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Association between CD24 Ala/Val polymorphism and multiple sclerosis risk

A meta analysis

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Abstract

Background: The aim of this study was to explore the association between CD24 Ala/Val polymorphism and susceptibility of multiple sclerosis (MS).

Methods: A comprehensive literature search for relevant studies was performed on google scholar, PubMed, Web of science, Embase, the Chinese National Knowledge Infrastructure and the Chinese Biology Medicine. This meta-analysis was conducted using the STATA 11.0 software and the pooled odds ratio with 95% confidence interval was calculated.

Results: Seven case-control studies were included in this meta-analysis. The results showed significant association between CD24 Ala/Val polymorphism and susceptibility to MS. Stratified analysis by areas also showed significant association in Asians. However, no association was found in Europeans.

Conclusion: This study suggested that the CD24 Val allele was associated with an increased risk of MS and larger-scale studies of populations are needed to explore the role of CD24 Ala/Val polymorphism during the pathogenesis of MS.

Abbreviations: CBM = Chinese Biology Medicine, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, CNS = central nervous system, HWE = Hardy-Weinberg equilibrium, MS = multiple sclerosis, OR = odds ratio.

Keywords: CD24, meta-analysis, multiple sclerosis, polymorphism

1. Introduction

Multiple sclerosis (MS) is a chronic central nervous system (CNS) disease that is characterized by demyelination, inflammation, and axonal loss.[1] MS is one of the most common causes of acquired neurological dysfunction during early to adulthood, and its onset is associated with many factors such as age, ethnicity, geography, and family history.[2] Although the etiology remains elusive, there is evidence that both environmental and genetic factors play roles in the susceptibility.

To date, several genes have been suspected to play roles in the pathogenesis of the disease in related studies.[3,4] These candidate genes are not considered to be causative factors but they are generally regarded as modifiers of either the individual's susceptibility to MS, in the patients' response to certain treatments or of its clinical course. One such gene is CD24, which has been studied deeply and considered as a factor that modifies the risk and the progress of the disease. It is located in the 6q21 region, a locus previously shown to be linked with MS and other autoimmune diseases. CD24 is a glycosyl phosphatidylinositol (GPI)-associated protein which is anchored to the cell surface and expressed in a broad range of cell types, such as activated B cells, T cells, and cells of the CNS. CD24 has also been identified as an important mediator in a CD28-independent costimulatory pathway in the activation of both CD8 and CD4 T cells.[5–7] Besides, CD24 plays an important role in binding the vascular cell adhesion molecule 1 and the adhesion molecules very late activation antigen 4.[8,9] These adhesion molecules are important in CNS in MS patients. Zhou et al has found a coding polymorphism in the CD24 gene (226C/T, rs 8734), which results in the replacement of an alanine (CD24 A) amino acid with valine (CD24 V).[10] This nonconservative amino acid change at the position which precedes the putative cleavage site for the GPI anchor has been confirmed to be associated with susceptibility of MS.

Recently, several studies have indicated that CD24 polymorphism might significantly relate to the increased risk of MS.[11,12] However, the results are inconsistent and controversial.

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Therefore, we attempt to perform this meta-analysis of all eligible studies to provide a more comprehensive and reliable conclusion by reevaluating the association between CD24 Ala/Val polymorphism and MS risk.

2. Methods

2.1. Search strategy

Studies which evaluated the association between CD24 Ala/Val polymorphism and MS risk were searched in the databases of google scholar, PubMed, Web of science, Embase, the Chinese National Knowledge Infrastructure (CNKI), and the Chinese Biology Medicine (CBM) with the following terms: CD24, rs8734/rs52812045, single nucleotide polymorphism, SNP, polymorphisms, mutation, variant, variants, multiple sclerosis, and MS. There is no limitation on languages. Besides, all references cited were also reviewed to identify additional studies. The meta-analysis did not include data related to patient personal information and therefore did not require ethical approval.

2.2. Inclusion criteria

Regarding MS susceptibility and the polymorphism, studies which met the following criteria were identified:

(1) Clinical case-control or cohort studies concentrated on the role of CD24 Ala/Val polymorphism in the pathogenesis of MS.
(2) All patients should be diagnosed according to the recommended diagnostic criteria (McDonald criteria and/or Poser criteria) for MS.
(3) The specific numbers or genotype frequency in case and control groups must be clearly showed in the articles.
(4) The genotype frequencies distribution of the controls should consist with Hardy-Weinberg equilibrium (HWE), which was performed for evaluating the qualities of the studies.

Studies were excluded if they did not in accordance with all the inclusion criteria.

2.3. Data extraction

Two authors extracted data from each included study independently according to the selection criteria. We compared the data and made decision by consensus of all members of our group. For included studies, data on first author, year of publication, study design, ethnicity of the study, number of cases and controls, mean age of participants, diagnostic standards of cases in each study, and the number of cases and controls for the variant were extracted.

2.4. Statistical analysis

Crude ORs with their 95% CIs were used to estimate the strength of association between the polymorphism and MS susceptibility. The pooled ORs were calculated for the allele contrasts, recessive genetic model, dominant genetic model, and additive comparison. Subgroup analyses were also performed by ethnicity.

A random or fixed effect model was employed based on the heterogeneity assumption.[13,14] Heterogeneity assumption was examined by the chi-square based Q test.[15] The random effect model was used as the pooling method in the presence of substantial heterogeneity ($I^2 > 50\%$), otherwise, the fixed effect was performed to assess the pooled odds ratio (OR). The genotypic frequency distribution in the control was checked for consistence with the HWE in all the included studies. The potential publication bias was estimated by Begg test or Egger linear regression test by visual examination of the funnel plot, and $P < .05$ was regarded as representative of statistically significant publication bias. To assess the stability of the results of the meta-analysis, case definition influence on the pooled evaluation, one-way sensitivity analyses were performed. All statistical tests were used with STATA version 11.0 (Stata Corporation, College station, TX). All P values tested were 2-tailed.

3. Results

3.1. The identification and characteristics of eligible studies

Figure 1 illustrates the study selection process. There were altogether 229 relevant papers under the search words (PubMed 28, google scholar 123, Web of science 35, Embase 42, CBM 5, and CNKI 106. However, 28 articles searched in PubMed, 35 articles searched in Web of science, and 42 articles searched in Embase can be found in google scholar and 5 articles searched in CBM can also be identified in CNKI), of which 186 were excluded and a total of 43 articles were identified through literature search and screening of title and/or abstract. Of these, 17 articles were not concentrated on CD24 gene, 5 articles were not related to CD24 Ala/Val polymorphism, 2 meta-analysis and 11 studies not related to MS. During the extraction of data, 1 study did not have clear data and was excluded. Seven articles met all inclusion criteria and were included in the meta-analysis.[10–12,16–19] Selected details of the individual studies are listed in Table 1.

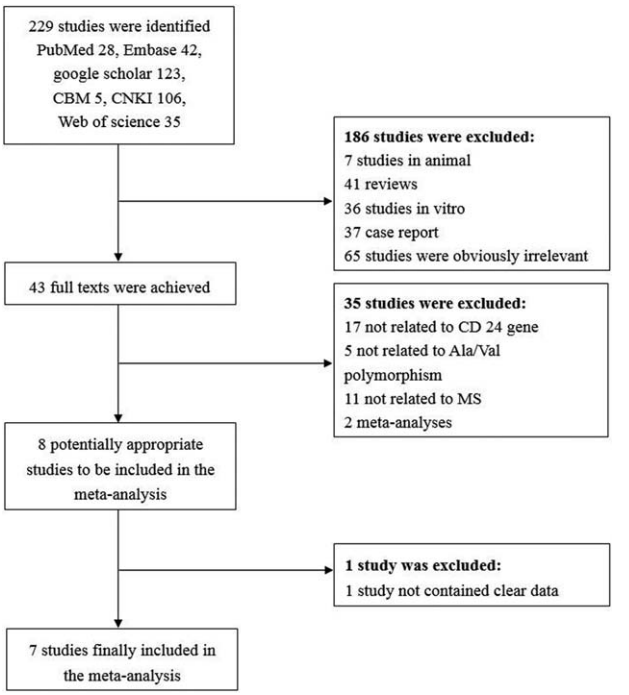

Figure 1. Flow diagram of the study selection process.

Table 1

Characteristics of studies included in the meta-analysis.

First author	Year	Region	Country	Mean age Case/Control	Diagnostic standard	Case/Control	Genotype method	NOS score
Zhou	2003	Mixed	America	NR/NR	McDonald criteria	242/297	PCR	7
Goris 1	2006	European	Belgian	NR/NR	Poser criteria	334/322	TaqMan	8
Goris 2	2006	European	UK	NR/NR	Poser criteria	846/846	TaqMan	8
Cui	2006	Asian	China	38.8/40.2	Poser criteria	83/110	PCR-RFLP	7
Otaegui	2006	European	Spain	NR/NR	McDonald criteria	135/285	PCR-RFLP	7
Ronaghi	2009	Asian	Iran	NR/NR	McDonald criteria	217/200	PCR	7
González	2011	Mixed	Argentina	35/37	McDonald criteria	102/205	PCR-RFLP	8
Kollaee	2011	Asian	Iran	38.2/37.2	McDonald criteria	120/120	PCR	8

NR = not report.

3.2. CD24 Ala/Val polymorphism and the risk of MS

In total, 7 articles provided data for 2079 cases and 2295 controls. The analysis performed by Goris et al was conducted within 2 studies in Belgian and UK, respectively.[16] Of all the studies, there were 3 studies performed in Europe and 3 in Asia. The results of HWE test for the distribution of the genotype in control population are shown in Table 2.

Table 3 lists the main results of this meta-analysis. Overall, when all eligible studies were pooled with random-effects model, significant associations were observed in allele contrasts (OR = 0.795, 95%CI 0.645–0.981, $P = .032$), and additive comparison (OR = 0.540, 95%CI 0.321–0.909, $P = .020$), dominant genetic model (OR = 0.570, 95%CI 0.356–0.913, $P = .019$), and additive comparison (OR = 0.540, 95%CI 0.321–0.909, $P = .020$). The Val allele might significantly increase MS risk. In order to explore potential association among population in different regions, a stratified analysis was conducted to assess effect estimated in subgroups defined by locations. The results suggested that the polymorphism was not associated with increased risk of MS in Europeans (allele contrasts, OR = 0.971, 95%CI 0.744–1.267, $P = .827$; recessive genetic model,

Table 2

Characteristics of case-control studies included in a meta-analysis of the link between the CD24 Ala/Val polymorphism and MS.

First author	Year	Region	Case			Control			*P* for HWE
			AA	AV	VV	AA	AV	VV	
Zhou	2003	Mixed	113	97	32	109	85	13	.39
Goris 1	2006	European	162	133	39	159	134	29	.92
Goris 2	2006	European	411	361	74	368	380	98	.99
Cui	2006	Asian	25	42	16	48	51	11	.64
Oategui	2006	European	59	69	7	145	136	4	.15
Ronaghi	2009	Asian	102	68	47	114	66	20	.43
González	2011	Mixed	43	50	9	96	91	18	.59
Kollaee	2011	Asian	56	40	24	63	49	8	.71

A = Ala, MS = multiple sclerosis, V = Val.

Table 3

Summary ORs and 95%CI for contrasts in CD24 Ala/Val polymorphism.

SNP	Contrast	Odds ratio OR (95%CI)	P_{OR}	Model	Heterogeneity I^2(%)	P_H
CD24	A vs V	0.795 (0.645–0.981)	.032	R	77.5	<.001
	AA vs AV+VV	0.845 (0.691–1.034)	.102	R	56.5	.024
	AA +AV vs VV	0.570 (0.356–0.913)	.019	R	76.9	<.001
	AA vs. VV	0.540 (0.321–0.909)	.020	R	79.4	<.001
Subgroup						
European						
	A vs V	0.971 (0.744–1.267)	.827	R	75.9	.016
	AA vs AV+VV	1.083 (0.932–1.259)	.300	F	61.9	.073
	AA +AV vs VV	0.790 (0.387–1.613)	.518	R	78.1	.010
	AA vs VV	0.779 (0.350–1.735)	.541	R	81.3	.005
Asian						
	A vs V	0.618 (0.504–0.758)	<.001	F	0	.973
	AA vs AV+VV	0.676 (0.514–0.889)	.005	F	0	.679
	AA +AV vs VV	0.382 (0.255–0.574)	<.001	F	0	.704
	AA vs VV	0.353 (0.230–0.542)	<.001	F	0	.897

95%CI = confidence interval, A = Ala, F = fixed-effects model, OR = odds ratio, R = random-effects model, V = Val.

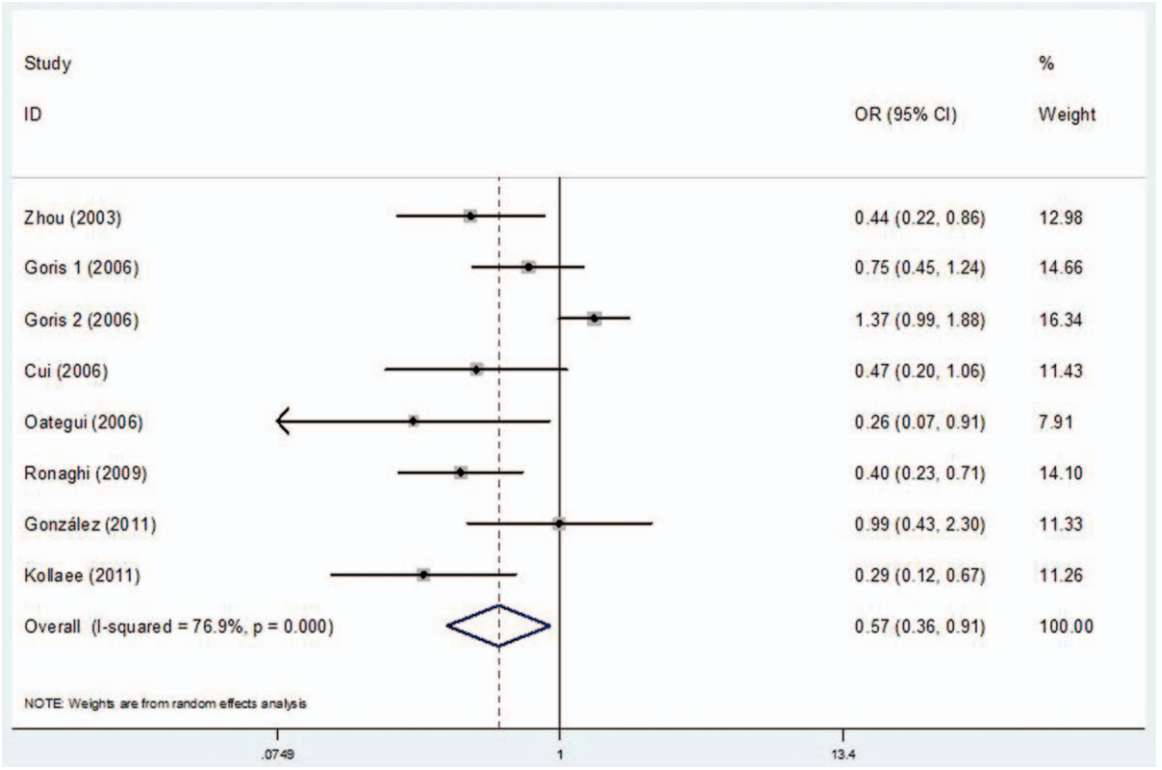

Figure 2. The association of CD 24 Ala/Val polymorphism and MS. Meta-analysis for the association between CD 24 Ala/Val polymorphism and MS under dominant genetic model (AlaAla + AlaVal vs ValVal) in the total populations using a random-effects model. The squares and horizontal lines correspond to the study specific OR and 95%CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95%CI. CI = confidence interval, MS = multiple sclerosis, OR = odds ratio.

OR = 1.083, 95%CI 0.932–1.259, $P = .300$; dominant genetic model, OR = 0.790, 95%CI 0.387–1.613, $P = .518$; additive comparison, OR = 0.779, 95%CI 0.350–1.735, $P = .541$). However, the stratified analysis in Asians showed that Val allele also significantly increased MS risk (allele contrasts, OR = 0.618, 95%CI 0.504–0.758, $P < .001$; recessive genetic model, OR = 0.676, 95%CI 0.514–0.889, $P = .005$; dominant genetic model, OR = 0.382, 95%CI 0.255–0.574, $P < .001$; additive comparison, OR = 0.353, 95%CI 0.230–0.542, $P < .001$) (Figs. 2 and 3).

3.3. Sensitivity analysis

Sensitivity analysis was performed to estimate the influence of each individual study on the pooled OR by omitting each individual study. The analysis results showed that no individual study significantly affected the pooled ORs under any genetic models of CD24 polymorphism (data were not shown).

3.4. Publication bias

Egger linear regression and Begg funnel plot test were used to assess the publication bias. The shape of the funnel plots did not reveal any evidence of obvious asymmetry under all the genetic model of CD24 Ala/Val polymorphism (Fig. 4). Egger test also did not display any statistical evidence of publication bias as well.

4. Discussion

MS is a chronic CNS disorder which affects nearly 0.1% of populations in Europeans and the incidence is increased among family members of affected individuals.[21] The concordance rate of the identical twins may be as high as 40%.[22] One of the whole-genome scans found a linkage disequilibrium in distal 6q whose identity has not been clearly revealed. CD24 is one of the interesting candidates in the region, which were suggested to be essential for the induction of experimental autoimmune encephalomyelitis (EAE) in mice.[20] The human genome contains 3 CD homologues located on chromosomes 6, 15, and Y, with evidences showing that the CD24 mRNA is derived from the chromosomes 6 copy.[23] The only coding polymorphism (rs 8734) from these homologues displayed in public databases is located on the Y chromosome and is therefore of no relevance in an analysis of the chromosomes 6 copy.[24]

In recent years, many studies have evaluated the association between CD24 Ala/Val polymorphism and MS risk, but the results remain inconsistent and controversial. This is the first meta-analysis to attempt to determine the potential role of CD24 Ala/Val polymorphism in MS susceptibility among populations from different regions and we combined data from published studies to estimate the genetic association. The results showed that the polymorphism is associated with susceptibility to MS, especially in Asians. However, no association was found in Europeans. Genetic association results coincided with most previous results, although the disease is complex and various genes, environmental factors, and genetic backgrounds contributed to MS development. The results supported a significant role of CD24 Val allele in the molecule pathogenesis of MS, which warrants further study. However, intriguingly, a European origin cohort study with large samples conducted in Belgium and UK did not show an association of CD24 Val allele with susceptibility of MS, which was consistent with our meta-analysis results.

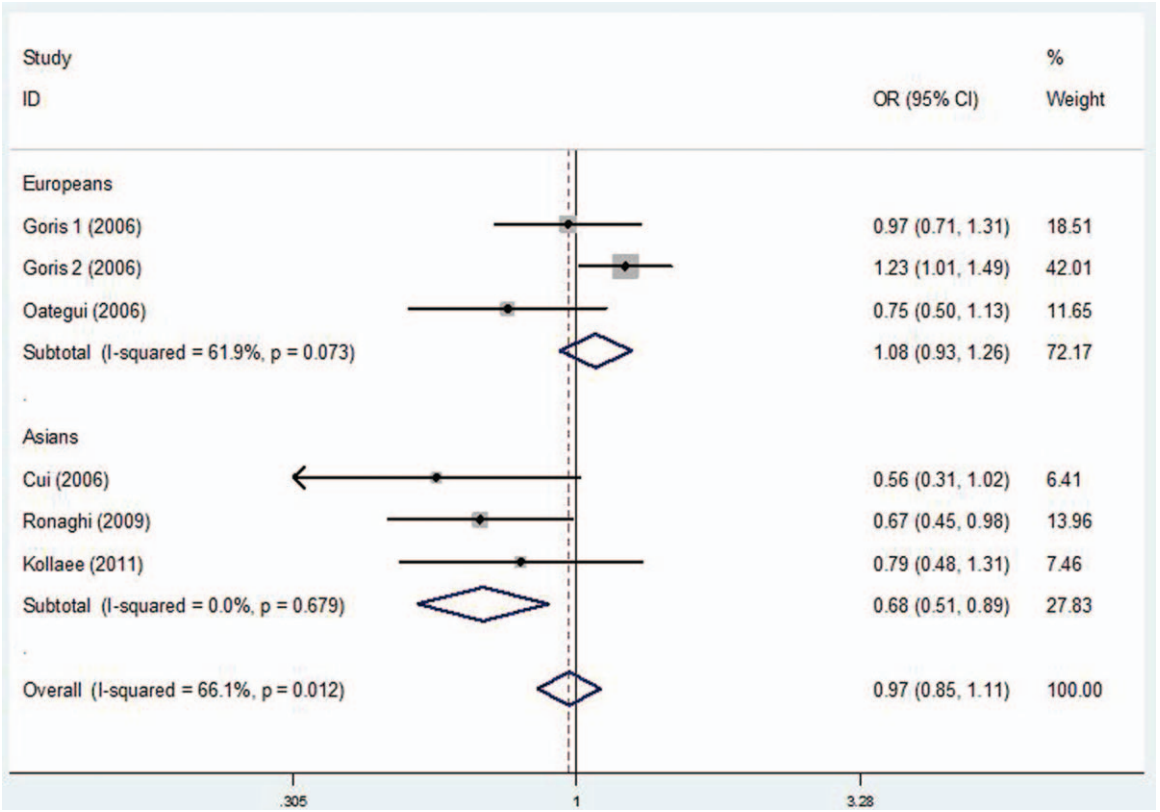

Figure 3. The association of CD 24 Ala/Val polymorphism and MS. Meta-analysis for the association between CD 24 Ala/Val polymorphism and MS under recessive genetic model (AlaAla vs AlaVal + ValVal) in the subgroup populations using a fixed-effects model. The squares and horizontal lines correspond to the study specific OR and 95%CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95%CI. CI = confidence interval, MS = multiple sclerosis, OR = odds ratio.

Similar to other meta-analyses, this analysis also has some shortages and limitations. First, the sample size of this meta-analysis is relatively small, which may not have abundant statistical power in assessing the role of CD24 Ala/Val polymorphism in the development of MS. Second, a language bias may have existed because this meta-analysis contained only English and Chinese articles due to database limitations. Some studies in coincidence with the inclusion criteria in other languages published in specific journals might not be identified and included in this meta-analysis. Besides, all included articles were published studies, and unpublished studies that had null results were missed, which also might bias the results. Third, although no publication biases were found by observing symmetry of funnel plot, Begg and Egger test, pooled analyses of original data could not be prevented from possible publication bias.

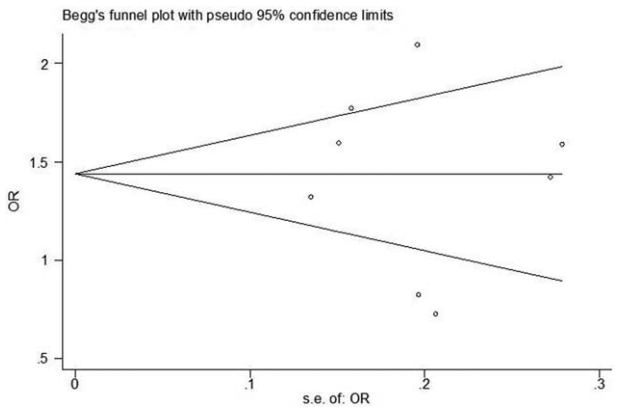

Figure 4. Begg funnel plot analysis was used to detect publication bias for the dominant genetic model (AlaAla vs ValVal) of CD 24 Ala/Val polymorphism. No asymmetry was found as indicated by the *P* value of the Egger test.

In conclusion, this meta-analysis of 7 relevant studies suggested that CD24 Ala/Val polymorphism was associated with an increased risk of MS, especially in Asians, but not in Europeans. However, the functional significance of CD24 polymorphism is still unclear. In particular, larger-scale studies of populations are needed to explore the roles played by CD24 Ala/Val polymorphism during the pathogenesis of MS.

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Author contributions

Conceptualization: Ling-Suo Kong.
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Formal analysis: Xing-Xing Zhu.
Funding acquisition: Lan-Ren Chen.
Investigation: Wan Yang.
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Project administration: Wan Yang.
Software: Rui-Xiang Wang.
Validation: Rui-Xiang Wang.
Visualization: Lan-Ren Chen.
Writing – original draft: Wan Yang.
Writing – review & editing: Lan-Ren Chen.

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