**Abstract**

**Objective:** Amyotrophic lateral sclerosis (ALS) is a fatal neurodegeneration disease affecting motor neurons in the brain and spinal cord, which is difficult to diagnose and treat. The objective of this study is to identify novel candidate genes related to ALS.

**Methods:** Transcriptome-wide association (TWAS) of ALS was conducted by using the genome-wide association study (GWAS) data from a previous study, including 1,234 ALS patients and 2,850 controls. The ALS-associated genes identified by TWAS were further compared with the differentially expressed genes detected by the mRNA expression profiles of the sporadic ALS (sALS). Functional enrichment and annotation analysis of identified genes were performed by a R package and the functional mapping and annotation (FUMA) software.

**Results:** TWAS identified 761 significant genes, 627 GO terms and 8 KEGG pathways for ALS (*P*TWAS<0.05), such as *C9orf72*, with three expression quantitative trait loci (eQTLs) were found significantly, rs2453554 (*P*TWAS CBRS=4.68×10-10, *P*TWAS CBRS=2.54×10-9), rs10967976 (*P*TWAS CBRS=7.85×10-10, *P*TWAS CBRS=8.91×10-9, *P*TWAS CBRS=1.49×10-7, *P*TWAS CBRS=5.59×10-7), rs3849946 (*P*TWAS CBRS=7.69×10-4, *P*TWAS YBL=4.02×10-2), Mitochondrion (*P*adj=4.22×10-16), Cell cycle (*P*adj=2.04×10-3). Moreover, 107 common genes, 4 KEGG pathways and 41 GO terms were detected for sALS, like *CPVL* (FC=2.06, *P*mRNA=6.99×10-6, *P*TWAS CBR=2.88×10-2, *P*TWAS CBR=4.37×10-2), Pyrimidine Metabolism (*P*adj=2.43×10-2) and Cell Activation (*P*adj=5.54×10-3).

**Conclusions:** Multiple candidate genes and pathways were detected for ALS. Our findings may provide novel clues for understanding the genetic mechanism of ALS.