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Unique characteristics of the genetics epidemiology of amyotrophic lateral sclerosis in China

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Continual discoveries of new genes and unraveling the genetic etiology in amyotrophic lateral sclerosis (ALS) have provided greater insight into the underlying pathogenesis in motor neuron degeneration, as well as facilitating the disease modeling and the testing of targeted therapeutics. While, the genetic etiology accounted for two-thirds of FALS and approximately 11% of SALS in Caucasians. However, the contributions of these causative genes to ALS vary among different populations. Furthermore, the prominent difference between Chinese population and other ethnics remains a source of ongoing debate. We systemically reviewed genetics literature of Chinese ALS populations and updated the mutation frequencies of the main ALS-implicated genes aiming to determine the genetic features of ALS in Chinese population. We also reviewed the associations between ALS-implicated single nucleotide polymorphisms (SNPs) and the risk of ALS in Chinese population. A total of 116 studies were included in this analysis (86 gene mutation study articles and 30 SNPs study articles). The results showed that the overall gene mutation rates of ALS-related causative genes were 55.0% in familial ALS (FALS) and 11.7% in sporadic ALS (SALS) in Chinese population. In Chinese FALS, the highest mutation frequency was found in *SOD1* gene (25.6%), followed by *FUS* (5.8%), *TARDBP* (5.8%), *DCTN1* (3.6%) and *C9orf72* (3.5%). In Chinese SALS, the highest mutation frequency was also identified in *SOD1* gene (1.6%), followed by *ANXA11* (1.4%), *FUS* (1.3%), *SQSTM1* (1.0%), *OPTN* (0.9%) and *CCNF* (0.8%). The associations between several SNPs and risk of ALS were also reported in Chinese population. The genetic features of ALS in Chinese population are significantly different from those in Caucasian population, indicating an association between genetic susceptibility and origin of population. Further explorations are required to understand the gene complexity of ALS, including the contribution of most minor genes and the molecular mechanisms in ALS pathologies.

amyotrophic lateral sclerosis, gene, mutation, single nucleotide polymorphisms

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons in the brain and spinal cord (Brown and Al-Chalabi, 2017). It is heterogeneous in its presentation, phenotypes, disease progression and prognosis. Although a growing number of studies are focusing on the etiology of ALS, the pathogenesis of ALS remains largely unclear. It is widely accepted that genetic factors and environmental risk factors both have equally important roles in the onset of ALS (Wingo et al., 2011). In terms of hereditary, ALS can be classified into two categories, familial and sporadic. Most cases are sporadic (SALS), and approximately 5%–10% of patients are considered as familial (FALS) with a Mendelian pattern of inheritance (Mitchell and Borasio, 2007). Continual discoveries of new genes and unraveling the genetic etiology in ALS have provided greater

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insight into the underlying pathogenesis in motor neuron degeneration, as well as facilitating the disease modeling and the testing of targeted therapeutics. Up to date, more than 30 causative genes have been found to be implicated in the pathogenesis of ALS. However, the mutation frequencies in ALS-implicated genes varied dramatically among different populations from different ethnic backgrounds (Zou et al., 2017). For example, studies have reported that chromosome 9 open reading frame 72 (*C9orf72*), copper/zinc superoxide dismutase-1 (*SOD1*), TAR DNA-binding protein (*TARDBP*) and Fused in sarcoma (*FUS*) are most common mutated genes in Caucasian population with ALS; the *C9orf72* repeat expansion accounts for a significantly high percentage among Caucasian population but is rare in Asian cases (Shahrizaila et al., 2016; Zou et al., 2017). In Caucasians, the genetic etiology accounts for two-thirds of FALS and approximately 11% of SALS (Caballero-Hernandez et al., 2016). While in the Asian population, the most common ALS-implicated genes are *SOD1*, *FUS*, *C9orf72* and *TARDBP* (Zou et al., 2017). Compared with the Caucasian and other Asian populations, Chinese population is quite different in ethic, social and cultural backgrounds; and Chinese ALS patients are an important component in this rare disease database (Huynh and Kiernan, 2015). Studies from Chinese ALS population suggested a younger age of disease onset and a lower percentage of FALS than other populations (Wei et al., 2015). The *SOD1* is the most common causative gene in Chinese ALS population, while the frequency of *C9orf72* gene is significantly lower than that in Caucasians (Chen et al., 2016; Wei et al., 2017).

The potentials of genome-wide association studies (GWAS) on different populations uncover the associations between genetics and the pathogenesis of ALS (Xie et al., 2014). Previous study indicated that GWAS could provide direct evidence of a genetic contribution to SALS, and approximately 8.5% of variance in liability could be tagged by common single nucleotide polymorphisms (SNPs) (Benyamin et al., 2017). Several susceptibility genes in various ethnic populations have been reported in previous studies, suggesting an important interaction between susceptible genes and SALS. Several previous studies also indicated the associations between different SNPs in gene and risk of ALS in Chinese population, such as polymorphisms in brain-derived neurotrophic factor (BDNF) (Xu et al., 2017), sterol regulatory element binding factor (SREBF1) gene (Yuan et al., 2018) and Nogo-A receptor gene (RTN4R) (Xu et al., 2018). These findings help to better understand the genetic etiology of ALS. Since the genetic cause of over 90% of SALS remains unknown, the genetic study of pathogenic genes and susceptible genes in Chinese ALS patients is of great significance.

However, the contributions to these ALS-implicated genes vary greatly among different populations and the prominent differences between Chinese and other ethnics remain a source of ongoing debate. Therefore, we reviewed all literature on genetics findings in Chinese ALS populations and updated the mutation frequencies of the main ALS-implicated genes to determine the genetic epidemiology of ALS in China. We also reviewed the associations between ALS-implicated SNPs and the risk of ALS in Chinese population.

RESULTS

We reviewed all eligible publications to investigate the contributions of these causative genes in Chinese ALS population, including *SOD1*, *TARDBP*, *FUS*, *C9orf72*, *Sequestosome 1* (*SQSTM1*), *Ataxin-2* (*ATXN2*), *Coiled-coil-helix-coiled-coil-helix domain containing 10* (*CHCHD10*), *TANK-binding kinase 1* (*TBK1*), *Profilin 1* (*PFN1*), *Angiogenin* (*ANG*), *Valosin-containing protein* (*VCP*), *Vesicle-associated membrane protein B* (*VAPB*), *Optineurin* (*OPTN*), *Ubiquilin 2* (*UBQLN2*), *Dynactin 1* (*DCTN1*), *matrin-3* (*MATR3*), *cyclin F* (*CCNF*), *Tubulin*, *Alpha 4A protein* (*TUBA4A*), *T-cell-restricted intracellular antigen-1* (*TIA1*), *ARHGEF28*, *GLE1*, *annexin A11* (*ANXA11*), and *kinesin family member 5A* (*KIF5A*). A total of 1,134 articles were identified after searching databases, and 175 duplicate articles were removed. Due to the types of studies (animal study, clinical trials) and types of articles (reviews, editorials), 843 articles were excluded. Finally, 116 studies were included in the analysis, including 86 gene articles and 30 SNPs articles. The flow diagram of the literature evaluation is presented in Figure 1. A large number of genetic studies were conducted in a single-center with hundreds of ALS patients in the mainland of China, such as Peking Union Medical College Hospital, Peking University Third Hospital, Xiangya Hospital of Central South University, and West China Hospital of Sichuan University. Only seven studies reported the gene mutations in a Taiwanese cohort.

The gene mutation rates of these ALS causative genes were 55.0% in FALS and 11.7% in SALS among Chinese ALS patients. In FALS, the highest mutation frequency was found in *SOD1* gene (25.6%), followed by *FUS* (5.8%), *TARDBP* (5.8%), *DCTN1* (3.6%), *C9orf72* (3.5%), *ANXA11* (3.3%), and other genes. In SALS, the highest mutation frequency was also identified in *SOD1* gene (1.6%), followed by *ANXA11* (1.4%), *FUS* (1.3%), *SQSTM1* (1.0%), *OPTN* (0.9%), *CCNF* (0.8%), *TBK1* (0.7%) and other genes.

In all Chinese ALS patients, *SOD1* mutations accounted for 5.1% cases, *FUS* accounted for 2.0%, but *C9orf72* only have 0.68%. *SOD1* mutations were reported in 11 studies, and *SOD1* mutations accounted for 25.6% in FALS cases and 1.63% in SALS cases. Six studies screened for *FUS* mutations, with mutation frequencies of 5.8% in FALS and 1.3% in SALS. *TARDBP* mutations and *C9orf72* repeat expansions

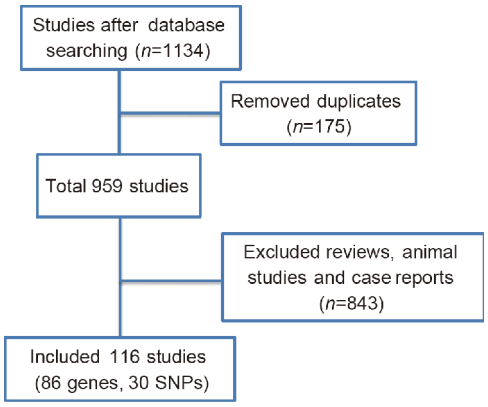

Figure 1 Flow diagram showing the studies selected for literature review.

were reported in 11 and 9 studies, respectively; *TARDBP* mutations accounted for 5.8% in FALS and 0.3% in SALS, and *C9orf72* only have 3.5% in FALS and 0.5% in SALS. The *DCTN1* gene mutations were reported in three studies, with high mutation frequencies of 3.6% in FALS and 0.7% in SALS. Two recent studies have shown *ANXA11* gene accounted for a high mutant frequency of 3.3% in FALS and 1.4% in SALS. Only one study reported the mutation of *KIF5A* gene, with a frequency of 0.41% in SALS. Table 1 and Figure 2 present the published studies and frequencies of these genes in Chinese population. Mutations in several other ALS-implicated genes have been reported as rare causes in Chinese patients. The mutations of *SQSTM1*, *CHCHD10*, *TBK1*, *PFN1*, *ANG*, *VCP*, *MATR3*, *CCNF*, *TUBA4A*, *TIA1*, *ARHGEF28*, and *GLE1* genes were not detected in FALS, while the mutations of *VCP*, *VAPB*, *TUBA4A*, and *GLE1* genes were not reported in SALS.

Thirty studies reported the associations between SNPs and risk of ALS in Chinese population, including Rs696880 in *RTN4R* gene, Rs9268856 in *HLA-DRA* gene, Rs56164415 in *BDNF* gene, Rs363371 in *VMAT2* gene, Rs3737597 in *DISC1* gene, Rs876016 and Rs2070872 in *P4HB* gene, Rs2275294 in *ZNF512B* gene, C (-1562) T in *MMP-9* gene, H63D in *HFE* gene, and Rs10493256 in *FLJ10986* gene. The results of the SNPs studies in the Chinese ALS population are presented in Table 2. Findings from other studies suggested that a lot of SNPs were not associated with ALS risk.

DISCUSSION

In this study, we conducted a literature review to determine the mutation frequencies of causative genes in Chinese ALS population and the association between SNPs in susceptibility genes and risk of ALS.

Our data showed that the overall gene mutation rates of these causative genes were 55.0% in FALS and 11.7% in SALS in China. In FALS, the most common mutations were *SOD1* gene, followed by *FUS*, *TARDBP*, *DCTN1*, *C9orf72* and other genes. In SALS, the highest mutation frequency was also in *SOD1* gene, followed by *ANXA11*, *FUS*, *SQSTM1*, *OPTN*, *CCNF*, *TBK1* and other genes. In contrast, the most frequently detected mutations in ALS were the *C9ORF72* repeat expansions in Caucasian populations (FALS 33.7%, SALS 5.1%), followed by *SOD1* (FALS 14.8%, SALS 1.2%), *TARDBP* (FALS 4.2%, SALS 0.8%), and *FUS* gene (FALS 2.8%, SALS 0.3%) in the meta-analysis (Zou et al., 2017). In FALS, the *SOD1* gene was detected in 11 eligible studies in China, accounting for 25.6% of cases, which is similar to the result (25.3%) from a previous Chinese review study with less included studies (Liu et al., 2018) and lower than the frequency of *SOD1* mutation in Asian population (30.0%), but this result is much higher than the frequency of *SOD1* mutation in European population (14.8% in FALS) (Chiò et al., 2008; Zou et al., 2017). The frequency of *C9orf72* repeat expansions in Caucasian population is much higher than that in Chinese ALS population, both in FALS and SALS. The mutation frequency of *TARDBP* in FALS, and the mutation frequency of *FUS* gene in both FALS and SALS were more common than those in Caucasians, while the mutation frequency of *TARDBP* gene in SALS was lower than that in Caucasians (Zou et al., 2017). These four majors ALS-implicated genes accounted for 40.7% in FALS and 3.7% in SALS in China, consistent with a Chinese summation article (40.2% in FALS and 4.1%) (Zou et al., 2016), which reviewed 10 studies on mainland Chinese. These results showed a significant difference of genetic features between Chinese and Caucasian populations, indicating an association between genetic susceptibility and origin of population. In European population, it is widely proposed that approximately 10% of cases with ALS reported a family history of the disease (Turner et al., 2013). But in Chinese population, the FALS frequency ranged from 1.2 to 2.7% in previous studies, which was lower than that in Caucasian population (Wei et al., 2015; Liu et al., 2018). In addition, the clinical manifestation may also be related with the genetic heterogeneity across populations. Distinct from Caucasians, Chinese ALS patients have a much younger age-of-disease-onset, which may be partially due to the genetic heterogeneity, for example, the higher frequency of *FUS* mutations in FALS and SALS patients in China (Wei et al., 2015; Liu et al., 2017).

Although mutations in several other genes have been reported as rare causes of ALS, *DCTN1* gene showed a high mutation frequency in Chinese FALS (3.6%) and SALS (0.7%), which were detected in three studies. A lower frequency of *DCTN1* gene has been reported in a Japanese population (2.6% in FALS and 1.1% in SALS) (Nakamura et al., 2016), and in Irish population (0% in FALS and 0.8% in SALS) (Kenna et al., 2013). *SQSTM1* gene mutation was rare; studies from China did not identify any *SQSTM1* gene

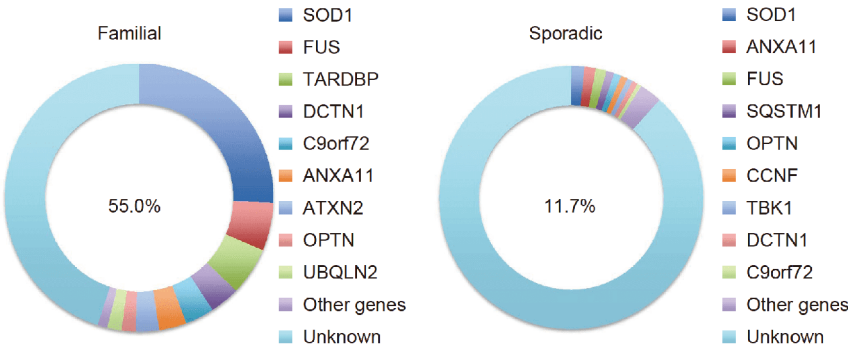

Figure 2 Genetic architecture of FALS and SALS in Chinese population. FALS, familial amyotrophic lateral sclerosis; SALS, sporadic amyotrophic lateral sclerosis.

Table 1 Mutation frequencies of common causative genes in Chinese ALS patients

Genes	FALS				SALS			
	Studies	*N*	*N* (mutation)	%	Studies	*N*	*N* (mutation)	%
SOD1	11	250	64	25.6	6	1,476	24	1.6
FUS	6	154	9	5.8	4	847	11	1.3
TRADBP	9	154	9	5.8	9	1,705	5	0.3
C9	7	173	6	3.5	7	3,051	16	0.5
SQSTM1	3	73	0	0	3	873	9	1
ATXN2	4	71	2	2.8	5	234	1	0.4
CHCHD10	4	123	0	0	4	1,332	3	0.2
TBK1	2	55	0	0	2	446	3	0.7
PFN1	5	88	0	0	4	1,229	1	0.1
ANG	5	94	0	0	2	558	1	0.1
VCP	4	78	0	0	3	689	0	0
VAPB	4	83	1	1.2	1	234	0	0
OPTN	3	58	1	1.7	3	876	8	0.9
UBQLN2	3	58	1	1.7	3	880	1	0.1
DCTN1	2	28	1	3.6	2	744	5	0.7
MATR3	1	32	0	0	2	684	2	0.3
CCNF	2	54	0	0	2	382	3	0.8
TUBA4A	1	80	0	0	1	500	0	0
TIA1	3	63	0	0	3	1,493	4	0.3
ARHGEF28	1	25	0	0	2	464	3	0.6
GLE1	1	20	0	0	1	230	0	0
ANXA11	2	30	1	3.3	2	573	8	1.4
KIF5A	0				1	960	4	0.4
Total (%)				55.0				11.7
Unknown				42.7				87.4

mutations in their FALS cohorts. However, in North American and French FALS patients, the mutation frequencies of *SQSTM1* gene were 1.76% and 1.11%. One study screened the *SQSTM1* gene mutation in 13 Chinese FALS patients with *SOD1* gene mutation, and found that the insertion of T in the intron 5 of *SQSTM1* gene may promote the ALS progression by damaging p62 function in the FALS-SOD1 G16A proband (Yang and Fan, 2014). The frequency of *OPTN* mutations was high in Japanese (3.8% in FALS, 0.29 in SALS) (Iida et al., 2012) and Chinese populations (1.7% in FALS, 0.9% in SALS), whereas these mutations ranged from 0% to 3.54% in Caucasian SALS patients (Li et al., 2015).

In European population, the *C9ORF72* repeat expansion

Table 2 Summary of single nucleotide polymorphisms studies conducted in Chinese ALS patients

Genes	Polymorphism	Authors	Samples	Results
SREBF1	*Rs11868035*	Yuan et al. (2018)	833 sALS, 814 HCs	The minor allele "G" Reduced risk for EOALS and female ALS
RTN4R	*Rs854971*	Xu et al. (2018)	499 sALS, 503 HCs	(–)
RTN4R	*Rs887765*	Xu et al. (2018)	499 sALS, 503 HCs	(–)
RTN4R	*Rs696880*	Xu et al. (2018)	499 sALS, 503 HCs	The minor allele "A" , Risk
RTN4R	*Rs1567871*	Xu et al. (2018)	499 sALS, 503 HCs	(–)
CTSD	*Rs17571*	Xi et al. (2018)	301 sALS, 474 HCs	(–)
SCFD1	*Rs10139154*	Chen et al. (2018)	1074 sALS, 927 HCs	(–)
HNMT and	*Thr105Ile*	Chen et al. (2018)	850 sALS, 836 HCs	(–)
STK39	*Rs2390669*	Chen et al. (2018)	850 sALS, 836 HCs	(–)
NMD3	*Rs34016896*	Chen et al. (2018)	850 sALS, 836 HCs	(–)
HLA-DRA/HLA-DRB5	*Rs9268877*	Yang et al. (2017)	400 sALS, 634 HCs	(–)
HLA-DRA/HLA-DRB5	*Rs9268856*	Yang et al. (2017)	400 sALS, 634 HCs	AA genotype, Risk
BTNL2	*Rs1980493*	Yang et al. (2017)	400 sALS, 634 HCs	(–)
RAB38/CTSC	*Rs302668*	Yang et al. (2017)	400 sALS, 634 HCs	(–)
BDNF	*Rs6265*	Xu et al. (2017)	499 sALS, 634 HCs	(–)
BDNF	*Rs56164415*	Xu et al. (2017)	499 sALS, 634 HCs	CT genotype and T allele, Risk
VMAT2	*Rs363371*	Hu et al. (2017)	863 sALS, 829 HCs	GG, Risk
VMAT2	*Rs363324*	Hu et al. (2017)	863 sALS, 829 HCs	(–)
TMEM106B	*Rs1990622*	Hu et al. (2017)	863 sALS, 829 HCs	(–)
TMEM106B	*Rs3173615*	Hu et al. (2017)	863 sALS, 829 HCs	(–)
DISC1	*Rs3737597*	Deng et al. (2017)	500 sALS, 500 HCs	Closely associated
P4HB	*Rs876016*	Yang et al. (2016)	322 sALS, 265 HCs	The minor allele "C" , Risk
P4HB	*Rs2070872*	Yang et al. (2016)	322 sALS, 265 HCs	The minor allele "G", Risk
GPNMB	*Rs156429*	Xu et al. (2016)	876 sALS, 829 HCs	(–)
SLC1A2	*Rs3794087*	Xu et al. (2016)	513 sALS, 437 HCs	(–)
ZNF512B	*Rs2275294*	Yang et al. (2015)	301 sALS, 457 HCs	CC genotype and C, Risk
ZNF512B	*Rs2275294*	Ju et al. (2015)	953 sALS, 1039 HCs	(–)
SNCA	*Rs3775444*	Chen et al. (2015)	885 sALS, 846 HCs	(–)
SNCA	*Rs3822086*	Chen et al. (2015)	885 sALS, 846 HCs	(–)
SNCA	*Rs11931074*	Chen et al. (2015)	885 sALS, 846 HCs	(–)
TREM2	*Rs75932628*	Chen et al. (2015)	868 sALS, 869 HCs	(–)
KRT18P55	*Rs34517613*	Chen et al. (2015)	869 sALS,871 HCs	(–)
C9orf72	*Rs3849942*	Chen et al. (2015)	869 sALS, 871 HCs	(–)
KRT18P55	*Rs34517613*	An et al. (2015)	298 sALS, 486 HCs	(–)
C9orf72	*Rs3849943*	An et al. (2015)	298 sALS, 486 HCs	(–)
SUSD2	*Rs8141797*	An et al. (2015)	298 sALS, 486 HCs	(–)
CAMK1G	*Rs6703183*	An et al. (2015)	298 sALS, 486 HCs	(–)
RAB7L1	*Rs1572931*	Guo et al. (2014)	778 sALS, 516 HCs	(–)
SNCA	*Rs2736990*	Guo et al. (2014)	778 sALS, 721 HCs	(–)
SNCA	*Rs356220*	Guo et al. (2014)	778 sALS, 721 HCs	(–)
9p21	*Rs2814707*	Chen et al. (2014)	397 sALS, 287 HCs	(–)
UNC13A	*Rs12608932*	Chen et al. (2014)	397 sALS, 287 HCs	(–)
TIMA1	*Rs13048019*	Chen et al. (2014)	397 sALS, 287 HCs	(–)
SCNN1A	*Rs2228576*	Chen et al. (2014)	397 sALS, 287 HCs	(–)
FGGY	*Rs6700125*	Cai et al. (2014)	397 sALS, 287 HCs	(–)

(*To be continued on the next page*)

(*Continued*)

Genes	Polymorphism	Authors	Samples	Results
FGGY	*Rs6690993*	Cai et al. (2014)	397 sALS, 287 HCs	(–)
MMP–9	*C(–1562)T*	He et al. (2013)	226 sALS, 351 HCs	Risk
ITPR2	*Rs2306677*	Chen et al. (2012)	395 sALS, 288 HCs	(–)
KIFAP3	*Rs1541160*	Chen et al. (2012)	395 sALS, 288 HCs	(–)
FLJ10986	*Rs6690993*	Chen et al. (2012)	395 sALS, 288 HCs	(–)
FLJ10986	*Rs6700125*	Chen et al. (2012)	395 sALS, 288 HCs	(–)
DPP6	*Rs10260404*	Chen et al. (2012)	395 sALS, 288 HCs	(–)
PON1	*Rs662*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON1	*Rs705381*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON1	*Rs705382*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON1	*Rs854548*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON1	*Rs854560*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON2	*Rs7493*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON2	*Rs11981433*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON3	*Rs757158*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
PON3	*Rs10487132*	Chen et al. (2012)	373 sALS, 248 HCs	(–)
9p21.2	*Rs2814707*	Iida et al. (2011)	684 sALS, 830 HCs	(–)
19p13.3	*Rs12608932*	Iida et al. (2011)	684 sALS, 830 HCs	(–)
HFE	*H63D*	He et al. (2011)	195 sALS, 405 HCs	Risk
DPP6	*Rs10260404*	Li et al. (2009)	58 sALS, 52 HCs	(–)
FLJ10986	*Rs10493256*	Fang et al. (2009)	57 sALS, 100 HCs	Risk
FLJ10986	*Rs1470407*	Fang et al. (2009)	57 sALS, 100 HCs	(–)
FLJ10986	*Rs6587852*	Fang et al. (2009)	57 sALS, 100 HCs	(–)
FLJ10986	*Rs333662*	Fang et al. (2009)	57 sALS, 100 HCs	(–)
FLJ10986	*Rs6700125*	Fang et al. (2009)	57 sALS, 100 HCs	(–)
FLJ10986	*Rs6690993*	Fang et al. (2009)	57 sALS, 100 HCs	(–)
VEGF	*C2578A*	Zhang et al. (2006)	115 sALS, 200 HCs	(–)

detected in 2011 was reported to account for 33.7% of FALS and 5.1% of SALS, 25% of familial FTD and a small fraction of sporadic FTD, indicating that *C9ORF72* is the major genetic factor in both diseases (van der Zee et al., 2013; Zou et al., 2017). The overlapping clinical syndromes in ALS and FTD have been confirmed in previous study, with around 15% of ALS cases showing a clear diagnosis of FTD and another 15% of FTD patients displaying ALS (Ji et al., 2017). Despite the high prevalence of *C9ORF72* in Caucasian population, Chinese population and the East Asian population had lower frequencies of *C9ORF72* repeat expansion in FALS and SALS (Konno et al., 2013). Along with *VCP* and *SQSTM1*, the mutations in these genes resulting in an ALS phenotype gave rise to another insight in the genetic links between ALS and FTD. Although *VCP* mutations have been reported in both FALS and SALS in Caucasian population, a lack of *VCP* mutation was reported in a Chinese ALS population (Zou et al., 2013). Intermediate-length expansions in *ATXN2* gene were reported to increase the risk of ALS in Western countries, and the similar results were found in Chinese patients from different regions (Lu et al., 2015).

Mutations in several other genes have been found to be rare or absent in Chinese ALS patients. The mutation of *SQSTM1*, *CHCHD10*, *TBK1*, *PFN1*, *ANG*, *MATR3*, *CCNF*, *TUBA4A*, *TIA1*, *ARHGEF28*, and *GLE1* genes was not detected in FALS, while the mutation of *VAPB*, *TUBA4A*, and *GLE1* genes was not reported in SALS. Only one study reported the mutation of *KIF5A* gene, with a frequency of 0.41% in SALS. A recent study reported that *ANXA11* gene accounted for a high mutant frequency of 5.6% (1/18) in FALS and 2.3% (8/353) in SALS, which is higher than the frequency in a European cohort (1% in FALS and 1.7% in SALS) (Zhang et al., 2018). However, another study included 286 unrelated Taiwanese SALS patients to investigate the ANXA11 mutations, and found no pathogenic *ANXA11* mutations in SALS patients (Tsai et al., 2018). These results highlighted the importance of regional difference in genetic heterogeneity. Several studies were conducted in Taiwanese ALS cohorts to determine the frequency of the ALS-im-

plicated genes, such as *SOD1*, *FUS*, *TARDBP*, *DCTN1*, *C9orf72*, *MATR4*, and *CCN*F (Tsai et al., 2011). In Taiwan, the *C9orf72* repeat expansion has been detected in 18.2% (4/22) of FALS and 2.0% (2/102) SALS patients (Tsai et al., 2012); *MATR3* and *CCN*F were detected approximately 0.6% and 0.9% in SALS, respectively (Lin et al., 2015; Tsai et al., 2018). These studies broaden the spectrum of the mutations causing ALS among different geographical backgrounds.

The potential investigation of GWAS in diverse worldwide populations provided substantial contributions to uncover the links between genetics and the pathogenesis of human complex diseases (Rosenberg et al., 2010), suggesting that the risk variants can vary in their occurrence across populations, and that the difference in allele frequencies among different populations in turn affects the detectability of these risk variants. Several recent GWAS studies have identified a number of loci that increase SALS susceptibility (Benyamin et al., 2017). Although most GWAS studies on ALS were performed in North American and European populations, 30 studies reported the associations between SNPs and risk of ALS in Chinese population. These studies presented an association between several SNPs and risk of ALS, such as from *HLA-DRA*, *BDNF*, and *VMAT2* gene, but the results only explained a few SALS risk (Xu et al., 2017; Yang et al., 2017). We have to admit that most genetic studies conducted in China were just replicated studies trying to verify the findings in Caucasians, which reflected a limitation for investigating the pathogenic mechanism underlying ALS neurodegeneration. A larger scale gene sequencing with novel technology such as whole genome sequencing, whole exome sequencing and GWAS should be performed in a large Chinese population from different areas to present the genetics of Chinese ALS cases. There is no doubt that genomics will continue to drive the research field forward. Genome sequencing will show greater insight into the genetic architecture of ALS by providing a large genetic data set and allowing us to explore the role of noncoding and intergenic genetic variation, as well as improving our understanding of motor neuron degeneration.

MATERIALS AND METHODS

Search strategy

To identify all eligible studies that reported the mutation frequencies of ALS-implicated genes or the association of SNPs with ALS in Chinese population, we conducted an intense literature search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Medline (National Library of Medicine), and China National Knowledge Internet (www.cnki.net) databases up to July 10th, 2018. The publication language was restricted to English or Chinese. A literature search strategy was designed and carried out using the following individual search terms, including “gene”, “genetic”, “mutation”, “single nucleotide polymorphism”, “single nucleotide polymorphisms”, “SNP”, “SNPs” in combination with “amyotrophic lateral sclerosis” or “ALS” or “motor neuron disease” or “MND” and “Chinese” or “Taiwanese” or “Hong Kong”.

Study selection criteria

All articles were screened according to the title and abstract. Studies with full text and original data were included for further evaluation and review, while abstracts published in relevant meetings were excluded. Only case-control studies or case series that reported mutation frequencies were included, and single case reports and review articles were excluded. Studies only focused on the gene functions and cellular mechanisms were excluded. ALS was diagnosed according to EI Escorial criteria, revised EI Escorial criteria, or Awaji criteria in these published studies. An identifiable family history of ALS among first, second or third-degree relatives was defined as FALS in these published articles (Byrne et al., 2011). Studies that only included the ALS-frontotemporal dementia (FTD) were excluded to avoid the potential selecting bias.

Data extraction and statistical analysis

Relevant data from all included studies were extracted by two authors (W-QQ and C-XP) independently. Inconsistencies were resolved by discussion with a third investigator (C-YP). The following data were extracted: surname of the first author, publication year, study design, ALS diagnostic criteria, sample size of patients and controls, exons sequenced, numbers of mutation carriers in FALS and SALS, and genotype and minor allele frequencies in cases and controls. Among FALS and SALS, the frequencies of gene mutations were calculated by the percentage of mutation carriers in each study. Studies had the same first author’s name, or partly overlapping participants were carefully screened. To release repeated data, we only selected the study with the most complete description of data or largest sample size.

CONCLUSION

Our study demonstrated that the overall gene mutation rates of ALS-implicated causative genes were 55.0% in FALS and 11.7% in SALS in China. The most common mutations were *SOD1* gene in both FALS and SALS. There was a significant difference of genetic features between Chinese and Caucasian populations, indicating an association between genetic

susceptibility and origin of population. Further explorations are required to understand the gene complexity of ALS, including the contribution of most minor genes and the molecular mechanisms in ALS pathologies.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

Table S1 The mutation frequencies of common causative genes in Chinese ALS patients from included studies

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