|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Gene | Variant | ACMG Classification | Age of Onset | Age at Testing | Site of Onset | Geoancestry | Family history |
| SOD1 | p.Ala5Val (4) | P | 63  64  59  28  65 | 64  65  59  29  65 | L  L  L  L  L | Caucasian  N/A  Hispanic  Caucasian  Caucasian | ALS\*^  ALS\*^  ALS\*  ALS\*^  ALS\*^ |
| p.Ile114Thr (2) | P | 46 | 60 | L | N/A | ALS\*\* |
| p.Gly42Ser | P | 70 | 71 | L/B | African | ALS\* |
| p.Asp102Gly | P | 37 | 37 | L | Caucasian | ALS\* |
| p.Gln23Leu | P | 38 | 38 | L | Hispanic | ALS^^ |
| p.Asp91Ala (2) | LP | 57  74 | 67  78 | L  B | Caucasian  Caucasian | ALS\*  ALS\* |
| p.Leu39Val | LP | 39 | 40 | L | Caucasian | ALS\* |
| p.Ala90Val | LP | 68 | 70 | L | Caucasian | ALS\* |
| p.Gly94Asp | LP | 34 | 35 | L | N/A | ALS^ |
| p.Glu101Lys (3) | LP | 49  47  45 | 50  48  47 | L  L  L | N/A  African  African | ALS\*^  ALS\*\*  ALS\*\* |
| p.Asn140Lys | LP | 43 | 44 | L | N/A | ALS\* |
| c.169+52\_169+58del | VUS | 73 | 76 | L | Caucasian | ALS^ |
| p.Val95Ala | VUS | 60 | 61 | L | N/A | ALS\* |
| p.Ile19Phe | VUS | 25 | 29 | L | Caucasian | ALS |
| TARDBP | p.Asn352Ser (3) | P | 69  66  70 | 70  68  75 | L  L  L | N/A  Caucasian  Caucasian | ALS\*  ALS\*\*  ALS\*^ |
| p.Ala315Thr (2) | P | 62  57 | 66  57 | L  L | Caucasian  Caucasian | ALS  ALS\* |
| p.Gly295Arg | LP | 58 | 59 | L | Caucasian | ALS\*\* |
| p.Ala321Gly | LP | 79 | 77 | L | Caucasian | ALS\* |
| p.Ala90Val | VUS | 42 | 45 | L | Caucasian | ALS\*^ |
| FUS | p.Arg521Gly (3) | P | 42  57  N/A | 44  58  42 | L  L  L | N/A  N/A  N/A | ALS\*^  ALS\*  ALS\* |
| p.Pro525Leu | P | 25 | 26 | B | Caucasian | ALS\* |
| p.Arg216Cys | P | 60 | 61 | L | N/A | ALS\* |
| p.Gly515\_Glu516insAsp | VUS | 22 | 22 | B | Caucasian | ALS\* |
| p.Ser135Asn | VUS | 67 | 70 | B | Caucasian | ALS\* |
| p.Gly228\_Gly229del | VUS | 67 | 70 | B | Caucasian | ALS^ |
| c.\*64T>G | VUS | 70 | 75 | B | N/A | N/A |
| c.\*182C>T | VUS | 63 | 64 | L | Caucasian | ALS\*^ |
| TBK1 | p.Asn22Lysfs\*8 | LP | 67 | 67 | L | Caucasian | ALS\* |
| p.Lys291Glu | VUS | 82 | 83 | B | Caucasian | ALS\* |
| p.Arg573His | VUS | 70 | 71 | L | Caucasian | ALS\* |
| VCP | p.Arg191Gln | P | 43 | 45 | L | Caucasian | ALS\* |

Supplementary Table 1. All variants identified via targeted panel testing

Legend: ALS, family history of ALS without information about affected family members; ALS\*, ALS in first-degree relative; ALS\*\*, ALS in multiple first-degree relatives; ALS^, ALS in second-degree relative; ALS^^, ALS in multiple second-degree relatives.

Abbreviations: P, pathogenic; LP, likely pathogenic; VUS, variant of uncertain significance; L, limb-onset ALS; B, bulbar-onset ALS; N/A, not available

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Characteristic | Total  (n = 573) | ALS  (n=490) | ALS/FTD  (n = 83) | fALS  (n = 234) | dALS  (n = 270) | fALS/dALS  (n = 67) |
| Ethnicity |  |  |  |  |  |  |
| African | 21 (3.7%) | 16 (3.3%) | 5 (6.0%) | 8 (3.4%) | 12 (4.4%) | 1 (1.5%) |
| Asian/Native American | 6 (1.0%) | 5 (1.0%) | 1 (1.3%) | 3 (1.3%) | 1 (0.4%) | 2 (3.0%) |
| European | 360 (62.8%) | 311 (63.5%) | 49 (59.0%) | 138 (59.0%) | 180 (66.7%) | 40 (59.7%) |
| Unknown/other | 186 (32.5%) | 158 (32.2%) | 28 (33.7%) | 85 (36.3%) | 77 (28.5%) | 24 (35.8%) |
| Age at Onset |  |  |  |  |  |  |
| Mean (min, max) | 58.2 (22, 85) | 57.4 (22, 85) | 64.5 (41, 85) | 58 (22, 85) | 58.3 (23, 85) | 59.1 (33, 80) |
| Age at testing |  |  |  |  |  |  |
| Mean (min, max) | 61 (22, 88) | 60.1 (22, 88) | 66.6 (36, 88) | 61 (22, 88) | 61.1 (25, 86) | 61.1 (34, 82) |
| Onset <50 |  |  |  |  |  |  |
| No | 371 (64.7%) | 314 (64.1%) | 57 (68.7%) | 149 (63.7%) | 174 (64.4%) | 47 (70.2%) |
| Yes | 110 (19.2%) | 104 (21.2%) | 6 (7.2%) | 48 (20.5%) | 52 (19.3%) | 10 (14.9%) |
| Unknown | 92 (16.1%) | 72 (14.7%) | 20 (24.1%) | 37 (15.8%) | 44 (16.3%) | 10 (14.9%) |

Supplementary Table 2. Demographic and disease characteristics of the tested cohort