HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2016 December 26.

Published in final edited form as:

Neurobiol Aging. 2015 October ; 36(10): 2906.e7–2906.11. doi:10.1016/j.neurobiolaging.2015.06.016.

HFE p.H63D polymorphism does not influence ALS phenotype and survival

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Disclosure statement

The authors have no actual or potential conflicts of interest.

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Abstract

It has been recently reported that the p.His63Asp polymorphism of the HFE gene accelerates disease progression both in the SOD1 transgenic mouse and in amyotrophic lateral sclerosis (ALS) patients. We have evaluated the effect of HFE p.His63Asp polymorphism on the phenotype in 1351 Italian ALS patients (232 of Sardinian ancestry). Patients were genotyped for the HFE p.His63Asp polymorphism (CC, GC, and GG). All patients were also assessed for C9ORF72, TARDBP, SOD1, and FUS mutations. Of the 1351 ALS patients, 363 (29.2%) were heterozygous (GC) for the p.His63Asp polymorphism and 30 (2.2%) were homozygous for the minor allele (GG). Patients with CC, GC, and GG polymorphisms did not significantly differ by age at onset, site of onset of symptoms, and survival; however, in SOD1 patients with CG or GG polymorphism had a significantly longer survival than those with a CC polymorphism. Differently from what

observed in the mouse model of ALS, the HFE p.His63Asp polymorphism has no effect on ALS phenotype in this large series of Italian ALS patients.

Keywords

Amyotrophic lateral sclerosis; HFE polymorphisms; phenotype; survival; SOD1

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of adult life characterized by a progressive loss of upper (cortical) and lower (bulbar and spinal) motor neurons. The disease has an invariably fatal course over a period of 3–5 years. No disease-modifying therapy is available, with the exception of riluzole, an antiexcytotoxic drug that prolongs patients' life by 3 months. The cause of ALS is still unknown. About 10% of ALS patients have a family history of ALS or frontotemporal dementia whereas in ~90% of cases the disease appears sporadically in the population. The most common genes related to ALS are C9ORF72, SOD1, TARDBP, and FUS, but at least 20 other rarer genes have been identified (Finsterer and Burgunder, 2014 and Renton et al., 2014). In addition, some genes have been found to modify the phenotype or the survival of ALS.

Polymorphisms of Unc-13 homolog A (UNC13 A) (Chiò et al., 2013 and Diekstra et al., 2012) of nonimprinted in Prader-Willi and Angelman syndrome 1 (NIPA1) (Blauw et al., 2012) genes and polyQ intermediate-length expansion of ATXN2 (Chiò et al., 2014) have been associated with a shorter survival, whereas a locus on 1p34.128 has been associated with a younger age at onset (Ahmeti et al., 2013).

Recently, it has been reported that the p.His63Asp polymorphism of the HFE gene accelerates disease progression in the ALS SOD1 transgenic mouse (Nandar et al., 2014). Conversely, in a small study on 35 ALS patients, it has been reported that patients carrying the p.H63D polymorphism of the HFE gene had a significantly longer survival than those with the wild-type gene (Su et al., 2013).

The aim of this study was to assess the influence of the p.H63D polymorphism of the HFE gene on the phenotype and survival of a large series of ALS patients of Italian and Sardinian ancestry.

2. Methods

2.1. Cases

ALS cases were collected through the Italian ALS Genetic (ITALSGEN) and the Sardinian ALS Genetic (SARDINIALS) consortia (Chiò et al., 2012 and Chiò et al., 2014). Cases were patients with definite, probable, probable-laboratory supported, and possible ALS diagnosed between 2006 and 2012. A total of 149 cases have been already reported (Restagno et al., 2007). All cases were also screened for most common ALS genes, that is, C9ORF72, SOD1, TARDBP, and FUS.

2.2. Controls

There were 1302 Italian and 121 Sardinian subjects without neurologic disorders, age- and gender-matched to cases. Of these, 162 Italian subjects have been previously reported (Restagno et al., 2007).

2.3. Genotyping

Cases and controls were genotyped using the Illumina NeuroX SNP array. The NeuroX platform consists of standard Illumina exome content of approximately 240,000 variants and over 24,000 custom content variants focusing on neurologic diseases (Nalls et al., 2015). Quality control parameters for genotype calling and filtering are as previously described (Nalls et al., 2015). Genotypes for rs1799945 (chr6:26091179, C > G, build 37) were extracted from the larger NeuroX dataset. SNP genotypes were not confirmed on another platform such as Sanger sequencing. However, the quality of genotyping has been assessed using Polar and Cartesian cluster plots for SNP rs1799945; the quality control metric of genotyping accuracy for this SNP was 0.835, indicating a high level of precision in assigning genotypes to samples (Supplementary Fig. 1).

2.4. Statistical methods

Comparisons between means were made with the Student's t-test or analysis of variance; comparison between categorical variables was made with the $\chi 2$ test; Levene's test was used to confirm the equality of variances. Survival was calculated from onset to death/tracheostomy or censoring date (October 31, 2014) using the Kaplan-Meier survival modeling, and differences in survival were measured by the log-rank test. No patients were lost to follow up. Multivariable analysis was performed with the Cox proportional hazards model (stepwise backward) with a retention criterion of $p < 0.1$. The significance level was set at $p < 0.05$. Data were processed using SPSS statistical package, version 22.0 (IBM Corporation, Chicago, IL, USA).

2.5. Ethical approval

The study has been approved by the ethical committees of the involved centers. All patients and controls signed a written informed consent. Databases were treated according to the Italian regulations for privacy.

3. Results

A total of 1119 Italian and 232 Sardinian ALS patients have been included in the study. Patients' clinical characteristics and genetic mutations are reported in Table 1.

3.1. HFE genotyping

The frequency of CC, GC, and GG genotypes in Italian and Sardinian ALS cases and controls is reported in Table 2. No significant differences were found in either population. Genotype frequencies are respected Hardy-Weinberg equilibrium in both cohorts (not shown).

3.2. Clinical characteristics of patients with different genotypes

Patients with CC, GC, and GG genotypes did not differ by age at onset and site of onset (Table 3 and Table 4). No difference of survival was found considering both the CC/GC/GG phenotypes and the presence of a G allele in either cohorts of patients (Fig. 1 and Fig. 2). This finding has been confirmed in Cox multivariable analysis.

We also assessed the possible effect of HFE phenotypes in patients carrying genetic mutations. A list of identified genetic mutations is reported in Supplementary Table 1. No difference was found in the groups of patients carrying C9ORF72, FUS, and TARDBP mutations. In the 26 patients with SOD1 mutations, we found an increased survival in patients with GC or GG compared with CC genotypes or in patients carrying the G allele (dominant assumption) ($p = 0.04$; Fig. 3). This finding is confirmed by the multivariable Cox model, where the G is retained as an independent prognostic factor ($p = 0.03$). A list of all SOD1 mutated cases with clinical details and HFE status is reported in Table 5.

4. Discussion

In 2 cohorts of Italian and Sardinian patients, we have found that the p.H63D polymorphism of the HFE gene does not represent a risk factor for ALS. Moreover, we showed that the presence of the G allele does not modify the overall patients' clinical phenotype and survival. However, patients with SOD1 mutations carrying the G allele had a better survival than other patients. In subjects with C9ORF72, TARDBP, and FUS mutations, the p.H63D polymorphism did not modify the phenotype and survival.

Several articles have suggested that the p.H63D polymorphism of HFE represents a risk factor for ALS (Goodall et al., 2005, Restagno et al., 2007 and Sutedja et al., 2007), but others did not confirm this finding; 2 meta-analyses of literature arrived at opposite conclusions (Li et al., 2014 and van Rheenen et al., 2013). This discrepancy may arise from several reasons: first, some articles are based on small, underpowered series; second, in some studies controls are not matched by ethnic origin to cases. A meta-analysis of worldwide HFE genotypes showed that the frequency of G polymorphism ranges from 30% in southern Europe, 20% in northern Europe, 15% in the Indian subcontinent, 5% in China, and 5% in sub-Saharan Africa (Hanson et al., 2001). Interestingly, the minor allele frequency observed for rs1799945 among the Italian samples analyzed in the present study (723 G alleles of 4842 alleles; minor allele frequency = 0.149) is comparable to its frequency reported in the ExAC browser (9128 G alleles of 66,738 alleles; minor allele frequency = 0.137; http://exac.broadinstitute.org/variant/6-26091179-C-G, accessed June 6, 2015).

In our 2 large cohorts of patients of Italian and Sardinian ancestry, compared with regionally matched controls, we have found that the p.H63D polymorphism of HFE does not increase the risk of developing ALS.

Recently, an article on a small series of ALS patients reported a significantly increased survival of subjects carrying the G allele compared with those who were homozygous for the C allele of the HFE gene (Su et al., 2013). The authors also found that the presence of the G

allele was associated with a reduction of SOD1 activity in the muscle and that SOD1 protein expression was negatively associated with total disease duration in ALS patients. In a subsequent article, the same group reported that a double transgenic mouse line (SOD1/H67D) carrying the H67D HFE (homolog of human H63D) and SOD1 (G93A) mutations have a shorter survival and an accelerated disease progression (Nandar et al., 2014); they therefore concluded that when HFE is combined with a mutation in an ALS gene the disease duration could be negatively impacted. The authors suggested that H63D HFE polymorphism can modify ALS pathophysiology via pathways involving oxidative stress, gliosis, and disruption of cellular functions.

Previously, the relationship between survival and HFE polymorphisms had been assessed only in a French series of ALS patients with negative results (Praline et al., 2012). However, in this article, no distinction between patients carrying or not-carrying SOD1 mutations was made.

In our series, we found that in both populations the presence of a G allele or GG/GC phenotypes did not influence overall patients' survival. We also looked at the patients carrying mutations of major ALS genes. No effect of HFE status was found in patients with C9ORF72, TARDBP, and FUS mutations. Conversely, in patients with SOD1 mutations the presence of a G allele was found to be significantly associated with a longer survival. This finding is in contrast with the reported shorter survival in the double transgenic mouse line (SOD1/H67D) (Nandar et al., 2014), highlighting the possibility that genetic interactions in mice compared with humans are biologically different. However, because of the small number of patients carrying a SOD1 mutation in this series, our finding should be considered with caution, because of the possibility of a type 1 error.

In conclusion, we found that in 2 large cohorts of Italian and Sardinian patients, HFE p.H63D polymorphism is not a risk factor for ALS and does not modify the phenotype and survival of patients with ALS. However, we found a possible interaction between the presence of a SOD1 genetic mutation and HFE genotype, with better survival in subjects carrying the G allele. Although based on a small cohort of patients, this interaction warrants further studies to better understand the genetic mechanisms underlying ALS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Adriano Chiò had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We thank the patient and her family for having collaborated to this study.

Funding/Support. This work was supported in part by the Intramural Research Programs of the US National Institutes of Health (NIH) and National Institute on Aging (Z01-AG000949-02). The work was also supported by the Packard Centre for ALS Research at Johns Hopkins, Fondazione Vialli e Mauro Onlus, Compagnia di San Paolo, European Community's Health Seventh Framework Programme (FP7/2007–2013) under grant agreement #259867, the Joint Programme–Neurodegenerative Disease Research (Sophia Project, granted by the Italian Health Ministry, and Strength Project, granted by the Italian Ministry of University and Research), the Agenzia Italian per la Ricerca sulla SLA (ARISLA, SARDINIALS grant), the Fondazione Mario e Anna Magnetto, and the Associazione Piemontese per l'Assistenza alla Sclerosi Laterale Amiotrofica (APASLA).

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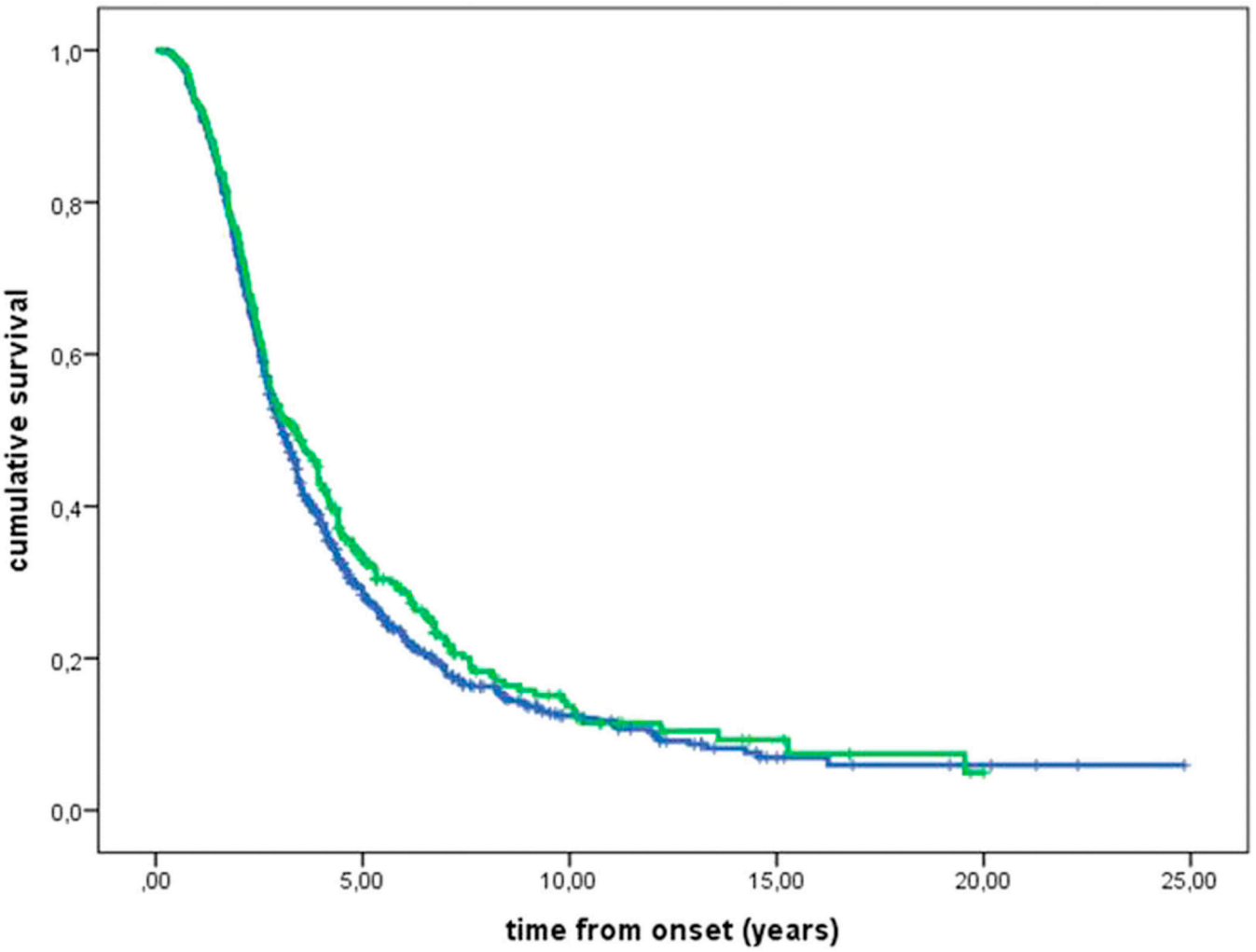

Fig. 1. Italian patients

Survival curves by HFE genotype. CC, median survival time 3.0 years (interquartile range 1.9–5.5); GC/GG, median survival time 3.4 years (interquartile range 2.0–6.7). p = n.s. CC, blue; GC/GG green.

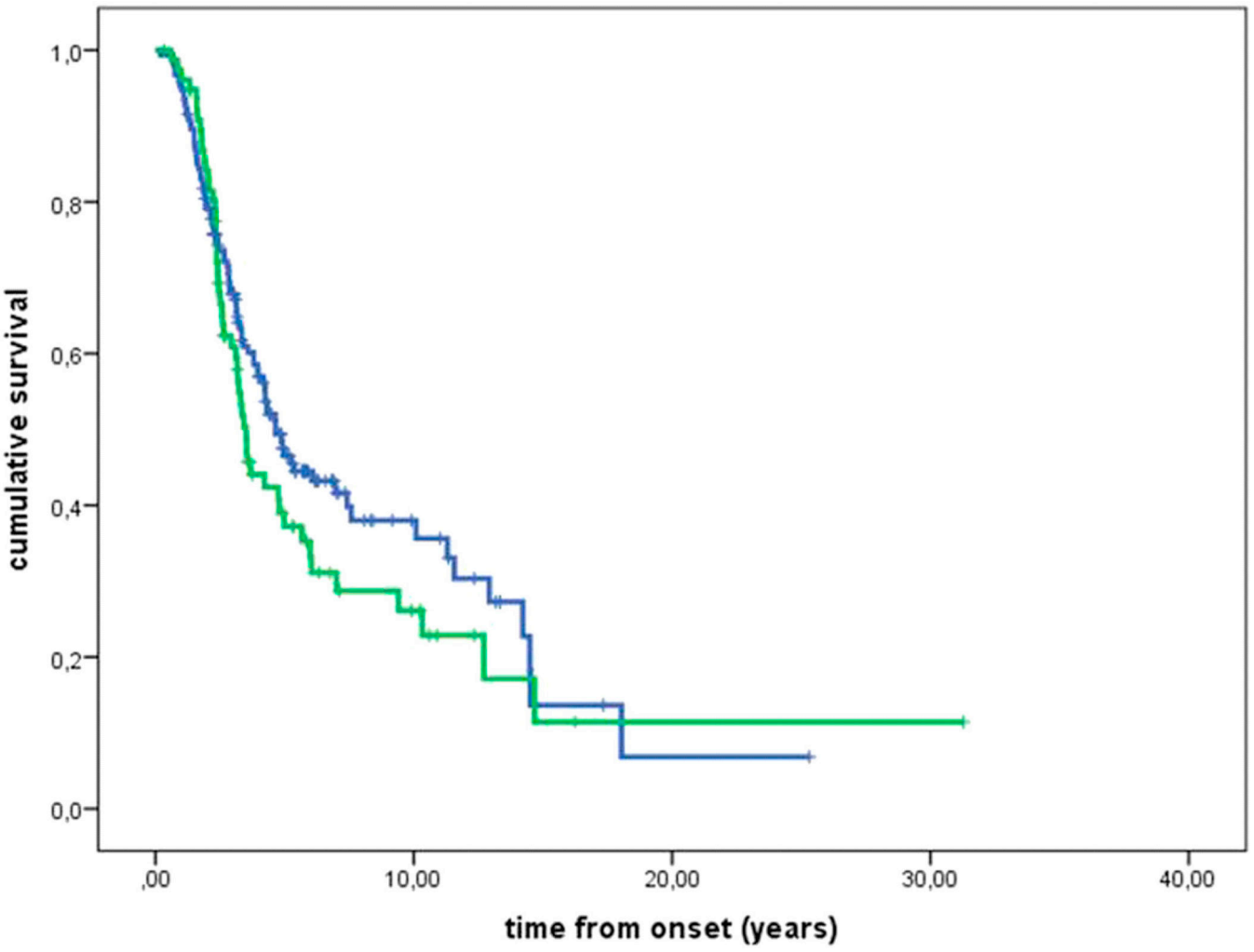

Fig. 2. Sardinian patients

Survival curves by HFE genotype. CC, median survival time 4.7 years (interquartile range 2.4–14.2); GC/GG, median survival time 3.5 years (interquartile range 2.3–10.3). p = n.s. CC, blue; GC/GG green.

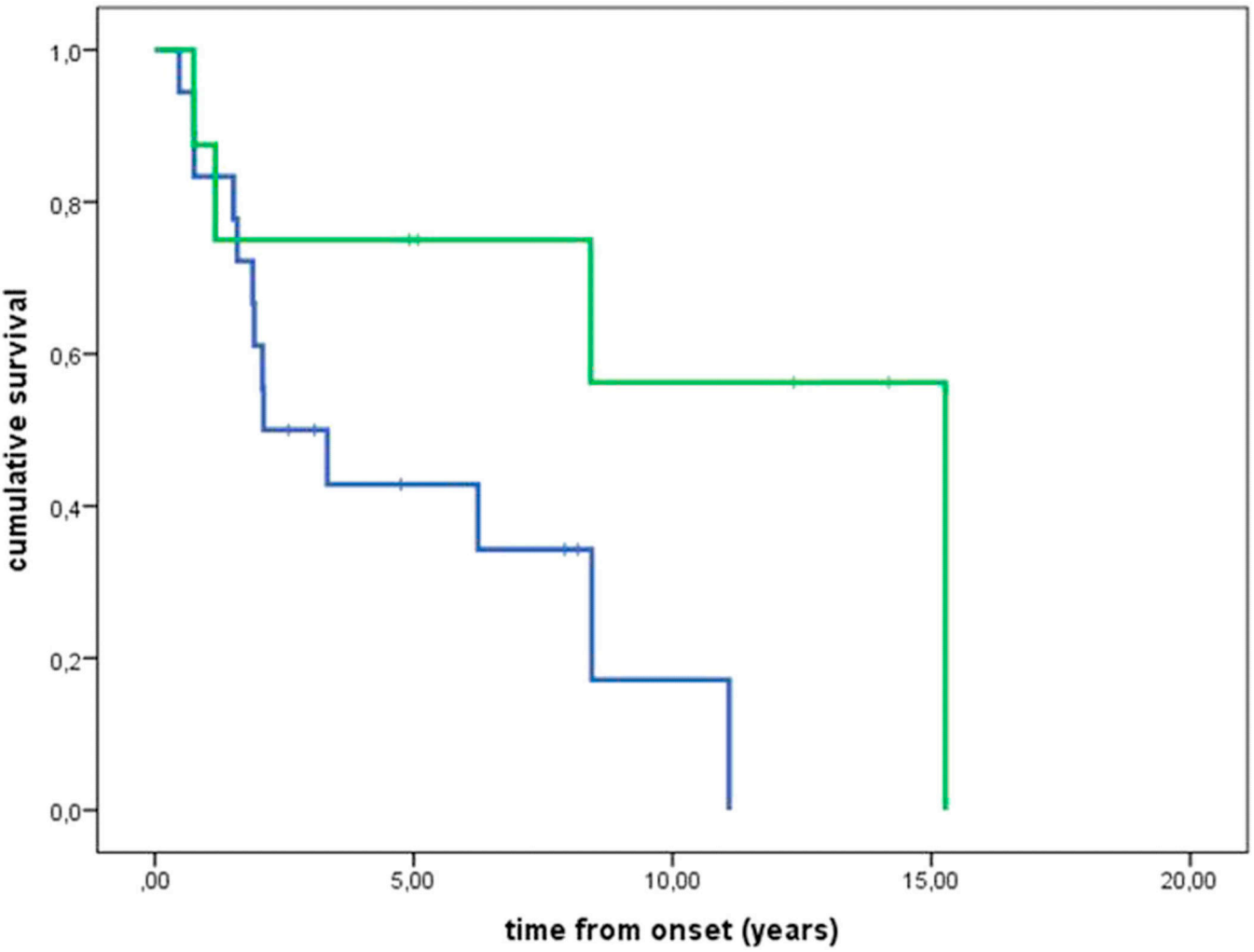

Fig. 3. Italian patients carrying SOD1 mutations

CC, median survival time 2.1 years (interquartile range 2.6–8.4); GC/GG, median survival time 15.3 years (interquartile range 1.2–15.3). p = 0.04. CC, blue; GC/GG green.

Table 1

Clinical characteristics of Italian and Sardinian ALS cases

	Italian ALS, *n* = 1119	**Sardinian ALS, *n* = 232**
Gender (female, %)	494 (44.1%)	92 (39.7%)
Mean age at onset (years)	62.2 (11.7)	60.5 (12.1)
Site of onset (Bulbar, %)	299 (26.7%)	48 (20.7%)
Genetic mutations		
Wild Type	1021 (91.2%)	139 (59.9%)
C9ORF72	50 (4.5%)	23 (9.9%)
SOD1	24 (2.1%)	2 (0.9%)
TARDBP	10 (0.9%)	68 (29.3%)
FUS	14 (1.3%)	0

Key: ALS, amyotrophic lateral sclerosis.

Table 2

Frequency of rs1799945 in Italian and Sardinian ALS patients and controls

Genotype	CC	GC	GG	Minor allele frequency	Total
Italians					
Cases	804 (71.8%)	293 (26.2%)	22 (2.0%)	0.151	1119
Controls	948 (72.8%)	322 (24.7%)	32 (2.5%)	0.148	1302
Sardinians					
Cases	154 (66.4%)	70 (30.2%)	8 (3.4%)	0.185	232
Controls	79 (65.3%)	38 (31.4%)	4 (3.3%)	0.190	121

Key: ALS, amyotrophic lateral sclerosis.

Table 3

Mean age at onset according to *HFE* H63D genotype

	CC	**GC**	**GG**	***p* Value**
Mean age at onset				
Italians	62.3 (11.2)	62.2 (11.7)	62.5 (11.2)	0.92
Sardinians	60.2 (12.8)	60.6 (10.5)	65.4 (10.3)	0.78

Table 4

Site of symptom onset according to *HFE H63D* genotype

Site of symptom onset	CC	GC	GG	*p* Value
Italians				
Bulbar	216	78	5	0.91
Spinal	588	215	17	
Sardinians				
Bulbar	31	15	2	0.93
Spinal	123	55	6	

Table 5

Clinical characteristics and HFE status in patients with SOD1 mutation

Code	Sardinian	*SOD1* mutation	Age at onset	Type of onset	Gender	HFE alleles	Alive/dead	Duration (years)
P02007-295	N	A4V	82.74	S	F	CC	D	2.10
SLA2011-362	N	G93D	60.02	S	M	CC	D	0.75
SLA2012-313	N	S134N	73.47	S	F	CC	D	2.08
FALS-SI24	N	G41S	52.03	S	M	CC	D	0.76
SLA2010-240	N	G93D	45.00	S	F	CC	D	6.24
SLA2008-201	N	D101G	50.21	S	F	CC	D	1.92
SLA2010-292	N	L38V	46.74	S	F	CC	D	0.47
512-SN	N	N19S	28.14	S	F	CC	D	11.09
SLA2009-24	N	E132del	53.20	S	M	CC	D	8.44
SLA2010-495	N	D90A heterozygous	85.52	B	F	CC	D	1.52
SLA2009-217	Y	A4T	45.68	S	M	CC	D	3.33
SLA2009-28	N	G93D	57.95	S	F	CC	D	1.89
2543-SE	N	N19S	77.70	S	F	CC	D	1.59
SLA2010-489	N	D109Y	56.68	S	F	CC	A	7.92
SLA2011-455	N	N19S	57.04	S	F	CC	A	3.09
SLA2009-107	N	I150T	45.38	S	F	CC	A	8.17
SLA2013-60	N	G93D	18.00	S	F	CC	A	2.58

Code	Sardinian	*SOD1* mutation	Age at onset	Type of onset	Gender	HFE alleles	Alive/dead	Duration (years)
SLA2009-02	N	L144F	44.63	S	F	CC	A	4.75
SLA2008-187	N	D11Y	56.25	S	F	GC	D	8.42
SLA2008-37	N	D90A heterozygous	44.20	S	M	GC	D	15.27
SLA2010-146	N	D90N	70.70	S	F	GC	D	0.75
SLA2011-30	N	A4V	70.67	S	F	GC	D	1.17
SLA2012-141	N	D11Y	40.31	S	M	GC	A	14.18
SLA2009-178	Y	A95G	69.18	S	M	GC	A	12.34
SLA2011-197	N	D109Y	57.51	S	F	GC	A	5.09
SLA2009-299	N	L84F	27.97	S	M	GG	A	4.92

Sardinian: N, no; Y, yes; type of onset: S, spinal; B, bulbar; gender: F, female, M, male; alive/dead: A, alive, D, dead.