Integrating transcriptome-wide association study and mRNA expression profile identified sensitive genes related to hand osteoarthritis

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Research article

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Abstract

Background
Osteoarthritis (OA) is a common skeletal system disease which proven partly related to genetic factors. The hand is a frequently affected part, which seriously affects the quality of life. But pathogenesis mechanism of hand osteoarthritis (hand OA) is still elusive.

Methods
The Genome-wide association study (GWAS) summary of hand OA was derived from the UK Biobank, which contains 452,264 White British individuals with 37782 osteoarthritis patients. The transcriptome-wide association study (TWAS) of hand OA was carried out using the Functional Summary-based Imputation (FUSION) using the gene expression references of muscle skeleton and blood. The significant genes identified by TWAS were further subjected to gene sets enrichment analysis (GSEA) by the Database for Annotation, Visualization and Integrated Discovery (DAVID) tool. Furthermore, we compared the identified genes and gene sets of TWAS with that of an OA mRNA expression profile to detect the genes and gene sets shared by TWAS and mRNA expression profiles of OA.

Results
TWAS identified 177 genes with $P$ value $< 0.05$ for muscle skeleton, such as ANKRD44 ($P = 0.0001$), RIC3 ($P = 0.0003$), AC005154.6 ($P = 0.0004$). TWAS identified 423 genes with $P$ value $< 0.05$ for blood, such as CRIM1 ($P = 0.0002$), ZNF880 ($P = 0.0002$), NCKIPSD ($P = 0.0003$). After comparing these results of TWAS to those of mRNA expression profile, we identified 5 common genes, such as DHRS3 (log2fold = -1.85, $P = 3.31 \times 10^{-9}$), SKP2 (log2fold = 1.36, $P = 1.62 \times 10^{-8}$). GSEA of TWAS identified genes detected 51 gene ontology (GO) terms for hand OA, for example, protein binding ($P = 0.0003$), cytosol ($P = 0.0020$). We also detected 6 common GO terms shared by TWAS and mRNA expression profiling of OA, such as protein binding ($P_{\text{TWAS}} = 2.54 \times 10^{-4}$, $P_{\text{mRNA}} = 3.42 \times 10^{-8}$), extracellular exosome ($P_{\text{TWAS}} = 0.02$, $P_{\text{mRNA}} = 1.18 \times 10^{-4}$), cytoplasm ($P_{\text{TWAS}} = 0.0183$, $P_{\text{mRNA}} = 0.0048$).

Conclusion
In this study, we selected 5 sensitive genes (DHRS3, SKP2, IRS2, TOB1, PPP1R15A) and 6 GO terms (protein binding, extracellular exosome, cytoplasm, oxidoreductase, cellular response to mechanical stimulus, oxidation-reduction process) related to the hand osteoarthritis, which may help to uncover the pathogenesis of hand osteoarthritis at the genetic and molecular levels.

Introduction
Osteoarthritis is a kind of musculoskeletal system disease, which always happens to the elderly. The hand is one of the parts where OA often occurs, especially for women, of which the main symptoms are joints stiff, painful, and may be swollen. It is affecting up to 10% of men and 13% of women all over the world[1]. Among women
aged 60 to 70 in the United States, the number of them with hand OA is as high as 75% [2]. The hand flexion and extension activity of hand OA patients is seriously affected, hand function and quality of life will be reduced as results. With the progress of an aging society, an increasing number of hand OA patients may be seen in the future.

With the development of bioinformatics, more and more studies focus on the extensive genetic association of OA. At the genetic level, there seem to be some potentially different mechanisms in hand OA compared to knee and hip OA [3]. After some genome-wide association studies (GWAS) of OA, researchers found some significantly associated loci, for example, chr12 near the matrix Gla protein (MGP) gene and at chr12 near the CCDC91 gene [4]. Functional polymorphisms were also found significantly between hand OA patients and normal subjects, such as ASPN D15, CILP rs2073711 TT [5]. Unfortunately, the genetic mechanism of hand OA is still not very clear yet.

GWAS are successfully applied for genes mapping of human complex diseases and traits. But it is limited in evaluating disease risk, for most GWAS-identified SNPs located in non-coding regions of the genome. The variant SNPs may play a role in gene expression levels [6]. And expression quantitative trait loci (eQTL) analysis aims to locate the genes related to variation in gene expression [7]. So, integrating GWAS and eQTL analysis does help researchers to identify causal genes associated with disease more effectively. Nowadays, the advantages of transcriptome-wide association study (TWAS) were highlighted gradually. It combines the pre-computed gene expression weights with summary statistical data from GWAS to recognize novel causal genes of elusive diseases [8]. In recent years, TWAS was utilized by more and more researchers to identify genetic loci associated with the disease. For example, a TWAS about 3000 subjects found 69 novel genes significantly related to BMI, lipids, and height which have a bearing on obesity [9]. A TWAS about Chronic low-grade inflammation recognized 448 genes related to inflammatory biologic age [10].

In this study, we utilized a wide GWAS dataset of hand OA and cartilage mRNA expression profiles. A TWAS was performed firstly to find genetic loci which may associate with hand OA. And then, gene ontology (GO) and pathway enrichment analysis were carried out for the notable genes screened by TWAS. In order to find the common genes and biological pathways, the significant genes identified by the TWAS were made comparisons with profiles analysis results of OA, as well as GO and pathway analysis.

**Material And Method**

**GWAS summary datasets of hand OA**

The GWAS summary of hand OA was derived from the UK Biobank (UK Biobank fields: 20002). Briefly, The UK Biobank cohort contains 452,264 White British individuals with 37782 osteoarthritis patients [11]. Various phenotypes have been informed for every participant. They gathered the blood samples when the subjects visited a UK Biobank assessment centre. Successively, DNA extracting and genotyping were performed in Affymetrix Research Services Laboratory. There're 623,94 genotyped variants that passed quality control through Applied Biosystems UK Biobank Axiom Array. This dataset Contains 9,113,133 imputed variants after filtering. They used the IMPUTE4 program to do the imputation (http://jmarchini.org/software/). Detailed information of the subjects, genotyping, imputation and quality control can be found in the published study.

**Gene expression profiles of cartilage**
The original mRNA expression profiling data of cartilage was acquired by Gene Expression Omnibus (accession number: GSE114007). This research collected normal human knee cartilage tissues from 5 female and 13 male (age 18–61, mean 38) who has never been suffered from joint disease or trauma. Cartilage invaded by osteoarthritis was gathered from 12 female and 8 male with knee replacement surgery (age 52–82, mean 66). The original image data was transformed into sequence data by the Illumina Genome Analyzer Pipeline Software (Casava v1.8.2). Expressed genes exhibited in the study were those whose log counts per million (log2CPM) were greater than 3.0 in one or more samples. Limma-voom was carried out for differential expression analysis. Significantly different expression (DE) genes were detected once the following two conditions are met: adjusted P-value of < 0.05 by the moderated t-statistic and a |log2FC| > 1[12].

**TWAS of hand OA**

The TWAS of hand OA was carried out using Functional Summary-based Imputation (FUSION) through integrating the GWAS data of hand OA and pre-computed gene expression reference weights of peripheral blood and muscle skeleton. In brief, we took advantage of the prediction models implemented in FUSION to calculate the gene expression firstly. The calculated tissue-related expression weights were then integrated with summary-level GWAS results to impute the association statistics between gene expression and target diseases. In this study, the gene-expression weight panels of peripheral blood and muscle skeleton were downloaded from the FUSION website (http://gusevlab.org/projects/fusion/).

**GO and pathway enrichment analysis**

The significant genes selected by TWAS were further analyzed by the Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/) tool for GO and pathway enrichment analysis. Similarly, DAVID was also applied to the differently expressed genes identified by the mRNA expression profiling of OA cartilage. To find the common GO and pathways detected both by TWAS and mRNA expression profiles, we made contrasts between the DAVID analysis results of TWAS and mRNA expression profiles of cartilage at length.

**Results**

**TWAS results of hand OA**

TWAS identified 177 genes with P value < 0.05 for muscle skeleton, such as ANKRD44 (P = 0.0001), RIC3 (P = 0.0003), AC005154.6 (P = 0.0004). TWAS identified 423 genes with P value < 0.05 for blood, such as CRIM1 (P = 0.0002), ZNF880 (P = 0.0002), NCKIPSD (P = 0.0003) (Supplementary Table S1). The top 10 significant genes selected by TWAS were shown in Table 1.

| Table 1. Top 10 genes selected by TWAS analysis |
| Tissue                      | Gene name | Chromosome | TWAS.Z | TWAS.P |
|-----------------------------|-----------|------------|--------|--------|
| muscle skeleton             | ANKRD44   | 2          | 3.8381 | 0.0001 |
|                             | RIC3      | 11         | 3.6172 | 0.0003 |
|                             | AC005154.6| 7          | 3.5112 | 0.0004 |
|                             | PARD3     | 10         | 3.4069 | 0.0007 |
|                             | GGCT      | 7          | 3.3363 | 0.0008 |
| peripheral blood            | CRIM1     | 2          | -3.6781| 0.0002 |
|                             | ZNF880    | 19         | 3.6694 | 0.0002 |
|                             | NCKIPSD   | 3          | -3.629 | 0.0003 |
|                             | CCR3      | 3          | -3.5323| 0.0004 |
|                             | R3HCC1    | 8          | 3.5037 | 0.0005 |

**GO and pathway analysis results of TWAS**

DAVID analysis of TWAS identified genes detected 51 GO terms for hand OA, such as protein binding (P value = 2.54×10^{-4}), cytosol (P value = 0.0012), membrane (P value = 0.0014). We also detected 5 biological pathway for hand OA, such as Biosynthesis of unsaturated fatty acids (P value =0.0034), Propanoate metabolism (P value = 0.0071) (Supplementary Table S2, S3).

**Integrative analysis of TWAS and mRNA expression profiling of OA**

Comparing the genes identified by TWAS with the differently expressed genes detected by mRNA expression profile detected 5 common genes, DHRS3 (log2fold=-1.85, P value = 3.31×10^{-9}), SKP2 (log2fold=1.36, P value = 1.62×10^{-8}), IRS2(log2fold= -2.00, P value = 2.11×10^{-9}), TOB1 (log2fold= -2.67, P value = 8.42×10^{-9}), PPP1R15A(log2fold= -2.13, P value = 2.83×10^{-8})(Table2).

**Table 2. Genes selected by both TWAS and mRNA expression profile of cartilage**

| Gene name | Chromosome | TWAS.Z | TWAS.P | log2fold change |
|-----------|------------|--------|--------|----------------|
| DHRS3     | 1          | -2.699 | 0.0070 | -1.8451        |
| SKP2      | 5          | 1.9814 | 0.0475 | 1.3556         |
| IRS2      | 13         | -2.130 | 0.0331 | 2.0001         |
| TOB1      | 17         | 1.9970 | 0.0458 | -2.6653        |
| PPP1R15A  | 19         | 2.2334 | 0.0255 | -2.1270        |

Comparing the GO enrichment analysis results of TWAS and mRNA expression profiles found 6 common GO terms, such as protein binding(P_{TWAS} = 2.54×10^{-4}, P_{mRNA} = 3.42×10^{-8}), extracellular exosome(P_{TWAS} =0.0225, P_{mRNA} = 1.18×10^{-4}),cytoplasm(P_{TWAS} =0.0183, P_{mRNA} = 0.0048), oxidoreductase(P_{TWAS} =0.0312, P_{mRNA} = 0.0259), cellular response to mechanical stimulus(P_{TWAS} =0.0324, P_{mRNA} = 0.0053), oxidation-reduction process(P_{TWAS} =0.0424, P_{mRNA} = 0.0294)(Table3).

**Table 3. GO terms selected by both TWAS and mRNA expression profile of cartilage**
| Term                                      | P value TWAS | P value mRNA expression | Genes TWAS                | Genes mRNA expression               |
|-------------------------------------------|--------------|-------------------------|---------------------------|-------------------------------------|
| GO:0005515~protein binding                | 0.0003       | 3.42E-08                | RAD51C, XRCC3...          | RBPMS2, LTBP1...                    |
| GO:0005737~cytoplasm                      | 0.0183       | 0.0048                  | RAD51C, XRCC3...          | RBPMS2, LDHC...                     |
| GO:0070062~extracellular exosome          | 0.0225       | 0.0001                  | ARSB, WASF3...            | S100A4, LDHC...                     |
| GO:0016491~oxidoreductase activity        | 0.0312       | 0.0259                  | SUOX, AKR1C2...           | ALDH1L1, ADHFE1...                  |
| GO:0071260~cellular response to mechanical stimulus | 0.0323       | 0.0053                  | CASP5, IRF1...            | PDE2A, PTGS2...                     |
| GO:0055114~oxidation-reduction process    | 0.0424       | 0.0294                  | TM7SF2, ALDH6A1...        | STEAP3, ALDH1L1...                  |

**Discussion**

Our study aims to detect candidate genes closely associated with hand osteoarthritis and try to explain the relationships between genes and the disease. We conducted a TWAS and functional gene set enrichment analysis and identified multiple genes and enriched GO terms and pathways for hand OA. Further integrative analysis of TWAS and mRNA expression profiling of OA identified 5 common genes and 6 common GO terms shared by TWAS and mRNA expression profile of OA. Our results provide novel clues for understanding the genetic mechanism of hand OA, focusing on the roles of abnormal transcription in the development of OA.

TWAS identified several candidate genes for hand OA, such as DHRS3, SKP2, IRS2, TOB1 and PPP1R15A.

IRS2 (insulin receptor substrate 2) is a kind of cytoplasmic adaptor molecules. It encodes some essential proteins related to insulin transduction and indeed plays a part in insulin resistance[13]. Runt-related transcription factor 1 (RUNX1) makes an important impact on bone growth and cellular differentiation. A previous study proved that IRS2 might make influence on chondrocytes differentiation through targeting RUNX1 via controlling the downstream of IGF1[14].

SKP2 was also detected simultaneously in TWAS and transcription levels. It is a gene that coding protein product Skp2 (S-phase kinase-associated protein 2), which acts as an essential regulator of the cell cycle. Other studies indicated that Skp2 might also play a direct role in cellular senescence[15]. As we all known, the prevalence of OA is positively correlated with age. The relationship between cellular aging and OA is well investigated by some researchers recently[16–18]. Combined with the results of our study, SKP2 is likely to have a specific relationship with the development of osteoarthritis, and the specific associations require further research.
CRIM1 gene encodes a human protein named cysteine-rich motor neuron protein1. Researchers have found that the extracellular domain of CRIM1 combines with bone morphogenetic protein (BMP), and E-Cadherin is positively correlated with CRIM1[19]. Furthermore, it has been proved that chondrocytes hypertrophy could be inhibited by depressing the BMPs signaling pathway, which helps to advance the treatment study of OA[20].

Another gene that was screened out sensitive to OA was DHRS3. DHRS3 encodes a kind of human enzyme named dehydrogenase reductase 3[6, 21]. It is thought to play a role in regulating all-trans-retinaldehyde in the human body, just as retinaldehyde reductase[6]. According to a study of genes associated with rheumatoid arthritis (RA), DHRS3 was detected as one of the sensitive genes in peripheral blood mononuclear cells samples, expressed in the RA case group twice as large as the control group[22].

GO enrichment analysis was conducted to explore the function of significant genes and how does they distribute in hand OA.

In our study, oxidoreductase activity was identified both by TWAS and mRNA expression profiles. Previous research shows that oxidoreductase activity was negatively related to collagen synthesis in osteoblasts[23]. Studies also indicated that osteoblasts dysregulation has strongly associated with osteoarthritis pathogenesis[24]. Combined with the result of our study, oxidoreductase activity may play a role in the mechanism of osteoarthritis.

The oxidation-reduction process has been proved closely related to human aging. And as we all know, osteoarthritis occurs more frequently in the old[25]. As for how does it work, we still need some further research.

Biosynthesis of unsaturated fatty acids is a pathway enrichment identified by TWAS. Its function in osteoarthritis has been investigated by many studies. For example, oleic acid is one of the unsaturated fatty acids, and research indicated that it could relieve OA symptoms by controlling the inflammation[26]. Eicosapentaenoic acid and docosahexaenoic acid also belong to unsaturated fatty acids. They were both identified as substances that could induce inflammation subsides[27].

TWAS also detected the E2F1 destruction pathway associated with hand OA. The E2F1 is a kind of transcription factor which has a critical function in controlling cell proliferation[28]. Previous research about osteoarthritis shows that E2F1 could boost osteoclastogenesis and induce inflammatory[29]. E2F1 destruction pathway may suggest a powerful therapy of OA.

In this study, we have compared the results of TWAS and mRNA expression profiling. As we all know, hand OA TWAS can detect significant genes at DNA-level, mRNA expression profiling could provide the information to explain regulatory mechanisms of OA pathogenesis at the expression level. The combination of TWAS and mRNA expression profiling contributes to identify sensitive genes more accurately.

It is worth noting that the GWAS data came from the UK biobank, which means that the genes were all about the European. The genes of other people have not been involved yet. On the other hand, the purpose of the study is to select genes associated with hand OA, but the mRNA expression profile was about knee cartilage. The difference in pathogenesis between hand OA and knee OA was still elusive. So the promotion of our research conclusions needs to be cautious.

Conclusion
In summary, we integrated the GWAS datasets of hand OA from the UK Biobank and pre-computed gene expression weights of peripheral blood and muscle skeleton to finish the TWAS. And then, we filtered genes expressed significantly different in cases. We also compare the results of GO and pathway enrichment analysis in gene and transcription levels. It turns out that 5 common genes and 6 GO terms were selected. We hope our results could promote the study of the mechanism of hand OA at the genetic and molecular level.

**Abbreviations**

DAVID: Database for Annotation, Visualization and Integrated Discovery

DE: different expression

eQTL: expression quantitative trait loci

FUSION: Functional Summary-based Imputation

GSEA: gene set enrichment analysis

GO: gene ontology

GWAS: Genome-wide association studies

OA: osteoarthritis

TWAS: transcriptome-wide association study

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and supporting materials**

The datasets analyzed during the current study are available from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/gds) accession number: GSE114007; 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 of 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,ZY,SHB were responsible for the collection of data. The analysis and interpretation of all data were finished by LY,LMY,ZJF. All authors read and approved the final manuscript.

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Not applicable

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