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## RESEARCH PAPER

## Defining SOD1 ALS natural history to guide therapeutic clinical trial design

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**ABSTRACT**

**Importance** Understanding the natural history of familial amyotrophic lateral sclerosis (ALS) caused by SOD1 mutations (ALS<sup>SOD1</sup>) will provide key information for optimising clinical trials in this patient population.

**Objective** To establish an updated natural history of ALS<sup>SOD1</sup>.

**Design, setting and participants** Retrospective cohort study from 15 medical centres in North America evaluated records from 175 patients with ALS with genetically confirmed SOD1 mutations, cared for after the year 2000.

**Main outcomes and measures** Age of onset, survival, ALS Functional Rating Scale (ALS-FRS) scores and respiratory function were analysed. Patients with the A4V (Ala-Val) SOD1 mutation (SOD1<sup>A4V</sup>), the largest mutation population in North America with an aggressive disease progression, were distinguished from other SOD1 mutation patients (SOD1<sup>non-A4V</sup>) for analysis.

**Results** Mean age of disease onset was 49.7 ±12.3 years (mean±SD) for all SOD1 patients, with no statistical significance between SOD1<sup>A4V</sup> and SOD1<sup>non-A4V</sup> (p=0.72, Kruskal-Wallis). Total SOD1 patient median survival was 2.7 years. Mean disease duration for all SOD1 was 4.6±6.0 and 1.4±0.7 years for SOD1<sup>A4V</sup>. SOD1<sup>A4V</sup> survival probability (median survival 1.2 years) was significantly decreased compared with SOD1<sup>non-A4V</sup> (median survival 6.8 years; p<0.0001, log-rank). A statistically significant increase in ALS-FRS decline in SOD1<sup>A4V</sup> compared with SOD1<sup>non-A4V</sup> participants (p=0.02) was observed, as well as a statistically significant increase in ALS-forced vital capacity decline in SOD1<sup>A4V</sup> compared with SOD1<sup>non-A4V</sup> (p=0.02).

**Conclusions and relevance** SOD1<sup>A4V</sup> is an aggressive, but relatively homogeneous form of ALS. These SOD1-specific ALS natural history data will be important for the design and implementation of clinical trials in the ALS<sup>SOD1</sup> patient population.

**INTRODUCTION**

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease affecting both upper and lower motor neurons, resulting in severe weakness and fatal respiratory failure within 2–5 years. The annual incidence of ALS is 1.7 in 100 000 people,<sup>1</sup>

yet the only Food and Drug Administration (FDA)-approved treatment, riluzole, has minimal effects on disease course.<sup>2</sup>

Inherited or familial ALS (FALS) accounts for roughly 10% of all ALS cases.<sup>3</sup> The second most common cause of FALS is the gene encoding copper zinc superoxide dismutase 1 (SOD1), which accounts for 10–20% of FALS and mostly follows an autosomal-dominant inheritance pattern,<sup>4</sup> although an aspartic acid to alanine (D90A) point mutation found in the Scandinavian population displays recessive inheritance.<sup>5</sup> Multiple efforts (ClinicalTrials.gov NCT00706147)<sup>6–17</sup> have focused on targeted therapeutic approaches for SOD1-related ALS (ALS<sup>SOD1</sup>).

To test the efficacy of SOD1-focused therapeutics, an ALS<sup>SOD1</sup> natural history data set is required to determine the patient sample size needed to observe the desired effect. Considering the rare nature of SOD1 mutations, these historical control data may also be used in future clinical trials provided that updated data show no change in disease measures. Given the heterogeneity among different SOD1 mutations,<sup>18</sup> it is important to clinically stratify mutations in SOD1 according to disease duration and rate of progression. The A4V (SOD1<sup>A4V</sup>) is known for an exceptionally aggressive disease course and relatively low interpatient clinical variability, and represents about 50% of ALS<sup>SOD1</sup> in the USA.<sup>18 19</sup>

We report the findings from a multicentre retrospective chart review of genetically confirmed ALS<sup>SOD1</sup> cases cared for after the year 2000 and discuss implications for future ALS<sup>SOD1</sup> clinical trials.

**METHODS****Data acquisition**

We corresponded with 37 sites within the Northeast ALS Consortium Network (NEALS), an international, independent, non-profit group of research sites who collaboratively conduct ALS clinical research. Sites performed a retrospective chart review of their respective patients with ALS<sup>SOD1</sup> cared for from the year 2000 to present. Data were sent to the coordinating centre at the Washington University in St Louis and entered into

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## Neurodegeneration

a central database. Information for all patients was de-identified, and data collection and processing were approved by the local Institutional Review Board (IRB) committees. The following 17 centres sent charts as part of this study: Washington University School of Medicine, Northwestern University Feinberg School of Medicine, University of Washington Medical Center, Neurology Clinical Research Institute at Massachusetts General Hospital, Mayo Clinic Florida, Emory University School of Medicine, Johns Hopkins University, Wake Forest School of Medicine, Perelman School of Medicine at the University of Pennsylvania, Methodist Neurological Institute at The Methodist Hospital, Neurosciences Institute at Albany Medical Center, University of Utah, Sunnybrook Health Sciences Centre, University of California Irvine, University of Michigan, University of Kansas Medical Center and Cedars-Sinai Medical Center.

### Data collection and analysis

All sites received a standardised form with the following items requested: gender, genetic mutation, month/year of birth, month/year of symptom onset, month/year of death, month/year of permanent ventilation (if applicable), ALS-Functional Rating Scale (ALS-FRS) at time points where available, and forced vital capacity (FVC) at time points where available. Symptom onset was defined as the first reported loss of function, such as limb weakness or dysarthria.

Genetic testing was performed by individual institutions at the time of diagnosis, and sites were asked to only report the specific *SOD1* mutation found. Data were collected and analysed from individual patients or families of index cases with confirmed *SOD1* mutations only; mutations recorded as 'self-reported' were not included in the analysis. All mutations are reported in this study using the traditional numbering nomenclature, that is, not counting the first (ATG) codon. When time of onset could not be narrowed down to more than a range of several months, for example, 'fall 2011', the onset was determined to be the midpoint of that range, for example, 'October 2011'. Patients still alive at the time of data collection were reported as such, and their last recorded FVC or ALS-FRS, whichever came later, was used for survival analyses. ALS-FRS is understood to be the revised scale (ALSFRS-R), a 12-item questionnaire with the highest, normal score being 48.<sup>20</sup> When both sitting and lying FVC readings were available, sitting values were used. Additional clinical features, such as site of onset and presence of non-motor symptoms and signs, were not analysed in this study.

### Statistical analysis

SAS V9.3 (Cary, North Carolina, USA) was used to perform all statistical analyses. Descriptive statistics were provided for gender, age and disease duration by mutation group (A4V and non-A4V) and total patients, respectively. Additionally, mean,

SD of age and disease duration were calculated for each interested mutation. The primary study end points included ALS-FRS and FVC while secondary end point was overall survival (OS). OS was defined as the date of symptom onset to death from any cause or last follow-up. Kaplan-Meier (KM) curves for OS were generated that provide unadjusted survival estimates for total sample and between mutation groups (non-A4V vs A4V), respectively. Difference between mutations groups were determined by log-rank testing.

The study sample includes ALS-FRS and FVC measurements for multiple visits. To account for correlations among repeated measures from the same patient, the longitudinal data were analysed using a generalised estimating equation (GEE) model with log link function to examine the change in ALS-FRS and FVC measurements over the first three time points recorded for a patient. The autoregressive of first order as working correlation structure was used and the patients with missing values at any assessment number were excluded from GEE analysis. The GEE model includes the group indicator, time points, the interaction term between group and time points. The p values of the interaction term from type 3 analysis in the GEE model were estimated to assess whether the measurements across all time points between A4V and non-A4V groups were significantly different. The least square mean and SEM were provided.

## RESULTS

### Descriptive features

Applicable data were collected from 15 medical centres. A total of 175 participants with confirmed *SOD1* mutations were analysed. Of participants collected, 63 had *SOD1*<sup>A4V</sup> mutations (36.4%), the most common mutation observed in this cohort. One hundred and twelve participants had *SOD1*<sup>non-A4V</sup> mutations (63.6%). There was a slight male dominance in this cohort with a male–female ratio of 1.30:1 in all *SOD1* participants, but there was no significant difference in the male–female ratio between *SOD1*<sup>A4V</sup> (1.33:1) and *SOD1*<sup>non-A4V</sup> (1.29:1) participants ( $p=0.91$ ,  $\chi^2$  testing; [table 1](#)).

A total of 36 distinct, missense *SOD1* mutations were found in this cohort. The most common *SOD1*<sup>non-A4V</sup> mutation was I113T (Ile-Thr) in 32 participants (18.3%), followed by G41D (Gly-Asp; 11 participants; 6.4%), and E40K (Glu-Lys; 10 participants; 5.7%). The frequencies and clinical characteristics of all participants included in this study are shown in [table 2](#).

### Age of disease onset

Age of onset data was provided for 162 (92.5%) total participants, with data for 57 *SOD1*<sup>A4V</sup> and 105 *SOD1*<sup>non-A4V</sup> patients available for analysis. The mean age of onset for all participants was 49.7±12.3 years (mean±SD). The mean age of onset varied across different mutations, with G37R (Gly-Arg) and D133A (Asp-Ala) mutations associated with the youngest and oldest mean ages at onset, respectively ([figure 1A](#)). There was no

**Table 1** Clinical characteristics of *SOD1*<sup>A4V</sup> versus *SOD1*<sup>non-A4V</sup> mutation populations in familial amyotrophic lateral sclerosis

	Total <i>SOD1</i>	<i>SOD1</i> <sup>A4V</sup>	<i>SOD1</i> <sup>non-A4V</sup>	p Value*
Number of participants (%)	175 (100)	63 (36.4)	112 (63.6)	
Male–female ratio	1.30:1	1.33:1	1.29:1	0.91
Mean age at onset (year)±SD (n)	49.7±12.3 (162)	50.0±12.4 (57)	49.5±12.3 (105)	0.72
Mean disease duration (year)±SD (n)	4.6±6.0 (134)	1.4±0.7 (51)	6.6±7.0 (83)	<0.0001
Median survival (year)	2.7	1.2	6.8	<0.0001

\* $\chi^2$  Test for categorical variable; Kruskal-Wallis test for continuous variable; log-rank test for overall survival.

**Table 2** Disease characteristics by mutation type in SOD1 familial ALS

Mutation*						
Exon	Codon	Substitution	Number of patients (%)	Mean age (year)±SD (n) at onset	Mean duration† (year)±SD (n)	Median duration (year)
1	4	Ala-Val	63 (36.6)	49.9±12.3 (57)	1.4±0.7 (51)	1.2
4	113	Ile-Thr	32 (18.3)	54.2±10.7 (29)	5.3±4.8 (22)	3.3
2	41	Gly-Asp	11 (6.4)	34.2±7.8 (8)	23.5±14 (4)	21
4	100	Glu-Lys	10 (5.7)	39.6±5.9 (10)	8.9±5.2 (8)	9.1
4	100	Glu-Gly	5 (2.9)	42.6±9.1 (5)	9±6.2 (4)	7.2
4	89	Ala-Val	4 (2.3)	56±10.4 (4)	8±1.6 (2)	8
1	4	Ala-Thr	3 (1.7)	50±10.1 (3)	0.8±0.05 (2)	0.8
4	90	Asp-Ala	3 (1.7)	57.7±9.6 (3)	9.7±5.4 (2)	9.7
4	93	Gly-Ala	3 (1.7)	49±12.5 (3)	2.2±0.6 (2)	2.2
5	137	Thr-Ala	3 (1.7)	38.3±9.2 (3)	9.6±7 (3)	6.4
1	14	Val-Gly	3 (1.7)	50.3±21.0 (3)	2.6±1 (2)	2.6
1	6	Cys-Ser	2 (1.2)	54±16.9 (2)	4.1±0.5 (2)	4.1
5	133‡	Glu-Ala	2 (1.2)	62±2.8 (2)	0.9±0.6 (2)	0.9
2	49	Glu-Lys	2 (1.2)	59±19.8 (2)	6.8±1.9 (2)	6.8
5	141	Gly- ---	2 (1.2)	42.5±2.1 (2)	1.1±0.7 (2)	1.1
2	37	Gly-Arg	2 (1.2)	26.5±6.4 (2)	7.8	
2	41	Gly-Ala	2 (1.2)	44.5±10.6 (2)	17.3±0 (2)	17.3
4	85	Gly-Arg	2 (1.2)	56.5±9.2 (2)	2.2±0.3 (2)	2.2
5	139	Asn-Lys	2 (1.2)	51±2.8 (2)	1.5±0.7 (2)	18.5
5	148	Val-Gly	2 (1.2)	49.5±0.7 (2)	0.7±0.4 (2)	0.7
1	4‡	Ala-His	1 (0.6)	50		
5	125‡	Asp-Ala	1 (0.6)	63	1.1	
3	76	Asp-Tyr	1 (0.6)	75	3.7	
4	108‡	Gly-Arg	1 (0.6)	67	1.7	
1	10‡	Gly-Ala	1 (0.6)	59	4.8	
5	141	Gly-Ala	1 (0.6)	43		
2	37	Gly-Val	1 (0.6)	36	4.6	
2	41	Gly-Ser	1 (0.6)	67	0.4	
4	93	Gly-Ser	1 (0.6)	45		
2	43	His-Arg	1 (0.6)	56	0.3	
2	46	His-Arg	1 (0.6)	47	23.4	
5	144	Leu-Phe	1 (0.6)	66	6.2	
5	144	Leu-Ser	1 (0.6)	56	7.8	
1	14	Val-Met	1 (0.6)	54	4.1	
4	87	Val-Met	1 (0.6)	39	8.8	
5	134	Thr-Cys	1 (0.6)	55		
	Unknown		1 (0.6)			
Total			175§ (100%)	162§	134§	

\*The mutations are ordered by decreasing number of affected patients. Nomenclature corresponds to amino acid sequence excluding ATG start codon.

†Censored data are included in determination of mean or median duration.

‡Mutations that are not listed in the ALSod Database as of 5/5/15.

§Total number of participants with available data.

ALS, amyotrophic lateral sclerosis.

significant difference in mean age of onset between SOD1<sup>A4V</sup> (50.0±12.4 years) and SOD1<sup>non-A4V</sup> (49.5±12.3 years) participants ( $p=0.72$ , Kruskal-Wallis; [table 1](#)).

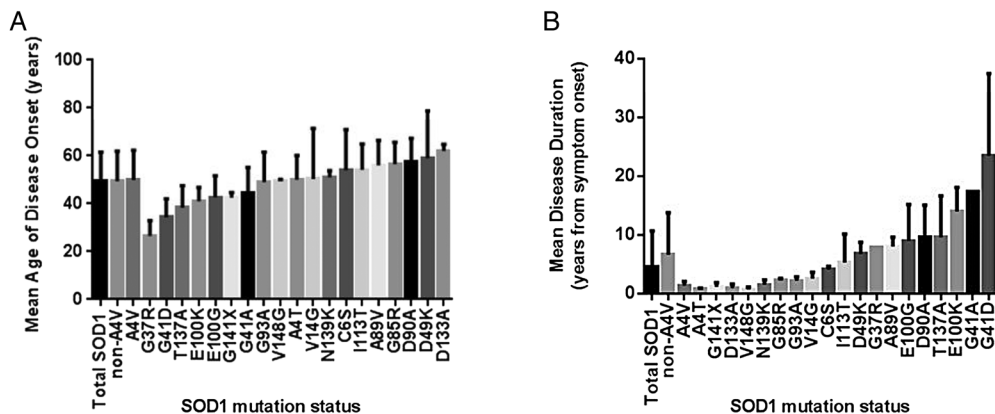
### Disease duration

Disease duration information was available for 134 (76.6%) of total participants, including 51 SOD1<sup>A4V</sup> and 83 SOD1<sup>non-A4V</sup> patients. The mean disease duration was 4.6±6.0 years for all SOD1 participants, 1.4±0.7 years for SOD1<sup>A4V</sup> participants, and 6.6±7.0 years for SOD1<sup>non-A4V</sup> ([table 1](#)). Disease duration varied between mutation type, ranging from rapidly progressing mutations such as A4T (Ala-Thr; 0.8±0.1 years) to slow progressing mutants such as G41D (Gly-Asp; 23.5±14.0 years; [figure 1B](#)).

KM survival analysis was performed comparing the survival probabilities from time of disease onset to death between SOD1<sup>A4V</sup> and SOD1<sup>non-A4V</sup> ([figure 2](#)). Of 120 participants analysed, 35 were SOD1<sup>A4V</sup> and 85 were SOD1<sup>non-A4V</sup>. The median survival for all participants was 2.7 years, 1.2 years for SOD1<sup>A4V</sup> and 6.8 for SOD1<sup>non-A4V</sup>. SOD1<sup>A4V</sup> median survival was significantly shorter than SOD1<sup>non-A4V</sup> by log-rank test ( $p<0.0001$ ). No SOD1<sup>A4V</sup> participants survived to 4 years ([figure 2B](#)).

### FRS and FVC

Only three data points were considered for FRS and FVC. Thirty SOD1<sup>A4V</sup> and 75 SOD1<sup>non-A4V</sup> participants were used for ALS-FRS and FVC analysis. The least mean and SE of ALS-FRS for SOD1<sup>A4V</sup> were 37.8±1.4, 30.0±2.0 and 22.3±3.7; while

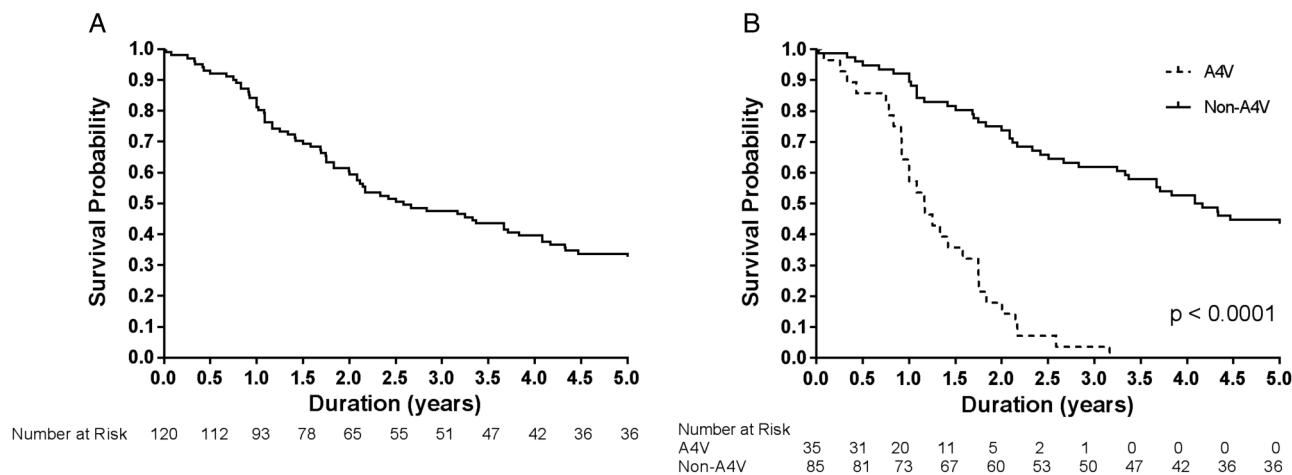


**Figure 1** Mean age at onset and disease duration for ALS<sup>SOD1</sup>. (A) The mean age at onset and (B) mean disease duration were reported for each mutation population with a minimum n=2. There was no statistical significance between all SOD1 patients (n=162), SOD1<sup>non-A4V</sup> patients (n=105), SOD1<sup>A4V</sup> patients (n=57; p=0.7217, Kruskal-Wallis). (A) Average age at onset varied among mutations, with the SOD1<sup>G37R</sup> and SOD1<sup>D133A</sup> mutations associated, respectively, with the youngest and oldest mean ages at onset among mutations with more than one patient. (B) Average disease duration varied with different mutations, with SOD1<sup>A4T</sup> and SOD1<sup>G41D</sup> mutations associated, respectively, with the shortest and longest disease durations. SOD1<sup>A4V</sup> disease duration (n=51) is significantly shorter than SOD1<sup>non-A4V</sup> disease duration (n=83; p<0.0001, Kruskal-Wallis). Error bars represent SD. ALS, amyotrophic lateral sclerosis.

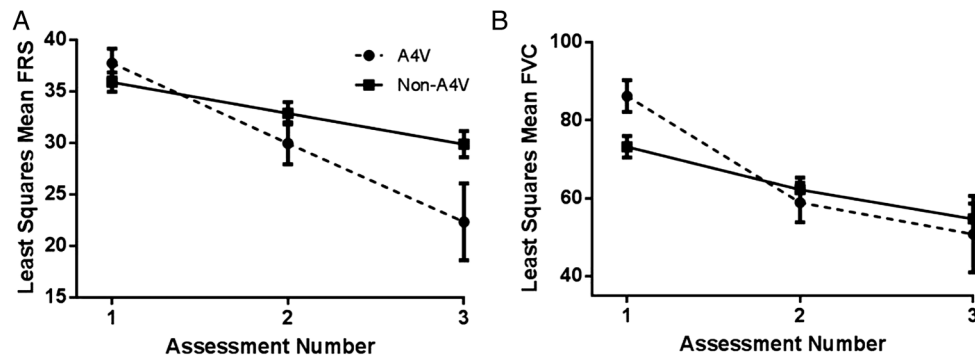
those of SOD1<sup>non-A4V</sup> were 35.9±0.9, 32.9±1.1 and 29.9±1.3 at time points 1, 2 and 3, respectively. A statistically significant difference was seen in ALS-FRS across three time points in SOD1<sup>A4V</sup> compared with SOD1<sup>non-A4V</sup> participants (p=0.02, figure 3A). Additionally, 37 SOD1<sup>A4V</sup> and 81 SOD1<sup>non-A4V</sup> participants were used for FVC analysis. Dates of permanent ventilation were rarely available (<5% of total participants), most likely due to death without receiving tracheal ventilation, and so were not included in final analysis. Similarly, a statistically significant increase in ALS-FVC decline was observed in SOD1<sup>A4V</sup> compared with SOD1<sup>non-A4V</sup> (p=0.02, figure 3B). The least mean and SE of FVC for SOD1<sup>A4V</sup> were 86.2±4.1, 58.8±5.1 and 50.7±9.8; while those of SOD1<sup>non-A4V</sup> were 73.2±2.8, 62.2±3.2 and 54.7±4.0 at time points 1, 2 and 3, respectively.

## DISCUSSION

We collected data from 15 North American centres, studying 175 participants with confirmed SOD1 mutations, cared for from the year 2000 to present. The number of patients available for this study represent the largest effort to study ALS<sup>SOD1</sup> natural history in almost 20 years.<sup>18</sup> Combining data from multiple studies<sup>18 19 21-27</sup> suggests mean disease duration for all SOD1 is 3.9±5.5 years and SOD1<sup>A4V</sup> is 1.4±0.9 years. Three of these studies<sup>18 19 25</sup> represent 92% of the 199 reported patients and use data collected more than 20 years ago and published in the 1990s. Our calculated disease duration for all SOD1 of 4.6±6.0 and SOD1<sup>A4V</sup> of 1.4±0.7 years indicates no significant change in the natural history of the disease since these historical data were collected. Our results provide updated



**Figure 2** Decreased survival probability from time of disease onset for SOD1<sup>A4V</sup> compared with SOD1<sup>non-A4V</sup> familial ALS. (A) Plot for survival probability of all SOD1 mutation patients. One hundred and twelve participants were analysed. The median survival for all SOD1 patients is 2.7 years. The survival probabilities for SOD1 patients and the corresponding 95% CIs were 0.82 (0.73 to 0.88), 0.51 (0.41 to 0.60) and 0.43 (0.33 to 0.53) at years 1, 3 and 5, respectively, after disease onset. (B) Plot for survival probability for SOD1<sup>A4V</sup> versus SOD1<sup>non-A4V</sup> mutation patients. Analysis consisted of 33 SOD1<sup>A4V</sup> and 79 SOD1<sup>non-A4V</sup>. The presence of SOD1<sup>A4V</sup> mutations was associated with shorter survival (p<0.0001, log-rank). The survival probability for SOD1<sup>A4V</sup> patients and the corresponding 95% CIs were 0.60 (0.41 to 0.75), 0.04 (0.00 to 0.15) and 0.00 (NA, NA) at years 1, 3 and 5, respectively, after disease onset. No SOD1<sup>A4V</sup> patients survived to year 4. The survival probability of SOD1<sup>non-A4V</sup> patients was 0.91 (0.82 to 0.96), 0.70 (0.59 to 0.79) and 0.60 (0.48 to 0.71) at 1, 3 and 5 years after disease onset. ALS, amyotrophic lateral sclerosis; NA, not available.



**Figure 3** SOD1<sup>A4V</sup> patients with ALS exhibit greater decline in ALS-FRS and FVC rates compared with SOD1<sup>non-A4V</sup> patients. (A) Least squares mean of ALS-FRS over multiple assessment periods. SOD1<sup>A4V</sup> patients decline from mean ALS-FRS 37.6 (35.1 to 40.6; 95% CI) at assessment point 1, 29.9 (26.2 to 34.3) at assessment point 2, to 22.3 (16.1 to 31.0) at assessment point 3. SOD1<sup>non-A4V</sup> patients decline from mean ALS-FRS 35.9 (34.1 to 37.8) at assessment point 1, 35.9 (34.1 to 37.8) at assessment point 2, to 29.9 (27.4 to 32.2) at assessment point 3. The SOD1<sup>A4V</sup> FRS decline is significantly increased compared to SOD1<sup>non-A4V</sup> ( $p=0.0168$ ). (B) Least squares mean of FVC over multiple assessment periods. SOD1<sup>A4V</sup> patients decline from mean ALS-FRS 86.2 (78.6 to 94.5; 95% CI) at assessment point 1, 58.8 (49.6 to 69.8) at assessment point 2, to 50.8 (34.8 to 74.0) at assessment point 3. SOD1<sup>non-A4V</sup> patients decline from mean FVC 74.7 (69.5 to 80.4) at assessment point 1, 63.4 (57.5 to 69.8) at assessment point 2, to 55.6 (48.4 to 64.0) at assessment point 3. The SOD1<sup>A4V</sup> FVC decline is significantly increased compared with SOD1<sup>non-A4V</sup> ( $p=0.0168$ ). Error bars represent SEM. ALS, amyotrophic lateral sclerosis; FRS, Functional Rating Scale; FVC, forced vital capacity.

survival data that could serve in the design and interpretation of future clinical trials specific for patients with ALS<sup>SOD1</sup>.

A total of 36 missense SOD1 mutations were captured, with the four most common (SOD1<sup>A4V</sup>, SOD1<sup>I113T</sup>, SOD1<sup>G41D</sup> and SOD1<sup>E100K</sup>) accounting for two-thirds of all participants. Our data show a smaller percentage (36.4%) of SOD1<sup>A4V</sup> among all ALS<sup>SOD1</sup> participants than previously reported (50%). This may reflect the recent expansion in genetic testing and improvement of ALS care, leading to increased detection of SOD1 mutations with less aggressive or typical presentations. Interestingly, male predominance was present, although mild, in ALS<sup>SOD1</sup> participants as a whole (M:F of 1.3). These findings may reflect potential bias in the data set, as they are in contrast to a recent literature review.<sup>28</sup> However, ALS<sup>SOD1</sup> cohorts published earlier report similar male predominance.<sup>18</sup> Age of onset for all SOD1 patients ( $49.7 \pm 12.3$  years) was not statistically different from SOD1<sup>A4V</sup> age of onset ( $50.0 \pm 12.4$  years), which might be unexpected due to the aggressive nature of SOD1<sup>A4V</sup>. However, these findings are consistent with previous reports<sup>18</sup> in which onset is similar between SOD1<sup>A4V</sup> and all SOD1 patients, while progression is more rapid in the SOD1<sup>A4V</sup> population.

Our results are limited by the design of this study as retrospective. As with all retrospective studies, inherent biases exist based on the availability of data collected. Of the original 37 NEALS medical centres which we corresponded, 17 participated in this study. No obvious variables such as geographic location or size of centre were linked to the 20 medical centres that did not respond. Correspondingly, data included in the study have come from clinical centres spanning wide geographical regions and likely capture a significant portion of the ALS<sup>SOD1</sup> population in North America. However, assumptions must be made when compiling survival data from multiple centres, including consistency of standard of care. Also, given that our data were drawn from large ALS referral centres, survival and progression rate numbers may be different than outcomes in the community.

Natural history data are optimally collected prospectively, and in fact a portion of our data from 2013 to 2014 was collected as such. Efforts to collect prospective natural history data on ALS<sup>SOD1</sup>, and FALS in general, should be considered in the future and will be better able to capture real-time clinical

information, such as site of onset and presence of extramotor findings, in addition to more closely documenting paraclinical end points such as ALS-FRS, FVC and time-to-permanent-ventilation. Despite these limitations, the rarity of ALS<sup>SOD1</sup> coupled with the urgent need for enabling new clinical trials helps justify the use of a retrospective study design.

In clinical trials with a rare disease population, such as ALS<sup>SOD1</sup>, historical controls may be implemented to assess outcomes. As recruitment of patients to a trial in a rare disease population is challenging, the use of historical controls would be valuable to design an adequately powered trial. However, it is important to validate if historical data have changed over time. In contrast to our results focusing on ALS<sup>SOD1</sup>, previous natural history studies<sup>29–30</sup> of the ALS population suggest an increase in survival and conclude this may reflect improvement in respiratory, nutritional and supportive clinical care. These findings may suggest that, although overall ALS survival has improved over time, ALS<sup>SOD1</sup> may represent a unique ALS sub-population. Although our data suggest the ALS<sup>SOD1</sup> has not changed over time, the use of historical controls in clinical trials is challenging, and key limitations exist in our data for direct implementation as historical controls. To properly match patients in trials with historical controls, additional data such as standard of care (riluzole use, non-invasive ventilation), cognitive status and site of disease onset must be collected, leading to enhanced comparisons with a future cohort. Future prospective studies will focus on these missing data in future prospective natural history studies in ALS<sup>SOD1</sup> or other ALS disease populations. Nevertheless, the data reported regarding updated survival statistics for this population are one important consideration in the use of historical controls.

The first reported cause of FALS was a mutation in SOD1, and it is now widely accepted that the pathogenesis of mutations in SOD1 is related to a gain of toxic function of the SOD1 protein. Therefore, global reduction of toxic SOD1 in ALS has been recognised as a possible therapeutic intervention. Our work with SOD1 antisense oligonucleotides<sup>6–10</sup> and others (ClinicalTrials.gov NCT00706147)<sup>11–17</sup> have focused on targeted SOD1-lowering therapeutics approaches for ALS<sup>SOD1</sup>. Given the heterogeneity of disease progression in different mutation carriers, one may envision the design of a trial that

stratifies results from patients with rapidly progressing disease as defined by unchanged natural history data. For example, our analysis of the SOD1<sup>A4V</sup> patient population in this study suggests that SOD1<sup>A4V</sup> disease characteristics are homogeneous, and natural history has remained unchanged over time with a median survival of 1.2 years. As SOD1<sup>A4V</sup> is the most common mutation found in North America, recruitment for a SOD1<sup>A4V</sup>-focused trial for therapeutic efficacy may be feasible. Assuming an accrual interval of 1 year and additional follow-up interval of 2 years, 52 SOD1<sup>A4V</sup> participants per group (new treatment and placebo) are needed to achieve at least 80% power at a 0.05 significance level to detect the statistical difference when the median survival in the treatment group is 2.4 years using two-sided log-rank test, where HR of new treatment to control is 0.5. In contrast, our findings suggest that the median survival in all SOD1 participants is 2.7 years, and thus 88 SOD1 participants per group (new treatment and placebo) are needed when the median survival probability in the treatment group is 5.4 years, where HR of new treatment to control is 0.5.

Overall, the data presented here will help guide clinical trial design and may serve as a historical control database for ALS<sup>SOD1</sup> interventional trials, with the hope of demonstrating that one of the upcoming therapies extends survival.

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