Integrating the analysis of transcriptome-wide association study and gene expression profile to identify genes associated with spondyloarthritis

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Research article

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Abstract

Background

Spondyloarthritis(SpA) is a group of multi-factorial bone diseases influenced by genetic factors, environment and lifestyles. However, the genetic and pathogenic mechanism of SpA is still elusive.

Methods

Firstly, the tissue-specific transcriptome-wide association study (TWAS) of SpA was performed by utilizing the genome-wide association study (GWAS, including 3966 SpA patients and 452264 controls) summary data and gene expression weights of the whole blood and skeletal muscle. Secondly, the SpA-associated genes identified by TWAS were further compared with the differentially expressed genes(DEGs) detected by gene expression profile of SpA acquired from the Gene Expression Omnibus database (GEO, accession number:GSE58667). Finally, FUMA and Metascape tools were used to conduct gene functional enrichment and annotation analysis.

Results

TWAS detected 28 significant genes associated with SpA both in the whole blood and skeletal muscle, such as CTNNAL1 (P_{SM}=0.0304, P_{WB}=0.0096). Further comparing with gene expression profile of SpA, we identified 20 candidate genes which overlapped in TWAS, such as MCM4 (P_{TWAS}=0.0132, P_{DEG}=0.0275), KIAA1109 (P_{TWAS}=0.0371,P_{DEG}=0.0467). The enrichment analysis of the genes identified by TWAS detected 93 significant GO terms 33 and KEGG pathways, such as mitochondrion organization (GO:0007005, $\log_{10}(P)$= -4.29) and axon guidance(hsa04360, $\log_{10}(P)$= -4.26).

Conclusion

We identified multiple candidate genes genetically related to SpA. Our study may provide some novel clues for the further study of the genetic mechanism, diagnosis and treatment of SpA.

Introduction

Spondyloarthritis (SpA) is a group of several related but phenotypically distinct disorders including psoriatic arthritis, arthritis related to inflammatory bowel disease, reactive arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis [1]. The symptoms of SpA include the inflammation of the axial skeleton, a typically asymmetric peripheral arthritis of the lower limbs, enthesitis, typical extra-articular manifestations and all subtypes of SpA shared a common genetic background [2]. The prevalence of SpA shows considerable differences among ethnic groups and populations, which varied from 0.01% in

Japan to 2.5 % in Alaska and the annual estimated incidence of SpA was 62.5/100.000 [3]. The worldwide prevalence of SpA has seriously affected the function of muscle-skeletal system and reduce the quality of life [3].

Recently, an increasing number of studies have focused on the genetic mechanisms of SpA. Through familial aggregation, previous studies have estimated that genetic risk factors contribute to 80–90% of the susceptibility to ankylosing spondylitis [1]. Genome-wide association study (GWAS) have deepen our understanding of genetic factors in the susceptibility to SpA [4]. By using GWAS approach, Díaz-Peña et al. revealed the potential involvement of mechanisms and pathways that were previously unsuspected in SpA, particularly with regard to aminopeptidases or IL23/IL17 pathways [4]. Unfortunately, the specific genetic mechanism of SpA is still unclear.

In recent years, GWAS is considered to be one of the primary tools for determining genetic links to diseases. But GWAS is only recommended for evaluating the risk of disease. The reason is most of GWAS-identified SNPs (single nucleotide polymorphisms) located in the non-coding regions of the genome and the interpretation of those variants at the gene expression level is limited [5]. Expression quantitative trait loci (eQTL) analysis is a way to identify genes related to variation in gene expression [6]. Therefore, integrating GWAS and eQTL analysis may help to identify the candidate genes which associated with disease more powerfully. In previous study, researchers have integrated publicly available GWAS summary data and eQTL reference datasets to evaluate the gene-trait relationships, called transcriptome-wide association study (TWAS) [7]. Different from GWAS, TWAS can drastically reduce the comparisons in statistical analysis and enhance the ability to detect the candidate genes of target diseases [8]. In recent years, TWAS is widely used to identify the genetic loci associated with the target diseases by an increasing number. For examples, Liao C et al. identified 9 transcriptome-wide significant hits of attention deficit/hyperactivity disorder (ADHD), of which 6 genes were not implicated in the original GWAS [9]. In addition, Mancuso N et al. identified 217 genes at 84 independent 1 Mb regions associated with prostate cancer risk through TWAS analysis, which can provide novel risk loci and prioritize putative causal genes at known risk loci of prostate cancer [10]. However, until now, there is few TWAS analysis focus on the SpA.

In this study, by integrating a large scale GWAS summary data of SpA and gene expression weights from two specific tissues, we conducted a TWAS analysis to identify genes associated with SpA. The significant genes identified by TWAS were further validated by gene expression profile of SpA. To further confirm the functional relevance of candidate genes, Functional Mapping and Annotation of genome wide association study (FUMA) and Metascape tools were then used to perform functional enrichment and annotation analysis. Our study may provide novel clues into the genetic mechanism, diagnosis and treatment of SpA.

Materials And Methods

The GWAS summary data set of SpA

A large-scale GWAS summary data set of SpA was obtained from the published study [11]. In short, the data set contains 4,033 diagnosed SpA and 458,900 controls of European from the UK Biobank [11]. The UK Biobank participants were genotyped using the Affymetrix UK Bileve AXIOM or UK Biobank AXIOM array and imputed against approximately 90 million genetic variations from the Haplotype Reference Consortium, 1000 genomes and the UK 10K project [11]. After filtering, the data set contains 9,113,133 imputed variants. The IMPUTE4 program was used to perform the imputation (http://jmarchini.org/software/). The summary data contains 3,966 SpA and 448,298 controls. Detailed information on the subjects, genotyping, imputation, and quality control can be found in the published study[11].

TWAS of SpA

The TWAS of SpA was carried out by using the Functional Summary-based Imputation software(FUSION http://gusevlab.org/projects/fusion/). FUSION is a new approach to identify genes whose expression is significantly associated with complex traits in individuals without directly measured the expression level by integrating the GWAS summary data and pre-calculated gene expression weights of different tissues[12]. The tissue of the whole blood and skeletal muscle were also used in previous biological studies of SpA [13, 14]. In this study, we used the pre-calculated gene expression weights of the whole blood and skeletal muscle by using the prediction models of FUSION. Then the calculated gene expression weights were combined with GWAS statistics to impute the association statistics between the gene expression level and SpA. The FUSION software and the gene expression weight panels for the skeletal muscle and the whole blood were all downloaded from the FUSION website (http://gusevlab.org/projects/fusion/).

Gene expression profile of SpA

The gene expression profile of SpA was acquired from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/GEO/, accession number: GSE58667). Briefly, DNA microarray gene expression was performed in 11 patients with juvenile spondyloarthritis (jSpA) and 4 healthy controls, along with bioinformatical analysis of retrieved data and then careful selected differentially expressed genes where analyzed by qRT-PCR in all participants of the study [15]. GEO2R tool was used to identify the differentially expressed genes. GEO2R presents a simple interface that allows users to perform sophisticated R-based analysis of GEO data to help identify and visualize differential gene expression[16]. Genes were identified as differentially expressed when the following two conditions were met: adjusted P value of < 0.05 by the moderated t statistic and $|\log2FC| > 1$ [15].

Gene annotation analysis and functional enrichment

In this study, we used the Metascape (https://metascape.org/gp/index.html) tool to perform Gene ontology and pathway enrichment analysis of candidate genes identified by TWAS and gene expression profile [17]. The significant Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were screened out by comparing the results of TWAS analysis and gene expression profile. Then the function of the significant genes shared by TWAS analysis and gene expression profile

were annotated, prioritized, visualized, and interpreted by using the FUMA (https://fuma.ctglab.nl/) tool [18].

Results

TWAS results of SpA

TWAS analysis identified 390 genes in the skeletal muscle and 138 genes in the whole blood with P value < 0.05 respectively. Comparing the significant genes of skeletal muscle (SM) and the whole blood (WB), 28 common genes were identified, such as CTNNAL1 (P_{SM}=0.0304, P_{WB}=0.0096), AC000078.5 (P_{SM}=0.0117, P_{WB}=0.0001), RP11-165J3.6 (P_{SM}=0.01861, P_{WB}=0.00184) and ZNF100 (P_{SM}=0.0030, P_{WB}=0.0028). The significant genes identified by TWAS are shown in Table 1.

Table 1
The common genes identified by TWAS analysis

Gene name	Chromosome	TWAS.P_{SM}	TWAS.P_{WB}
AC000078.5	22	0.0117	0.0001
RP11-165J3.6	9	0.0186	0.0018
ZNF100	19	0.0030	0.0028
ZNF493	19	0.0043	0.0044
ZNF429	19	0.0043	0.0062
STK17B	2	0.0304	0.0063
ZC3H3	8	0.0022	0.0070
ZNF738	19	0.0217	0.0075
CTNNAL1	9	0.0304	0.0096
GGTA1P	9	0.0078	0.0122
RP11-254F7.2	2	0.0149	0.0123
ARFGAP3	22	0.0288	0.0136
KLHL12	1	0.0064	0.0155
SRR	17	0.0254	0.0158
RP11-611E13.2	12	0.0161	0.0161
NT5C3B	17	0.0214	0.0172
MBLAC1	7	0.0388	0.0212
BNIP1	5	0.0288	0.0239
LRRC61	7	0.0442	0.0243
CCDC125	5	0.0248	0.0252
CHD1L	1	0.0104	0.0259
RP11-218M22.1	12	0.0370	0.0263
HLA-DQA1	6	0.0367	0.0297

Note: The GWAS summary dataset of SpA with the pre-calculated reference weights of gene expression profiles in the whole blood and skeletal muscle for TWAS analysis of SpA. Each TWAS.P value was calculated by transcriptome-wide association study analysis. (using the FUSION tool (http://gusevlab.org/projects/fusion/)). TWAS, Transcriptome-Wide Association Study; GWAS, Genome-Wide Association Study; SpA, spondyloarthritis; TWAS.P_{SM}, TWAS $P_{Skeletal\ Muscle}$ value; TWAS.$P_{WB,}$ TWAS $P_{Whole\ Blood}$ value; FUSION, Functional Summary-based Imputation.

Gene name	Chromosome	TWAS.P_{SM}	TWAS.P_{WB}
ZNF205	16	0.0386	0.0340
POLR2J3	7	0.0259	0.0378
RAPGEFL1	17	0.0334	0.0408
NUDCD3	7	0.0147	0.0445
AC091729.9	7	0.0395	0.0448

Note: The GWAS summary dataset of SpA with the pre-calculated reference weights of gene expression profiles in the whole blood and skeletal muscle for TWAS analysis of SpA. Each TWAS.P value was calculated by transcriptome-wide association study analysis. (using the FUSION tool (http://gusevlab.org/projects/fusion/)). TWAS, Transcriptome-Wide Association Study; GWAS, Genome-Wide Association Study; SpA, spondyloarthritis; TWAS.P_{SM}, TWAS $P_{Skeletal\ Muscle}$ value; TWAS.$P_{WB,}$ TWAS $P_{Whole\ Blood}$ value; FUSION, Functional Summary-based Imputation.

Integrative analysis of TWAS and gene expression profile of SpA

By comparing of the genes identified by TWAS analysis and gene expression profile of SpA, we screened 20 candidate genes differentially expressed in both TWAS and gene expression profile of SpA, such as MCM4 (P_{TWAS}=0.0132, P_{DEG}=0.0275), KIAA1109 (P_{TWAS}=0.0371, P_{DEG}=0.0467) and SFMBT2 (P_{TWAS}=0.0294, P_{DEG}=0.0245) (Table 2). The heat map of those candidate genes of SpA were shown in Figure 1. Through using FUMA software, we found that 20 candidate genes were differentially expressed in muscle-skeletal system. In addition, the expression of candidate genes were down-regulated in the tissue of muscle-skeletal (-log 10 P-value>4, Fig. 2).

Table 2
The common genes identified by both TWAS analysis and DEG identified by gene expression profiles of spondyloarthritis

Tissue	Gene	Chromosome	P_{TWAS}	P_{DEG}
skeletal muscle	BUD31	7	0.0132	0.0275
	MCM4	8	0.0337	0.0161
	ATRNL1	10	0.0434	0.0256
	CWF19L2	11	0.0406	0.0469
	RAB3IP	12	0.0151	0.0150
	DISP2	15	0.0099	0.0108
	G6PC3	17	0.0279	0.0063
	CYB5A	18	0.0183	0.0382
	TYMS	18	0.0031	0.0473
	ZNF738	19	0.0217	0.0307
	KIAA1109	4	0.0371	0.0467
	LINC01088	4	0.0451	0.0038
	DMGDH	5	0.0278	0.0159
whole blood	SFMBT2	10	0.0294	0.0245
	FRA10AC1	10	0.0400	0.0149
	ERVK13-1	16	0.0253	0.00002
	KLHL11	17	0.0221	0.0013
	C20orf194	20	0.0490	0.0193
	SAMD10	20	0.0224	0.0220
	SMG5	1	0.0043	0.0050

Note: Each P_{TWAS} value was calculated by transcriptome-wide association study (TWAS) analysis. Each P_{DEG} value was the differential expressed gene (DEG) derived from the published studies. TWAS, Transcriptome-Wide Association Study; DEG, Differential Expressed Gene; P_{TWAS}, $P_{Transcriptome-Wide\ Association\ Study}$ value; P_{DEG}, $P_{Differential\ Expressed\ Gene}$ value.

Table3. The 6 top-level GO terms and KEGG pathways identified by both TWAS and gene expression profiles of spondyloarthritis

Category	ID	Description	Count	Log10(P)
GO Biological Processes	GO:0007005	mitochondrion organization	22	-4.29
	GO:0006091	generation of precursor metabolites and energy	21	-4.29
	GO:0043985	histone H4-R3 methylation	3	-4.16
KEGG Pathway	hsa05416	Viral myocarditis	8	-4.92
	hsa04360	Axon guidance	12	-4.26
	hsa00230	Purine metabolism	11	-3.90

Note: Top 6 clusters with their representative enriched terms (one per cluster). "Count" is the number of genes in the user-provided lists with membership in the given ontology term. "Log10(P)" is the p-value in log base 10. TWAS, Transcriptome-Wide Association Study; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Gene annotation analysis and functional enrichment

FUMA and Metascape tools were used to conduct gene functional enrichment and annotation analysis. FUMA and Metascape tools identified 93 GO terms (Supplementary Table S1) enriched in SpA, such as mitochondrion organization (GO:0007005, log10(P)= -4.29), generation of precursor metabolites and energy (GO:0006091, log10(P)= -4.29), histone H4-R3 methylation (GO:0043985, log10(P)= -4.16) and so on. We also identified 33 KEGG pathways (Supplementary Table S2) for SpA, such as viral myocarditis (hsa05416, log10(P)= -4.92), axon guidance (hsa04360, log10(P)= -4.26), purine metabolism (hsa00230, log10(P)= -3.90) and so on. The top 6 GO terms and KEGG pathways were shown in the table 3.

Discussion

In this study, we aimed to identify the candidate genes associated with SpA. Firstly, we integrated a large scale GWAS summary data of SpA and gene expression weights from two specific tissues to conduct the TWAS analysis. The significant genes were further validated by gene expression profile of SpA. In addition, we used FUMA and Metascape tools to perform functional enrichment and annotation analysis associated with candidate genes. As far as we have known, this is the first study systematically identifying the candidate genes related to SpA by using the TWAS analysis. Our results may provide novel clues to study the genetic mechanism, diagnosis and treatment of SpA in the future.

TWAS identified several genes for SpA, such as SFMBT2, MCM4, KIAA1109, CTNNAL1. SFMBT2 protein is a member of polycomb group (PcG) of proteins. Hussain S et al. found SFMBT2 interference altered the expression of key metabolic genes in chondrocytes, SOX9 and COL2A1 were decreased, whereas MMP13 and ADAMTS4 were increased significantly [19]. Some studies have shown that up-regulation or down-regulation of these genes which altered by the SFMBT2 gene can lead to degeneration of cartilage

and further causes the pathogenesis of SpA [20]. In our study, ATRNL1 gene found in this study which can also regulate the expression of SOX9 and significantly highly expressed in cartilage tissues of patients with osteoarthritis[21]. To sum up, SFMBT2 and ATRNL1 have potential genetic mechanisms for the pathogenesis of SpA. we can regard SFMBT2 and ATRNL1 as candidate genes related to SpA and the genetic mechanisms between those genes and SpA need further research.

Another important candidate gene identified in this study is MCM4, MCM4 protein is a DNA replication licensing factor which is essential for DNA replication initiation and elongation in eukaryotic cells. In other words, MCM4 gene acts as an essential regulator of cell cycle. It has been proved that MCM4 can cause many diseases by regulating the cell cycle and inducing cell apoptosis [22, 23]. In addition, previous studies has shown that the pathogenesis mechanisms of SpA included thinning of the cartilage and by cartilage degeneration involving chondrocyte apoptosis and proteoglycan loss [24].

In addition, KIAA1109 was detected in both TWAS and gene expression profile of SpA. A candidate gene approach has shown that a 480 kb block on chromosome 4q27 encompassing KIAA1109/Tenr/IL-2/IL-21 gene cluster is associated with rheumatoid arthritis [25]. Zhernakova A et al. found the KIAA1109/Tenr/IL-2/IL-21 gene cluster is involved in susceptibility to multiple autoimmune diseases, implying that this locus is a general risk factor for multiple autoimmune diseases such as rheumatoid arthritis and celiac disease [26]. SpA is a subset of seronegative rheumatic-related autoimmune diseases and Bowes J et al. has already found the significant evidences for associations with susceptibility to SpA and IL-2,IL-21 genes [27, 28]. As far as we known, no researchers have studied whether KIAA1109 has an direct effect on SpA. So this is the first study exploring the genetic correlation between KIAA1109 and SpA.

CTNNAL1 (cadherin-associated protein, alpha-like 1) was found to be ubiquitously expressed in many tissues including skeletal muscle, pancreas and heart [29]. By comparing with psoriasis patients who did not have psoriatic arthritis and patients with psoriatic arthritis, Patrick MT et al. found significant loci overlapping the regulatory elements encompass genes differentially expressed in differentiated osteoblasts, including genes participating in the Wnt signaling such as RUNX1, FUT8, and CTNNAL1 [30]. The proteins in Wnt/β-catenin signaling play essential roles in the development of SpA. Xie W et al. found the Wnt proteins are critically essential in normal bone homeostasis, particular in osteoblastic new bone formation [31]. Therefore, Wnt proteins may also play roles in the process of new bone formation in ankylosing spondylitis and various components of the Wnt signaling molecules were found to be involved in maintaining bone mass [31]. To sum up, these results could provide the new clues for future study on the genetic mechanism of CTNNAL1.

In our study GO enrichment analysis and KEGG pathway were also conducted to explore the

functions of candidate genes and how they distributed in SpA. For example, mitochondrion organization (GO:0007005) was identified by both TWAS and gene expression profile. Cytochrome c is primarily known for its function in the mitochondria as a key participant in the life-supporting function of ATP synthesis [32]. Recently researchers found cytochrome c can interact with protease, which lead to the activation of apoptosis protease activation factor [33]. It has been demonstrated that this biological signal is

responsible for the apoptosis and activation of inflammatory process in the pathogenesis of psoriatic arthritis [33]. Combined with these study, these findings suggest the abnormal mitochondrion organization may play roles in the biological mechanism of SpA.

Axon guidance (KEGG:hsa04360) was also identified as enriched in SpA. Recently researchers found semaphorins as a family originally identified as axonal guidance molecules and semaphorins have affected the pathogenesis of multiple arthritis such as SpA, rheumatoid arthritis, osteoarthritis by regulating of immunity, angiogenesis, bone remodeling, apoptosis, cell migration and invasion [34]. In addition, semaphorins family can regulate the biological pathway of TNF-α/ADAMTS-4, blocking semaphorins can decrease the destruction of cartilage and bone, cell infiltration into the synovium, and production of TNFα and IL-6 [35]. The TWAS analysis and gene expression profile of SpA identified axon guidance as a susceptibility pathway for SpA, which was consistent with existing researches.

The strength of our study is that we conducted TWAS analysis by using the latest GWAS summary data of SpA [10]. The large sample size of GWAS summary data ensures the accuracy of our research results. In addition, we verified the candidate genes by comparing with the gene expression profile. These results may provide new clues for future research on the genetic mechanism of SpA.

This study also has some limitations. Firstly, the GWAS summary data are based on the European ancestry and may not apply to other ancestry studies. Therefore, it should be cautious to apply our results to other populations. Further TWAS analysis on other populations are needed to prove our results. Secondly, our results lacked sufficient mechanism-based experiments. So we need more mechanism-based experiments to further confirm the biological rationality and clarify the biological mechanism of our study results, which expect to participate in the development of SpA. Thirdly, to validate the TWAS results, we compared the significant genes identified by TWAS analysis of SpA with the gene expression profile of jSpA, but jSpA is just one subtype of within SpA. So our results should be interpreted with caution. Further biological studies should be conducted to confirm our findings.

Conclusions

In summary, we integrated the large scale GWAS summary data of SpA and gene expression weights from two specific tissues to conduct the TWAS analysis. Then the significant genes screened by TWAS analysis were further validated by gene expression profile of SpA. At last, to further confirm the functional relevance of candidate genes, we used FUMA and Metascape tools to perform functional enrichment and annotation analysis. Our study provide novel clues to study the genetic mechanism, diagnosis, and treatment of SpA in the future.

Abbreviations

eQTL
Expression quantitative trait loci

FUSION
Functional Summary-Based Imputation
FUMA
Functional Mapping and Annotation of Genome wide Association Study
GEO
Gene Expression Omnibus
GO
Gene ontology
GWAS
Genome-wide association study
KEGG
Kyoto Encyclopedia of Genes and Genomes
TWAS
Transcriptome-wide association study
SNP
single nucleotide polymorphisms
SpA
Spondyloarthritis

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are available from the Gene Expression Omnibus database(https://www.ncbi.nlm.nih.gov/gds) accession number: GSE58667; the UK biobank (http://geneatlas.roslin.ed.ac.uk/) fields: 20002

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. XJW designed this trial and wrote this manuscript. XJW, SHB, ZY were responsible for the collection of data. The analysis and interpretation of all data were finished by WYG, ZSY. All authors read and approved the final manuscript.

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Figures

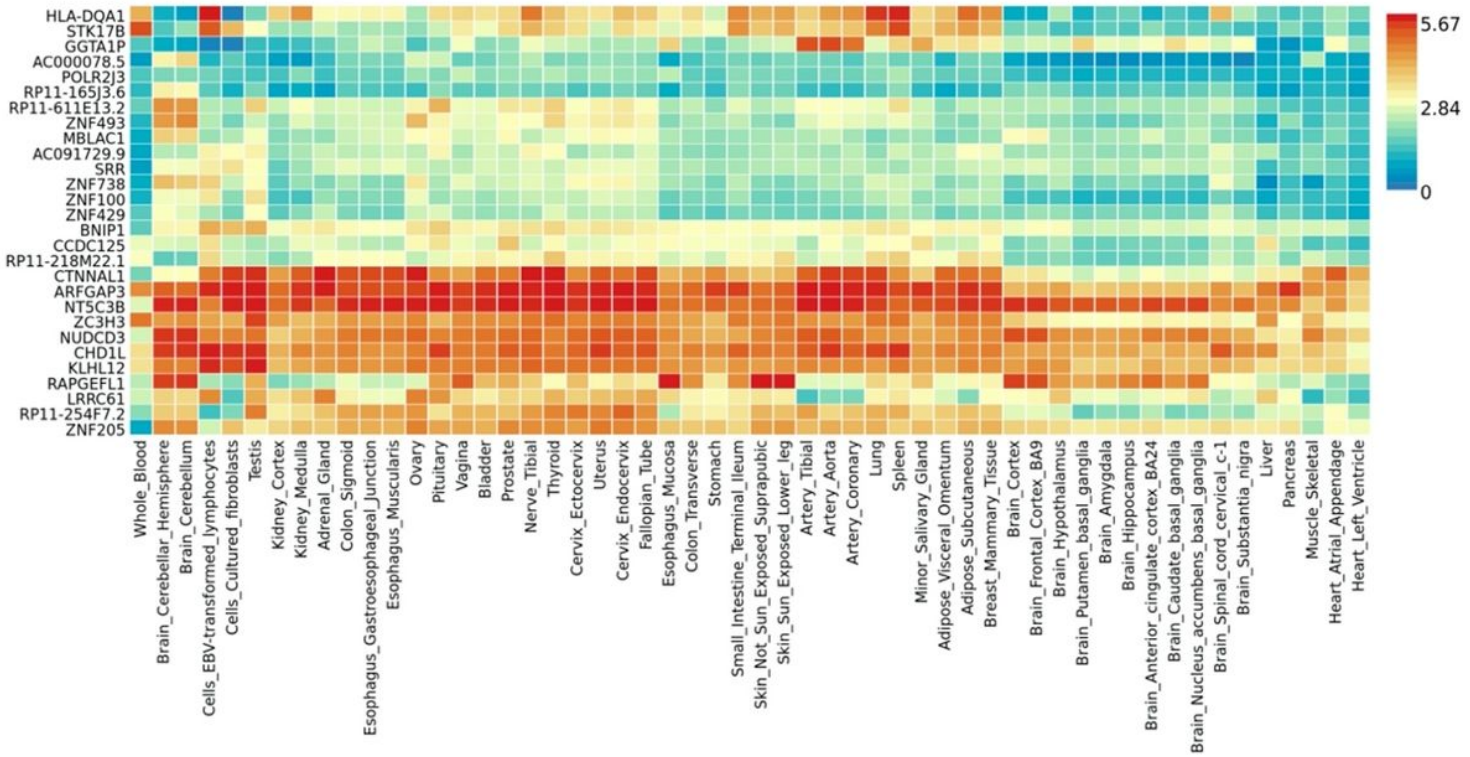

Figure 1

The heat map of genes expression of spondyloarthritis. Note: Gene expression heat map of the significant genes shared by transcriptome-wide association study (TWAS) and gene expression profile data of SpA. TWAS, transcriptome-wide association study; SpA, spondyloarthritis.

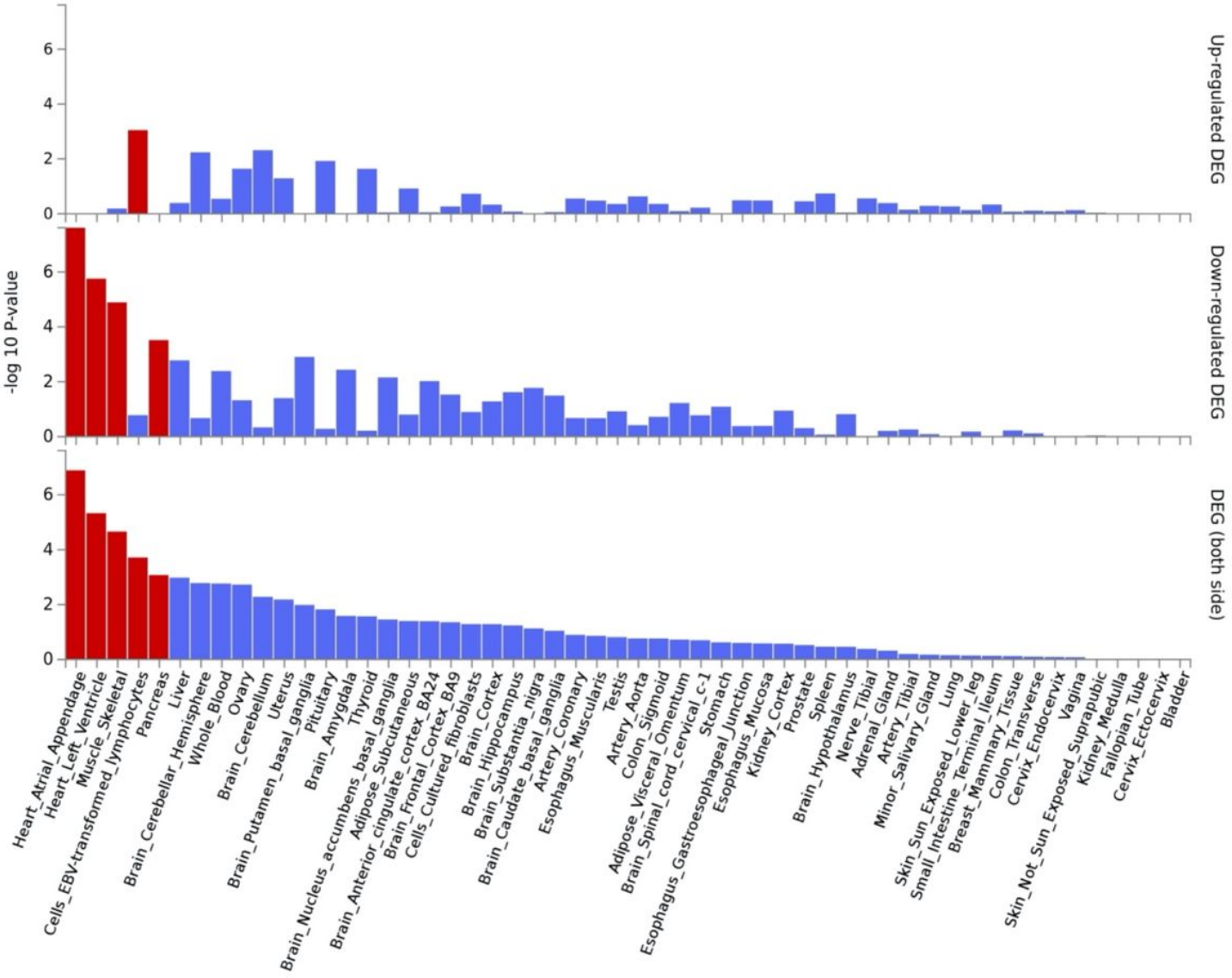

Figure 2

The expression of common genes of spondyloarthritis in different tissue sites. Note: Image showing the expression of significant genes of spondyloarthritis (SpA) in different tissue sites. We found that the significant genes shared by transcriptome-wide association study(TWAS) and gene expression profile data of SpA were differentially expressed in muscle-skeletal system. The bars in red show significant differential expression. TWAS, transcriptome-wide association study; SpA, spondyloarthritis.

Supplementary Files

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- SupplementaryTableS1.docx
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