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ORIGINAL ARTICLE

Meta-analysis of the association between *CHCHD10* Pro34Ser variant and the risk of amyotrophic lateral sclerosis

Baiyuan Yang[1] · Chenghui Yang[2] · Junwei Ren[3] · Chengqing Zhong[1] · Keting Liu[1] · Liusha Zhao[1] · Li Li[1] · Han Wang[1] · Mingling Zhu[1] · Zhenfang Lin[4]

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Abstract

Background Amyotrophic lateral sclerosis (ALS), one of the motor neuron diseases, appears to be caused by genetic and environmental risk factors. However, the influence of Pro34Ser variant of *CHCHD10* gene in increasing risk of ALS remains indeterminate. This study conducted a meta-analysis to establish the association between Pro34Ser variant of *CHCHD10* gene and risk of ALS.

Methods PubMed, Web of Science, and Embase databases were systematically searched for genome-wide association studies or case–control studies published up to March 28, 2020, on the association between Pro34Ser variant and risk of ALS. Data from eligible studies were extracted and analyzed.

Results Twelve case–control studies involving 7442 patients with sporadic ALS and 75,371 controls were analyzed. The Pro34Ser variant was not associated with increased risk of ALS disease based on fixed-effects meta-analysis (Pro34Ser-positive vs Pro34Ser-negative: OR 1.23, 95% CI 0.90 to 1.69, $P = 0.201$).

Conclusion Existing evidence suggests that Pro34Ser variant in *CHCHD10* is not associated with risk of ALS, particularly in Caucasian participants. However, our results ought to be validated using large, well-designed studies, especially in Asian and African populations.

Keywords Amyotrophic lateral sclerosis · *CHCHD10* · Pro34Ser · Variant · Meta-analysis

Introduction

Amyotrophic lateral sclerosis (ALS) is an idiopathic, fatal neurodegenerative disease of the human motor system [1]. Clinically, ALS is characterized by the presence of upper and lower motor neuron features involving brainstem and multiple spinal cord regions of innervation [1]. Progression of ALS is rapid, and most patients die within 3–5 years after

Baiyuan Yang, Chenghui Yang and Junwei Ren contributed equally to this work.

Heading
1. This manuscript provides what we believe to be the first report of the association between *CHCHD10* Pro34Ser variant and risk of amyotrophic lateral sclerosis.
2. This manuscript demonstrated that Pro34Ser variant in *CHCHD10* is not associated with risk of ALS, particularly in Caucasian participants.

✉ Zhenfang Lin
1326581972@qq.com

[1] Department of Neurology, Chengdu Seventh People's Hospital, 1188 Shuangxing Avenue, Shuangliu District, Chengdu 610213, Sichuan Province, China

[2] Department of Psychosomatic Medicine, Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital, 32# West. Section 2, 1st RingRoad, Chengdu 610072, Sichuan Province, China

[3] Department of Neurology, Fuling Central Hospital of Chongqing City, No.2, Gaosuntang Road, Fuling District, Chongqing 408000, China

[4] Department of Neurology, Affiliated Sichuan Provincial Rehabilitation Hospital of Chengdu University of TCM, 81, Ba Yi Road, Wenjiang, Chengdu 611135, Sichuan Province, China

onset of symptoms due to respiratory failure [2]. Pathogenesis of ALS has not been fully understood, although it has been reported that genetics and environmental risk factors contribute to its development [3].

Approximately 5–10% of ALS cases are familial, with a Mendelian pattern of inheritance, whereas the remaining 90% of ALS cases are sporadic [1]. Familial ALS has been associated with several gene mutations including *superoxide dismutase 1 (SOD1)*, *C9orf72*, *TARDNA-binding protein 43 (TARDBP-43)*, and *FUS* [4]. Seven novel genes, *MATR3*, *CHCHD10*, *TBK1*, *TUBA4A*, *NEK1*, *C21orf2*, and *CCNF*, which are associated with sporadic and familial ALS, have been identified based on population-based registers, genome-wide association studies (GWAS), whole genome studies, and exome sequencing technologies since 2014 [5]. *CHCHD10* is a 14-kDa nuclear-encoded, mitochondrial protein localized to the mitochondrial intermembrane space [6]. This protein is important for maintenance of mitochondrial dynamics and cellular bioenergetics [6]. *CHCHD10* was first linked to ALS after a study of a large French family, which identified a single heterozygous missense mutation p.S59L in exon 2 of *CHCHD10* [7]. *CHCHD10* was sequenced in 94 patients, and results revealed the presence of a novel heterozygous missense variant Pro34Ser in 2 unrelated frontotemporal dementia (FTD)-ALS individuals [8]. Consequently, there have been increasing studies to investigate Pro34Ser in other populations with ALS such as Italy [9], UK [10], and the Netherlands [11]. However, these results have not been consistent. We therefore conducted a meta-analysis to further evaluate whether *CHCHD10* Pro34Ser variant is a risk factor of ALS because of the inconsistencies in previous studies.

Materials and methods

Literature search and strategy

We searched PubMed, Web of Science, and Embase databases for studies on potential association between *CHCHD10* Pro34Ser variant and risk of ALS. The following search terms were used: "Amyotrophic lateral sclerosis" or "ALS" and "Pro34Ser" or "*CHCHD10*." No language restrictions were imposed. Our final search date was March 28, 2020.

Selection and exclusion criteria

Eligible studies had to meet the following criteria: (a) use of a case–control study design or a GWAS design to analyze patients with ALS and healthy controls, (b) evaluation of the association between Pro34Ser variant and ALS risk, and (c) report on frequency of a minor allele distribution for both cases and controls or other data necessary for estimating odds radio (OR) at 95% confidence interval (CI). Only large studies were included for studies with overlapping cohorts. Studies that did not report on the frequency of minor allele in Pro34Ser and studies in which it was impossible to calculate minor allele frequency based on data provided by the authors were excluded.

Data extraction

Two authors (BY Yang, CH Yang) independently assessed studies for inclusion or exclusion, and discrepancies were resolved by holding discussions with a third reviewer (ZF Lin). The following data were extracted from each study: name of the first author, publication year, ethnicity of the study cohort, sample size of ALS and control groups, allele distribution in case and controls, OR, and 95% CI.

Statistical analysis

Potential association between *CHCHD10* Pro34Ser variant and ALS risk was assessed using Stata 14.0 (StataCorp, College Station, TX, USA). Strength of the association was estimated using OR and 95% CI. OR was assessed using the allele model (Pro34Ser-positive vs Pro34Ser-negative). A P value equal to or less than 0.05 was considered to be statistically significant for all analyses. Cochran's Q test and I^2 statistic were used to assess heterogeneity among studies. Heterogeneity of studies was not considered if I^2 was $< 25\%$, low heterogeneity was indicated by $25\% \leq I^2 < 50\%$, moderate heterogeneity was indicated by $50\% \leq I^2 < 75\%$, and $I^2 \geq 75\%$ indicated substantial heterogeneity [12]. We applied fixed-effects model to perform meta-analysis of pooled data considered to be homogeneous or of low heterogeneity, and random-effects model to perform meta-analysis of data considered to be of moderate or substantial heterogeneity [13]. Begg's test was applied to evaluate publication bias [14].

Results

Literature search and included studies

A total of 65 potentially eligible articles were identified after searching PubMed, Web of Science, and Embase databases, and removing duplicates. We eliminated 49 articles based on titles and abstracts and read the remaining 16 articles excluding the following publications: 1 study which did not include ALS population [15], 2 studies which had no control population to compare with ALS patients [16, 17], 2 studies which did not have new data for letter response [18, 19], and 1 study which did not report minor allele frequency within a population of ALS, and it could not be derived from provided data [20].

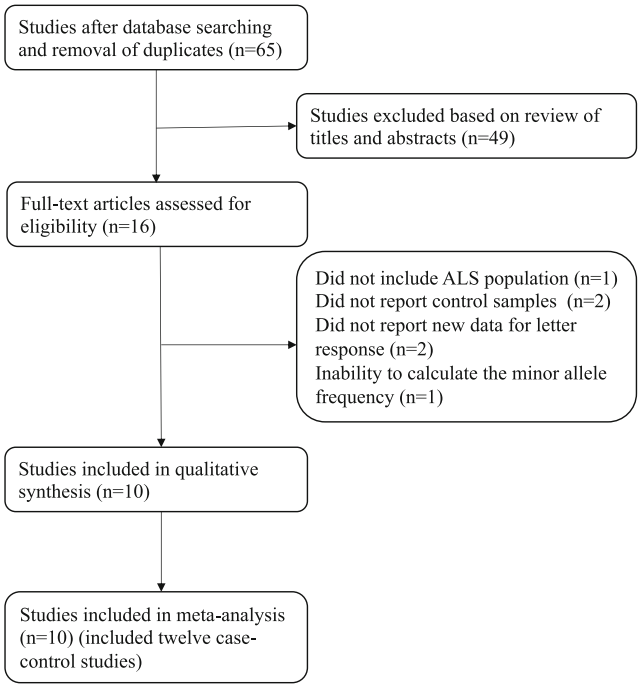

Fig. 1 Flowchart of study selection

The remaining 10 publications had a total of 7442 patients with sporadic ALS and 75,371 as controls. The 10 studies included 12 cohorts, which evaluated possible association between Pro34Ser variant and ALS risk (Fig. 1).

Characteristics of included studies

Tables 1 and 2 summarize key characteristics of studies included in the meta-analysis. Studies were conducted in populations from France [8], Italy [9, 21], UK [10, 22], Germany [23], Spain [24], Belgium [25], Australia [26], Netherlands, and other six different populations [11]. One study involving 635 ALS patients reported that individuals carrying Pro34Ser variant of *CHCHD10* were at higher risk of developing ALS than individuals without Pro34Ser variant [26]. The rest of the studies revealed no association between Pro34Ser variant and risk of ALS disease [8–11, 21–26].

Heterogeneity

Frequencies of the Pro34Ser allele exhibited heterogeneity based on a chi-squared test analysis ($\chi^2 = 10.72$; degrees of freedom, DF = 11, $P = 0.467$) and I^2 value (0%). Therefore, allele data were analyzed using a fixed-effects model.

Meta-analysis

Pooled OR for risk of ALS in the presence of Pro34Ser variant relative to absence of Pro34Ser was 1.23 (95% CI 0.90–1.69; Fig. 2), and the test for overall effect, $z = 1.28$ ($P = 0.201$).

Analysis of sensitivity and publication bias

Analysis of sensitivity indicated that none of the independent studies significantly influenced our results (Fig. 3). Our funnel plot was visually symmetrical indicating that there was no significant publication bias (Fig. 4). Begg's test revealed no significant risk of publication bias ($P = 0.064$).

Table 1 Characteristics of studies in our meta-analysis

First author	Year	Country	Patients	Male/female	Age	Asso (Y/N)	*p*	OR (95% CI)
Chaussenot	2014	French	80	—	65.6 ± 7.3	N	0.081	12.634 (0.603–264.628)
Chio	2015	Italy	224	101/123	65.9 ± 11.4	N	0.266	5.193 (0.267–100.879)
Abdelkarim	2015	UK	452	—	—	N	0.526	1.460 (0.512–4.162)
Wong	2015	UK	262	—	—	N	0.321	1.693 (0.537–5.338)
Ronchi	2015	Italy	217	—	—	N	0.431	3.962 (0.161–97.492)
Marroquin	2015	Germany	355	—	—	N	0.756	0.737 (0.207–2.621)
Dois-Icardo	2015	Spain	423	238/185	59.57 ± 14.05	N	1.000	0.754 (0.106–5.364)
Perrone	2016	Belgium	429	264/165	60.8	N	0.866	0.910 (0.304–2.724)
Project MinE ALS Sequencing Consortium	2018	7 different populations	4365	—	—	N	0.992	1.035 (0.568–1.889)
McCann (vs gnomAD NFE)	2019	Australia	635	—	62.085 ± 2.975	N	0.651	1.182 (0.527–2.648)
McCann (vs DACC)	2019	Australia	635	—	62.085 ± 2.976	Y	0.0038	19.888 (1.119–353.342)
McCann (vs MGRB)	2019	Australia	635	—	62.085 ± 2.977	N	0.507	0.674 (0.263–1.727)

Asso association between the Pro34Ser variant and ALS risk, *Y* yes, *N* no, *OR* odds radios, *CI* confidence intervals

Table 2 Distribution of Pro34Ser-(+) and Pro34Ser-(−) in each study

First author	Year	Country	*N*		Allele (ALS patients)		Allele (controls)	
			ALS	Control	Pro34Ser-(+)	Pro34Ser-(−)	Pro34Ser-(+)	Pro34Ser-(−)
Chaussenot	2014	French	80	200	2	158	0	400
Chio	2015	Italy	224	165	3	445	0	330
Abdelkarim	2015	UK	452	4777	4	900	29	9525
Wong	2015	UK	262	1216	4	520	11	2421
Ronchi	2015	Italy	217	286	1	433	0	572
Marroquin	2015	Germany	355	393	4	706	6	780
Dois-Icardo	2015	Spain	423	319	2	844	2	636
Perrone	2016	Belgium	429	703	5	853	9	1397
Project MinE ALS Sequencing Consortium	2018	7 different populations	4365	1832	37	8693	15	3649
McCann (vs gnomAD NFE)	2019	Australia	635	63,369	6	1264	507	126,231
McCann (vs DACC)	2019	Australia	635	967	6	1264	0	1934
McCann (vs MGRB)	2019	Australia	635	1144	6	1264	16	2272

N numbers, *Pro34Ser-(+)* Pro34Ser-positive, *Pro34Ser-(−)* Pro34Ser-negative

Discussion

To our knowledge, this is the first meta-analysis assessing existing data on association of Pro34Ser variant of *CHCHD10* with risk of ALS. Results from the present meta-analysis reveal that Pro34Ser variant of *CHCHD10* gene is not considerably associated with high risk of developing ALS, particularly among Caucasian participants.

Results of our study are in line with previous findings suggesting that Pro34Ser variant in *CHCHD10* is likely to be a benign polymorphism [15, 20, 25]. Dobson-Stone and others demonstrated Pro34Ser variant in a patient with FTD who harbors another established pathogenic mutation and its presence in 9/807 non-demented aged controls, six of whom were verified to be cognitively intact in their 70s–80s [15]. Meanwhile, non-pathogenicity was predicted in six out of eight functional predictive programs (PolyPhen-2, SIFT, FATHMM, MutationAssessor, PONP2, and Sibyl) [15]. The convergence of the above three evidence indicates that Pro34Ser is not a disease-causing mutation. In addition,

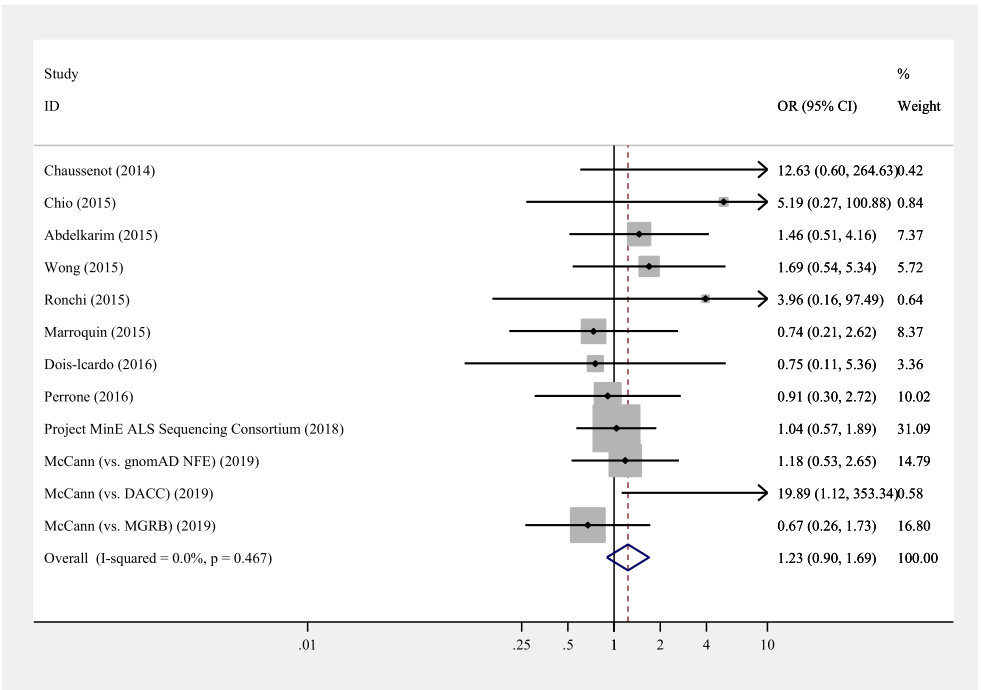

Fig. 2 Forest plot of the association between the Pro34Ser variant and amyotrophic lateral sclerosis susceptibility (Pro34Ser-positive vs Pro34Ser-negative)

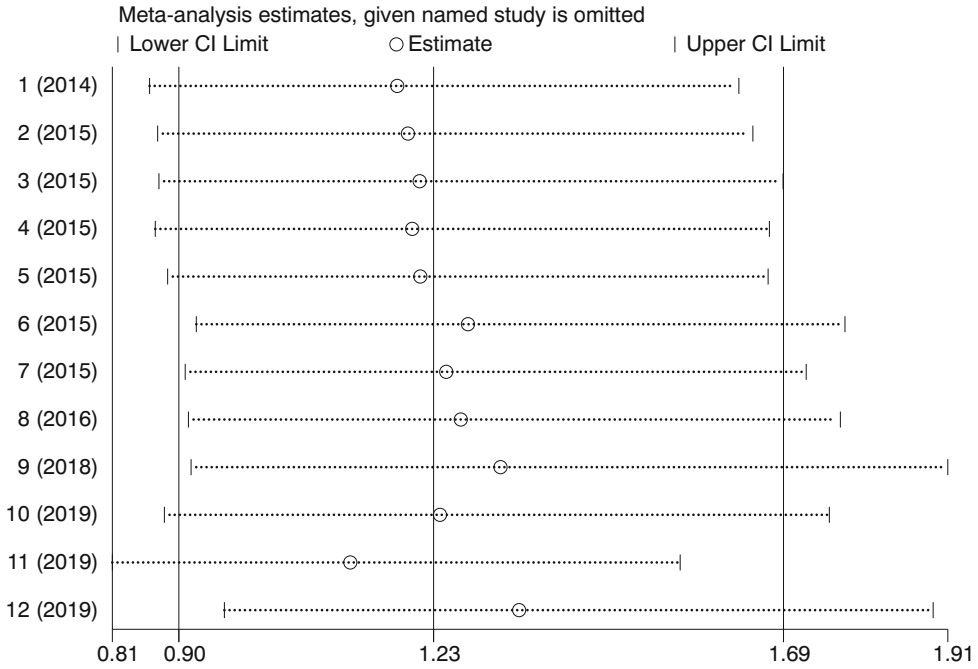

Fig. 3 Sensitivity analysis of the studies in the association between the Pro34Ser variant and sporadic amyotrophic lateral sclerosis susceptibility (Pro34Ser-positive vs Pro34Ser-negative)

Zhang and others analyzed 204 ALS and 158 FTD patients and established that the frequency of Pro34Ser variant substitution was comparable with the control samples (minor allele frequency = 0.0074), the 1000 genome project (minor allele frequency = 0.001), and the ExAC database (minor allele frequency = 0.003). This demonstrated that this variant is not pathogenic [20]. Moreover, time of median survival in four patients with Pro34Ser variant was 30 months, which corresponds with time of median survival of 29 months observed in total sporadic ALS cohorts that were tested. This contrasts with the gradual progression of the disease observed in most patients with motor neuron disease carrying a *CHCHD10* mutation for which pathogenicity is supported by co-segregation data [23].

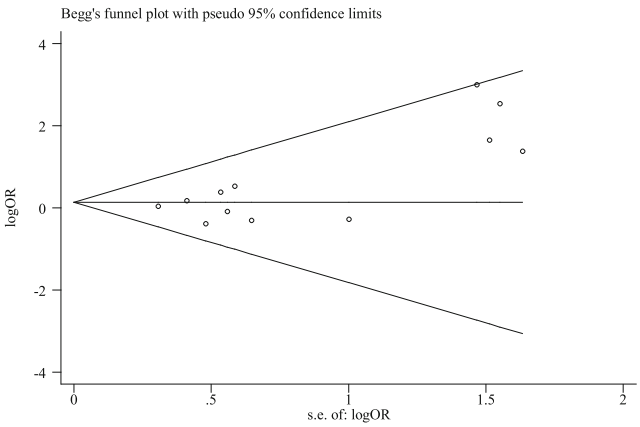

Fig. 4 Funnel plot of the association between the Pro34Ser variant and sporadic amyotrophic lateral sclerosis susceptibility (Pro34Ser-positive vs Pro34Ser-negative)

CHCHD10 genes are concentrated in exon 2 [9, 25] because this region is GC-rich (77.3% GC-content) and may not be effectively captured by oligonucleotide baits that are central to exome sequencing [22, 27]. Therefore, this variant is apparently absent or has low frequency in public databases and should not be solely relied on to elucidate its pathogenicity [15]. In addition, due to the low coverage of next-generation sequencing, the true frequency of Pro34Ser variation in the control group may indeed be higher, as reflected by Sanger sequencing data [22]. Although our meta-analysis does not confirm that Pro34Ser is a risk factor of ALS, there is need to perform large-scale studies to determine whether Pro34Ser variant is a risk allele for FTD-ALS with low penetrance.

Our meta-analysis provides the first comprehensive assessment of Pro34Ser variant in CHCHD10 and ALS risk. Our results should however be interpreted with caution because our study had several limitations. One of the limitations is that we did not perform a subgroup analysis based on gender and ethnicity due to limited data. Another limitation was that Begg's test revealed that there was no significant risk in publication bias, although this risk is always present. Finally, included studies were only performed among Caucasian populations; thus, correlation between Pro34Ser variant and ALS risk in other races requires further investigation.

In conclusion, our results suggest that Pro34Ser variant of *CHCHD10* is not associated with susceptibility to ALS, particularly in Caucasian populations. Future studies especially among African and Asian populations are required to validate and increase our understanding of the association between Pro34Ser variant and risk of ALS.

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Authors' contributions Conceptualization: Baiyuan Yang, Chenghui Yang, Junwei Ren, and Zhenfang Lin; Methodology: Baiyuan Yang, Chenghui Yang, and Chengqing Zhong; Formal analysis and investigation: Keting Liu, Liusha Zhao, Li Li, Han Wang, and Mingling Zhu; Writing-original draft preparation: Baiyuan Yang, Chenghui Yang, and Junwei Ren; Writing-review and editing: Baiyuan Yang and Zhenfang Lin; Supervision: Zhenfang Lin.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

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

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability The code used and/or analyzed during the current study is available from the corresponding author on reasonable request.

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