

# Clinical and Metabolic Signature of *UNC13A* rs12608932 Variant in Amyotrophic Lateral Sclerosis

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## Abstract

### Background and Objectives

To characterize the clinical and cognitive behavioral phenotype and brain <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose-PET (<sup>18</sup>F-FDG-PET) metabolism of patients with amyotrophic lateral sclerosis (ALS) carrying the rs12608932 variant of the *UNC13A* gene.

### Methods

The study population included 1,409 patients with ALS without *C9orf72*, *SOD1*, *TARDBP*, and *FUS* mutations identified through a prospective epidemiologic ALS register. Control participants included 1,012 geographically matched, age-matched, and sex-matched participants. Clinical and cognitive differences between patients carrying the C/C rs12608932 genotype and those carrying the A/A + A/C genotype were assessed. A subset of patients underwent <sup>18</sup>F-FDG-PET.

### Results

The C/C genotype was associated with an increased risk of ALS (odds ratio: 1.54, 95% confidence interval 1.18–2.01,  $p = 0.001$ ). Patients with the C/C genotype were older, had more frequent bulbar onset, and manifested a higher rate of weight loss. In addition, they showed significantly reduced performance in the letter fluency test, fluency domain of Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and story-based empathy task (reflecting social cognition). Patients with the C/C genotype had a shorter survival (median survival time, C/C 2.25 years, interquartile range [IQR] 1.33–3.92; A/A + C/C: 2.90 years, IQR 1.74–5.41;  $p = 0.0001$ ). In Cox multivariable analysis, C/C genotype resulted to be an independent prognostic factor. Finally, patients with a C/C genotype had a specific pattern of hypometabolism on brain <sup>18</sup>F-FDG-PET extending to frontal and precentral areas of the right hemisphere.

### Discussion

C/C rs12608932 genotype of *UNC13A* is associated with a specific motor and cognitive/behavioral phenotype, which reflects on <sup>18</sup>F-FDG-PET findings. Our observations highlight the importance of adding the rs12608932 variant in *UNC13A* to the ALS genetic panel to refine the individual prognostic prediction and reduce heterogeneity in clinical trials.

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## Glossary

**ALS** = amyotrophic lateral sclerosis; **ALSFRS-R** = amyotrophic lateral sclerosis functional rating scale – revised; **BIC** = Bayesian Information Criteria; **BMI** = body mass index; **CE** = cryptic exon; **CI** = confidence interval; **DR** = differed recall; **ECAS** = Edinburgh Cognitive and Behavioural ALS Screen; **FAS** = Letter Fluency test; **<sup>18</sup>F-FDG-PET** = <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose-PET; **FrSBe** = Frontal Systems Behavior Scale; **FTD** = frontotemporal dementia; **FVC** = forced vital capacity; **FWE** = family-wise error; **HCS** = healthy controls; **IQR** = interquartile range; **IR** = immediate recall; **MiToS** = Milano-Torino Staging; **OR** = odds ratio; **SET** = Story-Based Empathy Task; **SNP** = single-nucleotide polymorphism; **EA** = emotion attribution; **ToM** = theory of mind.

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of the CNS, characterized by the progressive involvement of several neuronal systems, namely the lower and upper motor neurons and neurons of the frontotemporal cortices. Approximately 10% of people with ALS have a familial history of ALS or frontotemporal dementia (FTD),<sup>1</sup> while the disease appears to be sporadic in the remaining participants. Moreover, at least 25% of patients with ALS carry a genetic mutation, which is the likely cause of the disease.<sup>2</sup>

ALS is a clinically heterogeneous disease with diverse clinical presentations and outcomes.<sup>1</sup> The modifiers of the ALS phenotype are only partially known; they include age, sex, and genetics<sup>3</sup> and likely environmental and lifestyle factors, such as exercise and elevated low density lipoproteins cholesterol.<sup>4,6</sup> The common variant rs12608932, located within an intron of *UNC13A* gene on chromosome 19p13.3, may influence susceptibility to disease and survival among patients with ALS<sup>7-9</sup> and may modulate response to pharmacologic treatment.<sup>10</sup>

While the biological mechanisms underlying the rs12608932 variant effect remain unclear, the phenotypic and MRI characteristics of patients carrying this variant have been recently reported in a cohort of patients with ALS of Dutch ancestry.<sup>11</sup> In this study, we used a large population-based cohort of Italian patients to characterize the clinical and behavioral/cognitive phenotype of patients with ALS carrying the rs12608932 variant of the *UNC13A* gene. We also assessed their metabolic correlates using brain <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose-PET (<sup>18</sup>F-FDG-PET).

## Methods

The rs12608932 variant of the *UNC13* gene was assessed in 1,584 patients with ALS identified through the Piemonte and Valle d'Aosta Register for ALS, a prospective population-based register active in Northern Italy since 1995. The characteristics of the register have been reported elsewhere.<sup>12</sup> For this study, we included cases with ALS diagnosed between 2007 and 2018. We excluded 175 patients with *C9orf72* (92), *SOD1* (30), *TARDBP* (20), and *FUS* (12) mutations. Patients met the revised El Escorial diagnostic criteria for definite, probable, and probable laboratory-supported ALS.<sup>13</sup> A total of 265 cases have already been reported in a previous study.<sup>8</sup>

Amyotrophic lateral sclerosis functional rating scale - revised (ALSFRS-R) mean monthly decline ( $\Delta$ ALSFRS-R) was calculated using the following formula:  $(48 - \text{ALSFRS-R score at diagnosis}) / (\text{months from onset to diagnosis})$ .<sup>14</sup> Similarly, weight mean monthly decline ( $\Delta$ Weight) was calculated as  $(\text{Weight at diagnosis} - \text{healthy body weight}) / \text{months from onset to diagnosis}$ .

A total of 565 patients underwent an extensive cognitive battery administered within 2 months of their diagnosis, encompassing executive function, memory, visuospatial function, language, and social cognition domains.<sup>15</sup> The battery included the following neuropsychological tests: Letter Fluency Test (FAS); Category Fluency Test; Frontal Assessment Battery; Trail Making Test A, B, and B-A; Rey-Osterrieth Complex Figure Test: immediate recall (IR) and differed recall (DR); Rey Auditory Verbal Learning Test: IR and DR; Babcock Story Recall Test: IR and DR; Digit Span Forward and Backward; Raven Colored Progressive Matrices (47); Mini-Mental State Examination; and the Story-Based Empathy Task (SET). The raw scores of all tests were age-corrected, sex-corrected, and education-corrected using the recent Italian normative.<sup>16</sup> Patients were classified into 5 categories according to the revised ALS-FTD Consensus Criteria.<sup>17</sup>

Neurobehavioral dysfunction was determined with the Frontal Systems Behavior Scale (FrSBe), using the family form evaluated by a close relative/caregiver (scores: normal  $\leq 59$ , borderline 60–64; and pathologic  $\geq 65$ ). For this study, we considered the change in points for each of the 3 domains of FrSBe (apathy, disinhibition, and executive) between the premorbid and postillness scores. If patients had scores reflecting a frontal systems abnormality both in the premorbid and postillness forms, they were considered pathologic only if there was an increase of  $\geq 10$  points between the premorbid and the disease scores.<sup>16</sup> Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale. The test item “I feel slowed down” was discussed with patients to have them not refer to physical disability.<sup>18</sup>

## Controls

Control participants consisted of 1,012 geographically matched, age-matched, and sex-matched Italian participants, identified through patients' general practitioners. Of them, 129 were tested with the cognitive battery.

## Genetic Analysis

All patients included in the study were tested for *SOD1* (all exons), *TARDBP* (exon 6 only), *FUS* (exons 14 and 15), and the *C9orf72* repeat expansion using the method described elsewhere.<sup>19</sup>

The *UNC13A* rs12608932 variant was genotyped by whole-genome sequencing on an Illumina HiSeqX10 sequencer in 1,319 cases and 771 controls. The remaining 265 cases and 241 controls were genotyped on Infinium HumanHap550 bead chips (Illumina, Inc., San Diego, CA) as per the manufacturer's specification. Sequencing methods have been detailed elsewhere.<sup>2,8</sup> These data are publicly available on the dbGAP repository ([ncbi.nlm.nih.gov/gap](https://ncbi.nlm.nih.gov/gap); phs001963.v1.p1 and phs000101.v3.p1).

## PET Acquisition

Before brain <sup>18</sup>F-FDG-PET, patients fasted for at least 6 hours, and blood glucose was less than 7.2 mmol/L in all cases. After a 20-minute rest, approximately 185 MBq of <sup>18</sup>F-FDG was injected. Data acquisition started 60 minutes after the injection. PET/CT scans were performed on a Discovery ST-E System (General Electric). Brain CT (slice thickness of 3.75 mm, 140 kV, 60–80 mAs) and PET scan were sequentially acquired, and the former was used for the attenuation correction of PET data. The PET images were reconstructed with 4 iterations and 28 subsets with an initial voxel size of 2.34 × 2.34 × 2.00 mm, and data were collected in 128 × 128 matrices.

## PET Statistical Analysis

SPM12 implemented in Matlab R2018b (MathWorks, Natick, MA) was used for image spatial normalization to a customized brain <sup>18</sup>F-FDG-PET template.<sup>20</sup> Normalization with a subcortical reference region was not performed because all brain regions have been demonstrated to be potentially affected in ALS. Intensity normalization was performed using the 0.8 default Statistical Parametric Mapping value of gray matter threshold, and images were smoothed with a 10-mm filter and submitted to statistical analysis. Patients carrying the A/A or the A/C genotypes were merged and compared with the group with the C/C genotype, using the 2-sample *t* test model of SPM12. To achieve a better characterization of patients' brain metabolic state, we compared each patient group (AA + AC and CC) with 40 healthy controls. We considered eligible as controls participants referred to the PET Center for suspected lung cancer, but for whom oncologic diseases were excluded, and brain PET scan, medical history for neurologic disorders, and neurologic examination resulted negative. Because the sample size of the 2 patient groups was unbalanced (AA + AC = 277, CC = 40), for the comparison with controls, 40 of 277 participants were randomly selected from the AA + AC group and then submitted to the analysis. In the comparison of each patient group with healthy controls (HCs) age at PET and sex were used as covariates. The height threshold was set at  $p < 0.001$  ( $p < 0.05$  family-wise error (FWE)-corrected at cluster level).

Age at PET, sex, site of onset (spinal/bulbar), and King stage at PET were used as covariates to compare the 2 groups of patients, and the height threshold was set at  $p < 0.001$  ( $p < 0.05$  FWE-corrected at cluster level). Only clusters containing >125 contiguous voxels were considered significant. Brodmann areas were identified at a 0–2 mm range from the Talairach coordinates of the SPM output isocenters corrected by Talairach Client ([talairach.org/index.html](http://talairach.org/index.html)).

## Statistical Methods

*UNC13A* rs12608932 was tested for association with the risk of developing disease under the following genetic models: additive (A/A vs A/C vs C/C genotypes), dominant (A/A vs A/C + CC), and recessive (A/A + A/C vs C/C). A  $p$  value < 0.05 was considered statistically significant. The genetic model underlying the association of this variant with disease risk was assessed using the max-statistic, which selects the largest test statistic from the dominant, recessive, and additive models. In addition, we calculated the Bayesian information criteria (BIC) and performed a likelihood ratio test on the residual deviance to compare the goodness of fit of the 3 genetic models. These analyses were performed using R (version 4.0). The Mann-Whitney *U* test was used for comparisons of continuous variables. Survival was calculated with Kaplan-Meier curves and compared using the log-rank test, setting the onset date as day 0 and the date of death or tracheostomy as the primary end point. The last day of follow-up for censored cases was December 31, 2020. None of the patients were lost to follow-up. Multivariable analysis for survival was performed with the Cox proportional hazards model (stepwise backward) with a retention criterion of  $p < 0.1$ . A  $p$  value < 0.05 was considered significant. The following variables were included in the model: age (continuous), diagnostic delay (continuous), sex (male vs female), site of onset (bulbar vs spinal), King staging,  $\Delta$ ALSFRS-R (continuous),  $\Delta$ FVC (forced vital capacity)% (continuous), and  $\Delta$ Weight (continuous). The cognitive tests were analyzed using the Mann-Whitney *U* test on age-matched, sex-matched, and education-corrected scores. A  $p$  value < 0.05 (2-tailed) was considered significant. These analyses were conducted using the SPSS 26.0 statistical package (SPSS, Chicago, IL).

## Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethical Committees of the 2 regional ALS Expert Centers (Comitato Etico Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino, and Comitato Etico Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara). Patients and controls provided written informed consent before enrollment. The databases were anonymized according to Italian law for the protection of privacy.

## Data Availability

Data will be available on motivated request by interested researchers.

## Results

The study population included 1,409 patients ([780, 55.4%] males, median onset age at onset of 67.8, interquartile range [IQR] 59.8–73.9) and 1,012 controls ([521, 51.5%] males, median age of 65.0, IQR 57–72). The patient and control cohorts did not differ for the main demographic variables (eTables 1 and 2, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551)).

Of the 1,409 patients included in the study, 662 (47.0%) carried the A/A genotype, 563 (40.0%) the A/C genotype, and 184 (13.1%) the C/C genotype. Allele frequencies were 0.67 (A) and 0.33 (C). The corresponding frequencies among controls were 509 for the A/A genotype (50.3%), 413 for the A/C genotype (40.8%), and 90 for the C/C genotype (8.9%). Allele frequencies in controls were 0.71 (A) and 0.29 (C). Allele frequency was significantly different among cases and controls ( $p = 0.001$ ). Allele frequency did not deviate from the Hardy-Weinberg equilibrium among controls ( $p = 0.92$ ), while the slight deviation observed among cases ( $p = 0.051$ ) likely reflects the increased risk associated with the C allele.

Patients with the C/C genotype had an increased risk of ALS (odds ratio [OR] = 1.54, 95% confidence interval [CI] = 1.18–2.01,  $p = 0.001$ ). Similarly, the C allele also increased the risk (OR = 1.19, 95% CI = 1.05–1.35,  $p = 0.006$ ). *UNC13A* rs12608932 was associated with an increased risk of developing ALS in additive ( $p = 7.8 \times 10^{-6}$ ), dominant ( $p = 0.0071$ ), and

recessive ( $p = 3.8 \times 10^{-6}$ ) models. Post hoc analysis demonstrated that the increased disease risk was indeed most prominent among C/C carriers (OR 1.76, 97.5% CI 1.40–2.21,  $p = 1.5 \times 10^{-6}$ ) rather than A/C carriers (OR 1.10, 97.5% CI 0.95–1.26,  $p = 0.196$ ): in this regard, recessive inheritance was selected as the model that maximized test statistics of the genetic case-control study. Model comparison also revealed that the recessive model was the best fit based on a lower BIC and a significant reduction in residual deviance ( $p = 0.01562$ ) when confronted with the additive and dominant models. According to those results, we adopted the recessive model for further analyses.

## Clinical Features

Clinical and demographic characteristics of patients with A/A + A/C vs C/C genotypes are summarized in Table 1. Patients with the C/C genotype had a higher age at onset ( $p = 0.04$ ), higher rate of bulbar-onset disease ( $p = 0.001$ ), and a higher  $\Delta$ Weight ( $p = 0.003$ ) compared with those with the A/A + A/C phenotype. The  $\Delta$ ALSFRS-R was also higher in the C/C genotype but did not reach statistical significance. The demographics of the cohorts are summarized in eTable 3, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551).

Comorbid FTD was diagnosed in 43 (8.4%) patients with A/A + A/C genotypes compared with 9 (10.8%) patients with the C/C genotype ( $p = 0.30$ ). A comparison of cognitive test age-adjusted and education-adjusted scores in non-ALS-FTD ALS patients A/A + A/C genotypes and C/C genotype with

**Table 1** Clinical and Demographic Characteristics of ALS Patients With A/A + A/C vs C/C rs12608932 *UNC13A* Genotypes

	A/A + A/C n = 1,225	C/C n = 184	p Value
Age at onset (y, median, IQR)	67.7 (59.5–73.8)	69.4 (62.5–75.4)	0.02
Sex (female)	539 (44.0%)	90 (48.9%)	0.21
Site of onset (bulbar)	361 (29.5%)	77 (41.8%)	0.001
Bulbar symptoms at diagnosis	624 (50.9%)	124 (67.4%)	0.001
Diagnostic delay (mo, median, IQR)	9.0 (5.1–13.2)	7.9 (5.1–12.0)	0.14
Education (median, IQR)	8.0 (5.0–13.0)	8.0 (5.0–11.0)	0.18
ALSFRS-R at diagnosis (median, IQR)	42 (38–45)	42 (36–45)	0.35
FVC% at diagnosis <sup>a</sup> (median, IQR)	91 (71–104)	85 (68–101)	0.09
BMI at diagnosis <sup>b</sup> (median, IQR)	24.2 (22.0–26.8)	24.4 (22.0–26.8)	0.91
$\Delta$ ALSFRS-R (points/mo, median, IQR)	0.63 (0.30–1.24)	0.72 (0.35–1.52)	0.10
$\Delta$ Weight <sup>b</sup> (kg/mo, median, IQR)	0.25 (0.0–0.85)	0.37 (0.0–1.12)	0.004
ALS-FTD <sup>c</sup>	43 (8.4%)	9 (10.8%)	0.30
King stage (1/2/3/4A + 4B) at diagnosis	541/385/248/45	77/50/51/6	0.15
MiToS stage (0/1/2/3/4) at diagnosis	833/336/38/9/3	130/45/6/3/0	0.62

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = amyotrophic lateral sclerosis functional rating scale - revised; BMI = body mass index; FVC = forced vital capacity; IQR = interquartile range; MiToS = Milano-Torino Staging.

p values are calculated with  $\chi^2$  (discrete variables) or Mann-Whitney U test (continuous variables).

<sup>a</sup> Available for 1,314 cases (A/A + A/C, 1,141; C/C, 173).

<sup>b</sup> Available for 1,373 cases (A/A + A/C, 1,193; C/C, 180).

<sup>c</sup> Available for 592 cases (509 A/A + A/C and 83 C/C).

controls is listed in eTable 4, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551). Overall, ALS patients had worse scores in several tests, exploring frontal function than population-based controls. In addition, we found significantly lower scores in patients with the C/C genotype in the FAS ( $p = 0.01$ ), SET–Emotion Attribution (SET-EA) ( $p = 0.01$ ), and SET–Global Score ( $p = 0.04$ ), as well as in the Fluency domain of Edinburgh Cognitive and Behavioural ALS Screen (ECAS) ( $p = 0.014$ ) (Tables 2 and 3). By contrast, no differences were found in the frequency of neurobehavioral symptoms and anxiety and depression scores.

## Survival

Patients with the C/C genotype had a shorter survival than those with AA + AC genotypes (C/C: median survival time = 2.25 years, IQR = 1.33–3.92; A/A + C/C: survival = 2.90, IQR = 1.74–5.41;  $p = 0.0001$ ) (Figure 1). Furthermore, the C/C genotype remained an independent predictor of survival in Cox multivariable analysis (eTable 5, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551)).

## PET Findings

The AA + AC participants showed a relative hypometabolism when compared with HCs in the left temporal and occipital

**Table 2** Median Values (Interquartile Range) of Age-Corrected and Education-Corrected Scores of Cognitive Tests in ALS Patients With A/A + A/C vs C/C *UNC13A* rs12608932 Genotypes

Test	A/a + A/C (n = 467)	C/C (n = 74)	p Value
MMSE	27.9 (26.7–30.0) n = 466	27.7 (26.2–29.4) n = 73	0.17
FAS	29.5 (23.6–37.2) n = 456	26.7 (18.5–34.1) n = 72	0.01
CAT	19.8 (16.3–22.3) n = 456	19.6 (15.5–22.0) n = 72	0.58
FAB	15.3 (13.7–16.9) n = 401	14.9 (13.3–16.3) n = 64	0.13
Digit span FW	5.7 (5.1–6.3) n = 420	5.5 (4.9–6.5) n = 63	0.28
Digit span BW	4.0 (3.5–4.5) n = 420	4.0 (3.3–4.6) n = 63	0.74
TMT A	36 (24–53.25) n = 422	41 (29–60) n = 63	0.13
TMT B	68.5 (34.25–146) n = 422	70 (48–188) n = 63	0.09
TMT B-A	34 (8–81) n = 422	38 (13–135) n = 63	0.21
RAVL-IR	40.2 (34–46.3) n = 238	38.9 (30–45.3) n = 43	0.08
RAVL-DR	7.0 (4.0–9.0) n = 238	6.0 (3.0–9.0) n = 43	0.45
BSRT-IR	5.7 (4.5–6.9) n = 246	5.7 (4.7–7.4) n = 36	0.64
BRRT-DR	6.7 (5.2–7.8) n = 246	6.5 (5.5–8.0) n = 36	0.68
ROCF-IR	32.0 (28.8–34.5) n = 335	31.9 (27.4–34.3) n = 54	0.52
ROCF-DR	12.3 (8.3–16.7) n = 335	12.2 (6.9–16.8) n = 54	0.66
CPM47	29.1 (25.3–32.0) n = 449	28.7 (24.3–32.7) n = 65	0.69
Clock <sup>a</sup>	4 (3–5) n = 392	4 (3–5) n = 58	0.78
SET-IA	4.9 (3.3–6.0) n = 78	4.2 (3.1–5.7) n = 17	0.49
SET-CI	4.6 (3.4–5.3) n = 78	4.0 (2.9–5.1) n = 17	0.16
SET-EA	5.0 (3.4–6.0) n = 78	3.2 (2.2–5.1) n = 17	0.01
SET-GS	14.0 (10.3–16.2) n = 78	10.1 (8.9–14.7) n = 17	0.04
HADS-A	7 (5–10) n = 370	8 (5–10.5) n = 57	0.27
HADS-D	5 (3–8) n = 370	5 (3–9) n = 57	0.73

Fifty-one patients with FTD have been excluded.

Abbreviations: ALS = amyotrophic lateral sclerosis; BSRT-DR = babcock story recall test-delayed recall; BSRT-IR = babcock story recall test-immediate Recall; CAT = category fluency test; Clock = Clock Drawing Test; CPM47 = Raven Colored Progressive Matrices; Digit Span BW = digit span backward; Digit Span FW = digit span forward; FAB = frontal assessment battery; FAS = letter fluency test; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression; MMSE = Mini-Mental State Examination; RAVL-DR = rey auditory verbal learning test-delayed recall; RAVL-IR = rey auditory verbal learning test-immediate recall; ROCF-DR = babcock story recall test-delayed recall; ROCF-IR = babcock story recall test-immediate recall; SET-CI = Story-Based Empathy Task-Causal Inference; SET-EA = Story-Based Empathy Task-Emotion Attribution; SET-GS = Story-Based Empathy Task-Global Score; SET-IA = Story-Based Empathy Task-Intention Attribution; TMT A = Trail Making Test A; TMT B = Trail Making Test B; TMT B-A = Trail Making Test B-A.

*p* values are calculated with the Mann-Whitney *U* test.

<sup>a</sup>The scores of the Clock test are not corrected by age and education because no Italian normative data are available.

**Table 3** Median Values (Interquartile Range) of Age-Corrected and Education-Corrected Scores of ECAS in ALS Patients With A/A + A/C vs C/C *UNC13A* rs12608932 Genotypes

Domains	A/A + A/C (n = 194)	C/C (n = 29)	p Value
Language	26 (23-27)	25 (21.5-26.5)	0.17
Fluency	16 (13.5-18)	14 (9-16)	0.014
Executive	30 (23-37)	30 (22.5-35)	0.56
Memory	17 (14-19.5)	16 (13-19.5)	0.20
Visuospatial	12 (11-12)	11 (11-12)	0.24
ALS-specific functions	72 (60-80)	69 (52.5-77.5)	0.17
ALS nonspecific functions	29 (25-31)	27 (23.5-32)	0.40
ECAS total score	100 (86-112)	96 (76.5-110)	0.19

Abbreviations: ALS = amyotrophic lateral sclerosis; ECAS = Edinburgh Cognitive and Behavioural ALS Screen; FTD = frontotemporal dementia. Patients with FTD have been excluded. *p* values are calculated with the Mann-Whitney *U* test.

cortex (Figure 2A, eTable 6, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551)). In comparison with HCs, the C/C group showed extensive clusters of relative hypometabolism encompassing bilateral frontal and temporal cortices, left occipital cortex, left precuneus, right caudate head and putamen, and right parietal cortex (Figure 2B; eTable 6, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551)).

Compared with the A/A + A/C genotypes, patients with the C/C genotype showed a significant ( $p = 0.000001$ ) relative hypometabolism in the right frontal cortex (middle and inferior frontal gyri and precentral gyrus) (Figure 2, eTable 7, [links.lww.com/NXG/A551](https://links.lww.com/NXG/A551)). No clusters of relative hypermetabolism were observed (Figure 3).

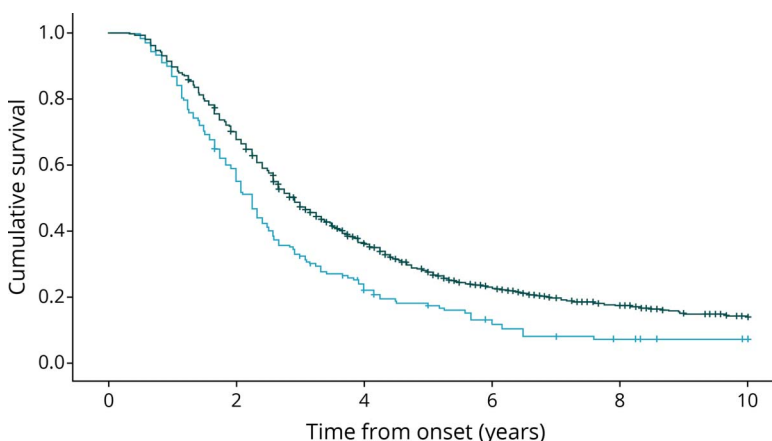
## Discussion

We have assessed a large population-based cohort of patients with ALS to identify the phenotypic characteristics of patients carrying the C/C genotype of the common variant

rs12608932 of the *UNC13A* gene. Based on a recessive model, patients carrying the C/C genotype were older, had more frequent bulbar-onset disease and manifested a higher rate of weight loss than those with the A/A + A/C genotype. We did not find an excess of patients with ALS-FTD in those carrying the C/C phenotype, but we observed a reduced performance in the FAS and the Fluency domain of ECAS and in social cognition (SET test). Patients with the C/C genotype had significantly shorter survival, and the presence of this genotype was independent of known outcome modifiers in Cox multivariable analysis. Finally, patients with the C/C genotype had a specific pattern of hypometabolism on brain  $^{18}$ F-FDG-PET extending to frontal and precentral areas of the right hemisphere.

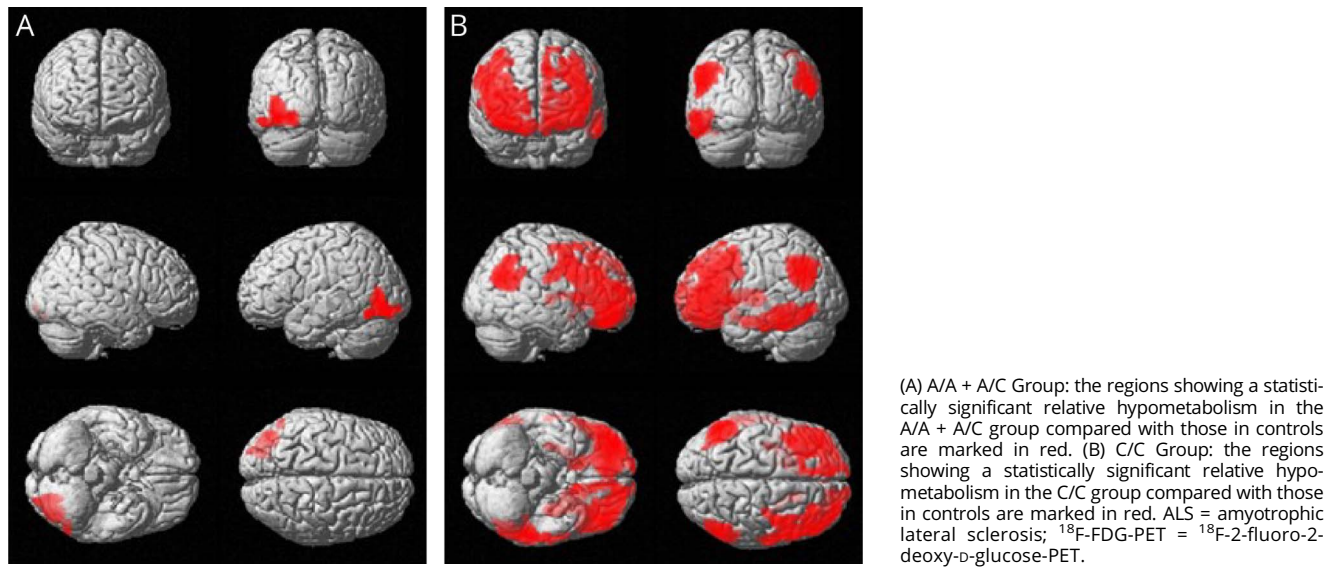
To date, the only study exploring the phenotype of *UNC13A* genotypes found that C/C carriers had an older age at symptom onset, displayed higher rates of bulbar-onset disease, had a higher incidence of ALS-FTD, and had a lower

**Figure 1** Survival From Onset According to a Recessive Model in Patients With ALS



Survival from onset according to a recessive model in patients with the C/C genotype (green line) vs A/A + A/C genotypes (blue line). Ticks indicate censored patients.  $p < 0.0001$ . ALS = amyotrophic lateral sclerosis.

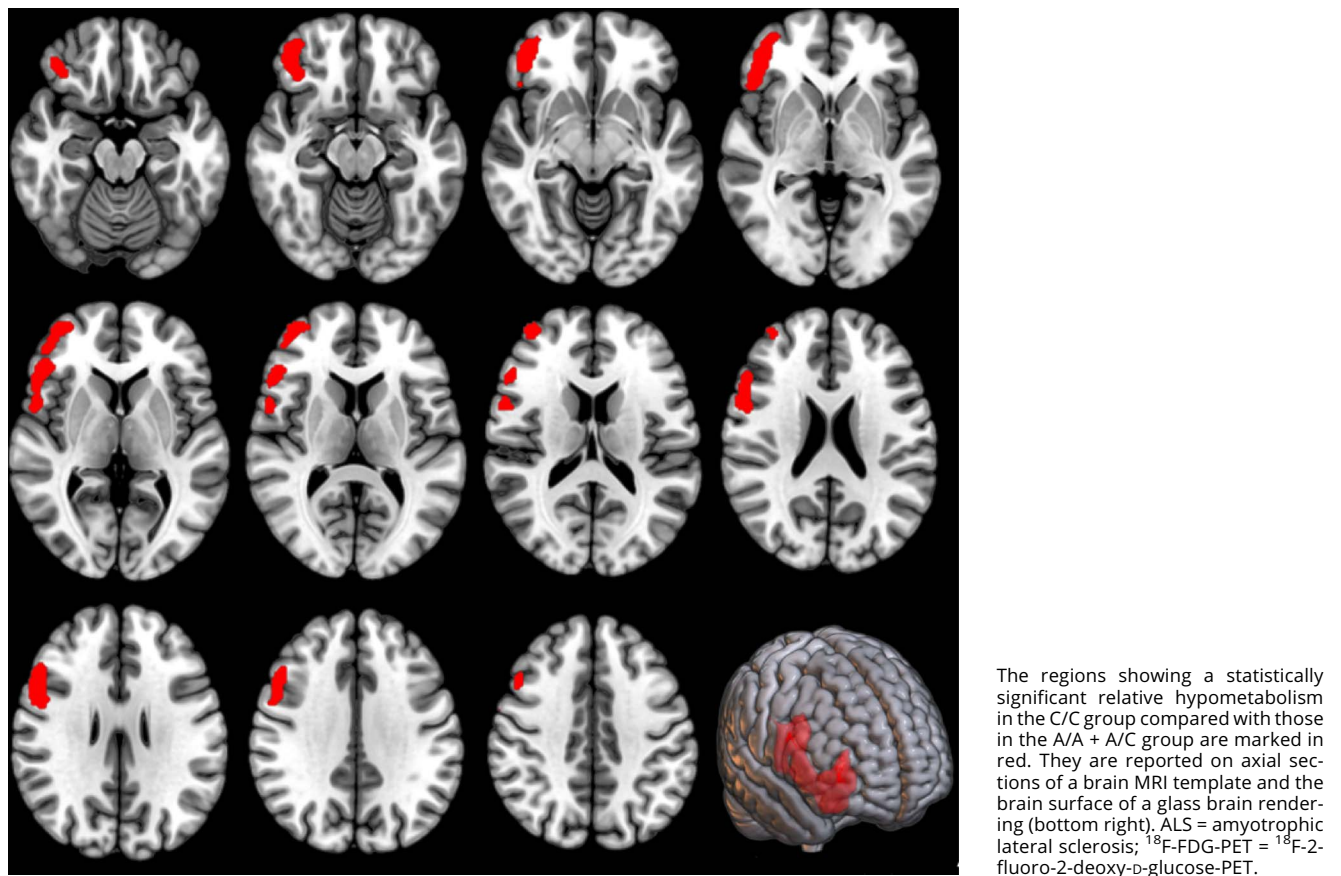
**Figure 2** 18FDG-PET Imaging of Cases With ALS vs Controls



forced vital capacity at diagnosis.<sup>11</sup> We did find that patients with C/C variant had lower FVC% values; however, in an exploratory analysis, we found that this difference

disappeared when stratifying FVC% according to the type of onset (bulbar onset, median values, C/C 79.5% (IQR 61–96), A/A + A/C 84% (IQR 62–100),  $p = 0.41$ ; spinal

**Figure 3** 18FDG-PET Imaging of *UNC13A* A/A+A/C vs C/C Group



onset, median values, C/C 96% (IQR 83–112), A/A + A/C 97% (IQR 81–108),  $p = 0.79$ ).

A relevant finding of our study is the higher rate of weight loss ( $\Delta$ Weight) in patients carrying the C/C variant, a difference that persisted when stratifying patients according to the presence of bulbar symptoms during diagnosis (bulbar symptoms present, C/C genotype 0.48 [IQR 0.10–1.21] kg/mo, A/A + A/C 0.43 [IQR 0–1.01] kg/mo,  $p = 0.04$ ; bulbar symptoms not present, median values, C/C 0.26 [IQR 0–0.85] kg/mo, A/A + A/C 0.07 [IQR 0–0.57] kg/mo,  $p = 0.01$ ). Therefore, more severe weight loss appears to be a specific feature of *UNC13A*, independent from the reduction of nutritional intake due to dysphagia, but likely related to other factors, such as increased energy expenditure (i.e., the so-called hypermetabolic state)<sup>21</sup> and central mechanisms (hypothalamic atrophy).<sup>22</sup>

In contrast with a previous study,<sup>11</sup> we did not observe a significantly higher incidence of ALS-FTD in the C/C genotype group. This difference is likely because we classified patients' cognitive impairment based on an extensive battery of cognitive/behavioral tests, as suggested by the revised ALS-FTD Consensus Criteria,<sup>17</sup> while another study<sup>11</sup> used only on ECAS. Of interest when moving to a single-test level, the C/C genotype group showed reduced performance in FAS and the Fluency domain of ECAS, i.e., 2 tests examining frontal functions. The only 2 other studies reporting cognitive tests showed impaired performance in C/C genotype patients in the language domain of ECAS<sup>11</sup> or in Digit Span backward test.<sup>23</sup>

Patients with ALS in our cohort have worse scores than controls in SET, a test exploring the theory of mind (ToM). Of interest patients with the C/C genotype had a significantly more severe impairment in this function than those with the A/A + A/C genotype, particularly the SET-EA subtest, indicating their reduced ability to attribute emotion to others in social situations.<sup>24</sup> Conversely, the 2 groups did not differ in cognitive ToM (SET-IA subtest). Concerning behavioral function in our cohort, patients with the C/C genotype showed a nonsignificant higher prevalence of disinhibition.

The negative influence of the *UNC13A* C/C genotype on ALS survival has been reported in populations with European and Chinese ancestry.<sup>7–9,25</sup> Three phenotypic characteristics of patients with the C/C phenotype observed in our cohort, i.e., older age, bulbar onset, and rate of weight loss, are well-known negative prognostic factors of ALS.<sup>26,27</sup> However, in our series, the C/C polymorphism remained an independent prognostic factor in Cox multivariable analysis, indicating that its effect on survival cannot be entirely explained by its phenotypic characteristics and is based on other still undisclosed mechanisms.

This study is the first to have assessed brain <sup>18</sup>F-FDG-PET in relation to *UNC13A* genotypes in ALS. We found that patients with the C/C genotype compared with those with A/A + A/C genotypes had a cluster of relative hypometabolism in a large area of the right frontal cortex, particularly the middle and inferior

frontal gyri and the precentral gyrus. Of interest a brain <sup>18</sup>F-FDG-PET study reported that in ALS, impairment in ToM was correlated to bilateral dorsomedial and dorsolateral prefrontal cortices hypometabolism.<sup>28</sup> In addition, in a previous PET study, the same areas were found to distinguish ALS patients with and without cognitive impairment, although bilaterally located,<sup>29</sup> indicating that selective cognitive impairment is a relevant feature of patients with ALS with the *UNC13A* C/C genotype. Studies assessing regional gray matter density with voxel-based morphometry and fMRI showed that affective ToM impairment was correlated to changes in right frontoinsula and anterior cingulate cortices.<sup>30,31</sup> Studies with MRI assessing cortical thickness in relation to *UNC13A* genotypes reported cortical thinning in bilateral frontal and temporal cortices in patients with the C/C genotype compared with those with the A/A + A/C genotype.<sup>11,22</sup> The difference between our PET findings and those related to MRI cortical thickness is probably due to the different characteristics of PET, which is a functional methodology, and MRI, which is mainly structural.

*UNC13A* protein has different functions, including regulating neurotransmitter and presynaptic vesicle release. However, it is unknown whether the intronic rs12608932 variant changes the function of the *UNC13A* protein or acts through different mechanisms or genetic variants that are in linkage disequilibrium with this single-nucleotide polymorphism (SNP). A recent study showed that TDP-43 depletion induces robust inclusion of a cryptic exon (CE) within *UNC13A*, resulting in nonsense-mediated decay and protein loss.<sup>32</sup> In particular, the rs12608932 risk allele modifies the binding of TDP-43 to the *UNC13A* pre-mRNA, probably making *UNC13A* CE more susceptible to even the partial TDP-43 loss, which occurs early in degenerating neurons.<sup>32</sup>

This study is not without limitations. Cognitive and behavioral function PET studies were not available for all cohort patients. However, the 2 subcohorts were similar to the whole cohort for all relevant clinical factors, and patients underwent cognitive testing and PET within 2 months of diagnosis, limiting the selection bias. Second, this study is based on a recessive genotype model. However, the recessive model both in our cohort and in literature has been consistently reported to be the best fit. The genotypic model through which *UNC13A* affects ALS will be determined only when we know its exact pathophysiologic mechanism. A notable feature of the study is its population-based nature, including some 80% of incident patients.

In conclusion, we have found that the C/C rs12608932 genotype of *UNC13A* is associated with a specific motor and cognitive/behavioral phenotype, which reflects on PET findings. We confirmed the polymorphism's effect on survival and added novel characteristics to its phenotype, such as the greater weight loss independent from bulbar involvement. We also extended its cognitive phenotype to encompass social cognition. Our observations highlight the importance of adding the *UNC13A* rs12608932 variant to the ALS genetic panel to refine the individual prognostic prediction and reduce heterogeneity in clinical trials.



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## Disclosure

B.J. Traynor holds the US, Canadian, and European patents on the clinical testing and therapeutic intervention for the hexanucleotide repeat expansion in C9orf72. A. Calvo has received a research grant from Cytokinetics. A. Canosa, C. Moglia, U. Manera, M. Grassano, R. Vasta, F. Palumbo, P. Cugno, S. Gallone, M. Brunetti, F. De Marchi, V. Arena, M. Pagani, L. Corrado, S. D'Alfonso, and L. Mazzini have no conflict of interest. A. Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, AC Immune, Biogen, Lilly, and Cytokinetics and has received a research grant from Biogen. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NG](https://www.neurology.org/NG).

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Continued

## Appendix (continued)

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## Clinical and Metabolic Signature of *UNC13A* rs12608932 Variant in Amyotrophic Lateral Sclerosis

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