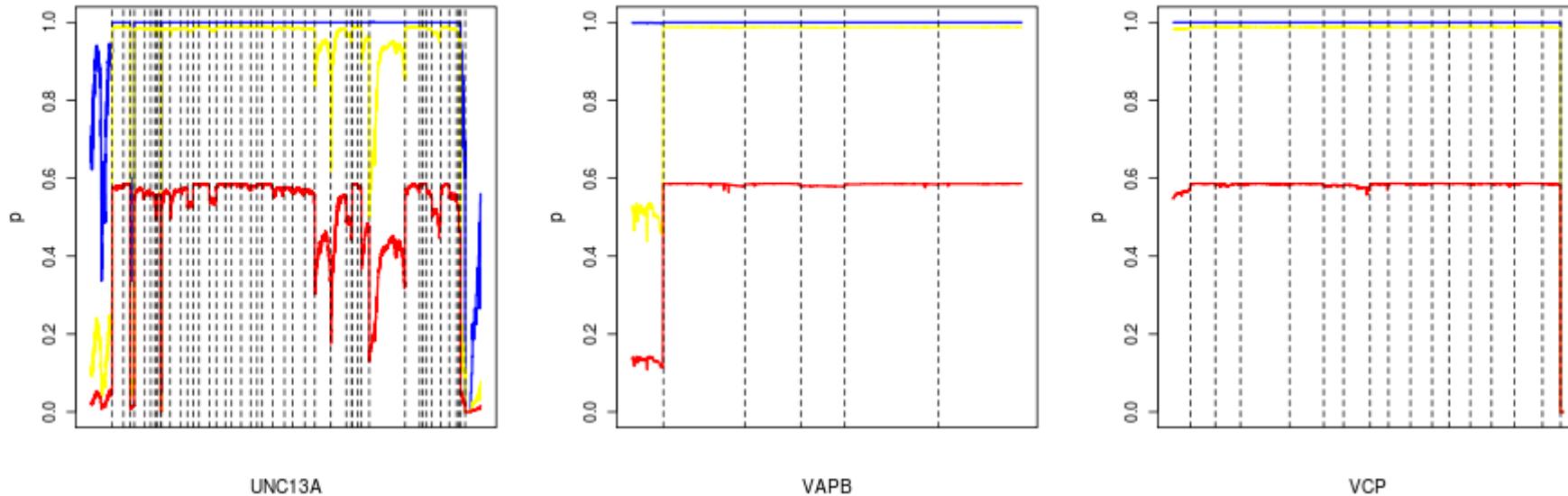


Figure S1: Variant detection power

The horizontal axes denote position within the coding sequence of each target gene. The vertical axes denote the probability that a variant with an allele frequency of 5% (blue line), 0.5% (yellow line) or 0.1% (red line) among Irish ALS patients was sampled during resequencing. The coding sequence of a target gene refers to the union of all coding transcripts reported in Ensembl 69. Exon boundaries are demarcated by vertical dotted lines.

Table S1: Target gene resequencing

Gene	Designation	% Sequenced (>=1 X coverage)	Mean Case Coverage
ALS2	Mendelian	100	35.6 + 25.4
ANG	Mendelian	100	30.4 + 22.2
ATXN2	Low penetrance/ tentative	87.1	21.4 + 26.7
C9orf72	Mendelian	100	36.7 + 27.1
CHMP2B	Low penetrance/ tentative	100	25.8 + 19.7
DCTN1	Low penetrance/ tentative	100	16.6 + 17.1
DPP6	Low penetrance/ tentative	98.8	20.6 + 22.2
ELP3	Low penetrance/ tentative	100	32.3 + 21.9
FGGY	Low penetrance/ tentative	100	30.8 + 20.1
FIG4	Low penetrance/ tentative	100	33.4 + 24.3
FUS	Mendelian	100	17.9 + 18.1
GRN	Low penetrance/ tentative	100	10.1 + 12.3
HFE	Low penetrance/ tentative	100	28.7 + 25.4
IFNK	Low penetrance/ tentative	100	38.8 + 21.6
ITPR2	Low penetrance/ tentative	100	31.6 + 21.3
MAPT	Low penetrance/ tentative	100	12.4 + 18.8
MOB3B	Low penetrance/ tentative	100	38.9 + 23.9
NEFH	Low penetrance/ tentative	97.7	11.4 + 13.5
NIPA1	Low penetrance/ tentative	96.1	22 + 20.7
OPTN	Mendelian	100	21.3 + 15.9
PARK7	Low penetrance/ tentative	100	26.7 + 18.1
PON1	Low penetrance/ tentative	100	37.1 + 24.7

PON2	Low penetrance/ tentative	99.9	34.7 + 25.3
PON3	Low penetrance/ tentative	100	32.7 + 22.2
PRPH	Low penetrance/ tentative	99.4	4.2 + 8.7
SETX	Mendelian	100	41.2 + 25.7
SIGMAR1	Low penetrance/ tentative	100	2.9 + 7.5
SOD1	Mendelian	100	29.7 + 24.6
SPG11	Low penetrance/ tentative	100	32.9 + 23.7
TARDBP	Mendelian	100	30.3 + 22.1
UNC13A	Low penetrance/ tentative	98.6	15.5 + 17.9
VAPB	Mendelian	100	31.8 + 22.3
VCP	Mendelian	99.2	34.1 + 23

Table S2: ALS gene variants

Gene	Class	Transcript	DNA	Amino.Acid	SIFT	Poly Phen	fALS	sALS	Irish	European	Global
ALS2	missense	*ENST00000264276, ENST00000467448	c.1102G>A, c.1102G>A	p.Val368Met, p.Val368Met	0, 0	0, 0	0,4,46	5,70,315	2,48,240	45,871,3894	145,1662,5633
ALS2	missense, splice region	*ENST00000264276	c.1115C>G	p.Pro372Arg	0	1	50,0,0	389,1,0	294,2,0	4742,22,0	7306,23,0
ALS2	missense	*ENST00000264276	c.1226C>G	p.Ala409Gly	0	0	48,0,0	358,12,0	252,23,0	252,23,0	252,23,0
ALS2	missense	*ENST00000264276	c.1265T>C	p.Met422Thr	1	0	50,0,0	388,1,0	302,0,0	4454,1,0	6399,1,0
ALS2	missense	*ENST00000264276	c.1283C>A	p.Thr428Asn	0	0	50,0,0	388,1,0	302,0,0	302,0,0	302,0,0
ALS2	missense	*ENST00000264276	c.1627G>A	p.Asp543Asn	1	2	47,0,0	290,0,0	247,4,0	4389,11,0	6357,11,0
ALS2	splice region, synonymous	*ENST00000264276	c.1641G>A	p.(=)			50,0,0	380,1,0	277,0,0	4388,4,0	6255,9,0
ALS2	synonymous	*ENST00000264276	c.2028A>G	p.(=)			50,0,0	383,0,0	267,1,0	267,1,0	267,1,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.2098A>G, c.34A>G	p.Thr700Ala, p.Thr12Ala	0, 0	0, 0	50,0,0	384,2,0	279,0,0	279,0,0	279,0,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.2155C>T, c.91C>T	p.Pro719Ser, p.Pro31Ser	1, 1	2, 2	50,0,0	389,0,0	282,1,0	282,1,0	282,1,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.2216C>T, c.152C>T	p.Ala739Val, p.Ala51Val	0, 0	0, 0	46,2,0	304,52,0	210,54,0	210,54,0	210,54,0
ALS2	synonymous	*ENST00000264276, ENST00000457679	c.2241C>T, c.177C>T	p.(=), p.(=)	,	,	50,0,0	388,1,0	295,1,0	4445,25,0	6403,28,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.2408A>G, c.344A>G	p.Lys803Arg, p.Lys115Arg	0, 0	1, 0	50,0,0	390,1,0	289,0,0	289,0,0	289,0,0
ALS2	synonymous	*ENST00000264276, ENST00000457679	c.2466G>A, c.402G>A	p.(=), p.(=)	,	,	8,25,15	57,175,145	37,117,102	750,2244,1719	2360,2984,1894
ALS2	missense	*ENST00000264276, ENST00000457679	c.2566A>G, c.502A>G	p.Thr856Ala, p.Thr168Ala	0, 0	1, 0	47,0,0	372,1,0	253,0,0	253,0,0	253,0,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.2606A>C, c.542A>C	p.Gln869Pro, p.Gln181Pro	1, 0	2, 1	50,0,0	389,1,0	290,0,0	290,0,0	290,0,0
ALS2	synonymous	*ENST00000264276, ENST00000457679	c.2796C>T, c.732C>T	p.(=), p.(=)	,	,	34,15,1	308,75,4	241,54,2	4029,745,31	6262,1120,53
ALS2	missense	*ENST00000264276, ENST00000467448,	c.280A>G, c.280A>G,	p.Ile94Val, p.Ile94Val,	0, 0, 0, 0	0, 0, 0, 0	47,3,0	371,15,1	285,14,0	4596,232,4	7069,445,7

		ENST00000409632, ENST00000410052	c.280A>G, c.280A>G	p.Ile94Val, p.Ile94Val							
ALS2	<i>synonymous</i>	*ENST00000264276, ENST00000457679	c.2992C>A, c.928C>A	p.(=), p.(=)	,	,	48,0,0	352,1,0	268,2,0	268,2,0	268,2,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.3046C>G, c.982C>G	p.Pro1016Ala , p.Pro328Ala	0, 0	0, 0	50,0,0	386,1,0	291,0,0	4445,1,0	6365,17,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.3094C>T, c.1030C>T	p.Arg1032Cys , p.Arg344Cys	1, 1	2, 2	49,0,0	374,1,0	274,0,0	274,0,0	274,0,0
ALS2	synonymous	*ENST00000264276, ENST00000457679	c.3129C>G, c.1065C>G	p.(=), p.(=)	,	,	50,0,0	387,1,0	294,0,0	294,0,0	294,0,0
ALS2	<i>splice donor</i>	*ENST00000264276, ENST00000457679	c.3182+2T >G, c.1118+2T >G		,	,	46,0,0	361,3,0	254,6,0	254,6,0	254,6,0
ALS2	<i>missense, splice region</i>	*ENST00000264276, ENST00000457679	c.3250T>G, c.1186T>G	p.Tyr1084Asp , p.Tyr396Asp	1, 1	1, 1	40,3,0	280,20,0	187,18,0	187,18,0	187,18,0
ALS2	missense	*ENST00000264276, ENST00000457679	c.3307C>A, c.1243C>A	p.His1103Asn , p.His415Asn	0, 1	0, 0	49,0,0	384,0,0	277,1,0	277,1,0	277,1,0
ALS2	synonymous	*ENST00000264276	c.3741T>G	p.(=)			50,0,0	385,1,0	282,0,0	4728,20,0	7267,20,0
ALS2	missense	*ENST00000264276	c.3863C>T	p.Pro1288Leu	0	0	50,0,0	375,1,0	302,0,0	4403,3,0	6299,3,0
ALS2	synonymous	*ENST00000264276	c.3885G>A	p.(=)			45,3,0	349,14,0	266,15,1	4404,366,7	6998,399,7
ALS2	synonymous	*ENST00000264276	c.4015C>T	p.(=)			0,3,44	1,57,288	0,25,218	25,682,3997	83,1354,5829
ALS2	synonymous	*ENST00000264276	c.4107G>A	p.(=)			46,0,0	352,1,0	245,0,0	245,0,0	245,0,0
ALS2	missense	*ENST00000264276	c.4119A>G	p.Ile1373Met	1	0	46,0,0	342,2,0	243,0,0	4664,43,0	7189,47,0
ALS2	missense	*ENST00000264276	c.4135C>A	p.Pro1379Thr	1	1	50,0,0	386,0,0	296,2,0	296,2,0	296,2,0
ALS2	missense	*ENST00000264276	c.4382G>A	p.Arg1461Gln	0	0	50,0,0	384,1,0	282,1,0	282,1,0	282,1,0
ALS2	synonymous	*ENST00000264276	c.4641G>A	p.(=)			49,0,0	387,1,0	277,2,0	277,2,0	277,2,0
ALS2	missense	*ENST00000264276	c.4957C>T	p.Arg1653Cys	1	1	50,0,0	356,0,0	239,1,0	4337,2,0	6197,3,0
ANG	missense	*ENST00000336811, ENST00000397990	c.122A>T, c.122A>T	p.Lys41Ile, p.Lys41Ile	1, 1	0, 0	50,0,0	361,5,0	283,5,0	4938,28,0	7850,32,0
ANG	missense	*ENST00000336811, ENST00000397990	c.208A>G, c.208A>G	p.Ile70Val, p.Ile70Val	0, 0	0, 0	50,0,0	387,1,0	301,2,0	4596,7,0	6797,9,0
ANG	synonymous	*ENST00000336811, ENST00000397990	c.330T>G, c.330T>G	p.(=), p.(=)	,	,	32,15,3	304,76,7	220,76,10	3725,1169,90	5982,1771,147
ANG	synonymous	*ENST00000336811,	c.363A>T,	p.(=), p.(=)	,	,	50,0,0	388,0,0	305,1,0	4978,6,0	7669,223,8

		ENST00000397990	c.363A>T								
ATXN2	missense	*ENST00000377617, ENST00000535949, ENST00000550104, ENST00000542287, ENST00000471866, ENST00000389153, ENST00000548492	c.1123G>A, c.256G>A, c.1123G>A, c.328G>A, c.151G>A, c.328G>A, c.352G>A c.363A>T	p.Asp375Asn, p.Asp86Asn, p.Asp375Asn, p.Asp110Asn, p.Asp51Asn, p.Asp110Asn, p.Asp118Asn	1, 1, 1, 1, 1, 1, 1	0, 0, 0, 0, 0, 0, 0	37,0,0	210,0,0	158,1,0	158,1,0	158,1,0
ATXN2	missense	*ENST00000377617, ENST00000535949, ENST00000550104, ENST00000542287, ENST00000389153	c.1472A>G, c.605A>G, c.1472A>G, c.677A>G, c.677A>G c.363A>T	p.Asn491Ser, p.Asn202Ser, p.Asn491Ser, p.Asn226Ser, p.Asn226Ser	0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0	36,1,0	206,4,0	163,0,0	4821,20,0	7733,24,0
ATXN2	missense, splice region, synonymous	*ENST00000377617, ENST00000542287, ENST00000550104, ENST00000389153, ENST00000389154, ENST00000535949, ENST00000482777	c.3000A>G, c.2205A>G, c.2939A>G, c.2211A>G, c.165A>G, c.2133A>G, c.57A>G c.363A>T	p.(=), p.(=), p.Tyr980Cys, p.(=), p.(=), p.(=), p.(=)	, , 0, ,, , ,, ,	, , 0, ,, , ,, ,	37,0,0	208,2,0	164,1,0	4803,40,0	7712,47,0
ATXN2	missense	*ENST00000377617, ENST00000550104	c.319C>G, c.319C>G	p.Leu107Val, p.Leu107Val	0, 0	,	0,0,0	0,0,0	0,0,0	19,122,237	416,351,324
ATXN2	missense	*ENST00000377617, ENST00000550844, ENST00000389154, ENST00000542287, ENST00000389153	c.3322C>T, c.97C>T, c.487C>T, c.2527C>T, c.2533C>T c.363A>T	p.Pro1108Ser , p.Pro33Ser, p.Pro163Ser, p.Pro843Ser, p.Pro845Ser	0, 0, 0, 0, 0	2, 2, 1, 2, 2	37,0,0	200,1,0	147,3,0	4811,17,0	7724,20,0
ATXN2	missense, synonymous	*ENST00000377617, ENST00000535949, ENST00000550844, ENST00000542287, ENST00000389154, ENST00000389153, ENST00000482777, ENST00000550889	c.3411C>T, c.2490C>T, c.186C>T, c.2616C>T, c.576C>T, c.2622C>T, c.414C>T, c.65C>T c.363A>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.Thr22Met	,,, , ,,, , ,,, ,	,,, , ,,, , ,,, ,	37,0,0	209,1,0	165,0,0	165,0,0	165,0,0

ATXN2	missense	*ENST00000377617, ENST00000550844, ENST00000389154, ENST00000482777, ENST00000550889, ENST00000389153, ENST00000535949, ENST00000542287	c.3491G>A, c.266G>A, c.656G>A, c.494G>A, c.145G>A, c.2702G>A, c.2570G>A, c.2696G>A	p.Ser1164Asn, p.Ser89Asn, p.Ser219Asn, p.Ser165Asn, p.Val49Ile, p.Ser901Asn, p.Ser857Asn, p.Ser899Asn	0, 0, 0, 0, , 0, 0, 0	0, 0, 0, 0, , 0, 0, 0	36,1,0	210,0,0	165,0,0	4464,1,0	6667,1,0
ATXN2	synonymous	*ENST00000377617, ENST00000389154, ENST00000550844, ENST00000542287, ENST00000389153, ENST00000535949, ENST00000482777	c.3708G>A, c.873G>A, c.483G>A, c.2913G>A, c.2919G>A, c.2787G>A, c.711G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , , ,	37,0,0	207,3,0	165,0,0	4805,38,0	7714,45,0	
ATXN2	missense	*ENST00000377617, ENST00000550104	c.743G>A, c.743G>A	p.Ser248Asn, p.Ser248Asn	0, 0	1, 0	36,0,0	197,3,0	145,4,0	4790,37,0	6858,776,108
C9orf72	synonymous	*ENST00000380003	c.1275G>A	p.(=)			48,0,0	362,0,0	252,1,0	4552,1,0	6752,2,0
C9orf72	synonymous	*ENST00000380003	c.1404C>T	p.(=)			49,1,0	383,3,0	270,6,0	4898,56,0	7809,61,0
C9orf72	missense	*ENST00000380003, ENST00000379995, ENST00000379997	c.620A>G, c.620A>G, c.620A>G	p.Asn207Ser, p.Asn207Ser, p.Asn207Ser	0, 0, 0	0, 0, 0	38,9,1	301,69,6	194,47,5	3788,1048,87	6523,1227,89
C9orf72	synonymous	*ENST00000380003	c.870C>T	p.(=)			35,12,3	275,95,16	193,84,11	3232,1534,200	5090,2459,333
CHMP2B	missense	*ENST00000263780, ENST00000494980	c.118A>G, c.118A>G	p.Lys40Glu, p.Lys40Glu	1, 1	1, 0	50,0,0	372,1,0	261,0,0	261,0,0	261,0,0
CHMP2B	missense	*ENST00000263780, ENST00000494980	c.123G>T, c.123G>T	p.Gln41His, p.Gln41His	1, 1	1, 2	50,0,0	372,1,0	263,0,0	263,0,0	263,0,0
CHMP2B	synonymous	*ENST00000263780, ENST00000494980	c.27C>T, c.27C>T	p.(=), p.(=)	,	,	24,4,0	135,42,3	104,26,1	4016,752,41	6298,1343,84
CHMP2B	synonymous	*ENST00000263780, ENST00000471660	c.312T>C, c.189T>C	p.(=), p.(=)	,	,	0,3,43	1,23,336	0,26,214	16,506,4396	467,1777,5590
CHMP2B	synonymous	*ENST00000263780, ENST00000471660, ENST00000494980	c.372A>C, c.249A>C, c.282A>C	p.(=), p.(=), p.(=)	, ,	, ,	33,8,1	248,53,4	176,36,0	4084,760,38	6382,1338,78
DCTN1	synonymous	*ENST00000361874,	c.1059C>T,	p.(=), p.(=),	, , ,	, , ,	46,0,0	274,1,0	211,1,0	211,1,0	211,1,0

		ENST00000394003, ENST00000409438, ENST00000409567, ENST00000409868, ENST00000407639, ENST00000409240	c.1038C>T, c.657C>T, c.999C>T, c.1008C>T, c.657C>T, c.948C>T	p.(=), p.(=), p.(=), p.(=), p.(=)	, ,	, ,					
DCTN1	missense	*ENST00000361874, ENST00000409567, ENST00000407639, ENST00000409438, ENST00000409240, ENST00000394003, ENST00000409868	c.1060G>A, c.1000G>A, c.658G>A, c.658G>A, c.949G>A, c.1039G>A, c.1009G>A	p.Ala354Thr, p.Ala334Thr, p.Ala220Thr, p.Ala220Thr, p.Ala317Thr, p.Ala347Thr, p.Ala337Thr	1, 1, 1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2, 2, 2	45,1,0	272,1,0	194,1,0	194,1,0	194,1,0
DCTN1	missense	*ENST00000361874, ENST00000409438, ENST00000394003, ENST00000407639, ENST00000409567, ENST00000409240, ENST00000409868	c.1231C>A, c.829C>A, c.1210C>A, c.829C>A, c.1171C>A, c.1120C>A, c.1180C>A	p.Arg411Ser, p.Arg277Ser, p.Arg404Ser, p.Arg277Ser, p.Arg391Ser, p.Arg374Ser, p.Arg394Ser	0, 0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0	41,0,0	246,2,0	167,0,0	167,0,0	167,0,0
DCTN1	missense	*ENST00000361874, ENST00000409868, ENST00000409567, ENST00000409240, ENST00000394003, ENST00000409438, ENST00000407639	c.1480G>A ,	p.Ala494Thr, p.Ala477Thr, p.Ala474Thr, p.Ala457Thr, p.Ala487Thr, p.Ala360Thr, p.Ala360Thr	0, 0, 0, 0, 0, 0, 0, 0, 0	2, 2, 0, 1, 0, 0, 0	37,0,0	203,1,0	178,1,0	4478,1,0	6676,6,0
DCTN1	missense	*ENST00000361874, ENST00000409868,	c.1484G>A, c.1433G>A,	p.Arg495Gln, p.Arg478Gln,	0, 0, 0, 0,	0, 0, 0, 0,	34,7,0	202,9,1	183,5,0	4687,178,1	7578,203,1

		ENST00000409567, ENST00000394003, ENST00000409240, ENST00000407639, ENST00000409438	c.1424G>A, c.1463G>A, c.1373G>A, c.1082G>A, c.1082G>A	p.Arg475Gln, p.Arg488Gln, p.Arg458Gln, p.Arg361Gln, p.Arg361Gln	0, 0, 0	0, 0, 0					
DCTN1	synonymous	*ENST00000361874, ENST00000394003, ENST00000409868, ENST00000409567, ENST00000407639, ENST00000409240, ENST00000409438	c.2019C>T, c.1998C>T, c.1968C>T, c.1959C>T, c.1617C>T, c.1908C>T, c.1617C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , ,	, , , ,	49,0,0	380,0,0	300,1,0	300,1,0	300,1,0
DCTN1	missense	*ENST00000361874, ENST00000409567, ENST00000409240, ENST00000407639, ENST00000409438, ENST00000409868, ENST00000394003	c.2209G>C, c.2149G>C, c.2098G>C, c.1807G>C, c.1807G>C, c.2158G>C, c.2188G>C	p.Glu737Gln, p.Glu717Gln, p.Glu700Gln, p.Glu603Gln, p.Glu603Gln, p.Glu720Gln, p.Glu730Gln	1, 1, 1, 1, 1, 1, 1, 1, 1	1, 0, 1, 0, 0, 1, 0	49,0,0	360,1,0	289,1,0	289,1,0	289,1,0
DCTN1	missense	*ENST00000361874, ENST00000407639, ENST00000409438, ENST00000409868, ENST00000409567, ENST00000394003, ENST00000409240	c.2339T>C, c.1937T>C, c.1937T>C, c.2288T>C, c.2279T>C, c.2318T>C, c.2228T>C	p.Ile780Thr, p.Ile646Thr, p.Ile646Thr, p.Ile763Thr, p.Ile760Thr, p.Ile773Thr, p.Ile743Thr	1, 1, 1, 1, 1, 1, 1, 1, 1	0, 0, 0, 0, 0, 0, 0	50,0,0	384,1,0	304,0,0	4603,1,0	6806,1,0
DCTN1	missense	*ENST00000361874, ENST00000409438, ENST00000407639, ENST00000394003, ENST00000409240, ENST00000409868, ENST00000409567	c.2353C>T, c.1951C>T, c.1951C>T, c.2332C>T, c.2242C>T, c.2302C>T, c.2293C>T	p.Arg785Trp, p.Arg651Trp, p.Arg651Trp, p.Arg778Trp, p.Arg748Trp, p.Arg768Trp, p.Arg765Trp	1, 1, 1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2, 2, 2	50,0,0	377,1,0	301,0,0	4594,7,0	6795,9,0
DCTN1	synonymous	*ENST00000361874, ENST00000409438,	c.2448A>G, c.2046A>G,	p.(=), p.(=), p.(=), p.(=),	, , , ,	, , , ,	48,0,0	369,4,0	301,2,0	4907,74,0	7613,281,3

		ENST00000409868, ENST00000407639, ENST00000409240, ENST00000394003, ENST00000409567	c.2397A>G, c.2046A>G, c.2337A>G, c.2427A>G, c.2388A>G	p.(=), p.(=), p.(=)							
DCTN1	missense	*ENST00000361874, ENST00000409438, ENST00000407639, ENST00000409240, ENST00000394003, ENST00000409868, ENST00000409567	c.2551C>G, c.2149C>G, c.2149C>G, c.2440C>G, c.2530C>G, c.2500C>G, c.2491C>G	p.Leu851Val, p.Leu717Val, p.Leu717Val, p.Leu814Val, p.Leu844Val, p.Leu834Val, p.Leu831Val	0, 0, 0, 0, 0, 0, 0, 0, 0 0	0, 0, 0, 0, 0, 0, 0, 0, 0 0	27,0,0	212,0,0	222,1,0	600,1,0	1312,2,0
DCTN1	synonymous	*ENST00000361874, ENST00000409240, ENST00000407639, ENST00000409567, ENST00000409868, ENST00000394003, ENST00000409438	c.2559C>T, c.2448C>T, c.2157C>T, c.2499C>T, c.2508C>T, c.2538C>T, c.2157C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	,,, ,, ,,	,,, ,, ,,	30,0,0	222,1,0	216,1,0	216,1,0	216,1,0
DCTN1	splice acceptor	*ENST00000361874, ENST00000409868, ENST00000409567, ENST00000394003, ENST00000409438, ENST00000407639, ENST00000409240	c.2887- 2A>G, c.2836- 2A>G, c.2827- 2A>G, c.2866- 2A>G, c.2485- 2A>G, c.2485- 2A>G, c.2776- 2A>G	,,, ,,, ,,, ,,, ,,, ,,, ,,,	,,, ,, ,,	,,, ,, ,,	39,0,0	237,2,0	246,0,0	246,0,0	246,0,0
DCTN1	synonymous	*ENST00000361874, ENST00000409567,	c.2952C>G, c.2892C>G,	p.(=), p.(=), p.(=), p.(=),	,,, ,,	,,, ,,	46,0,0	287,0,0	280,1,0	4579,2,0	6782,2,0

		ENST00000409868, ENST00000409240, ENST00000409438, ENST00000407639, ENST00000394003	c.2901C>G, c.2841C>G, c.2550C>G, c.2550C>G, c.2931C>G	p.(=), p.(=), p.(=)							
DCTN1	missense	*ENST00000361874, ENST00000409438, ENST00000394003, ENST00000409240, ENST00000407639, ENST00000409868, ENST00000409567	c.3146G>A, c.2744G>A, c.3125G>A, c.3035G>A, c.2744G>A, c.3095G>A, c.3086G>A	p.Arg1049Gln , p.Arg915Gln, p.Arg1042Gln , p.Arg1012Gln , p.Arg915Gln, p.Arg1032Gln , p.Arg1029Gln	0, 0, 0, 0, 0, 0, 0, 0, 0	2, 2, 2, 2, 2, 2, 2	47,0,0	313,4,0	273,2,0	4930,23,0	7845,24,0
DCTN1	synonymous	*ENST00000361874, ENST00000409868, ENST00000409567, ENST00000409438, ENST00000407639, ENST00000394003, ENST00000409240	c.3501C>T, c.3435C>T, c.3426C>T, c.3084C>T, c.3099C>T, c.3480C>T, c.3375C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , , ,	, , , , , ,	45,0,0	299,2,0	224,3,0	224,3,0	224,3,0
DCTN1	missense	*ENST00000361874, ENST00000407639, ENST00000409240, ENST00000394003, ENST00000409438, ENST00000409868, ENST00000409567	c.3746C>T, c.3344C>T, c.3620C>T, c.3725C>T, c.3329C>T, c.3680C>T, c.3671C>T	p.Thr1249Ile, p.Thr1115Ile, p.Thr1207Ile, p.Thr1242Ile, p.Thr1110Ile, p.Thr1227Ile, p.Thr1224Ile	1, 1, 1, 1, 1, 1, 1	0, 0, 0, 0, 0, 0, 0	41,0,0	272,3,0	266,4,0	4905,43,0	7816,48,0
DCTN1	missense	*ENST00000361874, ENST00000409438, ENST00000407639, ENST00000409868, ENST00000394003,	c.3788T>G, c.3371T>G, c.3386T>G, c.3722T>G, c.3767T>G,	p.Val1263Gly , p.Val1124Gly , p.Val1129Gly	1, 1, 1, 1, 1, 1, 1	2, 1, 1, 2, 1, 1, 2	32,3,0	135,52,0	114,52,0	114,52,0	114,52,0

		<i>ENST00000409567,</i> <i>ENST00000409240</i>	<i>c.3713T>G,</i> <i>c.3662T>G</i>	<i>,</i> <i>p.Val1241Gly</i> <i>,</i> <i>p.Val1256Gly</i> <i>,</i> <i>p.Val1238Gly</i> <i>,</i> <i>p.Val1221Gly</i>							
DCTN1	synonymous	*ENST00000361874, ENST00000394003, ENST00000409567, ENST00000458655, ENST00000417090	c.42C>T, c.42C>T, c.42C>T, c.63C>T, c.54C>T	p.(=), p.(=), p.(=), p.(=), p.(=)	,,,	,,,	37,0,0	275,1,0	221,1,0	221,1,0	221,1,0
DCTN1	missense	*ENST00000361874, ENST00000407639, ENST00000409567, ENST00000409240, ENST00000409438, ENST00000394003, ENST00000409868	c.586A>G, c.184A>G, c.526A>G, c.475A>G, c.184A>G, c.565A>G, c.535A>G	p.Ile196Val, p.Ile62Val, p.Ile176Val, p.Ile159Val, p.Ile62Val, p.Ile189Val, p.Ile179Val	0, 0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0	18,0,0	120,3,0	104,3,0	4711,69,2	7617,76,2
DCTN1	synonymous	*ENST00000361874, ENST00000409868, ENST00000409567, ENST00000409438, ENST00000409240, ENST00000394003, ENST00000407639	c.597G>A, c.546G>A, c.537G>A, c.195G>A, c.486G>A, c.576G>A, c.195G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	,,,	,,,	18,0,0	121,1,0	97,0,0	4393,0,0	6583,7,0
DCTN1	missense	*ENST00000361874, ENST00000394003, ENST00000409868, ENST00000409438, ENST00000409240, ENST00000409567, ENST00000407639	c.713G>T, c.692G>T, c.662G>T, c.311G>T, c.602G>T, c.653G>T, c.311G>T	p.Arg238Leu, p.Arg231Leu, p.Arg221Leu, p.Arg104Leu, p.Arg201Leu, p.Arg218Leu, p.Arg104Leu	1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2, 2, 2	26,0,0	164,0,0	146,1,0	146,1,0	146,1,0
DCTN1	synonymous	*ENST00000361874,	c.801G>A,	p.(=), p.(=),	,,,	,,,	16,0,0	128,1,0	143,0,0	143,0,0	143,0,0

		<i>ENST00000407639</i> , <i>ENST00000409567</i> , <i>ENST00000409438</i> , <i>ENST00000394003</i> , <i>ENST00000409868</i> , <i>ENST00000409240</i>	<i>c.399G>A</i> , <i>c.741G>A</i> , <i>c.399G>A</i> , <i>c.780G>A</i> , <i>c.750G>A</i> , <i>c.690G>A</i>	<i>p.(=), p.(=)</i> , <i>p.(=), p.(=)</i> , <i>p.(=)</i>	, ,	, ,					
DCTN1	missense	*ENST00000361874, ENST00000458655, ENST00000417090, ENST00000409868, ENST00000413111, ENST00000437375, ENST00000394003, ENST00000421392, ENST00000440727, ENST00000454119, ENST00000409567, ENST00000409240, ENST00000449655	<i>c.82C>T</i> , <i>c.103C>T</i> , <i>c.94C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i> , <i>c.82C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i> , <i>c.31C>T</i>	<i>p.Arg28Trp</i> , <i>p.Arg35Trp</i> , <i>p.Arg32Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg28Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i> , <i>p.Arg11Trp</i>	1, 1, 1, 1	1, 1, 2, 1, 1, 1, 1	45,0,0	308,0,0	235,2,0	235,2,0	235,2,0
<i>DPP6</i>	<i>synonymous</i>	* <i>ENST00000377770</i> , <i>ENST00000406326</i>	<i>c.114C>T</i> , <i>c.114C>T</i>	<i>p.(=), p.(=)</i>	,	,	0,1,0	0,1,0	0,0,0	0,0,0	0,0,0
DPP6	synonymous	*ENST00000377770, ENST00000332007, ENST00000404039, ENST00000427557	<i>c.1458C>T</i> , <i>c.1272C>T</i> , <i>c.1266C>T</i> , <i>c.1137C>T</i>	<i>p.(=), p.(=)</i> , <i>p.(=), p.(=)</i>	, , ,	, , ,	46,1,0	364,2,0	293,1,0	4469,8,0	6544,11,0
DPP6	missense	*ENST00000377770, ENST00000332007, ENST00000427557, ENST00000404039	<i>c.1459G>A</i> , <i>c.1273G>A</i> , <i>c.1138G>A</i> , <i>c.1267G>A</i>	<i>p.Val487Met</i> , <i>p.Val425Met</i> , <i>p.Val380Met</i> , <i>p.Val423Met</i>	1, 1, 1, 1	2, 2, 2, 2	49,0,0	364,0,0	298,1,0	298,1,0	298,1,0
<i>DPP6</i>	<i>missense</i>	* <i>ENST00000377770</i> , <i>ENST00000427557</i> , <i>ENST00000332007</i> , <i>ENST00000404039</i>	<i>c.1616T>C</i> , <i>c.1295T>C</i> , <i>c.1430T>C</i> , <i>c.1424T>C</i>	<i>p.Phe539Ser</i> , <i>p.Phe432Ser</i> , <i>p.Phe477Ser</i> , <i>p.Phe475Ser</i>	1, 1, 1, 1	2, 1, 1, 2	50,0,0	351,0,0	296,1,0	296,1,0	296,1,0
DPP6	missense	*ENST00000377770, ENST00000404039,	<i>c.1711A>C</i> , <i>c.1519A>C</i>	<i>p.Lys571Gln</i> , <i>p.Lys507Gln</i>	0, 0, 0, 0	0, 0, 0, 0	50,0,0	389,0,0	294,1,0	4770,8,0	7337,25,0

		ENST00000427557, ENST00000332007	c.1390A>C, c.1525A>C	p.Lys464Gln, p.Lys509Gln							
DPP6	synonymous	*ENST00000377770, ENST00000427557, ENST00000332007, ENST00000404039	c.1896A>G, c.1575A>G, c.1710A>G, c.1704A>G	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	2,9,0	18,56,10	29,49,2	1087,2329,122 6	1343,3452,2626
DPP6	synonymous	*ENST00000377770, ENST00000332007, ENST00000427557, ENST00000404039	c.1911G>A, c.1725G>A, c.1590G>A, c.1719G>A	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	5,10,1	33,72,14	35,58,4	1971,2118,580	3968,2838,652
DPP6	synonymous	*ENST00000377770, ENST00000332007, ENST00000404039, ENST00000427557	c.2127T>C, c.1941T>C, c.1935T>C, c.1806T>C	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	28,16,2	197,118,14	170,90,17	3275,1447,165	4371,2723,627
DPP6	synonymous	*ENST00000377770, ENST00000427557, ENST00000404039, ENST00000332007	c.2205C>T, c.1884C>T, c.2013C>T, c.2019C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	49,0,0	344,4,0	261,7,0	4756,43,0	7352,114,7
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000427557, ENST00000332007	c.2295A>G ,	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	49,0,0	356,2,0	296,0,0	296,0,0	296,0,0
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000427557, ENST00000332007	c.2103A>G ,	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	48,0,0	372,0,0	286,0,0	4841,6,0	7577,13,0
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000427557, ENST00000332007	c.2373C>T, c.2181C>T, c.2187C>T, c.2052C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	36,13,0	313,58,3	236,43,4	3799,975,60	6182,1258,109
DPP6	splice acceptor	*ENST00000377770, ENST00000332007,	c.2378-1G>A,	,,,	,,,	,,,	48,0,0	358,6,0	254,2,0	254,2,0	254,2,0

		<i>ENST00000427557, ENST00000404039</i>	<i>c.2192- 1G>A, c.2057- 1G>A, c.2186- 1G>A</i>								
DPP6	synonymous	*ENST00000377770, ENST00000427557, ENST00000332007, ENST00000404039	c.2427G>A, c.2106G>A, c.2241G>A, c.2235G>A	p.(=), p.(=), p.(=), p.(=)	,,	,,	34,14,2	299,86,6	226,62,5	3578,1116,101	4732,2251,422
DPP6	missense	*ENST00000377770, ENST00000332007, ENST00000404039, ENST00000427557	c.2561T>C, c.2375T>C, c.2369T>C, c.2240T>C	p.Leu854Pro, p.Leu792Pro, p.Leu790Pro, p.Leu747Pro	1, 0, 0, 0	0, 0, 0, 0	23,21,6	211,144,29	154,122,24	2637,1875,406	3479,3231,1056
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000332007	c.657C>T, c.465C>T, c.471C>T	p.(=), p.(=), p.(=)	,,	,,	4,28,17	39,167,182	31,127,124	419,1939,2397	910,3103,3299
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000332007	c.666C>T, c.474C>T, c.480C>T	p.(=), p.(=), p.(=)	,,	,,	48,2,0	382,9,0	282,3,0	4707,46,0	7261,52,0
DPP6	synonymous	*ENST00000377770, ENST00000332007, ENST00000404039	c.723A>G, c.537A>G, c.531A>G	p.(=), p.(=), p.(=)	,,	,,	0,8,41	4,52,324	3,49,245	51,812,3908	297,1822,5229
DPP6	<i>missense</i>	<i>*, ENST00000406326</i>	<i>c.785C>T</i>	<i>p.Ser262Leu</i>			<i>0,0,0</i>	<i>0,0,0</i>	<i>0,1,0</i>	<i>1946,400,23</i>	<i>3326,597,34</i>
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000332007, ENST00000427557	c.879T>C, c.687T>C, c.693T>C, c.558T>C	p.(=), p.(=), p.(=), p.(=)	,,	,,	50,0,0	388,1,0	296,0,0	296,0,0	296,0,0
DPP6	missense, splice region	*ENST00000377770, ENST00000332007, ENST00000427557, ENST00000404039	c.883G>A, c.697G>A, c.562G>A, c.691G>A	p.Glu295Lys, p.Glu233Lys, p.Glu188Lys, p.Glu231Lys	1, 1, 1, 1	2, 2, 2, 2	50,0,0	389,1,0	296,0,0	296,0,0	296,0,0
DPP6	synonymous	*ENST00000377770, ENST00000332007, ENST00000427557,	c.945C>T, c.759C>T, c.624C>T,	p.(=), p.(=), p.(=), p.(=)	,,	,,	45,3,0	325,44,2	248,49,1	4080,736,32	6300,1226,61

		ENST00000404039	c.753C>T								
DPP6	synonymous	*ENST00000377770, ENST00000404039, ENST00000427557, ENST00000332007	c.948C>T, c.756C>T, c.627C>T, c.762C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	47,0,0	371,1,0	292,0,0	4460,0,0	6472,3,0
DPP6	missense	*, ENST00000406326	c.982T>G	p.Cys328Gly			0,0,0	0,0,0	0,0,0	0,0,0	0,0,0
ELP3	synonymous	*ENST00000256398, ENST00000524103, ENST00000380353, ENST00000537665, ENST00000521015, ENST00000542181	c.1068G>A, c.852G>A, c.792G>A, c.711G>A, c.1026G>A, c.681G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	''''	''''	50,0,0	386,1,0	298,1,0	298,1,0	298,1,0
ELP3	missense	*ENST00000256398, ENST00000517975, ENST00000523357, ENST00000380353, ENST00000524103, ENST00000521015, ENST00000537665, ENST00000542181	c.1318G>A, c.97G>A, c.115G>A, c.1042G>A, c.1102G>A, c.1276G>A, c.961G>A, c.931G>A	p.Glu440Lys, p.Glu33Lys, p.Glu39Lys, p.Glu348Lys, p.Glu368Lys, p.Glu426Lys, p.Glu321Lys, p.Glu311Lys	1, 1, 1, 1, 1, 1, 1, 1, 1, 1	1, 2, 2, 1, 1, 1, 1, 1	49,0,0	363,1,0	259,2,0	4936,3,0	7852,3,0
ELP3	missense	*ENST00000256398, ENST00000521015, ENST00000521570, ENST00000524024, ENST00000521099, ENST00000520288, ENST00000520270	c.139G>A, c.97G>A, c.97G>A, c.139G>A, c.97G>A, c.97G>A, c.97G>A	p.Ala47Thr, p.Ala33Thr, p.Ala33Thr, p.Ala47Thr, p.Ala33Thr, p.Ala33Thr, p.Ala33Thr	1, 1, 1, 1, 1, 1, 1, 1, 1	0, 0, 0, 0, 0, 0, 0	50,0,0	380,3,0	302,0,0	4600,2,0	6803,2,0
ELP3	missense	*ENST00000256398, ENST00000380353, ENST00000521015, ENST00000542181, ENST00000524103, ENST00000523357, ENST00000537665	c.1459C>T, c.1183C>T, c.1417C>T, c.1072C>T, c.1243C>T, c.256C>T, c.1102C>T	p.Arg487Trp, p.Arg395Trp, p.Arg473Trp, p.Arg358Trp, p.Arg415Trp, p.Arg86Trp, p.Arg368Trp	1, 0, 1, 0, 0, 0, 0	2, 2, 2, 2, 2, 2, 2	46,0,0	330,1,0	199,1,0	4870,8,0	7786,8,0
ELP3	missense	*ENST00000256398,	c.206G>T,	p.Arg69Leu,	1, 1,	0, 0,	50,0,0	380,1,0	294,0,0	294,0,0	294,0,0

		ENST00000520288, ENST00000521570, ENST00000521015, ENST00000521099, ENST00000524024, ENST00000520270	c.164G>T, c.164G>T, c.164G>T, c.164G>T, c.206G>T, c.164G>T	p.Arg55Leu, p.Arg55Leu, p.Arg55Leu, p.Arg55Leu, p.Arg69Leu, p.Arg55Leu	1, 1, 1, 1, 1 1	0, 0, 0, 1, 0					
ELP3	initiator codon, missense	*ENST00000256398, ENST00000521099, ENST00000524103, ENST00000380353, ENST00000520288, ENST00000542181, ENST00000521570, ENST00000524024, ENST00000521015, ENST00000520270, ENST00000537665	c.326G>A, c.284G>A, c.110G>A, c.50G>A, c.284G>A, c.3G>A, c.284G>A, c.326G>A, c.284G>A, c.284G>A, c.33G>A	p.Cys109Tyr, p.Cys95Tyr, p.Cys37Tyr, p.Cys17Tyr, p.Cys95Tyr, p.Met1?, p.Cys95Tyr, p.Cys109Tyr, p.Cys95Tyr, p.Cys95Tyr, p.Met1Ile	1, 1, 1, 1, 1, , 1, 1, 1, 1, 1 1	2, 2, 2, 2, 2, 0, 2, 2, 2, 2, 0	49,1,0	389,1,0	278,0,0	4577,1,0	6780,1,0
<i>ELP3</i>	<i>splice region, synonymous</i>	<i>*, ENST00000523357</i>	<i>c.366G>A</i>	<i>p.(=)</i>			<i>0,0,0</i>	<i>0,0,0</i>	<i>0,0,0</i>	<i>287,82,9</i>	<i>833,223,35</i>
FGGY	synonymous	*ENST00000371218, ENST00000303721, ENST00000371210, ENST00000371212	c.1053A>G, c.1053A>G, c.156A>G, c.789A>G	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	389,1,0	281,2,0	4580,3,0	6783,3,0
FGGY	splice donor	*ENST00000371218, ENST00000303721, ENST00000371212, ENST00000371210	c.1221+2T >C, c.1221+2T >C, c.957+2T> C, c.324+2T> C	,,,	,,,	,,,	49,1,0	384,6,0	287,6,0	4924,47,0	7835,52,0
FGGY	missense	*ENST00000371218, ENST00000582567, ENST00000413489,	c.129T>G, c.129T>G, c.129T>G,	p.Asn43Lys, p.Asn43Lys, p.Asn43Lys,	0, 0, 0, 0, 0	0, 0, 0, 0, 0	17,24,8	143,187,31	117,139,46	1848,1892,521	2391,3053,1098

		ENST00000303721, ENST00000371212	c.129T>G, c.129T>G	p.Asn43Lys, p.Asn43Lys							
FGGY	synonymous	*ENST00000371218, ENST00000303721, ENST00000371212, ENST00000371210	c.1560C>T, c.1488C>T, c.1224C>T, c.591C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	46,0,0	310,0,0	285,1,0	285,1,0	285,1,0
FGGY	missense	*ENST00000371218, ENST00000371210, ENST00000303721, ENST00000371212	c.1716G>A, c.747G>A, c.1644G>A, c.1380G>A	p.Met572Ile, p.Met249Ile, p.Met548Ile, p.Met460Ile	0, 0, 0, 0	1, 1, 1, 1	48,0,0	375,1,0	285,0,0	285,0,0	285,0,0
FGGY	missense	*ENST00000371218, ENST00000413489, ENST00000303721, ENST00000371212	c.188G>C, c.188G>C, c.188G>C, c.188G>C	p.Cys63Ser, p.Cys63Ser, p.Cys63Ser, p.Cys63Ser	1, 1, 1, 1	1, 1, 1, 0	49,0,0	351,1,0	293,0,0	4251,2,0	6529,5,0
FGGY	<i>feature elongation, frameshift</i>	*ENST00000371218, ENST00000303721, ENST00000413489	<i>c.411_412i nsG,</i> <i>c.411_412i nsG,</i> <i>c.411_412i nsG</i>	<i>p.Val140Glyf sX25,</i> <i>p.Val140Glyf sX25,</i> <i>p.Val140Glyf sX25</i>	,,	,,	50,0,0	365,1,0	299,0,0	299,0,0	299,0,0
FGGY	missense	*ENST00000371218, ENST00000303721, ENST00000371212, ENST00000582567, ENST00000413489	c.49G>A, c.49G>A, c.49G>A, c.49G>A, c.49G>A	p.Val17Ile, p.Val17Ile, p.Val17Ile, p.Val17Ile, p.Val17Ile	1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2	47,1,0	308,2,0	225,1,0	3800,8,0	5367,9,0
FGGY	synonymous	*ENST00000371218, ENST00000371212, ENST00000413489, ENST00000303721	c.516G>A, c.252G>A, c.516G>A, c.516G>A	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	17,24,9	137,199,49	91,151,44	1899,2327,737	2388,3679,1812
FGGY	synonymous	*ENST00000371218, ENST00000413489, ENST00000371212, ENST00000303721	c.516G>C, c.516G>C, c.252G>C, c.516G>C	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	384,1,0	286,0,0	286,0,0	286,0,0
FGGY	missense	*ENST00000371218, ENST00000303721,	c.614G>A, c.614G>A,	p.Ser205Asn, p.Ser205Asn,	0, 0, 0	0, 0, 0	50,0,0	388,1,0	284,0,0	4582,2,0	6785,2,0

		ENST00000371212	c.350G>A	p.Ser117Asn							
FGGY	<i>missense</i>	*ENST00000371218, ENST00000303721, ENST00000371212	c.622A>G, c.622A>G, c.358A>G	p.Lys208Glu, p.Lys208Glu, p.Lys120Glu	0, 0, 0	0, 0, 0	50,0,0	389,0,0	280,1,0	280,1,0	280,1,0
FGGY	synonymous	*ENST00000371218, ENST00000371212, ENST00000303721	c.630T>A, c.366T>A, c.630T>A	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	387,1,0	281,0,0	281,0,0	281,0,0
FGGY	missense, splice region	*ENST00000371218, ENST00000371212, ENST00000303721	c.800G>T, c.536G>T, c.800G>T	p.Gly267Val, p.Gly179Val, p.Gly267Val	1, 1, 1	2, 2, 2	49,0,0	359,1,0	294,4,0	4958,18,0	7872,20,0
FGGY	missense	*ENST00000371218, ENST00000303721, ENST00000371212	c.857C>T, c.857C>T, c.593C>T	p.Thr286Met, p.Thr286Met, p.Thr198Met	0, 0, 1	1, 2, 1	39,5,2	292,55,3	238,46,8	4364,579,27	7223,635,28
FGGY	splice region, synonymous	*ENST00000371218, ENST00000371212, ENST00000303721, ENST00000371210	c.903G>T, c.639G>T, c.903G>T, c.6G>T	p.(=), p.(=), p.(=), p.(=)	, , ,	, , ,	50,0,0	357,1,0	302,1,0	4600,3,0	6803,3,0
FGGY	missense	*ENST00000371218, ENST00000303721, ENST00000371212, ENST00000371210	c.979A>C, c.979A>C, c.715A>C, c.82A>C	p.Asn327His, p.Asn327His, p.Asn239His, p.Asn28His	1, 1, 1, 1	0, 2, 2, 2	50,0,0	383,1,0	295,0,0	4586,9,0	6789,9,0
FIG4	missense	*ENST00000230124, ENST00000441478	c.1090A>T, c.259A>T	p.Met364Leu, p.Met87Leu	0, 0	0, 0	47,3,0	363,24,1	271,24,0	4611,355,7	7272,592,25
FIG4	missense	*ENST00000230124, ENST00000454215	c.122T>C, c.59T>C	p.Ile41Thr, p.Ile20Thr	1, 1	2, 2	46,0,0	360,1,0	238,2,0	4899,18,0	7814,19,0
FIG4	synonymous	*ENST00000230124, ENST00000441478	c.1305G>C, c.474G>C	p.(=), p.(=)	,	,	50,0,0	388,1,0	281,0,0	4579,2,0	6782,2,0
FIG4	missense	*ENST00000230124, ENST00000441478	c.1426C>T, c.595C>T	p.Arg476Cys, p.Arg199Cys	1, 1	0, 0	47,0,0	354,1,0	244,0,0	622,0,0	1334,1,0
FIG4	synonymous	*ENST00000230124, ENST00000441478	c.1525C>T, c.694C>T	p.(=), p.(=)	,	,	49,0,0	387,1,0	287,0,0	4586,1,0	6789,1,0
FIG4	synonymous	*ENST00000230124, ENST00000441478	c.1527G>A, c.696G>A	p.(=), p.(=)	,	,	50,0,0	387,0,0	287,1,0	287,1,0	287,1,0
FIG4	missense	*ENST00000230124, ENST00000441478,	c.1793T>A, c.962T>A,	p.Phe598Tyr, p.Phe321Tyr	0, 0, 0	0, 0, 0	38,0,0	336,0,0	219,1,0	219,1,0	219,1,0

		ENST00000415980	c.210T>A	p.Phe71Tyr							
FIG4	missense	*ENST00000230124, ENST00000441478	c.1961T>C, c.1130T>C	p.Val654Ala, p.Val377Ala	0, 0	0, 0	37,11,2	287,96,7	184,77,9	3552,1263,132	4030,2504,1329
FIG4	<i>missense</i>	*ENST00000230124, ENST00000419951, ENST00000441478	c.2200G>A , c.121G>A, c.1369G>A	p.Glu734Lys, p.Glu41Lys, p.Glu457Lys	0, , 0	0, 0, 1	41,0,0	216,1,0	216,1,0	4514,3,0	6717,3,0
FIG4	synonymous	*ENST00000230124, ENST00000441478	c.2559G>A, c.1641G>A	p.(=), p.(=)	,	,	13,22,1 5	107,190,79	92,139,49	1738,2355,865	3648,3195,1031
FIG4	<i>splice acceptor</i>	*ENST00000230124, ENST00000454215, ENST00000441478, ENST00000368941	c.447- 2A>T, c.384- 2A>T, c.9- 2A>T, c.216-2A>T	,,,	,,,	,,,	43,1,0	320,6,0	220,1,0	220,1,0	220,1,0
FUS	synonymous	*ENST00000254108, ENST00000380244, ENST00000568685	c.1080C>T, c.1077C>T, c.1083C>T	p.(=), p.(=), p.(=)	,,	,,	38,0,0	213,2,0	166,2,0	4841,5,0	7750,5,0
FUS	<i>inframe deletion</i>	*ENST00000254108, ENST00000568685, ENST00000380244	c.1204_12 06delAGT, c.1207_12 09delAGT, c.1201_12 03delAGT	p.Ser402del, p.Ser403del, p.Ser401del	,,	,,	50,0,0	364,1,0	296,0,0	296,0,0	296,0,0
FUS	synonymous	*ENST00000254108, ENST00000380244, ENST00000568685	c.132C>T, c.132C>T, c.132C>T	p.(=), p.(=), p.(=)	,,	,,	50,0,0	376,0,0	303,1,0	4601,3,0	6798,3,0
FUS	synonymous	*ENST00000254108, ENST00000380244, ENST00000568685	c.147C>A, c.147C>A, c.147C>A	p.(=), p.(=), p.(=)	,,	,,	29,13,6	173,158,44	133,137,33	2475,2086,420	4866,2551,474
FUS	synonymous	*ENST00000254108, ENST00000568685, ENST00000380244	c.153C>T, c.153C>T, c.153C>T	p.(=), p.(=), p.(=)	,,	,,	49,0,0	376,0,0	303,3,0	4947,37,0	7383,480,31
FUS	<i>synonymous</i>	*ENST00000254108, ENST00000380244, ENST00000568685	c.1545T>G, c.1542T>G, c.1548T>G	p.(=), p.(=), p.(=)	,,	,,	38,0,0	259,6,0	227,6,0	227,6,0	227,6,0

FUS	synonymous	*ENST00000254108, ENST00000568685, ENST00000380244	c.1566G>A, c.1569G>A, c.1563G>A	p.(=), p.(=), p.(=)	,,	,,	47,0,0	337,1,0	280,0,0	4940,18,0	7845,23,0
FUS	missense	*ENST00000254108, ENST00000568685, ENST00000380244	c.1574C>T, c.1577C>T, c.1571C>T	p.Pro525Leu, p.Pro526Leu, p.Pro524Leu	1, 1, 1	1, 2, 2	43,0,0	317,2,0	250,0,0	250,0,0	250,0,0
FUS	<i>inframe deletion</i>	*ENST00000254108, ENST00000568685, ENST00000380244	c.165_167 delTTC, c.165_167 delTTC, c.165_167 delTTC	p.Ser56del, p.Ser56del, p.Ser56del	,,	,,	48,0,0	372,0,0	304,1,0	304,1,0	304,1,0
FUS	<i>synonymous</i>	*ENST00000254108, ENST00000380244, ENST00000568685	c.231G>C, c.228G>C, c.231G>C	p.(=), p.(=), p.(=)	,,	,,	22,10,0	95,122,0	77,140,0	77,140,0	77,140,0
FUS	<i>missense</i>	*ENST00000254108, ENST00000568685, ENST00000380244	c.232A>C, c.232A>C, c.229A>C	p.Thr78Pro, p.Thr78Pro, p.Thr77Pro	0, 0, 0	,,	31,2,0	141,36,0	151,36,0	151,36,0	151,36,0
FUS	<i>synonymous</i>	*ENST00000254108, ENST00000568685, ENST00000380244	c.234T>C, c.234T>C, c.231T>C	p.(=), p.(=), p.(=)	,,	,,	33,0,0	173,10,0	184,9,0	184,9,0	184,9,0
FUS	synonymous	*ENST00000254108, ENST00000568685, ENST00000380244	c.291C>T, c.291C>T, c.288C>T	p.(=), p.(=), p.(=)	,,	,,	8,19,15	79,139,72	60,141,71	1000,2421,152 9	2398,3518,1944
FUS	synonymous	*ENST00000254108, ENST00000380244, ENST00000568685	c.339C>T, c.336C>T, c.339C>T	p.(=), p.(=), p.(=)	,,	,,	49,0,0	318,0,0	277,2,0	277,2,0	277,2,0
FUS	<i>missense</i>	*ENST00000254108, ENST00000380244, ENST00000568685	c.422A>C, c.419A>C, c.422A>C	p.Gln141Pro, p.Gln140Pro, p.Gln141Pro	0, 0, 0	,,	47,0,0	332,1,0	285,0,0	285,0,0	285,0,0
FUS	<i>missense</i>	*ENST00000254108, ENST00000380244, ENST00000568685	c.423A>T, c.420A>T, c.423A>T	p.Gln141His, p.Gln140His, p.Gln141His	0, 0, 0	,,	47,0,0	332,1,0	286,0,0	286,0,0	286,0,0
FUS	missense	*ENST00000254108, ENST00000380244,	c.74A>G, c.74A>G,	p.Tyr25Cys, p.Tyr25Cys,	1, 0, 1	,,	49,0,0	368,0,0	286,1,0	286,1,0	286,1,0

		ENST00000587387, ENST00000592783	c.99C>T, c.99C>T								
HFE	synonymous	*ENST00000357618, ENST00000317896, ENST00000461397, ENST00000309234, ENST00000470149, ENST00000336625	c.138G>A, c.138G>A, c.138G>A, c.138G>A, c.138G>A, c.138G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	',',',',',',	50,0,0	388,0,0	305,1,0	305,1,0	305,1,0	
HFE	missense	*ENST00000357618, ENST00000309234, ENST00000336625, ENST00000317896, ENST00000461397, ENST00000470149, ENST00000397022	c.157G>A, c.157G>A, c.157G>A, c.157G>A, c.157G>A, c.157G>A, c.88G>A	p.Val53Met, p.Val53Met, p.Val53Met, p.Val53Met, p.Val53Met, p.Val53Met, p.Val30Met	1,1,1,1,1,1 1,1,1,1,1,2	50,0,0	387,0,0	301,1,0	4979,1,0	7892,4,0	
HFE	missense	*ENST00000357618, ENST00000397022, ENST00000309234, ENST00000461397, ENST00000470149, ENST00000317896, ENST00000336625	c.187C>G, c.118C>G, c.187C>G, c.187C>G, c.187C>G, c.187C>G, c.187C>G	p.His63Asp, p.His40Asp, p.His63Asp, p.His63Asp, p.His63Asp, p.His63Asp, p.His63Asp	0,0,0,0,0,1 0,0,0,0,0,0	33,16,1	255,124,9	201,97,6	3558,1323,101	6275,1515,108	
HFE	missense	*ENST00000357618, ENST00000353147, ENST00000309234, ENST00000488199, ENST00000349999, ENST00000352392, ENST00000461397, ENST00000470149, ENST00000336625, ENST00000317896, ENST00000397022	c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C, c.18G>C	p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser, p.Arg6Ser	0,1,0,1,1,1, 0,0,1,1,0,0, 1,1,1,1,1,0	12,0,0	61,2,0	43,0,0	4336,6,0	6538,7,0	
HFE	missense	*ENST00000357618, ENST00000317896,	c.193A>T, c.193A>T,	p.Ser65Cys, p.Ser65Cys,	1,1,2,0, 1,1,2,0,	48,2,0	371,16,0	291,13,0	4829,150,3	7728,167,3	

		ENST00000470149, ENST00000336625, ENST00000397022, ENST00000309234, ENST00000461397	c.193A>T, c.193A>T, c.124A>T, c.193A>T, c.193A>T	p.Ser65Cys, p.Ser65Cys, p.Ser42Cys, p.Ser65Cys, p.Ser65Cys	1, 1, 1	1, 2, 2					
HFE	missense	*ENST00000357618, ENST00000488199, ENST00000349999, ENST00000309234, ENST00000461397, ENST00000470149, ENST00000397022	c.502G>C, c.238G>C, c.238G>C, c.502G>C, c.502G>C, c.502G>C, c.433G>C	p.Glu168Gln, p.Glu80Gln, p.Glu80Gln, p.Glu168Gln, p.Glu168Gln, p.Glu168Gln, p.Glu145Gln	1, 1, 1, 0, 1, 0, 1	2, 0, 1, 2, 2, 2, 1	44,0,0	264,0,0	224,2,0	4897,7,0	7813,7,0
HFE	missense	*ENST00000357618, ENST00000349999, ENST00000309234, ENST00000353147, ENST00000461397, ENST00000470149, ENST00000488199, ENST00000352392, ENST00000317896, ENST00000397022, ENST00000336625	c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T, c.50C>T	p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile, p.Thr17Ile	1, 1, 1, 1, 1	1, 2, 1, 1, 1, 1, 2,, 2, 2, 2	9,1,0	45,0,0	29,1,0	4317,12,0	6519,12,0
HFE	missense	*ENST00000357618, ENST00000336625, ENST00000470149, ENST00000317896, ENST00000309234, ENST00000397022, ENST00000353147, ENST00000488199, ENST00000349999, ENST00000461397	c.670C>T, c.352C>T, c.661C>T, c.394C>T, c.670C>T, c.601C>T, c.130C>T, c.364C>T, c.406C>T, c.628C>T	p.Arg224Trp, p.Arg118Trp, p.Arg221Trp, p.Arg132Trp, p.Arg224Trp, p.Arg201Trp, p.Arg44Trp, p.Arg122Trp, p.Arg136Trp, p.Arg210Trp	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2	49,1,0	385,1,0	296,0,0	4593,3,0	6795,4,0
HFE	missense	*ENST00000357618, ENST00000317896,	c.68G>A, c.68G>A,	p.Arg23His, p.Arg23His,	1, 1, 1, 1	2, 2, 2, 2,	7,1,0	23,0,0	17,0,0	4690,4,0	7600,9,0

		<i>ENST00000309234</i> , <i>ENST00000470149</i> , <i>ENST00000336625</i> , <i>ENST00000397022</i> , <i>ENST00000352392</i> , <i>ENST00000353147</i> , <i>ENST00000488199</i> , <i>ENST00000349999</i> , <i>ENST00000461397</i>	<i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i> , <i>c.68G>A</i>	<i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i> , <i>p.Arg23His</i>	1, 1, 1, 1, 0, 0, 1	2, 2, , 1, 2, 1, 2					
HFE	missense	* <i>ENST00000357618</i> , <i>ENST00000353147</i> , <i>ENST00000349999</i> , <i>ENST00000309234</i> , <i>ENST00000461397</i> , <i>ENST00000488199</i> , <i>ENST00000336625</i> , <i>ENST00000397022</i> , <i>ENST00000317896</i> , <i>ENST00000470149</i>	<i>c.766G>A</i> , <i>c.226G>A</i> , <i>c.502G>A</i> , <i>c.766G>A</i> , <i>c.724G>A</i> , <i>c.460G>A</i> , <i>c.448G>A</i> , <i>c.697G>A</i> , <i>c.490G>A</i> , <i>c.757G>A</i>	<i>p.Val256Ile</i> , <i>p.Val76Ile</i> , <i>p.Val168Ile</i> , <i>p.Val256Ile</i> , <i>p.Val242Ile</i> , <i>p.Val154Ile</i> , <i>p.Val150Ile</i> , <i>p.Val233Ile</i> , <i>p.Val164Ile</i> , <i>p.Val253Ile</i>	0, 1, 0, 0, 0, 0, 0, 0, 1, 0, 1, 0	0, 0, 0, 0, 0, 1, 0, 0, 0, 0	50,0,0	387,1,0	295,0,0	295,0,0	295,0,0
HFE	missense	* <i>ENST00000357618</i> , <i>ENST00000349999</i> , <i>ENST00000488199</i> , <i>ENST00000317896</i> , <i>ENST00000309234</i> , <i>ENST00000470149</i> , <i>ENST00000397022</i> , <i>ENST00000461397</i> , <i>ENST00000353147</i> , <i>ENST00000336625</i>	<i>c.829G>A</i> , <i>c.565G>A</i> , <i>c.523G>A</i> , <i>c.553G>A</i> , <i>c.829G>A</i> , <i>c.820G>A</i> , <i>c.760G>A</i> , <i>c.787G>A</i> , <i>c.289G>A</i> , <i>c.511G>A</i>	<i>p.Glu277Lys</i> , <i>p.Glu189Lys</i> , <i>p.Glu175Lys</i> , <i>p.Glu185Lys</i> , <i>p.Glu277Lys</i> , <i>p.Glu274Lys</i> , <i>p.Glu254Lys</i> , <i>p.Glu263Lys</i> , <i>p.Glu97Lys</i> , <i>p.Glu171Lys</i>	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2	50,0,0	382,1,0	299,1,0	4970,8,0	7883,11,0
HFE	missense	* <i>ENST00000357618</i> , <i>ENST00000488199</i> , <i>ENST00000317896</i> , <i>ENST00000470149</i> , <i>ENST00000309234</i> , <i>ENST00000349999</i> ,	<i>c.845G>A</i> , <i>c.539G>A</i> , <i>c.569G>A</i> , <i>c.836G>A</i> , <i>c.845G>A</i> , <i>c.581G>A</i>	<i>p.Cys282Tyr</i> , <i>p.Cys180Tyr</i> , <i>p.Cys190Tyr</i> , <i>p.Cys279Tyr</i> , <i>p.Cys282Tyr</i> , <i>p.Cys194Tyr</i>	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	1, 2, 2, 1, 1, 1, 2, 1, 2, 2	42,8,0	302,70,3	234,60,7	4345,608,26	7187,681,27

		ENST00000336625, ENST00000461397, ENST00000353147, ENST00000397022	c.527G>A, c.803G>A, c.305G>A, c.776G>A	p.Cys176Tyr, p.Cys268Tyr, p.Cys102Tyr, p.Cys259Tyr							
IFNK	missense	*ENST00000276943	c.263A>G	p.Tyr88Cys	1	2	50,0,0	390,1,0	287,1,0	4961,5,0	7832,50,0
IFNK	synonymous	*ENST00000276943	c.279G>A	p.(=)			50,0,0	391,0,0	287,1,0	287,1,0	287,1,0
IFNK	synonymous	*ENST00000276943	c.282C>T	p.(=)			50,0,0	391,0,0	287,1,0	287,1,0	287,1,0
<i>IFNK</i>	<i>feature elongation, frameshift</i>	<i>*ENST00000276943</i>	<i>c.30_31ins TGTT</i>	<i>p.Trp13Phefs X4</i>			44,6,0	366,21,0	269,14,0	269,14,0	269,14,0
IFNK	missense	*ENST00000276943	c.397A>G	p.Lys133Glu	0	0	0,0,49	0,4,386	0,2,274	0,83,4870	111,885,6873
<i>IFNK</i>	<i>stop gained</i>	<i>*ENST00000276943</i>	<i>c.43G>T</i>	<i>p.Glu15X</i>			46,3,0	330,31,0	205,37,0	205,37,0	205,37,0
IFNK	synonymous	*ENST00000276943	c.486G>C	p.(=)			49,0,0	385,0,0	280,1,0	280,1,0	280,1,0
ITPR2	stop gained	*ENST00000381340	c.1318C>T	p.Arg440X			49,0,0	384,0,0	275,1,0	275,1,0	275,1,0
ITPR2	missense	*ENST00000381340	c.1358C>T	p.Ala453Val	0	0	41,6,1	358,24,0	242,19,1	4318,413,8	6837,446,8
ITPR2	synonymous	*ENST00000381340	c.1674C>T	p.(=)			48,0,0	354,2,0	276,1,0	4396,2,0	6289,2,0
ITPR2	synonymous	*ENST00000381340	c.1857C>T	p.(=)			49,0,0	383,1,0	268,0,0	4702,22,0	7240,23,0
ITPR2	synonymous	*ENST00000381340	c.1905A>G	p.(=)			34,13,1	254,113,13	177,75,7	3241,1332,144	4465,2379,406
ITPR2	synonymous	*ENST00000381340	c.2016A>C	p.(=)			36,14,0	295,83,13	190,89,7	3294,1331,135	5101,1954,275
ITPR2	missense	*ENST00000381340	c.2018T>C	p.Met673Thr	0	0	50,0,0	390,1,0	287,0,0	4382,1,0	6240,1,0
ITPR2	synonymous	*ENST00000381340	c.2055A>G	p.(=)			15,27,8	183,154,51	113,137,33	1984,2198,593	3391,3137,860
ITPR2	synonymous	*ENST00000381340	c.2262A>C	p.(=)			40,9,1	334,52,3	244,60,1	3989,833,50	6660,918,52
ITPR2	synonymous	*ENST00000381340	c.2358C>T	p.(=)			36,14,0	284,83,12	196,92,7	3386,1347,135	5162,2144,306
ITPR2	synonymous	*ENST00000381340	c.2694C>T	p.(=)			30,16,4	223,129,28	141,109,15	2689,1726,310	4946,1980,328
ITPR2	missense	*ENST00000381340	c.2854C>T	p.Pro952Ser	0	0	48,0,0	304,1,0	274,1,0	4496,2,0	6598,2,0
ITPR2	synonymous	*ENST00000381340	c.2883C>T	p.(=)			9,29,6	72,146,94	42,140,54	1234,2385,121 1	1857,3718,2048
ITPR2	synonymous	*ENST00000381340	c.3117G>A	p.(=)			47,0,0	368,1,0	245,0,0	4687,2,0	7202,2,0
ITPR2	stop gained	*ENST00000381340	c.3358C>T	p.Arg1120X			49,0,0	363,0,0	256,1,0	256,1,0	256,1,0
ITPR2	synonymous	*ENST00000381340	c.3369A>G	p.(=)			50,0,0	369,10,0	267,8,0	4629,150,1	7222,159,1
ITPR2	missense	*ENST00000381340	c.3485T>G	p.Val1162Gly	0	0	44,1,0	354,1,0	249,0,0	4335,10,0	6173,12,0
ITPR2	missense	*ENST00000381340	c.3539G>A	p.Arg1180Gln	0	0	45,2,0	341,5,0	230,2,0	4631,68,0	7164,78,0
ITPR2	missense	*ENST00000381340	c.3614G>A	p.Arg1205Gln	0	2	50,0,0	370,1,0	266,0,0	266,0,0	266,0,0
ITPR2	missense	*ENST00000381340	c.3635C>T	p.Ala1212Val	0	1	50,0,0	373,0,0	261,3,0	261,3,0	261,3,0

ITPR2	missense	*ENST00000381340	c.3824G>A	p.Arg1275Gln	0	0	47,1,0	367,3,0	256,9,0	4771,51,0	7458,55,0
ITPR2	synonymous	*ENST00000381340	c.4023C>T	p.(=)			50,0,0	388,1,0	293,0,0	293,0,0	293,0,0
ITPR2	synonymous	*ENST00000381340	c.4125C>T	p.(=)			49,1,0	355,32,3	278,21,1	4596,244,6	7288,272,6
ITPR2	synonymous	*ENST00000381340	c.4239C>T	p.(=)			16,29,4	139,183,49	105,133,31	2087,2179,577	4220,2762,624
ITPR2	synonymous	*ENST00000381340	c.4305A>G	p.(=)			48,0,0	377,1,0	248,0,0	248,0,0	248,0,0
ITPR2	synonymous	*ENST00000381340	c.4407A>G	p.(=)			17,29,3	144,186,50	106,126,27	2044,2124,557	3976,2691,598
ITPR2	synonymous	*ENST00000381340	c.4482C>T	p.(=)			18,28,2	151,175,43	106,122,25	2194,2023,490	4106,2590,532
ITPR2	splice region, synonymous	*ENST00000381340	c.4962G>A	p.(=)			50,0,0	383,5,0	283,1,0	4804,34,1	7511,39,1
ITPR2	synonymous	*ENST00000381340	c.5118T>C	p.(=)			48,0,0	367,1,0	256,0,0	256,0,0	256,0,0
ITPR2	synonymous	*ENST00000381340	c.5175G>A	p.(=)			27,19,3	227,129,14	166,81,12	2888,1631,230	5279,1829,234
ITPR2	synonymous	*ENST00000381340	c.5331C>T	p.(=)			49,0,0	379,0,0	263,1,0	4360,2,0	6211,2,0
ITPR2	synonymous	*ENST00000381340	c.5569C>T	p.(=)			50,0,0	384,1,0	255,3,0	4698,18,0	7239,19,0
ITPR2	synonymous	*ENST00000381340	c.570G>C	p.(=)			48,0,0	382,1,0	281,3,0	281,3,0	281,3,0
ITPR2	missense	*ENST00000381340	c.6022G>A	p.Ala2008Thr	1	2	46,0,0	350,1,0	203,5,0	4302,6,0	6152,6,0
ITPR2	missense	*ENST00000381340	c.6346G>C	p.Ala2116Pro	1	2	48,1,0	375,5,0	263,4,0	263,4,0	263,4,0
ITPR2	missense	*ENST00000381340	c.6389C>T	p.Ser2130Leu	0	0	50,0,0	386,1,0	282,0,0	4404,1,0	6326,1,0
ITPR2	synonymous	*ENST00000381340	c.6390G>A	p.(=)			50,0,0	378,1,0	277,0,0	4402,1,0	6329,1,0
ITPR2	missense	*ENST00000381340	c.6529A>C	p.Lys2177Gln	1	0	50,0,0	390,0,0	278,1,0	4383,7,0	6242,7,0
ITPR2	missense	*ENST00000381340	c.6833T>C	p.Leu2278Pro	1	1	49,1,0	383,0,0	281,1,0	4757,2,0	7318,3,0
ITPR2	synonymous	*ENST00000381340	c.6966T>C	p.(=)			50,0,0	388,3,0	302,2,0	4420,5,0	6317,5,0
ITPR2	splice region, synonymous	*ENST00000381340	c.7401T>G	p.(=)			50,0,0	376,0,0	277,2,0	4357,3,0	6193,3,0
ITPR2	synonymous	*ENST00000381340	c.7518G>A	p.(=)			48,0,0	377,0,0	286,1,0	286,1,0	286,1,0
ITPR2	synonymous	*ENST00000381340	c.765A>G	p.(=)			8,32,10	120,175,94	76,152,55	1341,2380,105 5	3448,2822,1098
ITPR2	synonymous	*ENST00000381340	c.798G>A	p.(=)			47,2,0	346,30,3	255,13,0	4573,176,1	6327,896,117
ITPR2	missense	*ENST00000381340	c.8002G>A	p.Ala2668Thr	0	0	48,0,0	356,5,0	287,3,0	4884,28,0	7671,33,0
MAPT	missense	*ENST00000344290, ENST00000262410, ENST00000415613, ENST00000571987	c.1108C>T, c.1108C>T, c.1108C>T, c.1108C>T	p.Arg370Trp, p.Arg370Trp, p.Arg370Trp, p.Arg370Trp	1, 1, 1, 1 2, 1, 2, 1	2,2,1	28,37,5	24,44,9	2730,1552,217	5265,1777,229	
MAPT	missense	*ENST00000344290, ENST00000415613,	c.1280C>T, c.1280C>T,	p.Ser427Phe, p.Ser427Phe,	1, 1, 1, 1 2, 2, 2, 2	50,0,0	388,3,0	303,4,0	4962,23,0	7874,27,0	

		ENST00000571987, ENST00000262410	c.1280C>T, c.1280C>T	p.Ser427Phe, p.Ser427Phe							
MAPT	<i>missense</i>	*ENST00000344290, ENST00000415613, ENST00000262410, ENST00000571987	c.1306C>A, c.1306C>A, c.1306C>A, c.1306C>A	p.Pro436Thr, p.Pro436Thr, p.Pro436Thr, p.Pro436Thr	0, 0, 0, 0	0, 0, 0, 0	50,0,0	390,0,0	306,1,0	306,1,0	306,1,0
MAPT	missense	*ENST00000344290, ENST00000571987, ENST00000415613, ENST00000262410	c.1321T>C, c.1321T>C, c.1321T>C, c.1321T>C	p.Tyr441His, p.Tyr441His, p.Tyr441His, p.Tyr441His	0, 0, 0, 0	0, 0, 0, 0	37,12,1	257,126,8	210,87,9	3204,1578,202	5108,2414,378
MAPT	missense	*ENST00000344290, ENST00000571987, ENST00000415613, ENST00000262410	c.1339T>C, c.1339T>C, c.1339T>C, c.1339T>C	p.Ser447Pro, p.Ser447Pro, p.Ser447Pro, p.Ser447Pro	0, 0, 0, 0	0, 0, 0, 0	36,12,2	250,123,18	190,105,12	3019,1712,254	5642,1992,267
MAPT	<i>missense</i>	*ENST00000344290, ENST00000415613, ENST00000351559, ENST00000340799, ENST00000571987, ENST00000420682, ENST00000574436, ENST00000576518, ENST00000431008, ENST00000446361, ENST00000347967, ENST00000535772, ENST00000334239, ENST00000262410	c.1405G>A ,	p.Ala469Thr, p.Ala469Thr, p.Ala152Thr, p.Ala123Thr, p.Ala469Thr, p.Ala123Thr, p.Ala152Thr, p.Ala83Thr, p.Ala152Thr, p.Ala94Thr, p.Ala58Thr, p.Ala152Thr, p.Ala94Thr, p.Ala469Thr	0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 0, 0, 0	3,0,0	36,2,0	27,0,0	4679,25,1	7591,29,1
MAPT	<i>synonymous</i>	*ENST00000344290, ENST00000576518, ENST00000347967, ENST00000574436, ENST00000420682, ENST00000334239,	c.1479G>A, c.321G>A, c.246G>A, c.528G>A, c.441G>A, c.354G>A,	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , ,	, , , , ,	4,6,1	37,62,4	37,50,8	2856,1667,250	5518,1910,261

		ENST00000535772, ENST00000262410, ENST00000431008, ENST00000446361, ENST00000351559, ENST00000571987, ENST00000415613, ENST00000340799	c.528G>A, c.1479G>A, c.528G>A, c.354G>A, c.528G>A, c.1479G>A, c.1479G>A, c.441G>A	p.(=), p.(=)							
MAPT	synonymous	*ENST00000344290, ENST00000415613	c.1512T>C, c.1512T>C	p.(=), p.(=)	,	,	27,12,1	154,91,12	146,93,10	2556,1434,215	4607,1643,228
MAPT	synonymous	*ENST00000344290, ENST00000571987, ENST00000351559, ENST00000340799, ENST00000415613, ENST00000334239, ENST00000431008, ENST00000446361, ENST00000576518, ENST00000262410, ENST00000574436, ENST00000347967, ENST00000420682, ENST00000535772	c.1686A>G, c.1632A>G, c.681A>G, c.594A>G, c.1686A>G, c.507A>G, c.681A>G, c.507A>G, c.474A>G, c.1632A>G, c.681A>G, c.399A>G, c.594A>G, c.681A>G	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	'', '' '', '' '', '' '', '' '', '' '', '' '', '' '	9,7,0	57,31,1	52,24,3	2892,1625,240	5508,1912,253	
MAPT	missense	*ENST00000344290, ENST00000347967, ENST00000420682, ENST00000571987, ENST00000334239, ENST00000415613, ENST00000351559, ENST00000262410, ENST00000446361, ENST00000431008, ENST00000340799,	c.1720G>A, c.433G>A, c.628G>A, c.1666G>A, c.541G>A, c.1720G>A, c.715G>A, c.1666G>A, c.541G>A, c.715G>A, c.628G>A,	p.Ala574Thr, p.Ala145Thr, p.Ala210Thr, p.Ala556Thr, p.Ala181Thr, p.Ala574Thr, p.Ala239Thr, p.Ala556Thr, p.Ala181Thr, p.Ala239Thr, p.Ala210Thr,	0, 0, 0, 0	18,0,0	92,2,0	66,0,0	4354,12,0	6551,18,0	

		ENST00000535772, ENST00000576518, ENST00000574436	c.715G>A, c.508G>A, c.715G>A	p.Ala239Thr, p.Ala170Thr, p.Ala239Thr								
MAPT	synonymous	*ENST00000344290, ENST00000351559, ENST00000446361, ENST00000535772, ENST00000340799, ENST00000334239, ENST00000574436, ENST00000262410, ENST00000576518, ENST00000431008, ENST00000347967, ENST00000571987, ENST00000420682, ENST00000415613	c.1770T>C, c.765T>C, c.591T>C, c.765T>C, c.678T>C, c.591T>C, c.765T>C, c.1716T>C, c.558T>C, c.765T>C, c.483T>C, c.1716T>C, c.678T>C, c.1770T>C	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, ,, ,, ,, ,, ,, ,, ,	16,5,2	75,60,5	66,52,2	2887,1667,244	5509,1948,257		
MAPT	synonymous	*ENST00000344290, ENST00000446361, ENST00000574436, ENST00000351559, ENST00000571987, ENST00000334239, ENST00000420682, ENST00000347967, ENST00000340799, ENST00000576518, ENST00000535772, ENST00000431008, ENST00000415613, ENST00000262410	c.1815G>A, c.636G>A, c.810G>A, c.810G>A, c.1761G>A, c.636G>A, c.723G>A, c.528G>A, c.723G>A, c.603G>A, c.810G>A, c.810G>A, c.1815G>A, c.1761G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, ,, ,, ,, ,, ,, ,, ,	8,3,0	69,16,0	55,8,0	4319,414,8	7017,631,9		
MAPT	synonymous	*ENST00000344290, ENST00000446361, ENST00000571987, ENST00000420682,	c.2178G>A, c.999G>A, c.2124G>A, c.1086G>A,	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, ,, ,, ,	45,0,0	325,1,0	287,1,0	4585,3,0	6788,3,0		

		ENST00000334239, ENST00000535772, ENST00000576518, ENST00000415613, ENST00000340799, ENST00000351559, ENST00000431008, ENST00000347967, ENST00000262410, ENST00000574436	c.906G>A, c.1080G>A, c.873G>A, c.2178G>A, c.1086G>A, c.1173G>A, c.1080G>A, c.798G>A, c.2124G>A, c.1173G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)							
MAPT	missense	*ENST00000344290, ENST00000431008, ENST00000262410, ENST00000571987, ENST00000535772, ENST00000574436, ENST00000351559, ENST00000415613	c.284C>T, c.284C>T, c.284C>T, c.284C>T, c.284C>T, c.284C>T, c.284C>T, c.284C>T, c.284C>T	p.Thr95Met, p.Thr95Met, p.Thr95Met, p.Thr95Met, p.Thr95Met, p.Thr95Met, p.Thr95Met, p.Thr95Met, p.Thr95Met	0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	10,0,0	49,1,0	50,0,0	4348,1,0	6548,1,0
MAPT	missense	*ENST00000344290, ENST00000415613, ENST00000571987, ENST00000262410	c.605C>T, c.605C>T, c.605C>T, c.605C>T	p.Pro202Leu, p.Pro202Leu, p.Pro202Leu, p.Pro202Leu	0, 0, 0, 0	1, 1, 1, 1	0,2,0	0,8,1	7,12,1	2822,1566,254	5405,1839,268
MAPT	missense	*ENST00000344290, ENST00000262410, ENST00000415613, ENST00000571987	c.671T>G, c.671T>G, c.671T>G, c.671T>G	p.Val224Gly, p.Val224Gly, p.Val224Gly, p.Val224Gly	1, 1, 1, 1	1, 0, 1, 0	8,0,0	52,0,0	47,1,0	4684,39,0	7593,43,0
MAPT	missense	*ENST00000344290, ENST00000415613, ENST00000262410, ENST00000571987	c.689A>G, c.689A>G, c.689A>G, c.689A>G	p.Gln230Arg, p.Gln230Arg, p.Gln230Arg, p.Gln230Arg	1, 1, 1, 1	0, 0, 2, 2	9,3,0	71,9,0	63,6,1	4218,495,9	7028,586,11
MAPT	missense	*ENST00000344290, ENST00000262410, ENST00000415613, ENST00000571987	c.698C>T, c.698C>T, c.698C>T, c.698C>T	p.Pro233Leu, p.Pro233Leu, p.Pro233Leu, p.Pro233Leu	0, 0, 0, 0	2, 0, 2, 0	14,0,0	78,1,0	80,0,0	80,0,0	80,0,0
MAPT	stop gained	*, ENST00000576518	c.7A>T	p.Lys3X			26,10,1	154,88,12	126,75,9	352,205,31	991,272,38

MAPT	missense	*ENST00000344290, ENST00000571987, ENST00000262410, ENST00000415613	c.853G>A, c.853G>A, c.853G>A, c.853G>A	p.Asp285Asn, p.Asp285Asn, p.Asp285Asn, p.Asp285Asn	0, 0, 0, 0	0, 0, 0, 0	20,9,2	120,70,13	91,68,12	2910,1684,255	5532,1963,270
MAPT	synonymous	*ENST00000344290, ENST00000262410, ENST00000571987, ENST00000415613	c.855C>T, c.855C>T, c.855C>T, c.855C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	27,7,0	147,48,2	125,45,5	3756,1021,76	6277,1393,99
MAPT	missense	*ENST00000344290, ENST00000415613, ENST00000262410, ENST00000571987	c.866T>C, c.866T>C, c.866T>C, c.866T>C	p.Val289Ala, p.Val289Ala, p.Val289Ala, p.Val289Ala	0, 0, 0, 0	0, 0, 0, 0	24,9,2	124,74,14	119,80,11	2938,1696,254	5560,1976,268
MOB3B	synonymous	*ENST00000262244	c.414C>T	p.(=)			28,19,3	243,128,12	195,84,13	3304,1488,178	5880,1815,191
MOB3B	synonymous	*ENST00000262244	c.615G>A	p.(=)			50,0,0	390,0,0	303,1,0	303,1,0	303,1,0
MOB3B	missense	*ENST00000262244	c.98G>A	p.Arg33Gln	0	0	50,0,0	354,0,0	277,1,0	277,1,0	277,1,0
NEFH	missense	*ENST00000310624	c.1054C>A	p.Arg352Ser	1		31,0,0	184,2,0	142,10,0	4778,52,0	7687,59,0
NEFH	missense	*ENST00000310624	c.1105G>A	p.Ala369Thr	0		43,0,0	254,0,0	175,3,0	175,3,0	175,3,0
NEFH	synonymous	*ENST00000310624	c.1200C>T	p.(=)			28,16,0	172,91,7	125,62,18	3464,1310,109	6039,1631,129
NEFH	missense	*ENST00000310624	c.1387G>A	p.Glu463Lys	0		45,5,0	324,52,3	244,45,1	4066,852,50	6892,940,52
NEFH	missense	*ENST00000310624	c.1580C>T	p.Pro527Leu	0		47,0,0	354,1,0	279,2,0	279,2,0	279,2,0
NEFH	synonymous	*ENST00000310624	c.1740C>T	p.(=)			50,0,0	370,6,0	291,8,0	4857,119,1	7763,129,1
NEFH	missense	*ENST00000310624	c.1844C>T	p.Pro615Leu	1	2	30,17,2	217,147,12	170,109,13	3028,1715,227	5081,2490,315
NEFH	missense	*ENST00000310624	c.1933G>A	p.Glu645Lys	0	2	41,2,0	314,30,0	253,10,0	253,10,0	253,10,0
NEFH	<i>feature elongation, frameshift</i>	*ENST00000310624	c.1935_19 36insG	p.Ala646GlyfsX5			34,9,0	237,63,0	198,44,0	198,44,0	198,44,0
NEFH	synonymous	*ENST00000310624	c.1935A>G	p.(=)			39,5,0	292,41,0	246,21,0	246,21,0	246,21,0
NEFH	synonymous	*ENST00000310624	c.1938A>C	p.(=)			27,18,0	163,147,0	137,115,0	137,115,0	137,115,0
NEFH	synonymous	*ENST00000310624	c.1965A>T	p.(=)			16,29,0	118,206,0	129,125,0	129,125,0	129,125,0
NEFH	<i>inframe deletion</i>	*ENST00000310624	c.1970_19 75delAGGAAG	p.Glu658_Glu659del			24,23,0	189,148,0	187,79,0	187,79,0	187,79,0
NEFH	missense	*ENST00000310624	c.1973A>C	p.Glu658Ala	0	0	40,1,0	298,26,0	227,32,0	227,32,0	227,32,0
NEFH	missense	*ENST00000310624	c.1974A>C	p.Glu658Asp	0	2	45,1,0	323,15,0	248,14,0	248,14,0	248,14,0
NEFH	missense	*ENST00000310624	c.1975G>A	p.Glu659Lys	0	2	46,1,0	325,12,0	258,11,0	258,11,0	258,11,0

<i>NEFH</i>	<i>synonymous</i>	*ENST00000310624	c.1989T>A	p.(=)			43,2,0	332,22,0	300,0,0	300,0,0	300,0,0
<i>NEFH</i>	<i>synonymous</i>	*ENST00000310624	c.2082C>T	p.(=)			47,0,0	330,0,1	304,0,0	304,0,0	304,0,0
NEFH	synonymous	*ENST00000310624	c.2232T>C	p.(=)			2,18,29	14,145,216	12,107,179	230,1711,3035	321,2459,5112
<i>NEFH</i>	<i>inframe deletion</i>	*ENST00000310624	c.2368_23 70delAAG	p.Lys790del			48,0,0	324,1,0	278,0,0	278,0,0	278,0,0
NEFH	missense	*ENST00000310624	c.2414A>C	p.Glu805Ala	1	1	31,14,0	200,92,4	177,62,10	3518,1307,101	5785,1900,157
NEFH	synonymous	*ENST00000310624	c.2646C>T	p.(=)			37,0,0	281,0,0	199,2,1	199,2,1	199,2,1
NEFH	missense	*ENST00000310624	c.2740G>A	p.Val914Met	0		41,0,0	301,1,0	258,1,0	258,1,0	258,1,0
NEFH	synonymous	*ENST00000310624	c.2757C>T	p.(=)			39,1,0	266,6,0	201,3,0	4827,55,0	7724,74,0
NEFH	synonymous	*ENST00000310624	c.2784A>G	p.(=)			2,16,23	9,129,182	9,98,156	221,1706,3014	308,2459,5090
NEFH	missense	*ENST00000310624	c.2977A>G	p.Lys993Glu	1		38,0,0	315,0,0	265,1,0	265,1,0	265,1,0
<i>NIPA1</i>	<i>missense</i>	*ENST00000337435, ENST00000437912, ENST00000561183	c.233T>G, c.8T>G, c.8T>G	p.Val78Gly, p.Val3Gly, p.Val3Gly	0, 1, 1	0, 0, 0	32,1,0	174,51,0	200,46,0	200,46,0	200,46,0
NIPA1	synonymous	*ENST00000337435, ENST00000437912, ENST00000561183	c.441A>G, c.216A>G, c.216A>G	p.(=), p.(=), p.(=)	, ,	, ,	1,17,31	32,141,214	17,120,159	357,1937,2680	1027,3268,3595
OPTN	synonymous	*ENST00000263036, ENST00000378764, ENST00000378757, ENST00000378747, ENST00000378752, ENST00000378748	c.102G>A, c.102G>A, c.102G>A, c.102G>A, c.102G>A, c.102G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , ,	, , , , ,	24,16,3	120,112,12	104,102,14	2564,1980,354	5049,2389,376
OPTN	missense	*ENST00000263036, ENST00000378764, ENST00000378747, ENST00000378752, ENST00000378748, ENST00000378757	c.1192C>G, c.1174C>G, c.1192C>G, c.1174C>G, c.1192C>G, c.1192C>G	p.Gln398Glu, p.Gln392Glu, p.Gln398Glu, p.Gln392Glu, p.Gln398Glu, p.Gln398Glu	0, 0, 0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0, 0	50,0,0	367,1,0	243,0,0	243,0,0	243,0,0
OPTN	synonymous	*ENST00000263036, ENST00000378764, ENST00000378757, ENST00000378747, ENST00000378748, ENST00000378752	c.123G>A, c.123G>A, c.123G>A, c.123G>A, c.123G>A, c.123G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , ,	, , , , ,	39,2,0	225,8,0	224,9,0	4806,104,1	7710,116,1

OPTN	synonymous	*ENST00000263036, ENST00000378748, ENST00000378764, ENST00000378747, ENST00000378752, ENST00000378757	c.1569G>A, c.1569G>A, c.1551G>A, c.1569G>A, c.1551G>A, c.1569G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , ,	, , , , ,	48,0,0	341,1,0	279,0,0	279,0,0	279,0,0
OPTN	missense	*ENST00000263036, ENST00000378747, ENST00000378764, ENST00000378748, ENST00000430081, ENST00000378757, ENST00000378752	c.187C>A, c.187C>A, c.187C>A, c.187C>A, c.16C>A, c.187C>A, c.187C>A	p.Gln63Lys, p.Gln63Lys, p.Gln63Lys, p.Gln63Lys, p.Gln6Lys, p.Gln63Lys, p.Gln63Lys	0, 0, 0, 0, 1, 0, 0	2, 2, 2, 2, 2, 2, 2	49,0,0	361,1,0	271,1,0	271,1,0	271,1,0
OPTN	synonymous	*ENST00000263036, ENST00000378757, ENST00000430081, ENST00000378752, ENST00000378747, ENST00000378748, ENST00000378764	c.213G>A, c.213G>A, c.42G>A, c.213G>A, c.213G>A, c.213G>A, c.213G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , , ,	, , , , , ,	49,1,0	384,0,0	284,0,0	284,0,0	284,0,0
OPTN	missense	*ENST00000263036, ENST00000378764, ENST00000378747, ENST00000430081, ENST00000378757, ENST00000378752, ENST00000378748	c.287G>A, c.287G>A, c.287G>A, c.116G>A, c.287G>A, c.287G>A, c.287G>A	p.Arg96His, p.Arg96His, p.Arg96His, p.Arg39His, p.Arg96His, p.Arg96His, p.Arg96His	0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0	47,0,0	368,0,0	264,1,0	642,1,0	1354,2,0
OPTN	missense	*ENST00000263036, ENST00000378764, ENST00000378752, ENST00000430081, ENST00000378757, ENST00000378748, ENST00000378747	c.293T>A, c.293T>A, c.293T>A, c.122T>A, c.293T>A, c.293T>A, c.293T>A	p.Met98Lys, p.Met98Lys, p.Met98Lys, p.Met41Lys, p.Met98Lys, p.Met98Lys, p.Met98Lys	0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0	48,2,0	357,21,1	267,18,1	4654,303,7	6956,885,39
OPTN	synonymous	*ENST00000263036,	c.489A>G,	p.(=), p.(=),	, , ,	, , ,	50,0,0	388,1,0	306,0,0	4968,16,0	7881,19,0

		ENST00000378764, ENST00000378748, ENST00000430081, ENST00000378757, ENST00000378747, ENST00000378752	c.489A>G, c.489A>G, c.318A>G, c.489A>G, c.489A>G, c.489A>G	p.(=), p.(=), p.(=), p.(=), p.(=)	, ,	, ,					
OPTN	synonymous	*ENST00000263036, ENST00000378748, ENST00000430081, ENST00000378757, ENST00000378747, ENST00000378764, ENST00000378752	c.513C>T, c.513C>T, c.342C>T, c.513C>T, c.513C>T, c.513C>T, c.513C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , ,	, , , ,	50,0,0	384,0,0	299,1,0	4598,2,0	6801,2,0
OPTN	missense	*ENST00000263036, ENST00000378748, ENST00000378757, ENST00000378747, ENST00000378752, ENST00000378764	c.964A>G, c.964A>G, c.964A>G, c.964A>G, c.946A>G, c.946A>G	p.Lys322Glu, p.Lys322Glu, p.Lys322Glu, p.Lys322Glu, p.Lys316Glu, p.Lys316Glu	0, 0, 0, 0, 0, 0, 0, 0,	0, 0, 0, 0, 0, 0, 0, 0,	0,0,44	0,0,294	0,1,195	0,12,4862	2,138,7650
PARK7	synonymous	*ENST00000338639, ENST00000469225, ENST00000377491, ENST00000377488, ENST00000493678, ENST00000493373	c.234C>T, c.117C>T, c.234C>T, c.234C>T, c.234C>T, c.234C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , ,	, , , ,	48,0,0	345,1,0	240,0,0	4906,12,0	7317,490,27
PARK7	missense	*ENST00000338639, ENST00000493678, ENST00000377493, ENST00000469225, ENST00000377488, ENST00000493373, ENST00000377491	c.293G>A, c.293G>A, c.233G>A, c.176G>A, c.293G>A, c.293G>A, c.293G>A	p.Arg98Gln, p.Arg98Gln, p.Arg78Gln, p.Arg59Gln, p.Arg98Gln, p.Arg98Gln, p.Arg98Gln	0, 0, 0, 0, 0, 0, 0, 0, 0 0	0, 0, 0, 0, 0, 0, 0, 0, 0 0	46,0,0	294,3,0	239,6,0	4809,113,1	7715,123,1
PARK7	<i>missense</i>	*ENST00000338639, ENST00000493373, ENST00000377493,	c.49A>C, c.49A>C, c.49A>C,	p.Met17Leu, p.Met17Leu, p.Met17Leu,	1, 1, 1, 1, 1, 1	0, 0, 0, 0, 0, 0	49,0,0	375,1,0	283,0,0	661,0,0	1373,1,0

		<i>ENST00000493678,</i> <i>ENST00000377488,</i> <i>ENST00000377491</i>	<i>c.49A>C,</i> <i>c.49A>C,</i> <i>c.49A>C</i>	<i>p.Met17Leu,</i> <i>p.Met17Leu,</i> <i>p.Met17Leu</i>							
PARK7	synonymous	*ENST00000338639, ENST00000493373, ENST00000469225, ENST00000377493, ENST00000377488, ENST00000377491, ENST00000493678	c.501A>G, c.501A>G, c.414A>G, c.441A>G, c.501A>G, c.501A>G, c.501A>G	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	, , , , ,	, , , , ,	50,0,0	383,1,0	305,2,0	4967,18,0	7881,20,0
PARK7	missense	*ENST00000338639, ENST00000377493, ENST00000377491, ENST00000469225, ENST00000377488, ENST00000493373, ENST00000493678	c.535G>A, c.475G>A, c.535G>A, c.448G>A, c.535G>A, c.535G>A, c.535G>A	p.Ala179Thr, p.Ala159Thr, p.Ala179Thr, p.Ala150Thr, p.Ala179Thr, p.Ala179Thr, p.Ala179Thr	0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	50,0,0	378,0,0	303,1,0	4976,6,0	7890,8,0
PON1	missense	*ENST00000222381, ENST00000542556	c.163T>A, c.163T>A	p.Leu55Met, p.Leu55Met	1, 1	0, 2	18,26,6	159,176,54	109,128,43	1982,2264,712	4041,3035,798
<i>PON1</i>	<i>feature elongation, frameshift</i>	<i>*ENST00000222381,</i> <i>ENST00000542556</i>	<i>c.391dupG,</i> <i>c.391dupG</i>	<i>p.Val131Glyf sX15,</i> <i>p.Val131Glyf sX15</i>	,	,	<i>50,0,0</i>	<i>391,0,0</i>	<i>282,1,0</i>	<i>282,1,0</i>	<i>282,1,0</i>
PON1	synonymous	*ENST00000222381, ENST00000542556	c.468A>G, c.468A>G	p.(=), p.(=)	,	,	50,0,0	388,1,0	280,0,0	280,0,0	280,0,0
PON1	missense	*ENST00000222381, ENST00000542556	c.575A>G, c.575A>G	p.Gln192Arg, p.Gln192Arg	0, 0	0, 0	24,23,3	211,152,28	150,115,21	2544,2013,407	2905,3306,1669
PON1	missense	*ENST00000222381, ENST00000542556	c.602C>T, c.602C>T	p.Ala201Val, p.Ala201Val	0, 0	0, 0	50,0,0	386,2,0	278,3,0	4931,28,0	7844,31,0
PON1	synonymous	*ENST00000222381, ENST00000542556	c.603G>A, c.603G>A	p.(=), p.(=)	,	,	50,0,0	386,4,0	283,1,0	4946,16,0	7860,18,0
PON1	missense	*ENST00000222381, ENST00000542556	c.953C>T, c.953C>T	p.Thr318Ile, p.Thr318Ile	1, 1	0, 0	50,0,0	390,0,0	289,1,0	4588,2,0	6791,2,0
PON1, PON3	synonymous	*ENST00000265627, ENST00000427422,	c.63C>T, c.63C>T,	p.(=), p.(=), p.(=)	, ,	, ,	1,3,0	10,34,1	12,28,1	2607,1810,302	3945,3085,605

		ENST00000542556	c.63C>T								
PON1, PON3	stop gained	*ENST00000265627, ENST00000427422, ENST00000542556	c.94C>T, c.94C>T, c.94C>T	p.Arg32X, p.Arg32X, p.Arg32X	,,	,,	48,0,0	371,3,0	280,0,0	4937,21,0	7849,25,0
PON2	<i>feature truncation, frameshift</i>	*ENST00000222572, ENST00000433091, ENST00000536183	c.286delA, c.286delA, c.349delA	<i>p.Arg96GlyfsX5,</i> <i>p.Arg96GlyfsX5,</i> <i>p.Arg117GlyfsX5</i>	,,	,,	49,1,0	386,2,0	290,1,0	290,1,0	290,1,0
PON2	missense	*ENST00000222572, ENST00000433091, ENST00000536183	c.359T>G, c.359T>G, c.422T>G	p.Ile120Arg, p.Ile120Arg, p.Ile141Arg	1, 1, 0	0, 0, 1	50,0,0	389,0,0	287,1,0	287,1,0	287,1,0
PON2	missense	*ENST00000222572, ENST00000536183, ENST00000433091	c.443C>G, c.506C>G, c.407C>G	p.Ala148Gly, p.Ala169Gly, p.Ala136Gly	1, 1, 1	0, 0, 0	31,17,0	205,158,22	155,90,20	2924,1756,263	4445,2939,475
PON2	missense	*ENST00000222572, ENST00000433091, ENST00000536183	c.661T>G, c.625T>G, c.724T>G	p.Ser221Ala, p.Ser209Ala, p.Ser242Ala	0, 0, 0	0, 0, 0	49,0,0	380,1,0	257,0,0	257,0,0	257,0,0
PON2	missense	*ENST00000222572, ENST00000433091, ENST00000536183	c.827C>T, c.791C>T, c.890C>T	p.Ser276Leu, p.Ser264Leu, p.Ser297Leu	1, 1, 1	0, 0, 0	50,0,0	381,1,0	273,1,0	4572,2,0	6775,2,0
PON2	missense	*ENST00000222572, ENST00000536183, ENST00000433091	c.913C>T, c.976C>T, c.877C>T	p.Arg305Cys, p.Arg326Cys, p.Arg293Cys	1, 1, 1	2, 2, 2	48,1,0	384,2,0	276,0,0	4573,3,0	6776,3,0
PON2	missense	*ENST00000222572, ENST00000433091, ENST00000536183	c.932C>G, c.896C>G, c.995C>G	p.Ser311Cys, p.Ser299Cys, p.Ser332Cys	1, 1, 1	0, 0, 0	32,17,1	210,157,23	166,95,22	2934,1762,265	4447,2950,480
PON3	missense	*ENST00000265627, ENST00000427422	c.262A>G, c.262A>G	p.Met88Val, p.Met88Val	1, 0	0, 0	50,0,0	383,1,0	280,1,0	4943,16,0	7859,16,0
PON3	synonymous	*ENST00000265627, ENST00000427422	c.297G>A, c.297G>A	p.(=), p.(=)	,	,	17,20,1 2	93,199,91	85,121,72	1446,2454,105 6	1930,3805,2137
PON3	missense	*ENST00000265627, ENST00000427422	c.408G>T, c.408G>T	p.Met136Ile, p.Met136Ile	0, 0	0, 0	49,0,0	380,1,0	259,2,0	4554,7,0	6756,8,0
PON3	synonymous	*ENST00000265627,	c.609T>C,	p.(=), p.(=)	,	,	49,1,0	379,12,0	281,7,0	4908,57,1	7814,67,1

		ENST00000427422	c.609T>C								
<i>PON3</i>	<i>synonymous</i>	*ENST00000265627	<i>c.819T>C</i>	<i>p.(=)</i>			47,1,0	330,28,0	247,23,0	247,23,0	247,23,0
PON3	synonymous	*ENST00000265627	c.954C>T	p.(=)			49,0,0	376,1,0	285,0,0	4584,1,0	6787,1,0
PON3	missense	*ENST00000265627	c.971G>A	p.Gly324Asp	1	2	49,0,0	382,0,0	292,1,0	4935,35,0	7850,36,0
<i>PRPH</i>	<i>synonymous</i>	*ENST00000257860, ENST00000532332	<i>c.1083C>G, c.268C>G</i>	<i>p.(=), p.(=)</i>	,	,	0,0,0	1,2,0	1,0,0	4535,129,0	7383,188,0
<i>PRPH</i>	<i>synonymous</i>	*ENST00000257860, ENST00000532332	<i>c.1104A>G, , c.289A>G</i>	<i>p.(=), p.(=)</i>	,	,	0,0,0	9,0,0	7,0,0	4305,1,0	6507,1,0
<i>PRPH</i>	<i>synonymous</i>	*ENST00000257860, ENST00000532332	<i>c.1107A>G , c.292A>G</i>	<i>p.(=), p.(=)</i>	,	,	0,5,0	6,21,0	4,12,2	3018,1458,219	4431,2637,543
<i>PRPH</i>	<i>missense</i>	*ENST00000257860, ENST00000532332	<i>c.1225G>A , c.410G>A</i>	<i>p.Val409Met, p.Val138Met</i>	0, 0	0, 0	41,0,0	271,2,0	176,7,0	176,7,0	176,7,0
<i>PRPH</i>	<i>missense</i>	*ENST00000257860, ENST00000532332	<i>c.1231G>A , c.416G>A</i>	<i>p.Val411Ile, p.Val140Ile</i>	0, 0	0, 0	43,0,0	271,0,0	191,5,0	191,5,0	191,5,0
PRPH	missense	*ENST00000257860, ENST00000532332	c.1303C>T, c.488C>T	p.Arg435Trp, p.Arg164Trp	1, 1	2, 1	41,0,0	244,1,0	215,1,0	4889,5,0	7802,8,0
PRPH	missense	*ENST00000257860	c.26G>A	p.Arg9Gln	1	1	18,1,0	43,2,0	31,2,0	4585,111,1	7459,145,2
<i>PRPH</i>	<i>missense</i>	*ENST00000257860, ENST00000451891	<i>c.322T>C, c.79T>C</i>	<i>p.Phe108Leu, p.Phe27Leu</i>	1, 1	1, 2	2,0,0	4,1,0	5,0,0	5,0,0	5,0,0
PRPH	synonymous	*ENST00000257860	c.63C>T	p.(=)			24,0,0	74,7,0	45,5,0	4516,169,0	7272,309,2
<i>PRPH</i>	<i>missense</i>	*ENST00000257860, ENST00000532332	<i>c.829G>A, c.14G>A</i>	<i>p.Ala277Thr, p.Ala6Thr</i>	0, 0	0, 0	2,0,0	2,0,0	2,0,0	4511,169,0	7276,319,1
SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000393220	c.1077T>C, c.1077T>C, c.1077T>C	p.(=), p.(=), p.(=)	,	,	0,15,35	6,104,276	6,64,187	110,1280,3544	588,2589,4673
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.1655A>C, c.1655A>C, c.1655A>C	p.Gln552Pro, p.Gln552Pro, p.Gln552Pro	0, 0, 0	1, 1, 1	50,0,0	390,0,0	290,1,0	290,1,0	290,1,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.1750C>G, c.1750C>G, c.1750C>G	p.Leu584Val, p.Leu584Val, p.Leu584Val	1, 1, 1	2, 2, 2	50,0,0	390,1,0	278,2,0	278,2,0	278,2,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.1869A>C, c.1869A>C, c.1869A>C	p.Glu623Asp, p.Glu623Asp, p.Glu623Asp	1, 1, 1	2, 2, 2	50,0,0	385,0,0	267,1,0	4564,4,0	6767,4,0
SETX	synonymous	*ENST00000224140,	c.192A>G,	p.(=), p.(=),	,	,	48,1,0	377,5,0	256,2,1	4910,24,1	7824,26,1

		ENST00000393220, ENST00000372169	c.192A>G, c.192A>G	p.(=)							
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.1979C>G, c.1979C>G, c.1979C>G	p.Ala660Gly, p.Ala660Gly, p.Ala660Gly	0, 0, 0	0, 0, 0	43,7,0	339,44,1	234,33,0	4384,539,21	6103,1543,214
SETX	missense	*, ENST00000436441, ENST00000372169	c.2095C>T, c.7369C>T	p.Leu699Phe, p.Leu2457Ph e	0, 0	0, 0	6,0,0	58,3,0	72,3,0	2409,34,1	3995,37,1
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000372169	c.234G>A, c.234G>A, c.234G>A	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	384,0,0	262,2,0	4559,5,0	6761,6,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.2411T>C, c.2411T>C, c.2411T>C	p.Leu804Ser, p.Leu804Ser, p.Leu804Ser	1, 1, 1	0, 0, 0	49,0,0	378,1,0	253,0,0	4928,2,0	7843,2,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.2479A>G, c.2479A>G, c.2479A>G	p.Lys827Glu, p.Lys827Glu, p.Lys827Glu	0, 0, 0	0, 0, 0	49,0,0	378,1,0	246,0,0	4914,8,0	7828,9,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.2717C>T, c.2717C>T, c.2717C>T	p.Ser906Leu, p.Ser906Leu, p.Ser906Leu	0, 0, 0	0, 0, 0	49,0,0	380,1,0	258,0,0	4557,1,0	6760,1,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.2755G>C, c.2755G>C, c.2755G>C	p.Val919Leu, p.Val919Leu, p.Val919Leu	0, 0, 0	0, 0, 0	50,0,0	383,1,0	266,0,0	266,0,0	266,0,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.2842C>A, c.2842C>A, c.2842C>A	p.Pro948Thr, p.Pro948Thr, p.Pro948Thr	0, 0, 0	0, 0, 0	49,1,0	387,0,0	282,0,0	282,0,0	282,0,0
SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000393220	c.2964A>G, c.2964A>G, c.2964A>G	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	389,0,0	278,1,0	4577,2,0	6780,2,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.2975A>G, c.2975A>G, c.2975A>G	p.Lys992Arg, p.Lys992Arg, p.Lys992Arg	1, 1, 1	0, 0, 0	48,1,1	375,13,0	277,3,0	4799,159,0	7698,176,0
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000372169	c.3147C>T, c.3147C>T, c.3147C>T	p.(=), p.(=), p.(=)	, ,	, ,	42,8,0	336,53,1	228,36,2	4199,718,27	6767,1048,45

SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.3221A>G, c.3221A>G, c.3221A>G	p.Glu1074Gly , p.Glu1074Gly , p.Glu1074Gly	1, 1, 1	2, 2, 2	50,0,0	384,0,0	264,1,0	264,1,0	264,1,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.3229G>A, c.3229G>A, c.3229G>A	p.Asp1077As n, p.Asp1077As n, p.Asp1077As n	1, 1, 1	1, 1, 1	50,0,0	383,2,0	267,0,0	4936,9,0	7850,10,0
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000372169	c.3336T>C, c.3336T>C, c.3336T>C	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	383,4,0	267,2,0	4940,7,0	7853,10,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.3455T>G, c.3455T>G, c.3455T>G	p.Phe1152Cy s, p.Phe1152Cy s, p.Phe1152Cy s	1, 1, 1	1, 1, 1	47,3,0	362,25,0	263,13,0	4629,320,5	7166,679,25
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.3576T>G, c.3576T>G, c.3576T>G	p.Asp1192Glu , p.Asp1192Glu , p.Asp1192Glu	0, 0, 0	0, 0, 0	0,15,35	5,93,286	3,66,203	93,1168,3689	533,2448,4885
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.3754G>A, c.3754G>A, c.3754G>A	p.Gly1252Arg , p.Gly1252Arg , p.Gly1252Arg	0, 0, 0	0, 0, 0	0,15,35	6,107,276	8,70,212	118,1289,3561	1198,2588,4098
SETX	<i>feature elongation, frameshift</i>	*ENST00000224140, ENST00000372169, ENST00000393220	<i>c.3930dup A,</i> <i>c.3930dup A,</i> <i>c.3930dup</i>	<i>p.Arg1311Thr fsX2,</i> <i>p.Arg1311Thr fsX2,</i> <i>p.Arg1311Thr</i>	, ,	, ,	49,1,0	391,0,0	293,0,0	293,0,0	293,0,0

			A	fsX2								
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.4156A>G, c.4156A>G, c.4156A>G	p.Ile1386Val, p.Ile1386Val, p.Ile1386Val	0, 0, 0	0, 0, 0	0,15,35	6,107,277	8,68,191	112,1292,3541	1190,2591,4080	
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.4660T>G, c.4660T>G, c.4660T>G	p.Cys1554Gly ,	1, 1, 1	2, 2, 2	49,1,0	385,6,0	284,1,0	4922,41,0	7831,48,0	
SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000393220	c.4707T>C, c.4707T>C, c.4707T>C	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	391,0,0	288,1,0	288,1,0	288,1,0	
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.472T>G, c.472T>G, c.472T>G	p.Leu158Val, p.Leu158Val, p.Leu158Val	1, 1, 1	2, 2, 2	50,0,0	383,3,0	280,5,0	4910,53,0	7821,58,0	
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000372169	c.4755T>G, c.4755T>G, c.4755T>G	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	384,8,0	287,3,0	4888,80,0	7796,88,0	
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.506G>A, c.506G>A, c.506G>A	p.Arg169His, p.Arg169His, p.Arg169His	1, 1, 1	2, 2, 2	49,0,0	372,3,0	249,2,0	249,2,0	249,2,0	
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000372169	c.5271A>G, c.5271A>G, c.5271A>G	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	387,1,0	268,1,0	268,1,0	268,1,0	
SETX	synonymous	*ENST00000224140, ENST00000436441, ENST00000372169, ENST00000393220	c.5283A>G, c.9A>G, c.5283A>G, c.5283A>G	p.(=), p.(=), p.(=), p.(=)	, , ,	, , ,	49,0,0	375,1,0	263,0,0	4558,4,0	6761,4,0	
SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000393220	c.540A>G, c.540A>G, c.540A>G	p.(=), p.(=), p.(=)	, ,	, ,	50,0,0	385,1,0	279,0,0	279,0,0	279,0,0	
SETX	missense	*ENST00000224140, ENST00000436441, ENST00000372169, ENST00000393220	c.5563A>G, c.289A>G, c.5563A>G, c.5563A>G	p.Thr1855Ala, p.Thr97Ala, p.Thr1855Ala, p.Thr1855Ala	0, 0, 0, 0	0, 0, 0, 0	34,15,1	275,107,9	197,72,8	3541,1301,113	4078,2603,1190	

SETX	missense	*ENST00000224140, ENST00000372169, ENST00000436441, ENST00000393220	c.5587A>G, c.5587A>G, c.313A>G, c.5587A>G	p.Thr1863Ala, p.Thr1863Ala, p.Thr105Ala, p.Thr1863Ala	1, 1, 1, 1	2, 2, 2, 2	49,1,0	391,0,0	278,0,0	278,0,0	278,0,0
SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000393220, ENST00000436441	c.5811T>C, c.5811T>C, c.5811T>C, c.537T>C	p.(=), p.(=), p.(=), p.(=)	, , ,	, , ,	33,15,1	274,106,8	191,69,8	3532,1301,113	4070,2603,1189
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000436441, ENST00000393220	c.5842A>G, c.5842A>G, c.568A>G, c.5842A>G	p.Met1948Va , p.Met1948Va , p.Met190Val, p.Met1948Va 	1, 1, 1, 1	2, 2, 2, 2	50,0,0	387,1,0	279,0,0	279,0,0	279,0,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169, ENST00000436441	c.5998C>G, c.5998C>G, c.5998C>G, c.724C>G	p.Gln2000Glu ,	1, 1, 1, 0	1, 0, 0, 0	49,1,0	386,2,0	285,0,0	4959,4,0	7874,5,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.59G>A, c.59G>A, c.59G>A	p.Arg20His, p.Arg20His, p.Arg20His	0, 0, 0	0, 0, 0	49,0,0	380,5,0	288,9,0	4866,108,1	7771,119,1
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169, ENST00000436441	c.6005G>A ,	p.Arg2002His ,	1, 1, 1, 1	2, 2, 2, 2	50,0,0	375,1,0	268,2,0	268,2,0	268,2,0
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000372169, ENST00000436441	c.6024T>C, c.6024T>C, c.6024T>C, c.750T>C	p.(=), p.(=), p.(=), p.(=)	, , ,	, , ,	50,0,0	389,0,0	285,1,0	285,1,0	285,1,0
SETX	missense	*ENST00000224140,	c.6049A>G	p.Met2017Va	0, 0	2, 2	50,0,0	390,1,0	285,0,0	285,0,0	285,0,0

		<i>ENST00000393220, ENST00000436441, ENST00000372169</i>	, <i>c.6049A>G ,</i> <i>c.775A>G, c.6049A>G</i>	<i>I, p.Met2017Va I, p.Met259Val, p.Met2017Va I</i>	<i>0, 0</i>	<i>1, 1</i>					
SETX	synonymous	*ENST00000224140, ENST00000436441, ENST00000372169, ENST00000393220	c.6507G>A, c.1233G>A, c.6507G>A, c.6507G>A	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	383,7,0	279,16,0	4760,208,5	7653,231,5
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.654G>C, c.654G>C, c.654G>C	p.Lys218Asn, p.Lys218Asn, p.Lys218Asn	1, 1, 1	2, 2, 2	50,0,0	391,0,0	279,1,0	4951,7,0	7867,7,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	<i>c.6848C>A, c.6848C>A, c.1574C>A, c.6848C>A</i>	<i>p.Thr2283Lys ,</i> <i>p.Thr2283Lys ,</i> <i>p.Thr525Lys, p.Thr2283Lys</i>	1, 1, 1, 1	2, 2, 2, 2	48,0,0	357,3,0	241,8,0	241,8,0	241,8,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169	c.710A>G, c.710A>G, c.710A>G	p.Tyr237Cys, p.Tyr237Cys, p.Tyr237Cys	1, 1, 1	2, 2, 2	50,0,0	386,1,0	272,1,0	4570,3,0	6773,3,0
SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000436441	c.7119T>C, c.7119T>C, c.1845T>C	p.(=), p.(=), p.(=)	,,	,,	50,0,0	389,1,0	293,0,0	293,0,0	293,0,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000436441	c.7139G>A, c.7139G>A, c.1865G>A	p.Arg2380Gln , <i>p.Arg2380Gln ,</i> <i>p.Arg622Gln</i>	0, 0, 0	2, 1, 1	49,1,0	387,0,0	283,2,0	4582,3,0	6785,3,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000372169, ENST00000436441	c.7406T>C, c.7307T>C, c.7493T>C, c.2219T>C	p.Leu2469Pro , <i>p.Leu2436Pro ,</i> <i>p.Leu2498Pro ,</i> <i>p.Leu740Pro</i>	0, 0, 0, 0	0, 0, 0, 0	50,0,0	390,0,0	302,1,0	4601,2,0	6804,2,0

SETX	synonymous	*ENST00000224140, ENST00000372169, ENST00000436441, ENST00000393220	c.7524A>G, c.7611A>G, c.2337A>G, c.7425A>G	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	390,0,0	303,1,0	303,1,0	303,1,0
SETX	synonymous	*ENST00000224140, ENST00000436441, ENST00000372169, ENST00000393220	c.7590T>A, c.2403T>A, c.7677T>A, c.7491T>A	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	388,1,0	303,0,0	303,0,0	303,0,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000436441, ENST00000393220	c.7640T>C, c.7727T>C, c.2453T>C, c.7541T>C	p.Ile2547Thr, p.Ile2576Thr, p.Ile818Thr, p.Ile2514Thr	0, 0, 0, 0	0, 0, 0, 0	50,0,0	378,10,0	305,0,0	4913,69,1	7824,74,1
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	c.7645G>A, c.7546G>A, c.2458G>A, c.7732G>A	p.Val2549Ile, p.Val2516Ile, p.Val820Ile, p.Val2578Ile	1, 1, 0, 0	0, 0, 0, 0	50,0,0	387,2,0	305,0,0	4605,0,0	6807,1,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	c.7682C>T, c.7583C>T, c.2495C>T, c.7769C>T	p.Ser2561Leu ,	0, 0, 0, 0	0, 0, 0, 0	50,0,0	356,2,0	253,0,0	4552,1,0	6755,1,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	c.7709C>T, c.7610C>T, c.2522C>T, c.7796C>T	p.Pro2570Leu ,	1, 1, 0, 1	0, 0, 0, 0	50,0,0	362,0,0	297,1,0	297,1,0	297,1,0
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	c.7759A>G, c.7846A>G, c.7660A>G, c.2572A>G	p.Ile2587Val, p.Ile2616Val, p.Ile2554Val, p.Ile858Val	0, 0, 0, 0	0, 0, 0, 0	22,20,4	160,154,28	145,115,15	2472,2065,416	2770,3162,1937
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000436441,	c.7787C>G, c.7874C>G, c.2600C>G,	p.Ala2596Gly ,	1, 1, 0, 1	0, 0, 0, 0	9,4,0	125,19,0	142,16,0	142,16,0	142,16,0

		ENST00000393220	c.7688C>G	, <i>p.Ala867Gly,</i> <i>p.Ala2563Gly</i>							
SETX	missense	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	c.7834A>G, c.7735A>G, c.2647A>G, c.7921A>G	p.Ser2612Gly, p.Ser2579Gly, p.Ser883Gly, p.Ser2641Gly	0, 0, 0, 0 0, 0	0, 0, 0, 0 0, 0	34,2,0	202,19,1	176,15,0	4611,252,6	6595,1076,114
SETX	synonymous	*ENST00000224140, ENST00000393220, ENST00000436441, ENST00000372169	c.7944C>T, c.7845C>T, c.2757C>T, c.8031C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	37,0,0	220,1,0	180,0,0	4479,1,0	6682,1,0
SETX	missense	*ENST00000224140, ENST00000372169, ENST00000393220	c.814C>G, c.814C>G, c.814C>G	p.His272Asp, p.His272Asp, p.His272Asp	1, 1, 1	2, 2, 2	50,0,0	386,1,0	280,0,0	280,0,0	280,0,0
SIGMAR 1	missense	*ENST00000277010, ENST00000378892, ENST00000477726	c.595C>T, c.328C>T, c.502C>T	p.Leu199Phe, p.Leu110Phe, p.Leu168Phe	0, 0, 1	0, 0, 0	14,0,0	169,0,0	139,1,0	4437,3,0	6640,3,0
SIGMAR 1	missense	*ENST00000277010, ENST00000378892, ENST00000477726	c.622C>T, c.355C>T, c.529C>T	p.Arg208Trp, p.Arg119Trp, p.Arg177Trp	1, 1, 1	2, 2, 2	13,0,0	161,1,0	127,2,0	4788,19,0	7599,123,1
SPG11	missense	*ENST00000261866, ENST00000559193, ENST00000535302, ENST00000558319, ENST00000427534	c.1108G>A, c.1108G>A, c.1108G>A, c.1108G>A, c.1108G>A	p.Glu370Lys, p.Glu370Lys, p.Glu370Lys, p.Glu370Lys, p.Glu370Lys	0, 0, 0, 0, 0, 0, 0	0, 1, 0, 1, 0, 2	50,0,0	376,13,0	280,11,0	4768,198,1	7661,216,1
SPG11	synonymous	*ENST00000261866, ENST00000535302, ENST00000559193, ENST00000557866, ENST00000427534, ENST00000558319	c.1347C>T, c.1347C>T, c.1347C>T, c.45C>T, c.1347C>T, c.1347C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	387,3,0	288,5,0	4925,44,0	7720,155,5
SPG11	missense	*ENST00000261866, ENST00000558319, ENST00000559193, ENST00000557866,	c.1348A>G, c.1348A>G, c.1348A>G, c.46A>G,	p.Ile450Val, p.Ile450Val, p.Ile450Val, p.Ile16Val,	0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0	50,0,0	387,3,0	289,5,0	4925,45,0	7715,161,5

		ENST00000535302, ENST00000427534	c.1348A>G, c.1348A>G	p.Ile450Val, p.Ile450Val							
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000559193, ENST00000558319, ENST00000557866, ENST00000427534	c.1388T>C, c.1388T>C, c.1388T>C, c.1388T>C, c.86T>C, c.1388T>C	p.Phe463Ser, p.Phe463Ser, p.Phe463Ser, p.Phe463Ser, p.Phe29Ser, p.Phe463Ser	0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0	22,21,7	119,211,57	81,158,55	1494,2435,104 1	2163,3866,1852
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000427534, ENST00000558319, ENST00000559193, ENST00000557866	c.1529G>A, c.1529G>A, c.1529G>A, c.1529G>A, c.1529G>A, c.227G>A	p.Ser510Asn, p.Ser510Asn, p.Ser510Asn, p.Ser510Asn, p.Ser510Asn, p.Ser76Asn	0, 0, 0, 0, 0, 0, 0, 0	2, 2, 2, 1, 2, 2	50,0,0	388,1,0	282,0,0	282,0,0	282,0,0
SPG11	splice region, synonymous	*ENST00000261866, ENST00000535302, ENST00000427534, ENST00000559193, ENST00000558319, ENST00000557866	c.1605C>T, c.1605C>T, c.1605C>T, c.1605C>T, c.1605C>T, c.303C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	' , '' , ' , '' ,	' , '' ,	48,0,0	356,2,0	236,0,0	4909,3,0	7820,3,0
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000557866, ENST00000535302, ENST00000559193, ENST00000558319	c.1698T>G, c.1698T>G, c.396T>G, c.1698T>G, c.1698T>G, c.1698T>G	p.Asp566Glu, p.Asp566Glu, p.Asp132Glu, p.Asp566Glu, p.Asp566Glu, p.Asp566Glu	0, 0, 0, 0, 0, 0	0, 2, 0, 0, 1, 1	46,2,0	359,17,0	234,8,0	4740,177,0	7629,197,1
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000558319, ENST00000559193, ENST00000427534	c.1930A>T, c.1930A>T, c.1930A>T, c.1930A>T, c.1930A>T	p.Thr644Ser, p.Thr644Ser, p.Thr644Ser, p.Thr644Ser, p.Thr644Ser	0, 0, 0, 0, 0	0, 1, 2, 1, 2	48,1,0	382,0,0	265,0,0	265,0,0	265,0,0
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000427534, ENST00000559193,	c.2083G>A, c.2083G>A, c.2083G>A, c.2083G>A,	p.Ala695Thr, p.Ala695Thr, p.Ala695Thr, p.Ala695Thr,	1, 1, 1, 1, 1	2, 2, 2, 2, 2	48,0,0	343,11,0	234,7,1	4786,131,1	7681,147,1

		ENST00000558319	c.2083G>A	p.Ala695Thr							
SPG11	missense, splice region	*ENST00000261866, ENST00000535302, ENST00000558319, ENST00000427534	c.2318T>G, c.2318T>G, c.2318T>G, c.2318T>G	p.Val773Gly, p.Val773Gly, p.Val773Gly, p.Val773Gly	1, 1, 1, 1	2, 2, 2, 2	29,0,0	272,0,0	166,1,0	4812,4,0	7683,4,0
SPG11	<i>missense</i>	*ENST00000261866, ENST00000558319, ENST00000427534, ENST00000535302	c.2377G>A , c.2377G>A , c.2377G>A , c.2377G>A	<i>p.Val793Met,</i> <i>p.Val793Met,</i> <i>p.Val793Met,</i> <i>p.Val793Met</i>	1, 1, 1, 0	0, 0, 2, 0	44,0,0	345,2,0	212,3,0	212,3,0	212,3,0
SPG11	missense	*ENST00000261866, ENST00000558319, ENST00000535302, ENST00000427534	c.2577A>C, c.2577A>C, c.2577A>C, c.2577A>C	p.Gln859His, p.Gln859His, p.Gln859His, p.Gln859His	0, 0, 0, 0	0, 0, 1, 0	50,0,0	379,1,0	267,0,0	267,0,0	267,0,0
SPG11	synonymous	*ENST00000261866, ENST00000558319, ENST00000535302, ENST00000427534	c.2887A>C, c.2887A>C, c.2887A>C, c.2887A>C	p.(=), p.(=), p.(=), p.(=)	49,1,0	387,1,0	279,2,0	4943,14,0	7852,16,0
SPG11	missense, splice region	*ENST00000261866, ENST00000535302, ENST00000558319, ENST00000427534	c.3037A>G, c.3037A>G, c.3037A>G, c.3037A>G	p.Lys1013Glu, p.Lys1013Glu, p.Lys1013Glu, p.Lys1013Glu	0, 0, 0, 0	0, 0, 0, 0	49,1,0	375,7,0	269,2,0	4811,135,1	7712,145,1
SPG11	synonymous	*ENST00000261866, ENST00000559754, ENST00000558988, ENST00000427534, ENST00000535302, ENST00000558319	c.3420G>A, c.149G>A, c.147G>A, c.3420G>A, c.3420G>A, c.3420G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	''''	''''	44,6,0	355,35,0	259,25,2	4455,490,17	7301,554,18
SPG11	missense	*ENST00000261866, ENST00000559754, ENST00000427534, ENST00000558319, ENST00000558988,	c.3446T>C, c.175T>C, c.3446T>C, c.3446T>C, c.173T>C,	p.Leu1149Pro , p.Leu59Pro, p.Leu1149Pro , p.Leu1149Pro	1, 1, 1, 1, 1, 1, 1, 1	2, 2, 2, 2, 2, 2, 2, 2	50,0,0	391,0,0	285,1,0	285,1,0	285,1,0

		ENST00000535302	c.3446T>C	, p.Leu58Pro, p.Leu1149Pro							
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000558988, ENST00000535302, ENST00000558319	c.3680A>G, c.3680A>G, c.407A>G, c.3680A>G, c.3680A>G	p.Lys1227Arg, p.Lys1227Arg, p.Lys136Arg, p.Lys1227Arg, p.Lys1227Arg	0, 0, 1, 0, 0 0	0, 2, 0, 0, 2	49,1,0	390,0,0	302,0,0	302,0,0	302,0,0
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000558319, ENST00000427534, ENST00000559193	c.394A>G, c.394A>G, c.394A>G, c.394A>G, c.394A>G	p.Ser132Gly, p.Ser132Gly, p.Ser132Gly, p.Ser132Gly, p.Ser132Gly	0, 0, 0, 0, 0, 0, 0 0	0, 0, 0, 0, 0, 0, 0	50,0,0	390,1,0	279,0,0	279,0,0	279,0,0
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000558319, ENST00000535302	c.3980T>C, c.3980T>C, c.3980T>C, c.3980T>C	p.Ile1327Thr, p.Ile1327Thr, p.Ile1327Thr, p.Ile1327Thr	1, 1, 1, 1 1, 1	0, 2, 0, 0 0, 0	50,0,0	369,2,0	263,2,0	263,2,0	263,2,0
SPG11	missense	*ENST00000261866, ENST00000558319, ENST00000535302, ENST00000427534	c.3988C>G, c.3988C>G, c.3988C>G, c.3988C>G	p.Gln1330Glu ,	0, 0, 0, 0 0, 0 0, 0	0, 0, 0, 0 0, 1	49,0,0	364,3,0	265,1,0	4562,2,0	6760,2,0
SPG11	synonymous	*ENST00000261866, ENST00000535302, ENST00000427534, ENST00000558319	c.4026A>G, c.4026A>G, c.4026A>G, c.4026A>G	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	388,3,0	287,2,0	4576,11,0	6774,11,0
SPG11	synonymous	*ENST00000261866, ENST00000558319, ENST00000427534, ENST00000535302	c.4260C>T, c.4260C>T, c.4260C>T, c.4260C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	389,0,0	295,1,0	4590,4,0	6788,4,0
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000535302, ENST00000558319	c.4261G>A, c.4261G>A, c.4261G>A, c.4261G>A	p.Asp1421As n, p.Asp1421As n,	0, 0, 0, 0 0, 0 0, 0	0, 0, 0, 0 0, 0 0, 0	50,0,0	389,0,0	288,2,0	666,2,0	1378,3,0

				p.Asp1421Asn, p.Asp1421Asn							
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000558319, ENST00000535302	c.4343G>A, c.4343G>A, c.4343G>A, c.4343G>A	p.Cys1448Tyr, p.Cys1448Tyr, p.Cys1448Tyr, p.Cys1448Tyr	1, 1, 1, 1	1, 0, 1, 1	50,0,0	387,1,0	300,0,0	300,0,0	300,0,0
SPG11	missense, splice region	*ENST00000261866, ENST00000558319, ENST00000427534, ENST00000535302	c.5121G>T, c.5121G>T, c.5121G>T, c.5121G>T	p.Glu1707Asp, p.Glu1707Asp, p.Glu1707Asp, p.Glu1707Asp	1, 1, 1, 1	1, 1, 2, 1	50,0,0	389,0,0	302,1,0	4968,11,0	7878,12,0
SPG11	synonymous	*ENST00000261866, ENST00000558319, ENST00000427534, ENST00000535302, ENST00000559511	c.5361C>T, c.5361C>T, c.5361C>T, c.5361C>T, c.209C>T	p.(=), p.(=), p.(=), p.(=), p.(=)	, , , ,	, , , ,	46,1,0	340,1,0	243,0,0	4916,3,0	7826,4,0
SPG11	<i>feature truncation, frameshift</i>	<i>*ENST00000261866, ENST00000558319, ENST00000427534, ENST00000535302, ENST00000559511</i>	<i>c.5757_57 58delAG, c.5757_57 58delAG, c.5757_57 58delAG, c.5757_57 58delAG, c.605_606 delAG</i>	<i>p.Glu1921Ser fsX2, p.Glu1921Ser fsX2, p.Glu1921Ser fsX2, p.Glu1921Ser fsX2, p.Glu204Serf sX2</i>	, , , ,	, , , ,	50,0,0	389,1,0	302,0,0	302,0,0	302,0,0
SPG11	synonymous	*ENST00000261866, ENST00000427534,	c.5796T>C, c.5796T>C,	p.(=), p.(=), p.(=), p.(=),	, , , ,	, , , ,	50,0,0	380,0,0	299,1,0	4596,2,0	6794,2,0

		ENST00000559511, ENST00000535302, ENST00000558319	c.644T>C, c.5796T>C, c.5796T>C	p.(=)							
SPG11	missense	*ENST00000261866, ENST00000558319, ENST00000427534	c.5911A>G, c.5911A>G, c.5911A>G	p.Asn1971As p, p.Asn1971As p, p.Asn1971As p	0, 0, 0	0, 0, 0	50,0,0	383,0,0	293,1,0	293,1,0	293,1,0
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000558138, ENST00000535302	c.6224A>G, c.6224A>G, c.23A>G, c.5885A>G	p.Asn2075Ser ,	0, 0, 0, 0	0, 0, 0, 0	50,0,0	387,1,0	296,3,0	4925,50,0	7830,56,0
SPG11	synonymous	*ENST00000261866, ENST00000558138, ENST00000427534, ENST00000535302	c.6258G>T, c.57G>T, c.6258G>T, c.5919G>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	49,1,0	385,4,0	294,3,0	4916,57,0	7816,68,0
SPG11	synonymous	*ENST00000261866, ENST00000535302, ENST00000558138, ENST00000427534	c.6330G>A, c.5991G>A, c.129G>A, c.6330G>A	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	385,3,0	289,5,0	4917,53,0	7690,182,9
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000559511, ENST00000535302	c.6497T>C, c.6497T>C, c.868T>C, c.6158T>C	p.Ile2166Thr, p.Ile2166Thr, p.Ile290Thr, p.Ile2053Thr	1, 1, 1, 1	2, 2, 2, 1	50,0,0	386,1,0	303,0,0	4598,1,0	6794,1,0
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000559511, ENST00000427534, ENST00000558138	c.6632G>A, c.6293G>A, c.1003G>A, c.6632G>A, c.323G>A	p.Arg2211His, p.Arg2098His, p.Arg335His, p.Arg2211His, p.Arg108His	0, 0, 0, 0, 0, 0, 0	0, 0, 0, 2, 0	48,1,0	359,3,0	294,0,0	4577,15,0	6775,15,0
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000559511, ENST00000558138	c.6872G>A, c.6533G>A, c.1243G>A, c.563G>A	p.Cys2291Tyr ,	1, 1, 1, 1	2, 2, 2, 2	50,0,0	383,0,0	302,1,0	302,1,0	302,1,0

				p.Cys188Tyr								
SPG11	<i>feature elongation, frameshift</i>	*ENST00000261866, ENST00000558138, ENST00000535302, ENST00000559511	<i>c.6952dupC, c.643dupC, c.6613dupC, c.1323dupC</i>	<i>p.Arg2318ProfsX22, p.Arg215ProfsX22, p.Arg2205ProfsX22, p.Arg442ProfsX22</i>	,,,	,,,	30,5,0	156,51,0	166,44,0	166,44,0	166,44,0	
SPG11	synonymous	*ENST00000261866, ENST00000558138, ENST00000535302, ENST00000559511	c.7023C>T, c.714C>T, c.6684C>T, c.1394C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	46,4,0	353,30,0	257,18,0	4652,299,0	7533,328,1	
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000559511	c.7069C>T, c.6730C>T, c.1440C>T	p.Leu2357Phe, p.Leu2244Phe, p.Leu481Phe	0, 0, 1	2, 2, 2	49,1,0	383,2,0	275,1,0	4929,23,0	7834,29,0	
SPG11	synonymous	*ENST00000261866, ENST00000559511, ENST00000535302	c.7197G>A, c.1568G>A, c.6858G>A	p.(=), p.(=), p.(=)	,,	,,	50,0,0	382,7,0	278,4,0	4838,120,0	7740,129,0	
SPG11	missense	*ENST00000261866, ENST00000535302, ENST00000559511	c.7324G>C, c.6985G>C, c.1695G>C	p.Ala2442Pro, p.Ala2329Pro, p.Ala566Pro	1, 1, 1	2, 2, 2	50,0,0	390,1,0	282,0,0	282,0,0	282,0,0	
SPG11	missense	*ENST00000261866, ENST00000427534, ENST00000559193, ENST00000535302, ENST00000558319	c.808G>A, c.808G>A, c.808G>A, c.808G>A, c.808G>A	p.Val270Ile, p.Val270Ile, p.Val270Ile, p.Val270Ile, p.Val270Ile	0, 0, 0, 0, 0	1, 2, 2, 1, 2	50,0,0	389,1,0	282,4,0	4865,97,0	7729,144,0	
SPG11	missense	*ENST00000261866, ENST00000559193, ENST00000427534, ENST00000558319, ENST00000535302	c.979C>G, c.979C>G, c.979C>G, c.979C>G, c.979C>G	p.Leu327Val, p.Leu327Val, p.Leu327Val, p.Leu327Val, p.Leu327Val	0, 0, 0, 0, 0	0, 1, 0, 0, 0	50,0,0	386,0,0	274,1,0	651,2,0	1364,2,0	

TARDBP	synonymous	*ENST00000240185, ENST00000439080	c.1122T>C, c.774T>C	p.(=), p.(=)	,	,	50,0,0	385,0,0	301,1,0	4601,1,0	6803,2,0
TARDBP	missense	*ENST00000240185, ENST00000439080	c.1129T>A, c.781T>A	p.Ser377Thr, p.Ser261Thr	0, 0	1, 1	50,0,0	386,0,0	302,1,0	302,1,0	302,1,0
TARDBP	synonymous	*ENST00000240185, ENST00000473118, ENST00000315091, ENST00000476201	c.312C>T, c.312C>T, c.312C>T, c.435C>T	p.(=), p.(=), p.(=), p.(=)	,,,	,,,	50,0,0	382,1,0	270,0,0	270,0,0	270,0,0
TARDBP	missense	*ENST00000240185, ENST00000439080	c.859G>A, c.511G>A	p.Gly287Ser, p.Gly171Ser	0, 0	0, 0	50,0,0	388,2,0	300,0,0	300,0,0	300,0,0
TARDBP	synonymous	*ENST00000240185, ENST00000439080	c.975C>T, c.627C>T	p.(=), p.(=)	,	,	49,0,0	363,1,0	272,2,0	272,2,0	272,2,0
UNC13A	missense	*ENST00000519716, ENST00000428389, ENST00000252773, ENST00000552293, ENST00000551649, ENST00000550896	c.1031T>C, c.1295T>C, c.1031T>C, c.1031T>C, c.1031T>C, c.1031T>C	p.Leu344Pro, p.Leu432Pro, p.Leu344Pro, p.Leu344Pro, p.Leu344Pro, p.Leu344Pro	0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 0, 0, 2	15,2,0	109,4,0	96,2,0	4219,15,0	6313,16,0
UNC13A	<i>inframe deletion</i>	<i>c.1049_10 51delAGG,</i> <i>c.1049_10 51delAGG,</i> <i>c.1313_13 15delAGG,</i> <i>c.1049_10 51delAGG,</i> <i>c.1049_10 51delAGG,</i> <i>c.1049_10 51delAGG,</i> <i>c.1049_10 51delAGG,</i>	<i>p.Glu350del,</i> <i>p.Glu350del,</i> <i>p.Glu438del,</i> <i>p.Glu350del,</i> <i>p.Glu350del,</i> <i>p.Glu350del,</i>	,,,	,,,	14,0,0	89,6,0	67,7,0	67,7,0	67,7,0	
UNC13A	missense	*ENST00000519716, ENST00000551649, ENST00000428389, ENST00000252773, ENST00000550896,	c.1075G>A, c.1075G>A, c.1339G>A, c.1075G>A, c.1075G>A,	p.Ala359Thr, p.Ala359Thr, p.Ala447Thr, p.Ala359Thr, p.Ala359Thr,	0, 0, 0, 0, 0, 0, 0, 0, 1, 0	0, 0, 0, 0, 0, 0, 0, 0, 1, 0	7,14,3	38,85,17	32,70,10	1562,2142,979	3649,2792,1092

		ENST00000552293	c.1075G>A	p.Ala359Thr							
UNC13A	<i>synonymous</i>	*ENST00000519716, ENST00000428389, ENST00000550896, ENST00000252773, ENST00000551649, ENST00000552293	c.1188C>T, c.1452C>T, c.1188C>T, c.1188C>T, c.1188C>T, c.1188C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	'''' ,	'''' ,	1,0,0	5,0,0	3,0,0	4155,6,0	6144,6,0
UNC13A	<i>synonymous</i>	*ENST00000519716, ENST00000551649, ENST00000552293, ENST00000428389, ENST00000252773, ENST00000550896	c.1368C>T, c.1368C>T, c.1368C>T, c.1632C>T, c.1368C>T, c.1368C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	'''' ,	'''' ,	20,2,0	81,0,0	71,2,0	4334,20,0	6519,20,0
UNC13A	<i>splice region, synonymous</i>	*ENST00000519716, ENST00000552293, ENST00000550896, ENST00000428389, ENST00000551649, ENST00000252773	c.153C>T, c.153C>T, c.153C>T, c.417C>T, c.153C>T, c.153C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	'''' ,	'''' ,	48,1,0	360,2,0	302,3,0	4424,12,0	6330,12,0
UNC13A	<i>synonymous</i>	*ENST00000519716, ENST00000551649, ENST00000428389, ENST00000550896, ENST00000552293, ENST00000252773	c.1767C>G, c.1767C>G, c.2031C>G, c.1761C>G, c.1767C>G, c.1767C>G	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	'''' ,	'''' ,	25,5,0	108,38,3	64,12,3	3943,781,33	6017,1536,119
UNC13A	<i>missense</i>	*ENST00000519716, ENST00000252773, ENST00000551649, ENST00000552293, ENST00000550896, ENST00000428389	c.182C>T, c.182C>T, c.182C>T, c.182C>T, c.182C>T, c.446C>T	p.Thr61Met, p.Thr61Met, p.Thr61Met, p.Thr61Met, p.Thr61Met, p.Thr149Met	0, 0, 0, 0, 0, 0	1, 2, 1, 1, 2, 2	50,0,0	366,1,0	296,1,0	4810,19,0	7475,24,0
UNC13A	<i>missense</i>	*ENST00000519716, ENST00000551649, ENST00000428389, ENST00000252773,	c.2068G>A ,	p.Ala690Thr, p.Ala690Thr, p.Ala778Thr, p.Ala690Thr,	1, 1, 1, 1, 1, 1	2, 2, 2, 2, 1, 2	45,0,0	291,0,0	269,1,0	269,1,0	269,1,0

		<i>ENST00000550896</i> , <i>ENST00000552293</i>	<i>c.2332G>A</i> , <i>c.2068G>A</i> , <i>c.2062G>A</i> , <i>c.2068G>A</i>	<i>p.Ala688Thr</i> , <i>p.Ala690Thr</i>							
UNC13A	synonymous	*ENST00000519716, ENST00000428389, ENST00000252773, ENST00000552293, ENST00000551649, ENST00000550896	c.2289T>C, c.2553T>C, c.2289T>C, c.2289T>C, c.2289T>C, c.2283T>C	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	,,, ,	,,, ,	48,0,0	333,1,0	294,0,0	4559,1,0	6709,1,0
UNC13A	missense	* <i>ENST00000519716</i> , <i>ENST00000552293</i> , <i>ENST00000428389</i> , <i>ENST00000550896</i> , <i>ENST00000551649</i> , <i>ENST00000252773</i>	<i>c.2626C>A</i> , <i>c.2626C>A</i> , <i>c.2890C>A</i> , <i>c.2620C>A</i> , <i>c.2626C>A</i> , <i>c.2626C>A</i>	<i>p.Gln876Lys</i> , <i>p.Gln876Lys</i> , <i>p.Gln964Lys</i> , <i>p.Gln874Lys</i> , <i>p.Gln876Lys</i> , <i>p.Gln876Lys</i>	1, 1, 1, 1, 1, 1	2, 2, 2, , 2, 2	36,2,0	214,15,0	180,16,0	180,16,0	180,16,0
UNC13A	missense, splice region	*ENST00000519716, ENST00000552293, ENST00000252773, ENST00000551649, ENST00000428389, ENST00000550896	c.3080C>T, c.3080C>T, c.3080C>T, c.3080C>T, c.3344C>T, c.3074C>T	p.Pro1027Leu , p.Pro1027Leu , p.Pro1027Leu , p.Pro1027Leu , p.Pro1115Leu , p.Pro1025Leu	0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 0, 2	45,2,0	336,2,0	253,4,0	4383,58,0	6369,65,0
UNC13A	missense	*ENST00000519716, ENST00000551649, ENST00000428389, ENST00000550896, ENST00000552293,	c.3098T>A, c.3098T>A, c.3362T>A, c.3092T>A, c.3098T>A,	p.Val1033Asp , p.Val1033Asp , p.Val1121Asp	0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0	49,0,0	371,1,0	286,0,0	286,0,0	286,0,0

		ENST00000252773	c.3098T>A	,	p.Val1031Asp						
				,	p.Val1033Asp						
				,	p.Val1033Asp						
UNC13A	missense	*ENST00000519716, ENST00000551649, ENST00000428389, ENST00000550896, ENST00000252773, ENST00000552293	c.3101T>C, c.3101T>C, c.3365T>C, c.3095T>C, c.3101T>C, c.3101T>C	p.Leu1034Pro ,	0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0	0,0,50	0,0,373	0,0,287	0,0,665	0,0,1378
UNC13A	synonymous	*ENST00000519716, ENST00000551649, ENST00000428389, ENST00000550896, ENST00000552293, ENST00000252773	c.3108G>A, c.3108G>A, c.3372G>A, c.3102G>A, c.3108G>A, c.3108G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	' '' , ,	' '' , ,	46,4,0	345,29,3	255,37,0	4245,548,16	6795,624,17
UNC13A	missense	*ENST00000519716, ENST00000552293, ENST00000252773, ENST00000551649, ENST00000550896, ENST00000428389	c.3397G>T, c.3397G>T, c.3397G>T, c.3397G>T, c.3391G>T, c.3661G>T	p.Ala1133Ser, p.Ala1133Ser, p.Ala1133Ser, p.Ala1133Ser, p.Ala1131Ser, p.Ala1221Ser	0, 0, 0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0, 1, 0	40,9,1	306,67,0	260,42,0	4122,784,28	6898,851,28
UNC13A	missense	*ENST00000519716, ENST00000428389, ENST00000552293, ENST00000550896, ENST00000252773, ENST00000551649	c.3461A>G ,	p.Asp1154Gly	1, 1,	1, 0,	37,0,0	215,3,0	231,7,0	231,7,0	231,7,0
			c.3725A>G ,	p.Asp1242Gly	1, 1,	0, 1,					
			c.3461A>G ,	p.Asp1154Gly	1, 1	1, 1					

			<i>c.3455A>G</i> , <i>c.3461A>G</i> , <i>c.3461A>G</i>	<i>p.Asp1152Gly</i> , <i>p.Asp1154Gly</i> , <i>p.Asp1154Gly</i>							
UNC13A	synonymous	*ENST00000519716, ENST00000428389, ENST00000550896, ENST00000252773, ENST00000552293, ENST00000551649	c.3552A>G, c.3816A>G, c.3546A>G, c.3552A>G, c.3552A>G, c.3552A>G	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	',',',',',','	49,1,0	377,1,0	301,2,0	4864,44,0	7694,49,0	
UNC13A	synonymous	*ENST00000519716, ENST00000551649, ENST00000552293, ENST00000252773, ENST00000428389, ENST00000550896	c.3576T>C, c.3576T>C, c.3576T>C, c.3576T>C, c.3840T>C, c.3570T>C	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	',',',',',','	24,23,3	182,162,44	140,130,35	2152,2111,638	2520,3078,2119	
UNC13A	synonymous	*ENST00000519716, ENST00000252773, ENST00000552293, ENST00000550896, ENST00000428389, ENST00000551649	c.3687C>T, c.3687C>T, c.3687C>T, c.3681C>T, c.3951C>T, c.3687C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	',',',',',','	50,0,0	346,33,1	273,31,0	4328,552,17	7029,650,17	
UNC13A	synonymous	*ENST00000519716, ENST00000552293, ENST00000252773, ENST00000550896, ENST00000428389, ENST00000551649	c.4029C>T, c.4029C>T, c.4029C>T, c.4023C>T, c.4293C>T, c.4029C>T	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	',',',',',','	40,0,0	237,30,1	153,26,1	4251,541,18	7061,602,18	
UNC13A	<i>synonymous</i>	<i>*ENST00000519716, ENST00000428389, ENST00000252773, ENST00000551649</i>	<i>c.4251G>A</i> , <i>c.4515G>A</i> , <i>c.4251G>A</i> , <i>,</i>	<i>p.(=), p.(=),</i> <i>p.(=), p.(=)</i>	<i>,,,</i>	<i>33,1,0</i>	<i>171,20,0</i>	<i>123,19,0</i>	<i>123,19,0</i>	<i>123,19,0</i>	

			<i>c.4251G>A</i>								
<i>UNC13A</i>	<i>missense</i>	*ENST00000519716, ENST00000428389, ENST00000252773, ENST00000551649	<i>c.4259C>A,</i> <i>c.4523C>A,</i> <i>c.4259C>A,</i> <i>c.4259C>A</i>	<i>p.Pro1420Gln</i> , <i>p.Pro1508Gln</i> , <i>p.Pro1420Gln</i> , <i>p.Pro1420Gln</i>	<i>0, 0,</i> <i>0, 0,</i> <i>0, 0,</i> <i>0, 0</i>	<i>30,7,0</i>	<i>114,86,1</i>	<i>63,117,0</i>	<i>63,117,0</i>	<i>63,117,0</i>	
UNC13A	synonymous	*ENST00000519716, ENST00000428389, ENST00000252773, ENST00000551649, ENST00000552293, ENST00000550896	c.4380G>C, c.4644G>C, c.4380G>C, c.4380G>C, c.4305G>C, c.4299G>C	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	' '' '' ''	45,0,0	299,0,0	255,1,0	255,1,0	255,1,0	
UNC13A	synonymous	*ENST00000519716, ENST00000552293, ENST00000550896, ENST00000428389, ENST00000252773, ENST00000551649	c.4497G>A, c.4422G>A, c.4416G>A, c.4761G>A, c.4497G>A, c.4497G>A	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	' '' '' ''	24,19,4	165,148,28	161,99,23	2827,1789,286	5371,2036,296	
UNC13A	synonymous	*ENST00000519716, ENST00000552293, ENST00000252773, ENST00000550896, ENST00000428389, ENST00000551649	c.474G>C, c.474G>C, c.474G>C, c.474G>C, c.738G>C, c.474G>C	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	' '' '' ''	1,10,39	12,100,270	4,61,233	89,1095,3618	214,1818,5405	
<i>UNC13A</i>	<i>synonymous</i>	*ENST00000519716, ENST00000552293, ENST00000551649, ENST00000252773, ENST00000550896, ENST00000428389	<i>c.5079C>A,</i> <i>c.5061C>A,</i> <i>c.5136C>A,</i> <i>c.5079C>A,</i> <i>c.4998C>A,</i> <i>c.5343C>A</i>	<i>p.(=), p.(=),</i> <i>p.(=), p.(=),</i> <i>p.(=), p.(=)</i>	<i>' '' '' ''</i>	<i>0,0,0</i>	<i>0,1,0</i>	<i>0,0,0</i>	<i>3702,654,30</i>	<i>5596,1285,89</i>	
UNC13A	missense	*ENST00000519716, ENST00000550896, ENST00000552293,	c.694C>T, c.694C>T, c.694C>T,	p.Pro232Ser, p.Pro232Ser, p.Pro232Ser,	0, 0, 0, 0, 0, 0	50,0,0	367,0,0	305,1,0	305,1,0	305,1,0	

		ENST00000551649, ENST00000252773, ENST00000428389	c.694C>T, c.694C>T, c.958C>T	p.Pro232Ser, p.Pro232Ser, p.Pro320Ser							
UNC13A	<i>synonymous</i>	*ENST00000519716, ENST00000428389, ENST00000550896, ENST00000252773, ENST00000552293, ENST00000551649	c.771C>G, c.1035C>G, c.771C>G, c.771C>G, c.771C>G, c.771C>G	p.(=), p.(=), p.(=), p.(=), p.(=), p.(=)	'''' ,	'''' ,	6,0,0	49,3,0	35,3,0	4432,85,0	7098,97,0
UNC13A	<i>missense</i>	*ENST00000519716, ENST00000550896, ENST00000552293, ENST00000551649, ENST00000252773, ENST00000428389	c.905A>C, c.905A>C, c.905A>C, c.905A>C, c.905A>C, c.1169A>C	p.His302Pro, p.His302Pro, p.His302Pro, p.His302Pro, p.His302Pro, p.His390Pro	0, 0, 0, 0, 0, 0	0, 1, 0, 2, 0, 1	14,1,0	75,5,0	76,3,0	76,3,0	76,3,0
UNC13A	<i>missense</i>	*ENST00000519716, ENST00000551649, ENST00000552293, ENST00000252773, ENST00000550896, ENST00000428389	c.907T>C, c.907T>C, c.907T>C, c.907T>C, c.907T>C, c.1171T>C	p.Ser303Pro, p.Ser303Pro, p.Ser303Pro, p.Ser303Pro, p.Ser303Pro, p.Ser391Pro	0, 0, 0, 0, 0, 0	0, 2, 1, 2, 1, 1	11,1,0	70,8,0	72,8,0	72,8,0	72,8,0
VAPB	<i>inframe deletion</i>	*ENST00000475243	c.474_476 delTTC	p.Ser159del			50,0,0	386,2,0	278,0,0	278,0,0	278,0,0
VAPB	missense	*ENST00000475243	c.510G>A	p.Met170Ile	0	0	50,0,0	385,4,0	279,1,0	4939,19,0	7854,20,0
VCP	<i>synonymous</i>	*ENST00000358901	c.1641G>A	p.(=)			50,0,0	386,1,0	299,0,0	299,0,0	299,0,0
VCP	synonymous	*ENST00000358901	c.1704A>G	p.(=)			48,1,0	373,5,0	298,5,0	4930,50,1	7835,61,1
VCP	<i>missense</i>	*ENST00000358901	c.2092G>C	p.Ala698Pro	1	2	49,0,0	341,7,0	272,7,0	272,7,0	272,7,0
VCP	missense	*ENST00000358901	c.2249A>G	p.Asn750Ser	0	0	50,0,0	388,1,0	306,0,0	306,0,0	306,0,0
VCP	<i>synonymous</i>	*ENST00000358901	c.2406T>C	p.(=)			45,0,0	282,0,0	262,0,0	4559,3,0	6762,3,0

* Denotes canonical transcript

SIFT prediction values of “0” and “1” denote “tolerated” and “deleterious” predictions respectively

PolyPhen prediction values of “0”, “1” and “2” denote “benign”, “possibly damaging” and “probably damaging” predictions respectively

Mutations failing variant quality control (supplementary materials and methods) are shown in bold/ italics. It should be noted that these are anticipated to include true variants in addition to sequencing artefacts.

Table S3: Co-occurrence of Mendelian ALS gene variants

*Frequency Threshold	Cases with 1 mutation	Cases with 2 mutations	Controls with 1 mutation	Controls with 2 mutations	**p
0	55	3	12	0	0.36
0.0005	63	4	17	0	0.45
0.005	79	7	34	0	0.76
0.05	114	16	49	7	0.72

*Denotes the cut-off carrier frequency for variants among European and Global reference cohorts. Variants exceeding a given threshold were excluded from analysis. Reference cohorts included individuals resequenced by NHLBI exome sequencing and 1000 genomes project only. Only nonsynonymous and splice variants were included in analyses.

** Probability that the observed frequency of cases carrying multiple Mendelian ALS gene variants is in excess of chance expectation (see Materials and Methods for details)

Total number of cases=444, total number of controls =311

Table S4: Co-occurrence of ALS gene variant

*Frequency Threshold	Cases with 1 variant	Cases with 2 variants	Controls with 1 variant	Controls with 2 variants	**p
0	77	6	34	4	0.85
0.0005	103	9	50	7	0.99
0.005	151	30	95	13	1.00
0.05	247	90	160	72	1.00

*Denotes the cut-off carrier frequency for variants among European and Global reference cohorts. Variants exceeding a given threshold were excluded from analysis. Reference cohorts included individuals resequenced by NHLBI exome sequencing and 1000 genomes project only. Only nonsynonymous and splice variants were included in analyses.

** Probability that the observed frequency of cases carrying multiple ALS gene variants is in excess of chance expectation (see Materials and Methods for details)

Total number of cases=444, total number of controls =311

Table S5: Carriers of established and possible ALS variants

Gene	Mutation	C9orf72 Repeat Expansion	Family History	Gender	Site Of Onset	Cognitive Status	Age Of Onset (Years)	Survival (Months)
ALS2	c.2098A>G(p.Thr700Ala)	-	-	M	spinal	NA	67	39
ALS2	c.3094C>T(p.Arg1032Cys)	-	-	M	bulbar	co-morbid FTD	57	>61
ALS2	c.2408A>G(p.Lys803Arg)	-	-	M	spinal	NA	58	>44
ALS2	c.2606A>C(p.Gln869Pro)	-	-	M	spinal	normal	57	>55
ALS2, SETX	c.2098A>G(p.Thr700Ala), c.7682C>T(p.Ser2561Leu)	-	-	M	spinal	NA	84	58
C9orf72		+	+	M	spinal	NA	35	70
C9orf72		+	+	M	bulbar	NA	NA	NA
C9orf72		+	-	M	both	NA	34	67
C9orf72		+	-	F	spinal	NA	51	13
C9orf72		+	-	F	bulbar	NA	60	20
C9orf72		+	-	M	bulbar	NA	47	30
C9orf72		+	-	M	spinal	NA	66	8
C9orf72		+	-	M	spinal	NA	44	23
C9orf72		+	-	F	bulbar	NA	43	36
C9orf72		+	-	F	bulbar	NA	52	17
C9orf72		+	-	M	spinal	NA	68	NA
C9orf72		+	+	F	bulbar	NA	82	12
C9orf72		+	-	F	spinal	NA	42	54
C9orf72		+	-	M	spinal	NA	NA	NA
C9orf72		+	-	F	spinal	normal	55	30
C9orf72		+	+	F	both	normal	44	50
C9orf72		+	-	M	spinal	cognitively impaired	55	24

C9orf72		+	-	M	spinal	co-morbid FTD	62	52
C9orf72		+	+	M	spinal	co-morbid FTD	56	16
C9orf72		+	-	F	spinal	normal	44	37
C9orf72		+	+	F	spinal	co-morbid FTD	65	16
C9orf72		+	+	M	spinal	co-morbid FTD	65	25
C9orf72		+	-	M	spinal	behaviourally impaired	48	>66
C9orf72		+	-	F	bulbar	normal	63	14
C9orf72		+	-	F	spinal	cognitively impaired	49	37
C9orf72		+	-	F	spinal	cognitively impaired	62	18
C9orf72		+	+	M	bulbar	normal	59	19
C9orf72		+	+	F	bulbar	normal	64	41
C9orf72		+	+	F	bulbar	cognitively impaired	65	33
C9orf72		+	+	M	bulbar	normal	66	32
C9orf72		+	-	M	spinal	co-morbid FTD	36	46
C9orf72		+	-	M	bulbar	NA	59	25
C9orf72		+	-	F	spinal	NA	72	>87
C9orf72		+	-	M	bulbar	No	44	29
C9orf72		+	+	M	spinal	cognitively and behaviourally impaired	59	17
C9orf72		+	+	F	spinal	NA	52	>41
C9orf72, CHMP2B	c.123G>T(p.Gln41His)	+	-	M	spinal	NA	55	48
C9orf72, SETX	c.2842C>A(p.Pro948Thr)	+	+	M	bulbar	co-morbid FTD	58	17
C9orf72, SPG11	c.3680A>G(p.Lys1227Arg)	+	+	M	spinal	NA	65	43
CHMP2B	c.118A>G(p.Lys40Glu)	-	-	M	spinal	NA	61	NA

DCTN1	c.2887-2A>G()	-	-	M	spinal	NA	63	26
DCTN1, SPG11	c.2887-2A>G(), c.1529G>A(p.Ser510Asn)	-	-	M	spinal	NA	63	42
DPP6	c.883G>A(p.Glu295Lys)	-	-	F	bulbar	normal	62	21
ELP3	c.326G>A(p.Cys109Tyr)	NA	-	F	spinal	NA	68	12
ELP3	c.206G>T(p.Arg69Leu)	-	-	F	bulbar	cognitively impaired	68	21
ELP3	c.326G>A(p.Cys109Tyr)	-	+	M	bulbar	normal	67	NA
FGGY	c.1716G>A(p.Met572Ile)	-	-	M	spinal	NA	75	11
FUS	c.1574C>T(p.Pro525Leu)	NA	-	M	spinal	NA	13	17
FUS	c.1574C>T(p.Pro525Leu)	-	-	F	bulbar	normal	21	11
HFE	c.766G>A(p.Val256Ile)	-	-	M	spinal	cognitively impaired	76	7
ITPR2	c.3614G>A(p.Arg1205Gln)	-	-	F	bulbar	NA	79	19
MAPT	c.698C>T(p.Pro233Leu)	-	-	M	spinal	normal	57	>55
MAPT	c.284C>T(p.Thr95Met)	-	-	F	spinal	normal	81	>48
OPTN	c.1192C>G(p.Gln398Glu)	-	-	F	spinal	NA	NA	NA
PON2	c.661T>G(p.Ser221Ala)	-	-	F	spinal	co-morbid FTD	58	12
SETX	c.7645G>A(p.Val2549Ile)	-	-	F	spinal	NA	64	24
SETX	c.5842A>G(p.Met1948Val)	-	-	M	spinal	NA	47	NA
SETX	c.2755G>C(p.Val919Leu)	-	-	M	bulbar	co-morbid FTD	68	15
SETX	c.7682C>T(p.Ser2561Leu)	-	-	M	spinal	cognitively impaired	57	33
SETX	c.5587A>G(p.Thr1863Ala)	-	+	F	other	NA	61	>103
SETX	c.7645G>A(p.Val2549Ile)	-	-	F	bulbar	cognitively and behaviourally impaired	76	26
SETX	c.2975A>G(p.Lys992Arg)	-	+	M	bulbar	NA	78	14
SPG11	c.4343G>A(p.Cys1448Tyr)	-	-	M	spinal	NA	63	33

SPG11	c.1930A>T(p.Thr644Ser)	-	+	F	bulbar	NA	68	27
SPG11	c.394A>G(p.Ser132Gly)	-	-	M	spinal	normal	51	>42
SPG11	c.2577A>C(p.Gln859His)	-	-	F	bulbar	NA	59	NA
SPG11	c.7324G>C(p.Ala2442Pro)	-	-	M	spinal	NA	60	21
TARDBP, ALS2	c.859G>A(p.Gly287Ser), c.2566A>G(p.Thr856Ala)	-	-	M	bulbar	normal	67	>51
TARDBP, SETX	c.859G>A(p.Gly287Ser), c.814C>G(p.His272Asp)	-	-	F	bulbar	NA	66	49
UNC13A	c.3098T>A(p.Val1033Asp)	-	-	M	spinal	NA	80	25
VCP	c.2249A>G(p.Asn750Ser)	-	-	F	bulbar	NA	63	>35

ALS2 - ENST00000264276; *CHMP2B* - ENST00000263780; *DCTN1* - ENST00000361874; *DPP6* - ENST00000377770; *ELP3* - ENST00000256398;
FGGY - ENST00000371218; *FUS* - ENST00000254108; *HFE* - ENST00000357618; *ITPR2* - ENST00000381340; *MAPT* - ENST00000344290;
OPTN - ENST00000263036; *PON2* - ENST00000222572; *SETX* - ENST00000224140; *SPG11* - ENST00000261866; *TARDBP* - ENST00000240185;
UNC13A - ENST00000519716; *VCP* - ENST00000358901