**Methods**

**GWAS summary data of ALS**

The GWAS summary data of ALS were obtained from a previous study[7]. Briefly, a Chinese sample from 1,234 ALS cases and 2,850 controls were adopted for a genome-wide association analysis. The cases were diagnosed by a neurologist specializing in ALS using the revised El Escorial criteria. Genomic DNA was extrated from whole blood by using the DNA extration Kit. The Illumina HumanOmni ZhongHua-8 v1.0 arrays were used for genome-wide genotyping in the discovery cohort. Detailed discription of the sample charateristics, experimental design and statistical analysis could be found in the publish study[7].

**mRNA expression profiles of sALS**

The mRNA exprssion profiles of sALS were derived from a published study[13]. Briefly, 12 sALS and 10 control lumbar spinal cords acquired for genomic studies. The sALS nervous system were from patients who had been followed during the clinical course of their illness and met El Escorial criteria for definite ALS. Control samples were from patients the hospital critical care unit when life support was withdrawn, patient on hospice and from the Pennsylvania Tissue Repository. The GeneChip Human Exon 1.0 ST Arrays (Affymetrix) were used for exon array hybridization. RNA was isolated, amplified for mRNA and profiled whole genome exon splicing. Finally, 17,864 genes were idenfied in sALS patients compared with control subjects. Detailed informations were given in the published study[13].

**TWAS of ALS**

TWAS of ALS was performed by the FUSION software brain RAN-seq splicing through integrating the ALS GWAS summary data and pre-computed gene expression weights of different tissues, including CBRS, CBR, NBL and YBL (http://gusevlab.org/projects/fusion/)[10]. The gene expression weights reference of CBR, CB, NBL and YBL were obtained from the FUSION software. FUSION is capable to detect the associations of each gene with target diseases among different tissues. The gene expression weights were firstly calculated by FUSION. Then, the GWAS results of ALS were combined with the calculated expression weights to impute association statistics between gene expression levels and target disease. The association test statistics between predicted gene expression and target diseases were defined as TWAS Z-score, and calculated using the formula below[10]:

ZTWAS = WZ/(W Σs,s Wt )1/2

Z stands for the scores of ALS, W for the weights, and S for the SNP-correlation covariance matrix. The imputed expression is predicted as a linear model of genotypes with weights based on the association between SNPs and gene expression by calculating linkage disquilirium among SNPs[10]. In this study, the permutation test was run 2,000 times for each TWAS gene to control the potential impact on multiple test problems, and TWAS *P* value was estimated for each gene by Z-test within CBRS, CBR, NBL and YBL. The significant genes were defined as *P*TWAS<0.05. After that, the candidate genes identified by TWAS were compared with the significant expressed genes detected by mRNA expression profiles of sALS to identify the common genes for sALS.

**Functional enrichment and annotation analysis**

Gene ontology (GO) and pathway enrichment analyses of the genes identified by TWAS and integrative analysis with mRNA expresssion profiles were performed by a R package and the functional mapping and annotation (FUMA) software[14, 15].