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ORIGINAL ARTICLE

UNC13A variant rs12608932 is associated with increased risk of amyotrophic lateral sclerosis and reduced patient survival: a meta-analysis

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease associated with both genetic and environmental risk factors. Previous studies trying to find an association between ALS and *unc-13 homolog A* (*UNC13A*) gene variants have shown inconsistent results. This study aimed to conduct a meta-analysis of the association between the C allele of rs12608932, a single-nucleotide polymorphism located in an intron of *UNC13A*, and risk of ALS and patient survival.

Methods PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure, Wanfang, and SinoMed databases were systematically searched for genome-wide association studies or case-control studies published up to January 2019 on the association between this variant in *UNC13A* and risk and/or prognosis of ALS. Data from eligible studies were extracted and analyzed.

Results The pooled data (28,072 patients with sporadic ALS and 56,545 controls) showed that rs12608932(C) was associated with an increased risk of ALS (OR = 1.13, 95%CI 1.07–1.20). Subgroup analysis revealed that rs12608932(C) increased the risk of sporadic ALS in non-Asian individuals, including those from the USA and Europe (OR 1.17, 95%CI 1.10–1.25, $P < 0.000$), but not in Japanese or Chinese subjects (OR 1.01, 95%CI 0.92–1.10, $P = 0.85$). The available data demonstrated that the CC genotype decreased the survival time of patients with ALS (OR 1.33, 95%CI 1.19–1.49, $P < 0.001$).

Conclusion The present meta-analysis suggests that rs12608932(C) is associated with increased ALS susceptibility, especially in Caucasian and European subjects, and that the CC genotype of rs12608932 is associated with reduced ALS patient survival.

Keywords Amyotrophic lateral sclerosis · *UNC13A* · rs12608932 · Meta-analysis · Risk · Survival

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by muscle weakness and loss of control voluntary movement caused by degeneration of both the upper and lower motor neurons [1]. The progression of ALS is rapid and usually results in paralysis and death from respiratory failure [2]. The average survival time of patients with ALS ranges from 3 to 5 years [3]. The pathophysiology of the disease remains partially elusive, although it has been reported that genetic and environmental risk factors contribute to ALS development [3].

In some patients, the disease is considered an inherited disorder following a Mendelian pattern. Within populations of European descent, up to 20% of individuals with ALS have a family history of either ALS or frontotemporal dementia. Seventy percent of familial ALS cases are linked to mutations in four genes: *superoxide dismutase 1 (SOD1)*, *C9orf72*, *TAR DNA-binding protein 43 (TARDBP-43)*, and *FUS*. Based on population-based registers, genome-wide association studies (GWAS) of sporadic ALS suggested that several genetic variants are associated with an increased risk of ALS. These studies have shed light on the association of *DPP6*, *ITPR2*, *SUNC1*, *9p21.2*, and *UNC13A* genes with ALS [4]. Among these genetic risk factors, one locus in chromosome 9p21 is the only one successfully identified across all the studies. The rs12608932 variant in *UNC13A* gene was first identified as a risk single-nucleotide

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polymorphism (SNP) associated with ALS [4], and similar results were obtained in ALS patients from the Netherlands [5], Italy [6], USA, and Europe [7], but these results were not replicated in studies in France [8], UK [9], Japan [10], or China [10, 11]. Interestingly, another publication using an independent cohort and data from the original study found that a minor allele in rs12608932 was associated with a shorter survival of ALS patients [5]. Similar observations were made in ALS patients from Italy [6] but not Spain [12]. In view of the inconsistence of these studies, we conducted a meta-analysis to further verify whether rs12608932 was a risk factor for ALS and/or modify the survival of ALS patients.

Materials and methods

Literature search strategy

Pubmed, Embase, Web of Science, Wanfang, Chinese National Knowledge Infrastructure, and SinoMed databases were searched for eligible studies published up to January 2019. The following search terms were applied: "*UNC13A*," "*unc-13 homologue A gene*," "rs12608932," "Genome-wide association studies," and "amyotrophic lateral sclerosis.". No language restrictions were applied.

Study selection criteria

To be included in the meta-analysis, studies had to fulfill all the following criteria: (i) use a GWAS design or case-control study design to analyze patients with ALS (diagnosed according to the El Escorial criteria) [13] and healthy controls; (ii) evaluate the association between the rs12608932 variant and ALS risk and/or the association between rs12608932 and prognosis of ALS; and (iii) report the minor allele frequency (MAF) distributions for both cases and controls. If there were studies on overlapping cohorts, only the largest study was included. Studies were excluded if they did not report the MAF of rs12608932 or if it was impossible to calculate the MAF based on the data provided by the authors.

Data extraction

Two investigators (BY Yang and B Liu) independently searched the literature and extracted data. Disagreements were resolved by the corresponding author (XL Yang). The following data were extracted from the original article: surname of the first author, year of publication, ethnicity of the study cohort, sample size of ALS and control groups, allele frequencies in cases and controls, the odds ratio (OR), and 95% confidence intervals (CI) for survival.

Statistical analysis

We evaluated the association between ALS risk with the C allele of rs12608932 expressed as OR and 95% CI. Cochran's Q test and I^2 statistics were used to assess the heterogeneity among studies. If $I^2 < 25\%$, no heterogeneity among studies was considered; $25\% \le I^2 < 50\%$ indicated low heterogeneity; $50\% \le I^2 < 75\%$ indicated moderated heterogeneity; while $I^2 \ge 75\%$ indicated substantial heterogeneity [14]. A fixed-effect model was used to analyze pooled data classified as homogeneous or with low heterogeneity, and a random-effect model was applied to assess data classified as of moderate or substantial heterogeneity [15]. Egger's and Begg's tests were applied to evaluate the publication bias [15, 16]. Stata version 12.0 (StataCorp, College Station, TX, USA) was used to perform the analyses. A P value of less than 0.05 was considered the threshold for statistical significance in all the analyses.

Results

Literature search and study selection

A total of 49 potentially eligible articles were identified after database search and removal of duplicates. After eliminating 28 articles based on the title and abstract, the remaining 21 were read and the following publications were excluded: 2 review articles, 3 GWAS studies not providing detailed information on rs12608932 [17–19], 1 GWAS study conducted in China that did not detect rs12608932 and that deviated significantly from the Hardy-Weinberg equilibrium [20], 1 study not following a case-control design, and 4 publications not assessing the relationship between the rs12608932 variant and ALS risk or survival.

The remaining 10 publications included a total of 28,072 patients with sporadic ALS and 56,545 controls. These 10 studies included 12 cohorts and evaluated the possible association between the rs12608932 C variant and ALS risk in Europe [4], France [8], UK and other European countries [9], The Netherlands [5], Italy [6], USA and Europe [7, 21], Japan [10], and China [10, 11] (Fig. 1). Four studies including six cohorts examined the association between the rs12608932 variant and survival of patients with ALS [4–6, 12].

The rs12608932(C) variant and risk of sporadic ALS

Data from the nine GWAS and case-control studies were pooled to analyze the potential association between the rs12608932 variant and risk of sporadic ALS (Table 1). Frequencies of the C allele showed heterogeneity based on a chi-squared test ($\chi^2 = 42.79$; degrees of freedom, DF = 11;

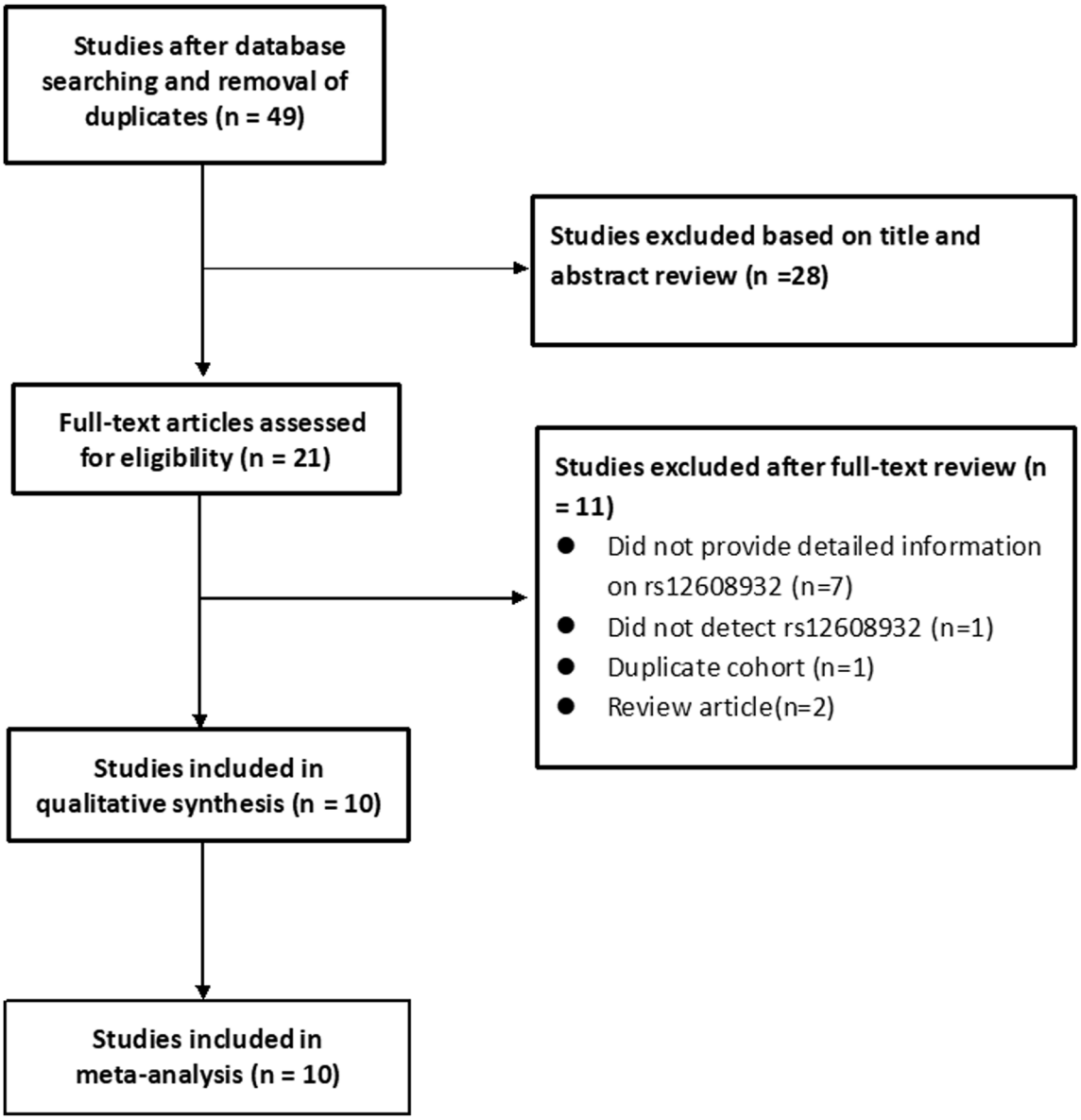

Fig. 1 Flow diagram for publication selection in the present meta-analysis. OR, odds ratio

$P < 0.001$) and the I^2 value (74.3.1%). Therefore, allele data were analyzed using a random-effects model.

The pooled OR for ALS risk in the presence of the C allele relative to the A allele was 1.13 (95%CI 1.07–1.20; Fig. 2), and the Z test for overall effect was 4.26 ($P < 0.000$). Sensitivity analysis indicated that none of the studies significantly affected the results in an independent fashion (Figs. 3 and 4). The funnel plot was visually symmetrical indicating that there was no significant publication bias (Fig. 3). Neither Egger's test ($P = 0.945$) nor Begg's test ($P = 0.598$) showed significant risk of publication bias.

Geographical differences were also evaluated between rs12608932(C) and risk of sporadic ALS. Our analyses revealed that the C allele of rs12608932 increased the risk of sporadic ALS in non-Asian subjects, including those from the USA and Europe (OR 1.17, 95%CI 1.10–1.25, $P < 0.000$), while a significant association was not found in Japanese or Chinese (OR 1.01, 95%CI 0.92–1.10, $P = 0.85$) (Fig. 2).

The rs12608932(C) variant and survival of ALS patients

Data were pooled from six cohorts in four studies (Table 2), and a fixed-effect model was applied because the data were homogeneous ($I^2 = 0$, DF = 4, $P = 0.587$). Pooled hazard ratio (HR) for survival of ALS patients with the CC genotype relative to those without this genotype was 1.33 (95%CI 1.19–1.49, $P < 0.001$; Fig. 5). The funnel plot was visually symmetrical, indicating that there was no significant publication bias

Table 1 Characteristics of the studies included in the present meta-analysis of the association between the rs12608932(C) variant and risk of amyotrophic lateral sclerosis

Study	Year	Country	ALS (*n*)	C (*n*)	ALS (MAF, *n* (%))	(MAF, *n* (%))	Genotyping method
van Es [4]	2009	Europe (genome-wide phase)	2323	9013	1858/4646 (0.4)	6129/18026 (0.34)	GWAS
		Europe (replication phase)	2532	5940	1874/5064 (0.37)	4039/11880 (0.34)	GWAS
Daoud [8]	2010	France	285	285	196/570 (0.344)	193/570 (0.339)	TaqMan SNP genotyping assay
Shatunov [9]	2010	UK	599	4144	438/1198 (0.366)	1074/3033 (0.354)	SNP seq
Iida [10]	2011	Japan	1179	1645	1759/2358 (0.746)	2438/3290 (0.741)	Multiplex PCR, direct sequencing
		China	684	830	932/1368 (0.681)	1120/1660 (0.675)	
Diekstra [5]	2012	The Netherlands	412	481	338/824 (0.41)	346/962 (0.36)	Capillary sequencing
Chiò [6]	2013	Italy	500	1457	325/1000 (32.5)	832/2914 (28.6)	SNP seq
Ahmeti [7]	2013	USA and Europe	4243	5112	3224/8486 (0.38)	3476/10224 (0.34)	iPLEX assay
Chen [11]	2014	China	397	287	505/794 (0.636)	378/574 (0.6585)	iPLEX assay
Vidal-Taboada [12]	2015	Spain	136	487	102/272 (0.375)	280/974 (0.287)	SNP seq
Rheenen [21]	2016	USA and Europe	14,791	26,864	10,737/29582 (0.363)	18,605/53728 (0.346)	GWAS

ALS, amyotrophic lateral sclerosis; *GWAS*, genome-wide association study; *iPLEX assay*, increased Plexing Efficiency and Flexibility for MassARRAY; *MAF*, minor allele frequency; *SNP*, single-nucleotide polymorphism

(Fig. 6). Neither Egger's test ($P = 0.110$) nor Begg's test ($P = 0.452$) showed significant risk of publication bias.

Discussion

Results from the present meta-analysis revealed that rs12608932(C) variant in *UNC13A* gene was significantly associated with a higher risk of developing ALS in Caucasian and European subjects, but not in Japanese or Chinese cohorts. Besides, the present data support *UNC13A* as a modifier of prognosis among sporadic ALS.

These results are in line with previous evidence suggesting that *UNC13A* may play a role in the pathophysiology of ALS. *UNC13A* is a member of a large family of presynaptic brain proteins. *UNC13A* protein regulates not only presynaptic vesicle priming but also glutamate release at neuromuscular synapses. In vitro experiments using glutamatergic hippocampal neurons from mice lacking the *UNC13A* gene showed arrested synaptic vesicle maturation and disrupted glutamatergic transmission [22]. A dysfunction in glutamate metabolism has been hypothesized to play a key role in the pathophysiology of ALS and, in fact, the only drug currently approved for ALS treatment, riluzole, is a glutamate release inhibitor [23]. Experiments with *Caenorhabditis elegans* suggest that *UNC13A* contributes to motor neuron degeneration through interaction with TARDBP-43 [24], which has been proposed as a pathological biomarker of ALS [1].

Our subgroup analysis indicated that rs12608932(C) influences the risk of sporadic ALS in Caucasian and European populations (OR 1.19, 95%CI 1.13–1.26, $P < 0.001$), but not in Japanese or Chinese subjects. These results are consistent with numerous individual studies in the literature. One reason for this ethnic bias may be the fact that the Japanese and Chinese subjects had relatively small samples, increasing risk of non-generalizable results. Another reason may be ethnic differences: as evidence from the public database among Caucasian and European healthy study subjects in our meta-analysis, even among the seven studies based on Caucasian and European subjects, studies from France and UK did not detect an association between the (C) variant and risk of ALS. We therefore hypothesize that the rs12608932(C) variant may be a susceptibility SNP for ALS in some specific populations. In fact, a role for ethnic-specific gene variants has been described in other neurodegenerative diseases. For example, several SNPs in the microtubule-associated protein tau (MAPT) locus have been strongly associated with increased risk of Parkinson's disease in the European population, while a recent GWAS study conducted in multiple Asian nations failed to identify any association [25]. The SNP rs10139154 in the gene encoding Sec1 family domain containing 1 (SCFD1) protein was identified as a risk SNP for ALS in European

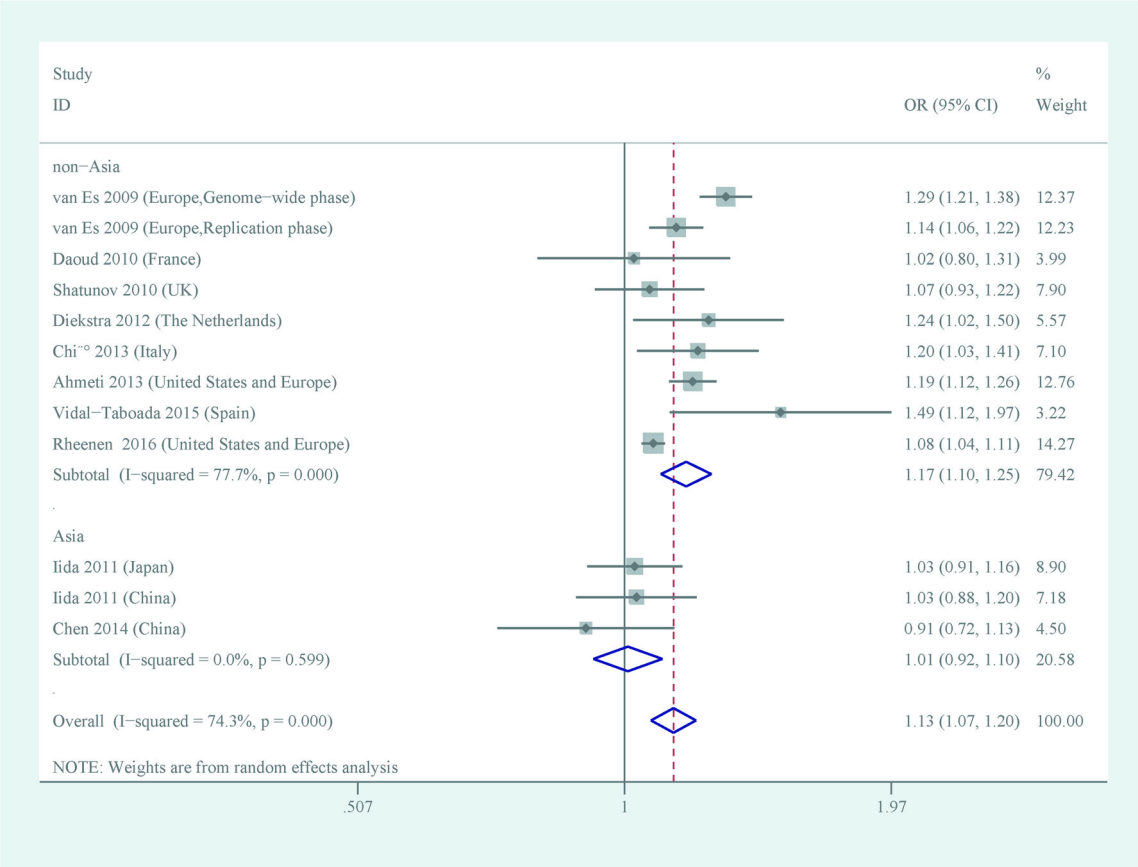

Fig. 2 Forest plot of the association between the rs12608932 variant and amyotrophic lateral sclerosis susceptibility (C vs. A allele)

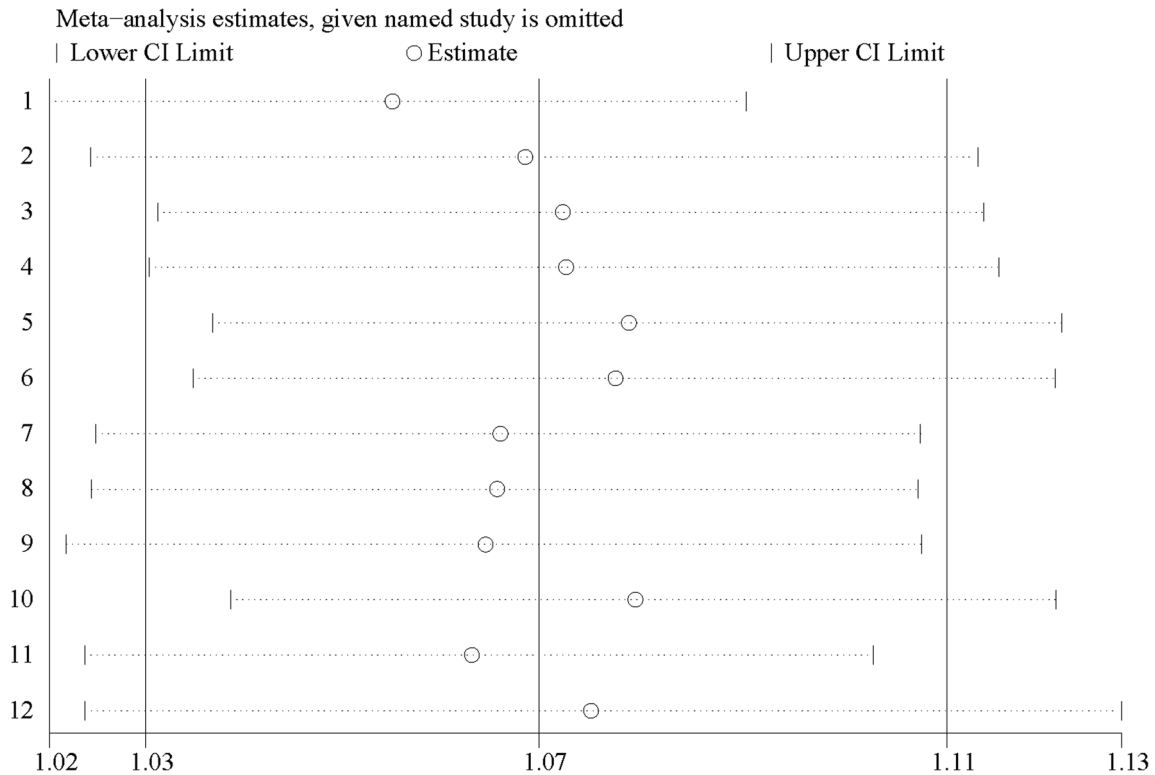

Fig. 3 Sensitivity analysis of the studies in the association between the rs12608932 variant and amyotrophic lateral sclerosis susceptibility (C vs. A allele).

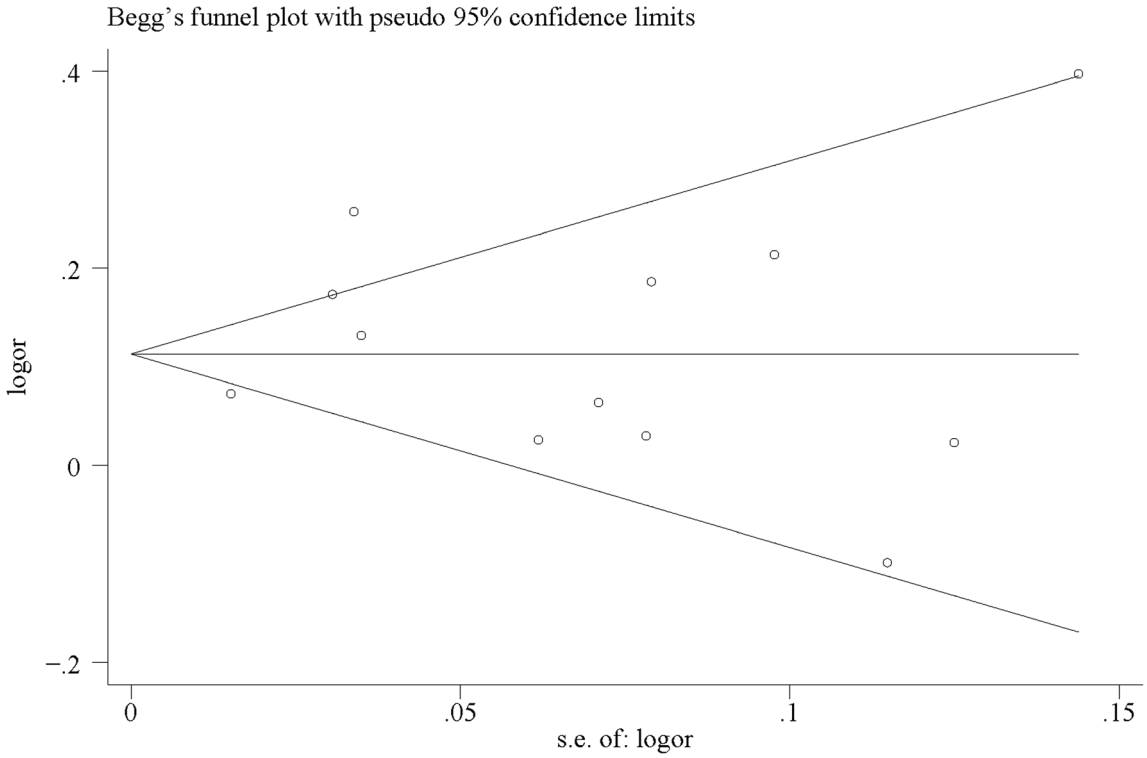

Fig. 4 Funnel plot of the association between the rs12608932 variant and sporadic amyotrophic lateral sclerosis susceptibility (C vs. A allele)

populations [17] but not in a large cohort of Chinese patients [26]. ALS is a complex disease involving genetic and environmental risk factors and, therefore, it is extremely difficult to find risk SNPs common to different regions or ethnicities.

Although the mechanisms by which UNC13A influences survival remain unclear, the present study found that the CC genotype of rs12608932 significantly decreased the survival time of ALS patients. In the past 20 years, significant efforts have been directed at exploring the factors determining ALS patient survival. Survival is longer in patients who are younger or in whom symptom onset begins in the limbs, as well as in individuals who are diagnosed longer after symptom onset [27]. In addition, missense mutations in the FUS gene and pathogenic repeat expansions of C9ORF72 gene have been shown to adversely influence survival. Previous research conducted by our group indicated that Chinese ALS patients carrying the AA genotype of rs9268856 have shorter survival [28]. However, larger independent studies are still necessary to establish a definitive role for UNC13A in ALS survival.

Table 2 Characteristics of the studies included in the present meta-analysis of the association between the rs12608932 (CC genotype) variant and survival of amyotrophic lateral sclerosis patients

Study	Year	Country	ALS cases (*n*)	OR	ll	ul
van Es	2009	Netherlands	1011	1.18	0.97	1.44
van Es	2009	Belgium	298	1.22	0.89	1.67
van Es	2009	Sweden	458	1.46	1.00	2.12
Diekstra	2012	Netherlands	412	1.62	1.16	2.26
Chiò	2013	Italy	500	1.40	1.05	1.87
Vidal-Taboada	2015	Spain	136	1.44	1.10	1.87

ALS, amyotrophic lateral sclerosis; *OR*, odds ratio

While our meta-analysis offers the largest pooled comprehensive evaluation of the rs12608932(C) variant and ALS risk and survival, some limitations should be taken into consideration. Firstly, although we searched six international and Chinese databases, and Egger's and Begg's tests suggested no significant risk of such publication bias; this risk is always present. Although this meta-analysis included 28,072 patients with sporadic ALS and 56,545 controls from multiple ethnicities, potential heterogeneity may still be present, even if a random-effect model was applied. Therefore, our results should be interpreted with caution. In addition, there were only four studies involving six cohorts that assessed the relationship between rs12608932 and prognosis of ALS. These studies were performed only in Caucasian and European populations; whether rs12608932 confers survival in other ethnicities requires further verification.

In conclusion, our results suggest that the C allele of rs12608932 is associated with ALS susceptibility, especially in Caucasian and European populations. Furthermore, the CC genotype was confirmed as a modifier of ALS patient survival.

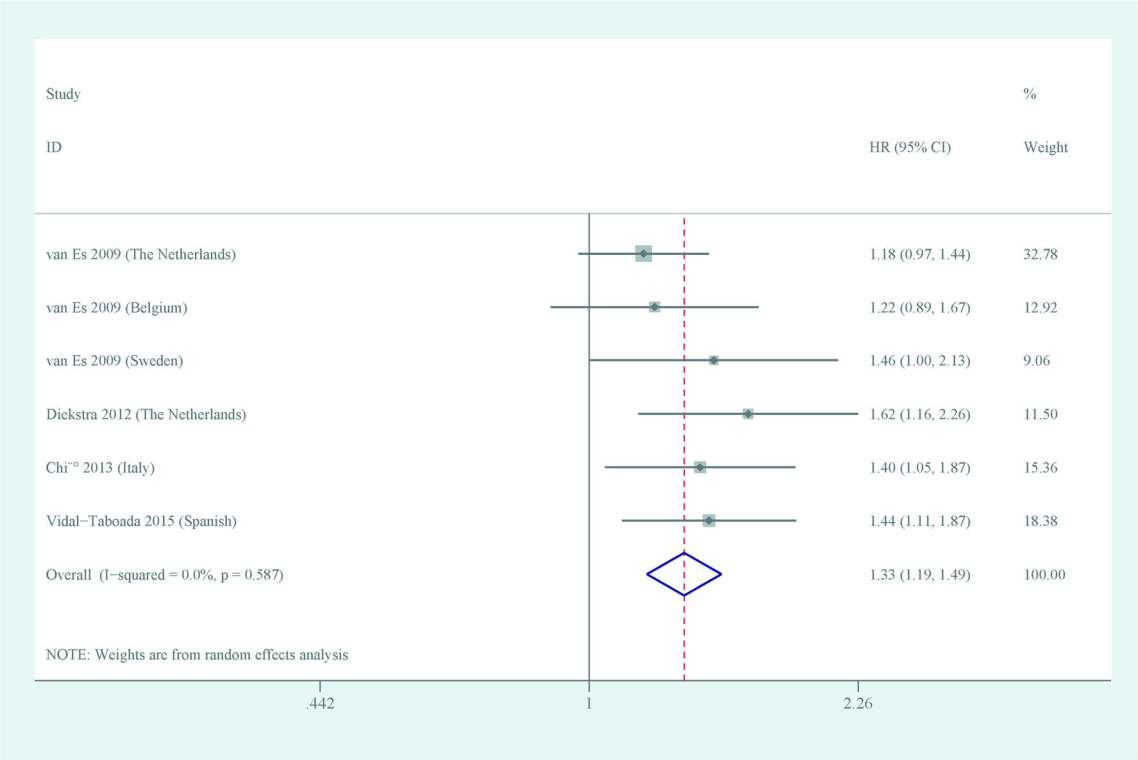

Fig. 5 Funnel plot of the studies in the association between the rs12608932 (CC genotype) variant and survival of amyotrophic lateral sclerosis patients

However, further well-designed, larger studies involving more ethnicities are needed to validate these results. Similarly, functional studies addressing the pathogenic mechanisms linking *UNC13A* and ALS are required. Ultimately, the UNC13A pathophysiological pathway may be identified as a potential therapeutic target that could help prolong the survival of ALS patients.

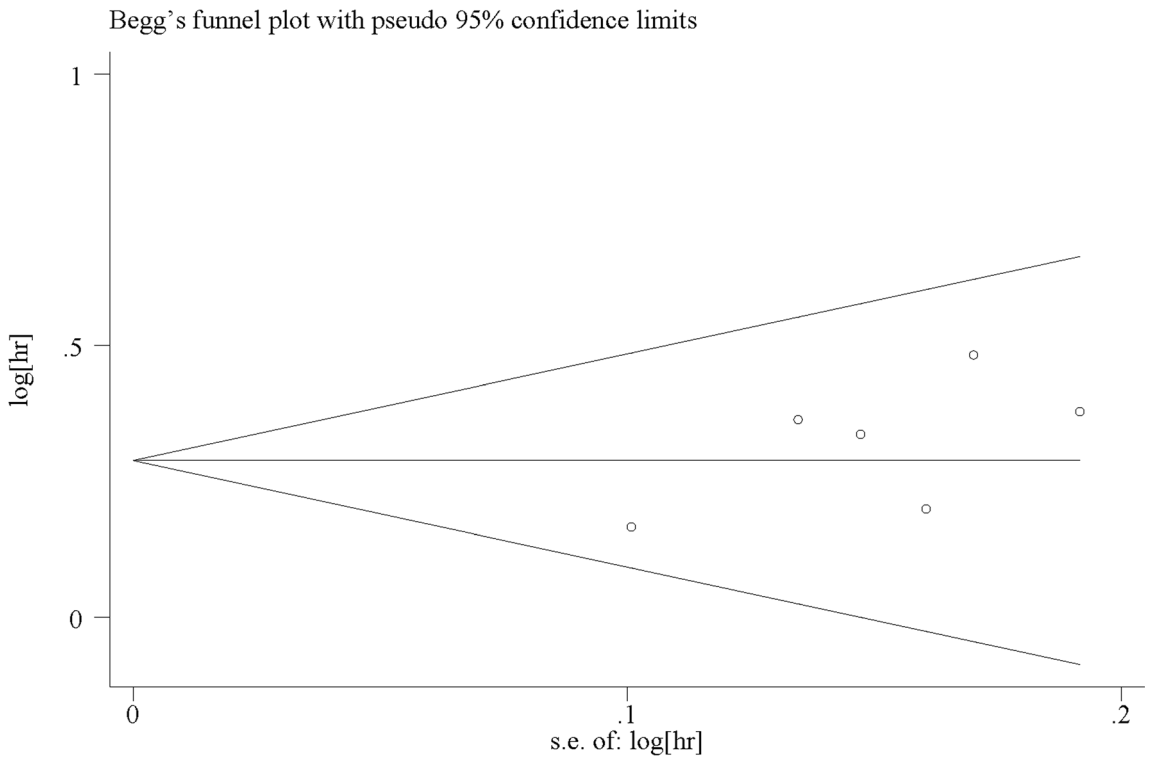

Fig. 6 Funnel plot of the association between the rs12608932 (CC genotype) variant and survival of amyotrophic lateral sclerosis

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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