**Table e1 Phenoconverters: clinical signs or symptoms indicating manifest disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Genotype** | **Site of onset** | **Reported symptom(s)** | **Neuromuscular examination finding(s)** | **Abnormal EMG finding(s)** 1 | **Cognition and behavior finding(s)** |
| **In region(s) with weakness** | **In other region(s)** |
| SOD1 A4V | Limb | Weakness | Weakness, atrophy, reduced tone, absent reflexes | Yes | No | Not examined |
| Limb | Weakness | Weakness, atrophy, diminished reflexes | Yes | No | Not examined |
| Limb | Weakness, fasciculations, cramps | Weakness, abnormal reflexes  | Yes | No | Normal |
| Bulbar | Dysarthria | Dysarthria, tongue weakness, fasciculations with slow tongue movements | No | Yes | Not examined |
| Limb | Weakness | Weakness, fasciculations, reduced tone, brisk reflexes with extensor plantar response | Yes | Yes | Not examined |
| Limb | Weakness | Weakness, brisk reflexes | Yes | Yes | Not examined |
| Limb | Weakness | Weakness, fasciculations, diminished reflexes | Yes | No | Normal |
| Bulbar | Facial fasciculations | Facial weakness and fasciculations. Mild proximal weakness and fasciculations in both arms.  | Yes | Yes | Normal |
| Limb | Weakness | Weakness, fasciculations, atrophy, diminished reflexes | Yes | No | Normal |
| SOD1nonA4V | Breathing & limb | Shortness of breath; limb weakness | Slow vital capacity: 91% erect, 75% supine Limb: weakness, atrophy, fasciculations | Yes | Yes | Normal |
| Limb | Weakness | Weakness, atrophy, diminished tone, brisk reflexes | Yes | Yes | Normal |
| FUS | Limb | Weakness | Weakness with brisk reflexes in two limbs; atrophy and weakness in a third limb. | Yes | Yes | Normal |
| C9ORF72 | Limb | None | Unilateral extensor plantar response | N/A | Yes | Normal |
| Fronto-temporal | Personality change (per informant/caregiver) | Diffusely diminished reflexes | N/A | Yes | Impaired 2  |

1 EMG regions include bulbar, cervical (arms), thoracic, and lumbosacral (legs). Per El Escorial criteria, cervical and lumbosacral regions are considered affected if there is evidence of ongoing denervation and chronic reinnervation in at least two muscles innervated by different peripheral nerves and nerve roots; cranial and thoracic regions are considered abnormal based on ongoing denervation in a single muscle.

2 Cognitive and behavioral impairment based on ECAS and neuropsychological battery.

**Table e2. Baseline serum and CSF pNfH levels vs. age**

|  |  |  |
| --- | --- | --- |
|  | **Serum** | **CSF** |
| **Control** | At-risk | Both | **Control** | At-risk | Both |
| **Baseline only** | r = 0.11p = 0.5(N=34) | r = 0.08p = 0.5(N=79) | r = 0.09p = 0.3(N=113) | r = 0.71p = 0.0028 (N=15) | r = 0.49p = 0.0005 (N=46) | r = 0.57p < 0.0001 (N=61) |

r = Spearman rank correlation

**Table e3. Baseline serum and CSF pNfH levels, by sex**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control** | **At-Risk** | **Converter** | **Affected** |
| ***Baseline serum pNfH, log-transformed a, Mean ± SD:*** |
|  **Female** | 2.98 ± 1.53(N=19) | 2.71 ± 1.20(N=51) | 2.65 ± 1.95(N=7) | 4.55 ± 1.77(N=10) |
|  **Male** | 2.39 ± 1.30(N=15) | 2.81 ± 1.24(N=28) | 2.98 ± 0.82(N=7) | 3.99 ± 1.67(N=12) |
| ***Baseline CSF pNfH, log-transformed a, Mean ± SD:*** |
|  **Female** | 5.22 ± 0.89(N=8) | 5.44 ± 0.46(N=32) | 5.72 ± 1.45(N=2) | 7.97 ± 0.93(N=4) |
|  **Male** | 5.82 ± 0.92(N=7) | 5.59 ± 0.33(N=14) | 6.87 ± 1.02(N=5) | 7.37 ± 0.82(N=5) |

*a* Natural algorithm

**Table e4. Baseline serum and CSF pNfH levels in At-Risk group, by genotype**

|  |  |
| --- | --- |
|  | **At-Risk Group, By Genotype:** |
|  | ***SOD1*** **A4V** | ***SOD1*** **nonA4V** | ***C9orf72*****HRE** | **Other Genes** |
| **Baseline serum pNfH****Log-transformed a, Mean ± SD**  | 2.77 ± 1.14(N=27) | 2.67 ± 1.30(N=22) | 2.82 ± 1.32(N=25) | 2.50 ± 0.77(N=5) |
| **Baseline CSF pNfH****Log-transformed a, Mean ± SD**  | 5.43 ± 0.39(N=15) | 5.55 ± 0.53(N=10) | 5.49 ± 0.43(N=17) | 5.48 ± 0.38(N=4) |

*a* Natural algorithm