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The epidemiology and genetics of Amyotrophic lateral sclerosis in China

Xiaolu Liu^a, Ji He^a, Fen-Biao Gao^b, Aaron D. Gitler^c, and Dongsheng Fan^{a,*}

^aDepartment of Neurology, Peking University Third Hospital, Beijing 100191, PR China

^bDepartment of Neurology, University of Massachusetts Medical School, Worcester, MA 01605, USA

^cDepartment of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA

Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder associated with loss of motor neurons. Previous knowledge of the disease has been mainly based on studies from Caucasian ALS patients of European descent. Here we review the epidemiological characteristics of ALS among the Chinese population in order to compare the similarities and differences between Chinese ALS cases and those from other countries. We describe a potential lower incidence and prevalence of ALS, a younger age of onset and a lower proportion of familial ALS cases in the Chinese population. Additionally, we highlight potential genetic differences between Chinese and Caucasian ALS patients. Most notably, the frequency of GGGGCC repeat expansions in *C9ORF72* in Chinese ALS is significantly lower than in Caucasians. Since some conclusions might not be consistent across all of the studies around China to date, we suggest that it is necessary to carry out a prospective population-based study and large-scale gene sequencing around to better define epidemiological and genetic features of Chinese ALS patients.

Keywords

Amyotrophic lateral sclerosis; *C9ORF72*; China; Epidemiology; Genetics; *SOD1*

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disease caused by the progressive degeneration of upper and lower motor neurons in the brain and spinal cord (Brown and Al-Chalabi, 2017). The drugs riluzole and edaravone, approved by the US Food and Drug Administration for the treatment of ALS, improve survival but only to a limited extent. New therapeutic strategies are needed and it is hoped that a better understanding of ALS pathogenesis will lead to improved treatment strategies.

*Corresponding author. dsfan@aliyun.com (D.Fan).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.brainres.2018.02.035>.

The El Escorial diagnostic criteria, which were first developed in 1994 and underwent several revisions, are used by clinicians to diagnose ALS patients. Nevertheless, the heterogeneity in clinical presentation and lack of diagnostic biomarkers make early diagnosis a great challenge (Huynh and Kiernan, 2015). Currently, the pathogenesis of ALS remains largely unclear, but it is widely accepted that ALS is a syndrome rather than a single disease. The onset and progression of ALS is considered to be the result of environmental risk factors and aging acting on a pre-existing risk genetic background (Al-Chalabi and Hardiman, 2013).

There has been a large body of ALS research based on epidemiological and genetic studies of ALS patients from Caucasian populations of European origin. Compared to Caucasians, Chinese represent a significantly different population in terms of ethnic, social and cultural backgrounds. Therefore, it is valuable to consider the similarities and differences in ALS epidemiological and genetic features between China and other countries.

2. Epidemiologic characteristics of Chinese ALS patients

Here we review nine epidemiological studies of Chinese ALS populations (Table 1). The latter four studies, based on data drawn from the National Health Insurance Research Database in Taiwan or the computer system of Hospital Authority in Hong Kong, were considered population-based studies. While in Mainland China, a medical record system covering the whole country has not been established yet, the epidemiological studies were conducted based on data collected by one or several ALS referral centers.

The annual incidence of ALS is 0.51/100,000/year in Taiwan (Tsai et al., 2015) and 0.31–0.6/100,000/year in Hong Kong (Fong et al., 1996; 2005). Compared to worldwide figures, the incidence in China is lower than that in Japan (2.2/100,000/year) (Doi et al., 2014), Europe (2.16/100,000/year) (Logroscino et al., 2010) and Australia (2.74/100,000/year) (Kiernan et al., 2006). While the prevalence is 1.97/100,000/year in Taiwan and 0.95–3.04/100,000/year in Hong Kong, which is equally lower than that in Japan (9.9/100,000/year) (Doi et al., 2014) and Australia (8/100,000/year) (Kiernan et al., 2006). It was reported that the incidence of ALS is lower in an ethnically mixed population (Zaldivar et al., 2009). One potential explanation is that heterogeneous populations are less likely to share ALS risk genes (Shahrizaila et al., 2016). China is a multi-ethnic country. Among the 1.3 billion people in Mainland China, in addition to the Han Chinese, 8.49% of the population is ethnic minorities. Similarly, about 6.7% of the population in Taiwan is ethnic minorities and 7.5% of the population in Hong Kong is non-Chinese. In many regions throughout China, there are likely many inter-ethnic marriages resulting in a large genetic and ethnic mixed population, which might be one of the reasons for the low incidence and prevalence of ALS in China. Comparing the two population-based studies from Hong Kong, an increase in both prevalence and incidence has been observed (Table 1) (Fong et al., 1996; 2005), which was in accordance with the worldwide trend. It is projected that the number of ALS patients across the global will increase 69% from 2015 to 2040, predominantly due to aging of the population with improving healthcare and economic conditions (Arthur et al., 2016).

The mean age of onset in Chinese ALS patients is 49.8–54.3 years old in hospital-based studies and 55.5–58.76 years old in population-based studies (Table 1). In Japan and Europe, the mean age of onset is 62.1 (Furuta et al., 2013) and 62.1–66.3 years old (Al-Chalabi et al., 2014), respectively. However, in India, it is 46.2 years old (Nalini et al., 2008), lower than that in most other regions around the world. Compared with Mainland China, economic development and life expectancy in Taiwan and Hong Kong are closer to those in developed countries. It has been suggested that age of onset is younger in less developed regions with shorter life expectancy. Older and more severe patients are less likely to be referred to regional or national referral centers, which also partially explains for the documented younger age of onset. Another potential contributing factor is higher level of environmental pollution in less developed areas.

It is widely accepted that the frequency of familial ALS (fALS) is about 10% (Brown and Al-Chalabi, 2017). Although not all the studies above included fALS patients, the percentage of fALS is only 1.2–2.7% in Chinese patients (Table 1). The rate is similar to that in southern Europe, but lower than other regions around the world (Byrne et al., 2011). Unfortunately, the definition of fALS in each of the studies is not consistent, making the comparison difficult. Further detailed prospective population-based studies of fALS are required to confirm this rate.

Although the above mentioned studies share some common characteristics, some conclusions drawn from these studies are inconsistent. The proportion of bulbar-onset patients, reported by the largest single-center in Mainland China, is only 14% (Chen et al., 2015), while the proportion from a multi-center study is 30.9% (Liu et al., 2014a). It's commonly accepted that about 25% of ALS patients develop initial symptoms in the bulbar-innervated muscles (Al-Chalabi et al., 2016), so it is hard to regard the percentage of bulbar-onset as a specific feature of Chinese patients. The median survival time is also inconsistent among different studies. In the cohort from the largest single-center in Mainland China and the data from Taiwan, it's about 71 (Chen et al., 2015) and 66.6 months (Lee et al., 2013), respectively. While in the cohort from another single-center located in the southeast of China and the data from Hong Kong, it is only 29.67–33.6 months (Fong et al., 1996; Yang et al., 2011). It has been demonstrated that up to 70% of ALS patients die within 3 years of disease onset by the population-based registers from European countries (Hardiman et al., 2017). The inclusion criteria of each study were diverse. Some included the atypical phenotypes with better prognosis than classical ALS, such as flail arm syndrome (FAS) and progressive muscular atrophy (PMA), while some studies included only classical ALS patients. Thus, it is too early to make firm conclusions of survival time in Chinese ALS patients.

3. Genetic characteristics of Chinese ALS patients

With the progress of genetic research in ALS, it cannot be ignored that the prominent genetic differences between Chinese and Caucasian ALS patients could be a primary reason underlying the distinct clinical features (Fig. 1).

The GGGGCC (G₄C₂) repeat expansion in *C9ORF72*, the most common genetic cause of ALS and frontotemporal dementia (FTD) in Caucasian, accounting for about 33.7% and

5.1% of fALS and sporadic ALS (sALS) in European patient populations, is scarcely detected in Chinese ALS patients (Zou et al., 2017). Among the eleven studies focusing on the G₄C₂ repeat expansion conducted in China, the mutation was found in only 0–18.2% of fALS and 0–2.0% of sALS cases (Supplementary Table S1). In contrast, the low frequencies of the expanded G₄C₂ repeats have been reported in other East Asian population, including 3.4% of fALS and 0% of sALS in Japanese patients (Konno et al., 2013) and none in Korean fALS and sALS patients (Jang et al., 2013). Compared to the cohorts in Mainland China, the frequency of the mutation in Taiwan seems much higher. The admixture with Dutch and Spanish in the 17th century in Taiwan might be a reasonable explanation (Tsai et al., 2012). Among the patients with expanded G₄C₂ repeats, four of them were reported to have a phenotype of ALS-FTD or a family history of FTD (Jiao et al., 2014; Soong et al., 2014), another three patients exhibited cognitive impairment (Chen et al., 2016b). An intermediate length of G₄C₂ repeats might also be pathological in Caucasian ALS patients (Byrne et al., 2014), while the phenomenon was not detected in the studies of Chinese patients (Chen et al., 2016b; Jiao et al., 2014; Liu et al., 2016a). Interestingly, a patient with a heterozygous splice site mutation (c.601–2A > G) was identified using the method of targeted sequencing of coding regions. Functional analysis indicated that the splice site mutation created a premature stop codon (p. I201fsX235) with a decreased mutant messenger RNA levels, supporting the potential loss-of-function mechanism in the pathogenesis of *C9ORF72* mutation (Liu et al., 2016a).

Additionally, a single founder risk haplotype has been reported in most G₄C₂ repeat expansion-carrying ALS cases in diverse European populations (Mok et al., 2012). Four studies conducted the haplotype analysis including 8 to 23 SNPs surrounding the G₄C₂ repeats (Supplementary Table S2). Overall, the SNPs detected in 5 out of 15 patients with the expansion mutation were exactly consistent with the European risk haplotype. Four patients didn't carry the risk allele in no less than 5 SNPs flanking the G₄C₂ repeats including rs3849942. The frequencies of risk alleles (A in rs2814707, A in rs3849942, C in rs774359 and G in rs1982915) in Han Chinese are much lower than those in Caucasian, which is one reason for the risk alleles relatively less common in Chinese expansion carriers. Additionally, it could not be excluded that recombination events occurred from generation to generation. It is too early to make a firm conclusion that G₄C₂ repeat expansion in Chinese ALS patients was a result of founder effect or some unrelated mutation events (Chen et al., 2016a).

In contrast, mutations in *SOD1* account for 25.3% of Chinese fALS cases, which has been identified as the most frequently mutated ALS gene in China, followed by *TARDBP* (5.8%) and *FUS* (5.8%) (Supplementary Table S1). In contrast, among Caucasian fALS cases, the percentage of mutations in *SOD1*, *TARDBP* and *FUS* was 14.8%, 4.2% and 2.8%, respectively (Zou et al., 2017). In Chinese sporadic cases, mutations in *FUS* (1.3%) are more common than those in Caucasians (0.3%) (Supplementary Table S1) (Zou et al., 2017). In several studies focusing on juvenile ALS (jALS) cases in China, mutations in *FUS* were the most frequent in this rare group with the age of onset younger than 25 years old, which is consistent with Caucasians (Hübbers et al., 2015; Liu et al., 2017b; Zou et al., 2013a, 2016). The early age of onset in Chinese ALS may be partially due to the relatively higher frequency of *FUS* mutations in familial and sporadic cases.

Intermediate CAG repeat expansions in *ATXN2* were identified as a genetic risk factor for ALS in multiple Caucasian ethnicities (Elden et al., 2010; Gellera et al., 2012; Neuenschwander et al., 2014; Van Langenhove et al., 2012). Several studies conducted in China confirmed the association between intermediate CAG repeat expansions and ALS risk, rather than the phenotype, in Chinese population from different regions (Chen et al., 2011; Liu et al., 2013; Lu et al., 2015). Variants in *SQSTM1* and *OPTN* were detected in around 1% of sALS Chinese patients respectively, but it will be necessary to carry out more functional studies to verify the pathogenicity of these variants (Chen et al., 2014; Li et al., 2015; Liu et al., 2016b; Yang et al., 2015). By contrast, mutations in some other genes previously reported to be linked to ALS, including *VAPB*, *ANG*, *VCP*, *UBQLN2* and *DCTN1*, had been found to be rare or absent in Chinese ALS patients (Huang et al., 2017; Liu et al., 2016b, 2017a; Soong et al., 2014; Zou et al., 2012, 2013b). In recent years, the development of whole exome sequencing (WES), expedited the discovery of ALS genes. *PFN1*, *HNRNPA1*, *CHCHD10*, *MATR3*, *TBK1*, *TUBA4A* and *CCNF* were identified disease-causing one after another based on the analysis of WES performed in several ALS families or large cohorts of familial and sporadic ALS cases with Caucasian origin (Bannwarth et al., 2014; Cirulli et al., 2015; Freischmidt et al., 2015; Johnson et al., 2014; Kim et al., 2013, 2016; Smith et al., 2014; Wu et al., 2012). Unfortunately, mutations in above-mentioned genes are quite rare in Chinese population, suggesting genes may not be informative of the genetics in Chinese ALS patients (Chen et al., 2013; Li et al., 2016; Lin et al., 2015; Pan et al., 2017; Shen et al., 2017; Shu et al., 2016; Soong et al., 2014; Tsai et al., 2016, 2017; Xu et al., 2016; Zhou et al., 2017; Zou et al., 2013c). Targeted next-generation sequencing (NGS), a cost-effective approach for variant screening in known ALS genes, has been applied primarily in fALS and jALS (Liu et al., 2014b, 2017b). In addition, based on the data from targeted NGS, the cooccurrence of two or more variants of known ALS genes detected in one patient has been reported in 25% of fALS and 3.0% of sALS, respectively (Liu et al., 2016b). An extensive use of targeted NGS will provide more evidence for the existence of oligogenic basis for ALS.

In recent years, several studies have attempted to define new candidate loci or genes for ALS using genome-wide association study (GWAS) and WES in Chinese population. Two new susceptibility loci, rs6703183 covering *CAMK1G* and rs8141797 located in the region harboring *CABIN1* and *SUSD2*, were found in GWAS analysis in Han Chinese ALS (Deng et al., 2013). Afterwards, it was identified that a significant association of rs10463311 spanning *GPX3-TNIP1* with ALS in the meta analysis of GWAS data from Chinese and European cohorts (Benyamin et al., 2017). Recently, *NEK1* was reported a risk ALS gene based on the meta-analysis of WES data from large cohorts of Chinese and European ancestry (Gratten et al., 2017), which was consistent with the two studies from several European countries (Brenner et al., 2016; Kenna et al., 2016) and considered the first study to define a new gene with WES data in Chinese ALS.

4. Limitations and future directions

In the cohort studies conducted in Mainland China, significant inclusion bias cannot be ignored. First, younger, better-educated and higher-income patients are more likely to visit a national or regional referral hospital. Second, some patients visit more than one hospital thus

are included in different databases. Third, limited by geographic factors and population scales, the retrospective population-based studies completed in Taiwan and Hong Kong are not representative of all China. A prospective population-based registration around China, named China ALS Research (CHALSR), is ongoing and dedicated to filling in gaps in ALS epidemiological research in China. Moreover, genetic mutations in many genes cause both ALS and FTD and several downstream molecular pathways are dysregulated in both disorders (Gao et al., 2017). Yet, diagnosis and research on cognitive deficits in Chinese ALS patients remains rudimentary. Finally, the aims of most genetic studies conducted in China were to confirm the findings in Caucasians. A larger scale gene sequencing with novel technology such as whole genome sequencing (WGS), WES and GWAS should be performed to collect comprehensive genetic information and define the genetics of Chinese ALS cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Genetic architecture of fALS and sALS in Chinese and Caucasian populations.

Table 1

Summary of epidemiological studies of ALS patients conducted in China.

Study	Yang et al. (2011)	Liu et al. (2014a)	Cui et al. (2014)	Chen et al. (2015)	Wei et al. (2015)	Lee et al. (2013)	Tsai et al. (2015)	Fong et al. (1996)	Fong et al. (2005)
Study/location	Mainland	Mainland	Mainland	Mainland	Mainland	Taiwan	Taiwan	HongKong	HongKong
Study/type	Single-center cohort	Multicenter cohort	Multicenter cohort	Single-center cohort	Single-center cohort	Population based	Population based	Population based	Population based
Follow-up	Yes	Yes	No	Yes	No	Yes	No	No	No
Study/duration(year)	2004–2010	2009–2010	2009–2010	2003–2012	2006–2014	1999–2008	1999–2008	1989–1992	1997–2002
Number/case	139	455	461	1624	1131	1149	1136	84	218
Incidence(per10 ⁵)	/	/	/	/	/	/	0.51	0.31	0.6
Prevalence(per10 ⁵)	/	/	/	/	/	/	1.97	0.95	3.04
Meanage/onset	50.54	52.4	52.6	49.8	54.3	56.27	56.6	55.5	58.76
Gender/ratio(M:F)	/	1.63	1.6	1.7	1.45	1.65	1.67	1.98	1.72
Survivaltime(months)	29.67	/	/	71	/	66.6	/	33.6	/
Percentage of bulbar-onset	/	30.90%	20.30%	14.00%	20.30%	/	/	/	/
Percentage of fALS	/	/	2.7%	/	1.8%	/	/	1.2%	/
Percentage of riluzole-use	/	/	28.90%	32.30%	35%	60.75%	56%	/	/
Percentage of NIPPV-use	/	/	34.50%	10%	3.70%	16.80%	/	/	/
Percentage of invasive ventilation	/	/	18.00%	/	/	20.97%	16.5–20.5%	/	/
Percentage of PEG-use	/	/	27.10%	/	1.30%	3.80%	/	/	/

* Abbreviations: M: male; F: female; NIPPV: noninvasive positive pressure ventilation; PEG: percutaneous endoscopy.