Neurobiology of Aging 35 (2014) 1778.e9–1778.e23

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

A genome-wide association study combining pathway analysis for typical sporadic amyotrophic lateral sclerosis in Chinese Han populations

Tong Xie [a], Libin Deng [b], Puming Mei [b], Yiyi Zhou [a], Bo Wang [a], Jie Zhang [a], Jiari Lin [b], Yi Wei [b], Xiong Zhang [c], Renshi Xu [a,*]

[a] Department of Neurology, the First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[b] Institute of Translational Medicine, Nanchang University, Nanchang, Jiangxi, China
[c] Department of Neurology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangdong Neuroscience Institute, Guangzhou, China

ARTICLE INFO

Article history:
Received 21 August 2013
Received in revised form 20 December 2013
Accepted 12 January 2014
Available online 17 January 2014

Keywords:
Sporadic amyotrophic lateral sclerosis
Genome-wide association study
Locus
Pathway
Chinese Han populations

ABSTRACT

Sporadic amyotrophic lateral sclerosis (sALS) is a severe neurodegenerative disease that causes progressive motor neuron death. Although the etiology of sALS remains unknown, genetic variants are thought to predispose individuals to the disease. Several recent genome-wide association studies have identified a number of loci that increase sALS susceptibility, but these only explain a small proportion of the disease. To extend the current genetic evidence and to identify novel candidates of sALS, we performed a pooling genome-wide association study by 859,311 autosomal single-nucleotide polymorphisms of IlluminaHumanOmniZhongHua-8 combining pathway analysis in 250 typical sALS cases precluding age, clinical course, and phenotype interference and 250 control subjects from Chinese Han populations (CHP). The results revealed that 8 novel loci of 1p34.3, 3p21.1, 3p22.2, 10p15.2, 22q12.1, 3q13.11, 11q25, 12q24.33, and 5 previously reported loci of CNTN4 (kgp11325216), ATXN1 (kgp8327591), C9orf72 (kgp6016770), ITPR2 (kgp3041552), and SOD1 (kgp10760302) were associated with sALS from CHP. Furthermore, the pathway analysis based on the Gene Set Analysis Toolkit V2 showed that 10 top pathways were strongly associated with sALS from CHP, and among them, the 7 most potentially candidate pathways were phosphatidylinositol signaling system, Wnt signaling pathway, axon guidance, MAPK signaling pathway, neurotrophin signaling pathway, arachidonic acid metabolism, and T-cell receptor signaling pathway, a total of 39 significantly associate genes in 7 candidate pathways was suggested to involve in the pathogenesis of sALS from CHP. In conclusion, our results revealed several new loci and pathways related to sALS from CHP and extend the association evidence for partial loci, genes, and pathways, which were previously identified in other populations. Thus, our data provided new clues for exploring the pathogenesis of sALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease. It causes the degeneration of motor neurons in the primary motor cortex, brain stem, and spinal cord, which subsequently results in rapidly progressive paralysis of the skeletal muscles. Individuals suffering from this disease ultimately die because of respiratory failure, which usually occurs within 3–5 years after disease onset. Most of ALS cases are acquired spontaneously (sporadic ALS; sALS), whereas only 10%–15% of ALS cases are inherited (familial ALS) (Ludolph et al., 2012). However, the etiology of sALS is less clear and is considered multifactorial and polygenic in most cases. Several interdependent and interacting mechanisms have been shown to induce motor neuron damage in sALS, which are excitotoxicity, aberrant RNA processing, altered axonal transport, protein misfolding aggregation, mitochondrial dysfunction, toxicity of non-neuronal (glial) cells, oxidative stress (Contestabile, 2011), virus infection, autoimmune reaction, abnormal apoptotic processes, and gene mutations (Liscic & Breljak, 2011). Although there has been no conclusive evidence that any of these factors are responsible for even a small fraction of sALS cases, several genetic

* Corresponding author at: Department of Neurology, the First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China. Tel.: +86 91 88603798.
E-mail address: xurenshi@yahoo.com (R. Xu).

0197-4580/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.01.014

factors have been recently suggested to play an important role in the pathogenesis of sALS (Ravits et al., 2013). However, until the recent development of genome-wide association study (GWAS), little was known of the genetic evidence of sALS. Recent breakthroughs in genetics have enlarged the number of known mutations causing sALS, but these mutations only explain a few of sALS risk (Pasinelli & Brown, 2006).

Putative susceptible genes of sALS have been proposed by recent studies (Lattante et al., 2012), including vascular endothelial growth factor (Lambrechts et al., 2003), angiogenin (Greenway et al., 2006), apurinic endonuclease (Greenway et al., 2004), hemochromatosis (Sutedja et al., 2007), survival motor neuron (SMN1, SMN2) (Corcia et al., 2006; Veldink et al., 2005), the cluster of paraoxonase on chromosome 7q (PON1, PON2, PON3) (Slowik et al., 2006), TARDBP and FUS (Lattante et al., 2013), C9orf72 (Debray et al., 2013), ataxin-1 and ataxin-2 (Conforti et al., 2012), and PFN1 (Tiloca et al., 2013). However, to date, no gene has been conclusively determined to be responsible for the pathogenesis of sALS.

The potential of GWAS on disparate populations to uncover the links between genetics and the pathogenesis of human complex diseases has been generally studied (Rosenberg et al., 2010), suggesting that the risk variants can vary in their occurrence across populations (Dhandapany et al., 2009; Goldstein & Hirschhorn, 2004), and that the difference in allele frequencies among different populations in turn affects the detectability of these risk variants. The identification of a variant might be easier in the same population when compared with that of complex populations because the particular histories of recombination, mutations, and divergences of genealogical lineages in various populations affect the ability to map the variant (Adeyemo & Rotimi, 2010; Myles et al., 2008). In addition, Stranger et al. (2011) also indicated that studying additional populations in GWAS might provide valuable insights for current and future research studies in medical genetics. To date, nearly all GWAS on ALS have been performed on North American and European populations and only a few partial Asian populations have been studied, thus, further investigations are required on diverse populations to identify and extend the current results, particularly in Chinese Han populations (CHP) because they constitute nearly 20% of the world population.

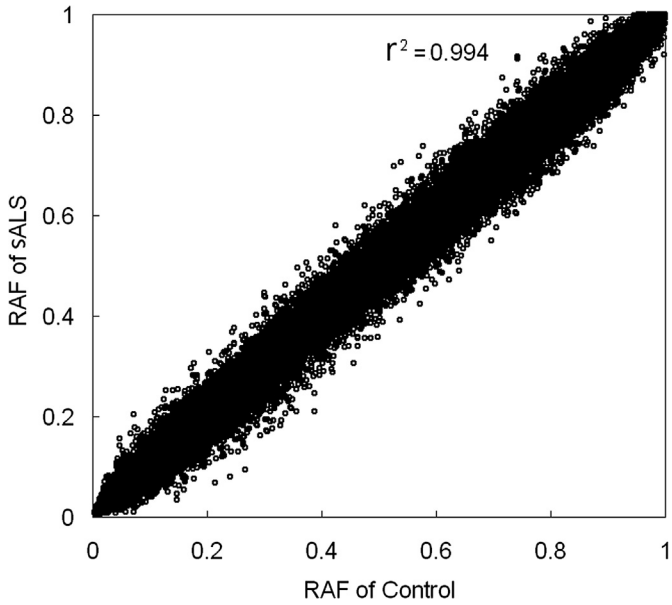

Fig. 1. Scatter plot of pooling genotypic data. Predicted allele frequencies of 859,311 randomly selected SNPs in sALS case and control DNA pools, $r^2 = 0.994$. Abbreviations: sALS, sporadic amyotrophic lateral sclerosis; SNPs, single-nucleotide polymorphisms.

Many examples of GWAS have indicated the scarcity of the many potential variants that contribute to the explanation of a small percentage of the estimated heritability for complex diseases, which constitutes a major challenge in the identification of risk single-nucleotide polymorphisms (SNPs) that are specific to a complex disease or in developing genetic risk prediction tests (Couzin & Kaiser, 2007; Dermitzakis & Clark, 2009; Eichler et al., 2010; Gibson, 2010; Holtzman et al., 2011; Manolio et al., 2009; Shriner et al., 2007; Williams et al., 2007; Wray et al., 2007). Multiple factors (e.g., SNPs, microRNAs, and metabolic and epigenetic factors) may target different sets of genes in the same pathway to affect the pathway's function. In contrast to isolated molecules, network and pathway oriented analyses are thought to be more beneficial to capture pathologic perturbations and to better explain predispositions to a disease (Schadt & Björkegren,

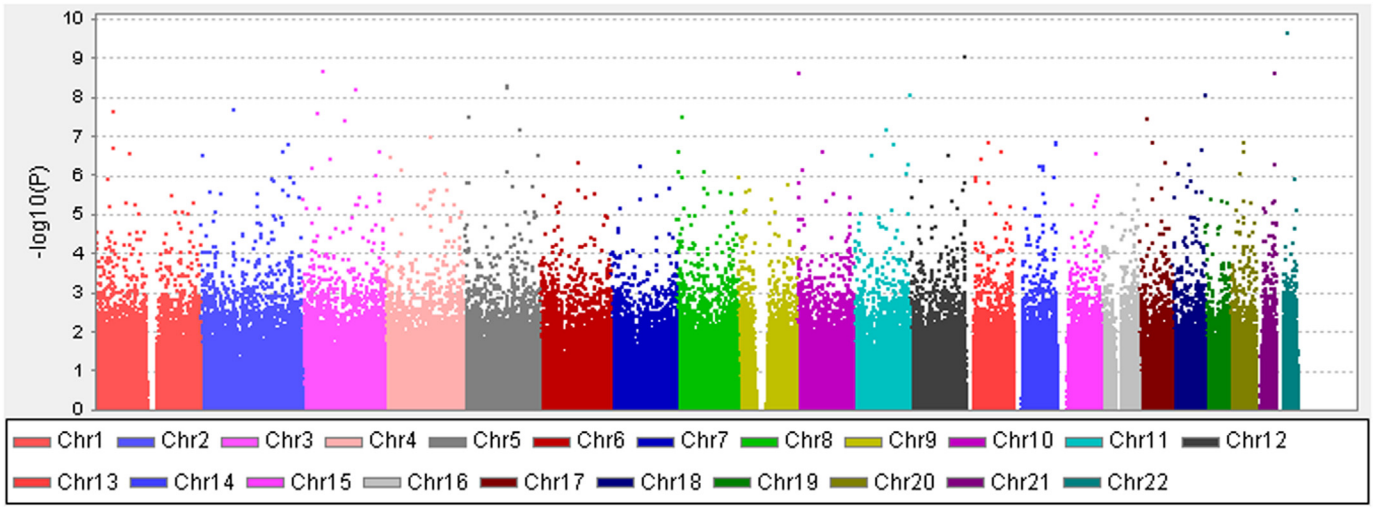

Fig. 2. Genome-wide association *p* value. The Manhattan plot of the GWAS shows the *p* values for the association of 859,311 autosomal SNPs with sALS from CHP. The x-axis shows the chromosomal positions. The y-axis shows the −log10 *p* value. Logistic analysis corrected for the genomic inflation of the Genome-wide signal plots. Negative log base 10 ranking *p* value from the Z combination test was plotted against the genomic position. Abbreviations: CHP, Chinese Han populations; GWAS, genome-wide association studies; sALS, sporadic amyotrophic lateral sclerosis; SNPs, single-nucleotide polymorphisms.