Supplemental Table 1. ALS susceptibility genes and their association with ALS, FTD or ALS-FTSD (sorted by chromosome)

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus** | **Gene ID/Locus MIM number** | **Chromosome** | **Protein; functional changes** | **Inheritance** | **Clinical Phenotype** | | | | **Reference** |
|  |  |  |  |  | **FTD** | **ALS** | **ALS-FTSD** | **other** |  |
|  | *CAMTA1* | 1p36.31-p36.23 | Calmodulin-binding transcription activator gene 1 | sporadic | n/a | + | n/a | Cerebellar ataxia with mental retardation | (1) |
|  | *KIFAP3* | 1q24.2 | Kinesin-associated protein 3; small G protein | sporadic | n/a | + (3) | n/a |  | (2) |
|  | *DCTN1* | 2p13.1 | Dynactin 1; axonal transport | AD | + (9) | + | n/a | Perry syndrome | (3;4) |
| ALS17 | *CHMP2B* | 3p11.2 | Charged multivesicular body protein 2B (also known as chromatin-modifying protein 2B); Vesicle trafficking | sporadic | + | + | n/a |  | (5;6) |
|  | *NEK1* | 4q33 | Serine/threonine kinase NIMA (never in mitosis gene-A)-related kinase | sporadic |  | + |  |  | (7;8) |
|  | *ARHGEF28* | 5q13.2 | Rho guanine nucleotide exchange factor 28 | AD | n/a | + | n/a |  | (9-11) |
|  | *SMN1* | 5q13.2 | Survival of motor neuron 1 | AD, sporadic | n/a | + | n/a |  | (12;13) |
|  | *MATR3* | 5q31.2 | Matrin 3; Nuclear matrix RNA/DNA binding protein | AD | + (10) | + |  | Distal asymmetric myopathy | (14;15) |
|  | *SQSTM1* | 5q35.3 | Sequestome 1; scaffold protein, NFkB signaling pathway | AD, sporadic | + | + | + | Paget’s disease of bone | (16;17) |
|  | *HFE* | 6p22.1 | Hemochromatosis; iron absorption | sporadic | n/a | + (4) | n/a |  | (18;19) |
| ALS11 | *FIG4* | 6q21 | Factor-Induced gene 4 (FIG4) homolog, SAC1 lipid phosphatase domain containing (*Saccharomyces cerevisiae*); polyphosphoinositide phosphatase | AD, sporadic | n/a | + (8) | n/a | PLS, CMT | (20) |
|  | *PON1* | 7q21.3 | Paraoxonase; organophosphate hydrolysis | sporadic | n/a | + | n/a |  | (21) |
|  | *ELP3* | 8p21.1 | Elongator acetyltransferase complex subunit 3; transcript elongation | sporadic | n/a | + | n/a |  | (22) |
| ALS16 | *SIGMAR1* | 9q13.3 | Sigma non-opioid intracellular receptor 1; Ion channel regulation | AR | + | + |  |  | (23;24) |
|  | *ITPR2* | 12p12.1-11.23 | INOSITOL 1,4,5-triphosphate receptor type 2 | sporadic | n/a | + (1) | n/a |  | (25) |
|  | *PRPH* | 12q13.12 | Peripherin; cytoskeleton | AD, sporadic | n/a | + (6) | n/a |  | (26;27) |
|  | *DAO* | 12q24.11 | D-amino-acid oxidase; Oxidative stress | AD |  | + |  |  | (28) |
| ALS13 | *ATXN 2* | 12q24.12 | Ataxin 2; Oxidative stress | sporadic | n/a | + | n/a | SCA2 | (29;30) |
| ALS9 | *ANG* | 14q11.2 | Angiogenin, ribonuclease, RNase A family; DNA/RNA processing | AD, sporadic | n/a | + | + (7) | PD | (31;32) |
|  | *TAF15* | 17q12 | TAF15 RNA polymerase II, TATA box binding protein (TDP)-associated factor, 68 kDa; DNA/RNA processing | AD | + | + (5) | n/a |  | (33;34) |
|  | *PGRN* | 17q21.31 | Progranulin; cell growth regulator | sporadic | + | + (2) | n/a |  | (35) |
|  | *UNC13A* | 19p13.12 | Unc-13 homologue A (*Caenorhabditis elegans*); Synaptic neurotramsmitter release | sporadic | + | + | + |  | (36) |
|  | *NEFH* | 22q12.1-q13.1 | Neurofilament, heavy polypeptide; cytoskeleton | sporadic | n/a | + | n/a |  | (37) |
|  | *CHCHD10* | 22q11.23 | Coiled-coil-helix-coiled-coil-helix domain-containing protein 10; mitochondrial protein of the intermembrane space | AD | + | + (11) |  |  | (38-42) |

AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CMT, Charcot-Marie-Tooth; FTD, frontotemporal dementia; NEK1, NIMA (never in mitosis gene) kinase 1; PD, Parkinson’s disease; PMA, progressive muscular atrophy; SCA2, spinocerebellar atrophy 2

n/a – no literature reports of either the association or lack of association of specific gene mutations with either FTD or ALS-FTD

1. Note failure to replicate the association with ALS in a second study (43;44). This may imply a lack of association or a population-specific association.
2. Single case reports of ALS-FTD and limb onset ALS with PGRN missense mutation variants of uncertain biological significance
3. Initial report as a modifier of survival in ALS (2) have not been replicated (45;46)
4. Initial reports as being associated with ALS (18;19) have not been replicated (47;48)
5. Single variant identified in a mutational analysis (34); the bulk of the data relates specifically to neuropathological studies of the FET proteins in ALS.
6. Single mutation (27) or sequence variants in both fALS and sALS (26).
7. A single case report of ALS-FTD with a K171 *ANG* mutation (32).
8. Initial report as a susceptibility gene for ALS have not been replicated (49)
9. Single family in which ALS and FTD occur with a heterozygous R1101K mutation in the *DCTN1* gene (50)
10. A single family reported in which ALS and FTD occur; not replicated in French (51), Australian population studies (52) or Taiwanese (53) studies.
11. Note several population studies in which no pathogenic mutations have been observed amongst specific geographic populations, suggesting a degree of regional specificity (54;55)

Reference List

(1) Fogh I, Lin K, Tiloca C, Rooney J, Gellera C, Diekstra FP, et al. Association of a Locus in the CAMTA1 Gene With Survival in Patients With Sporadic Amyotrophic Lateral Sclerosis. JAMA Neurol 2016.

(2) Landers JE, Melki J, Meininger V, Glass JD, Van den Berg LH, van Es MA, et al. Reduced expression of *kinesin-associated protein3* (KIFAP3) gene increases survival in sporadic amyotrophic lateral sclerosis. Proc Natl Acad Sci USA 2009;106:9004-9.

(3) Farrer MJ, Hulihan MM, Kachergus JM, Dachsel JC, Stoessl AJ, Grantier LL, et al. DCTN1 mutations in Perry syndrome. Nat Genet 2009;41:163-5.

(4) Munch C, Sedlmeier R, Meyer T, Homberg V, Sperfeld AD, Kurt A, et al. Point mutations of the p150 subunit of dynactin (DCTN1) gene in ALS. Neurology 2004;63:724-6.

(5) Cox LE, Ferraiuolo L, Goodall EF, Heath PR, Higginbottom A, Mortiboys H, et al. Mutations in CHMP2B in lower motor neuron predominant amyotrophic lateral sclerosis (ALS). PLoS One 2010;5:e9872.

(6) Parkinson N, Ince PG, Smith MO, Highley R, Skibinski G, Andersen PM, et al. ALS phenotypes with mutations in CHMP2B (charges multivesicular body protein 2B). Neurology 2006;67:1074-7.

(7) Kenna KP, van Doormaal PT, Dekker AM, Ticozzi N, Kenna BJ, Diekstra FP, et al. NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. Nat Genet 2016.

(8) Brenner D, Muller K, Wieland T, Weydt P, Bohm S, Lule D, et al. NEK1 mutations in familial amyotrophic lateral sclerosis. Brain 2016;139:e28.

(9) Droppelmann CA, Wang J, Campos-Melo D, Keller B, Volkening K, Hegele RA, et al. Detection of a novel frameshift mutation and regions with homozygosis within ARHGEF28 gene in familial amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2013.

(10) Ma Y, Tang L, Chen L, Zhang B, Deng P, Wang J, et al. ARHGEF28 gene exon 6/intron 6 junction mutations in Chinese amyotrophic lateral sclerosis cohort. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:309-11.

(11) Zhang M, Xi Z, Ghani M, Jia P, Pal M, Werynska K, et al. Genetic and epigenetic study of ALS-discordant identical twins with double mutations in SOD1 and ARHGEF28. J Neurol Neurosurg Psychiatry 2016.

(12) Corcia P, Mayeux-Portas V, Khoris J, de Toffol B, Autret A, Muh JP, et al. Abnormal SMN1 gene copy number is a susceptibility factor for amyotrophic lateral sclerosis. Ann Neurol 2002;51:243-6.

(13) Wang XB, Cui NH, Gao JJ, Qiu XP, Zheng F. SMN1 duplications contribute to sporadic amyotrophic lateral sclerosis susceptibility: evidence from a meta-analysis. J Neurol Sci 2014;340:63-8.

(14) Johnson JO, Pioro EP, Boehringer A, Chia R, Feit H, Renton AE, et al. Mutations in the Matrin 3 gene cause familial amyotrophic lateral sclerosis. Nat Neurosci 2014;17:664-6.

(15) Leblond CS, Gan-Or Z, Spiegelman D, Laurent SB, Szuto A, Hodgkinson A, et al. Replication study of MATR3 in familial and sporadic amyotrophic lateral sclerosis. Neurobiol Aging 2016;37:209-21.

(16) Le B, I, Camuzat A, Guerreiro R, Bouya-Ahmed K, Bras J, Nicolas G, et al. SQSTM1 mutations in French patients with frontotemporal dementia or frontotemporal dementia with amyotrophic lateral sclerosis. JAMA Neurol 2013;70:1403-10.

(17) Fecto F, Yan J, Vemula SP, Liu E, Yang Y, Chen W, et al. SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis. Arch Neurol 2011;68:1440-6.

(18) Wang XS, Lee S, Simmons Z, Boyer P, Scott K, Liu W, et al. Increased incidence of the Hfe mutation in amyotrophic lateral sclerosis and related cellular consequences. J Neurol Sci 2004;227:27-33.

(19) Goodall EF, Greenway MJ, van M, I, Carroll CB, Hardiman O, Morrison KE. Association of the H63D polymorphism in the hemochromatosis gene with sporadic ALS. Neurology 2005;65:934-7.

(20) Chow CY, Landers JE, Bergren SK, Sapp PC, Grant AE, Jones JM, et al. Deleterious variants of FIG4, a phosphoinositide phosphatase, in patients with ALS. Am J Hum Genet 2009;84:85-8.

(21) Saeed M, Siddique N, Hung WY, Usacheva E, Liu E, Sufit RL, et al. Paraoxonase cluster polymorphisms are associated with sporadic ALS. Neurology 2006;67:771-6.

(22) Simpson CL, Lemmens R, Miskiewicz K, Broom WJ, Hansen VK, van Vught PW, et al. Variants of the elongator protein 3 (ELP3) gene are associated with motor neuron degeneration. Hum Mol Genet 2009;18:472-81.

(23) Al-Saif A, Al-Mohanna F, Bohlega S. A mutation in sigma-1 receptor causes juvenile amyotrophic lateral sclerosis. Ann Neurol 2011;70:913-9.

(24) Belzil VV, Daoud H, Camu W, Strong MJ, Dion PA, Rouleau GA. Genetic analysis of SIGMAR1 as a cause of familial ALS with dementia. Eur J Hum Genet 2013;21:237-9.

(25) van Es MA, van Vught PW, Blauw HM, Franke L, Saris CG, Andersen PM, et al. ITPR2 as a susceptibility gene in sporadic amyotrophic lateral sclerosis: a genome-wide association study. Lancet Neurol 2007;6:869-77.

(26) Gros-Louis F, Larivière RC, Gowing G, Laurent S, Camu W, Bouchard J-P, et al. A frameshift deletion in peripherin gene associated with amyotrophic lateral sclerosis. J Biol Chem 2004;in press.

(27) Corrado L, Carlomagno Y, Falasco L, Mellone S, Godi M, Cova E, et al. A novel peripherin gene (PRPH) mutation identified in one sporadic amyotrophic lateral sclerosis patient. Neurobiol Aging 2011;32:552-6.

(28) Mitchell J, Paul P, Chen HJ, Morris A, Payling M, Falchi M, et al. Familial amyotrophic lateral sclerosis is associated with a mutation in D-amino acid oxidase. Proc Natl Acad Sci U S A 2010;107:7556-61.

(29) Elden AC, Kim HJ, Hart MP, Chen-Plotkin AS, Johnson BS, Fang X, et al. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. Nature 2010;466:1069-75.

(30) Borghero G, Pugliatti M, Marrosu F, Marrosu MG, Murru MR, Floris G, et al. ATXN2 is a modifier of phenotype in ALS patients of Sardinian ancestry. Neurobiol Aging 2015;36:2906-5.

(31) Greenway MJ, Andersen PM, Russ C, Ennis S, Cashman S, Donaghy C, et al. ANG mutations segregate with familial and 'sporadic' amyotrophic lateral sclerosis. Nat Genet 2006;34:411-3.

(32) van Es MA, Diekstra FP, Baas F, Bourque PR, Schelhaas HJ, Strengman E, et al. A case of ALS-FTD in a large FALS pedigree with a K17I ANG mutation. Neurology 2009;72:287-8.

(33) Hand CK, Khoris J, Salachas F, Gros-Louis F, Simoes Lopes AA, Mayeux-Portas V, et al. A novel locus for familial amyotrophic lateral sclerosis on chromosome 18q. Am J Hum Genet 2002;70:251-6.

(34) Ticozzi N, Vance C, Leclerc AL, Keagle P, Glass JD, McKenna-Yasek D, et al. Mutational analysis reveals the FUS homolog TAF15 as a candidate gene for familial amyotrophic lateral sclerosis. Am J Med Genet B Neuropsychiatr Genet 2011;156B:285-90.

(35) Schymick JC, Yang Y, Andersen PM, Vonsattel JP, Greenway M, Momeni P, et al. Progranulin mutations and amyotrophic lateral sclerosis or amyotrophic lateral sclerosis-frontotemporal dementia phenotypes. J Neurol Neurosurg Psychiat 2007;78:754-6.

(36) Shatunov A, Mok K, Newhouse S, Weale ME, Smith B, Vance C, et al. Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. Lancet Neurol 2010;9:986-94.

(37) Al-Chalabi A, Andersen PM, Nilsson D, Chioza B, Andersson JL, Russ C, et al. Deletions of the heavy neurofilament subunit tail in amyotrophic lateral sclerosis. Hum Mol Genet 1999;8:157-64.

(38) Bannwarth S, Ait-El-Mkadem S, Chaussenot A, Genin EC, Lacas-Gervais S, Fragaki K, et al. A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement. Brain 2014;137:2329-45.

(39) Chaussenot A, Le B, I, Ait-El-Mkadem S, Camuzat A, De SA, Bannwarth S, et al. Screening of CHCHD10 in a French cohort confirms the involvement of this gene in frontotemporal dementia with amyotrophic lateral sclerosis patients. Neurobiol Aging 2014;35:2884.

(40) Chio A, Mora G, Sabatelli M, Caponnetto C, Traynor BJ, Johnson JO, et al. CHCH10 mutations in an Italian cohort of familial and sporadic amyotrophic lateral sclerosis patients. Neurobiol Aging 2015;36:1767-6.

(41) Dols-Icardo O, Nebot I, Gorostidi A, Ortega-Cubero S, Hernandez I, Rojas-Garcia R, et al. Analysis of the CHCHD10 gene in patients with frontotemporal dementia and amyotrophic lateral sclerosis from Spain. Brain 2015;138:e400.

(42) Zhou Q, Chen Y, Wei Q, Cao B, Wu Y, Zhao B, et al. Mutation Screening of the CHCHD10 Gene in Chinese Patients with Amyotrophic Lateral Sclerosis. Mol Neurobiol 2016.

(43) Chio A, Schymick JC, Restagno G, Scholz SW, Lombardo F, Lai SL, et al. A two-stage genome-wide association study of sporadic amyotrophic lateral sclerosis. Hum Mol Genet 2009;18:1524-32.

(44) Fernandez-Santiago R, Sharma M, Berg D, Illig T, Anneser J, Meyer T, et al. No evidence of association of FLJ10986 and ITPR2 with ALS in a large German cohort. Neurobiol Aging 2011;32:551-4.

(45) Traynor BJ, Nalls M, Lai SL, Gibbs RJ, Schymick JC, Arepalli S, et al. Kinesin-associated protein 3 (KIFAP3) has no effect on survival in a population-based cohort of ALS patients. Proc Natl Acad Sci U S A 2010;107:12335-8.

(46) van Doormaal PT, Ticozzi N, Gellera C, Ratti A, Taroni F, Chio A, et al. Analysis of the KIFAP3 gene in amyotrophic lateral sclerosis: a multicenter survival study. Neurobiol Aging 2014;35:2420-4.

(47) Yen AA, Simpson EP, Henkel JS, Beers DR, Appel SH. HFE mutations are not strongly associated with sporadic ALS. Neurology 2004;62:1611-2.

(48) Chio A, Mora G, Sabatelli M, Caponnetto C, Lunetta C, Traynor BJ, et al. HFE p.H63D polymorphism does not influence ALS phenotype and survival. Neurobiol Aging 2015;36:2906-11.

(49) Verdiani S, Origone P, Geroldi A, Bandettini Di PM, Mantero V, Bellone E, et al. The FIG4 gene does not play a major role in causing ALS in Italian patients. Amyotroph Lateral Scler Frontotemporal Degener 2013;14:228-9.

(50) Munch C, Rosenbohm A, Sperfeld AD, Uttner I, Reske S, Krause BJ, et al. Heterozygous R1101K mutation of the DCTN1 gene in a family with ALS and FTD. Ann Neurol 2005;58:777-80.

(51) Millecamps S, De SA, Teyssou E, Daniau M, Camuzat A, Albert M, et al. Genetic analysis of matrin 3 gene in French amyotrophic lateral sclerosis patients and frontotemporal lobar degeneration with amyotrophic lateral sclerosis patients. Neurobiol Aging 2014;35:2882-5.

(52) Fifita JA, Williams KL, McCann EP, O'Brien A, Bauer DC, Nicholson GA, et al. Mutation analysis of MATR3 in Australian familial amyotrophic lateral sclerosis. Neurobiol Aging 2015;36:1602.

(53) Lin KP, Tsai PC, Liao YC, Chen WT, Tsai CP, Soong BW, et al. Mutational analysis of MATR3 in Taiwanese patients with amyotrophic lateral sclerosis. Neurobiol Aging 2015;36:2005-4.

(54) Teyssou E, Chartier L, Albert M, Bouscary A, Antoine JC, Camdessanche JP, et al. Genetic analysis of CHCHD10 in French familial amyotrophic lateral sclerosis patients. Neurobiol Aging 2016;42:218-3.

(55) Wong CH, Topp S, Gkazi AS, Troakes C, Miller JW, de MM, et al. The CHCHD10 P34S variant is not associated with ALS in a UK cohort of familial and sporadic patients. Neurobiol Aging 2015;36:2908.