RESEARCH ARTICLE

Drug Repurposing for Frozen Shoulder; a Bioinformatics Meta-Analysis

Yashar Shahbaz, MD; Taimoor Ali, MBBS; Atieh Nouralishahi, MD; Kazem Ansari, MD; Salwa Usman, MD; Syed Mohammad Mohtashim Ali, MD; Mohammad Zarenezhad, MD; Lohrasb Taheri, MD; Shahram Shafa, MD; Mansoor Deilami, MD

Research performed at Jahrom University of Medical Sciences, Jahrom, Iran

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Abstract

Objectives: Adhesive capsulitis (AC), commonly known as frozen shoulder (FS), is characterized by glenohumeral joint capsule contraction, resulting in pain, stiffness, and dysfunction. Genetic factors have been implicated in the etiology of AC, prompting a bioinformatics investigation to explore potential therapeutic targets.

Methods: A systematic review of Gene Expression Omnibus (GEO) datasets was conducted using keywords related to Frozen Shoulder and Adhesive Capsulitis. The gene expression profiles from GSE238052, GSE190023, and GSE140731 were analyzed using the i-DEP package. Differential gene expression analysis, Gene Ontology (GO) enrichments, and drug-gene enrichments were performed through biclustering of GO pathways with the Drug.GeneSet database and dpGSEA Python application.

Results: Among 58,825 genes in 67 samples, 1,036 upregulated and 378 downregulated genes were identified in the case-control comparison. Upregulated pathways included skeletal muscle adaptation, fiber transition, myofibril assembly, and regulation of muscle fiber development. Drug.GeneSet database analysis highlighted adenosine and its derivatives as potential therapeutic targets. Further dpGSEA analysis revealed a significant influence of adenosine on the disease.

Conclusion: This study provides information about the genomic landscape of adhesive capsulitis, identifying potential therapeutic avenues centered around adenosine-related interventions. While topical or intra-articular injection of adenosine is evident in the literature, this finding should be validated through experimental studies.

Level of evidence: V

Keywords: Adhesive capsulitis, Bioinformatics analysis, Frozen shoulder, Gene expression omnibus

Introduction

Adhesive capsulitis (AC), or frozen shoulder (FS), involves shoulder stiffness and pain, progressing through stages of initial pain to severe stiffness.[1] AC is characterized by chronic soreness and discomfort, accompanied by an increasing inability to use the shoulder.[2] It has an approximate prevalence of 2% to 5% in the general population, with the mean age of onset typically around 55 years.[3,4] Risk increases with age, and women over 40 are more susceptible to adhesive capsulitis.[5] The exact pathology of adhesive capsulitis is not fully understood, but several hypotheses exist. The most commonly accepted hypothesis suggests that inflammation initially occurs within the joint capsule, leading to pain, stiffness, and dysfunction.[4] The condition involves the glenohumeral joint capsule becoming contracted and adherent to the humeral head, resulting in scar tissue formation and reduced space for arm movement.[2] It is considered an idiopathic disease with principal characteristics of pain and limited range of motion.[4] HLA-B27, is a protein involved in the immune system, and AC. Patients with axial spondyloarthritis, a condition often associated with HLA-B27, are at an

Corresponding Author: Shahram Shafa, Department of Orthopedics, School of Medicine, Peymanie Hospital, Jahrom University of Medical Sciences, Iran

Email: researcher0439827@yahoo.com

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increased risk of developing AC.[6] Specifically, HLA-B27 has been found to be significantly more common in individuals with FS compared to control groups, suggesting a potential genetic predisposition to this condition.[7] Recent research, including Genome-Wide Association Studies (GWAS), has revealed a genetic aspect in AC, as well as the WNT7B, POU1F1, and MAU2 genes.[8] These investigations identified distinct genes and uncovered a common genetic structure linking AC with conditions such as Dupuytren disease, a myofibroplastic disease of the hands.[9] Additionally, hyper-low-density lipoproteinemia and hyper-non-high-density lipoproteinemia, have been linked to AC in individuals with diabetes mellitus.[10] Examining 19 genes in patients with FS, rotator cuff tear (RCT), or shoulder instability (SI), a study found increased matrix metalloproteinases, pro-inflammatory cytokines, and collagen-related genes in FS. Chondrogenesis and fibrosis-related genes were highly expressed in FS, particularly in the axillary recess (AX), suggesting AX analysis may unveil FS pathogenesis and its impact on shoulder motion.[11]

Microscopic examinations of impacted shoulder capsules disclose uniform pathological alterations marked by reparative inflammatory mechanisms. These encompass degeneration, vascular restoration, and a general reduction in capsular volume.[12] Researchers have developed various methods to induce AC in rats for experimental purposes. Extra-articular internal fixation of the shoulder has been shown to induce AC in rats.[13] Another study demonstrated that a rat FS model using immobilization generates the pathophysiologic process of inflammation leading to AC.[14] While it is a chronic condition, it might resolve self-limited; however, as symptoms are annoying, invasive treatments might be necessary. One prospective trial emphasized the significant relief provided by injecting a steroid into the shoulder without image guidance.[15] Another systematic review of randomized trials assessed the effectiveness of interventions for primary frozen shoulder, such as arthroscopic capsular release (ACR) and steroid injection.[16] A randomized controlled trial investigated the use of suprascapular nerve blocks in the treatment of AC. The trial found that suprascapular nerve blocks are considered a safe and effective method for relieving pain and restoring function in patients with AC.[17]

Materials and Methods

Data Retrieval and Processing

In conducting a systematic review of Gene Expression Omnibus (GEO) datasets, an exhaustive search was conducted on the GEO database using appropriate Medical Subject Headings (MeSH) terms and keywords [("Frozen shoulder"[MeSH Terms] OR "Adhesive capsulitis")]. All available gene expression profiles related to AC or FS were retrieved [Table 1].

In the preprocessing stage, several steps were undertaken to prepare gene expression data for further analysis. Firstly, genes with extremely low expression were filtered out. Subsequently, gene IDs were converted to Ensembl gene IDs or STRING-db gene IDs. Finally, transformations were applied to the data. Regarding counts data filtering, genes that were either not expressed in any samples or expressed at extremely low levels were removed from further analysis. By default, a gene must have more than 0.5 counts per million (CPM) in at least one sample; otherwise, it is excluded. Counts were normalized by calculating CPMs, which involves dividing read counts by the total counts per sample. The filtering process was achieved using R commands, and the resulting data is normalized by the cpm function in edgeR.

Table 1. Characteristics of included Gene datasets

Dataset	Condition	platform	Objective	Key Findings
GSE238052	Frozen Shoulder (FS)	Illumina NovaSeq 6000 (Homo sapiens)	Elucidate key molecules in pathologic fibrosis and explore therapeutic targets for FS	Elevated CD36 expression was detected in FS; Salvianolic acid B (SaB) inhibits CD36, attenuating inflammation and fibrosis; CD36 promotes pathologic fibrosis by activating the PI3K-Akt pathway; SaB treatment in rats improves the range of motion (ROM) and reduces collagen fiber deposition.
GSE190023	Adhesive Capsulitis (AC)	Illumina NovaSeq 6000 (Homo sapiens)	Investigate the underlying mechanisms of severe AC	Integrated transcriptomic and metabolomic analysis identifies pathways related to muscle development and myogenesis correlating with severe AC progression. The arginine-citrulline gene-compound network is identified as central in severe AC, and two phospholipids are recognized as potential serum markers for severe AC.
GSE140731	Adhesive Capsulitis (AC) vs. Shoulder Instability	Illumina NovaSeq 6000 (Homo sapiens)	Identify potential biomarkers specific to AC	Increased expression of PDGFB, COL18A1, and MMP9 in AC patients; reduced TNFA expression; RNA sequencing and real-time RT-PCR were used for transcriptomic analysis and validation.

Identifying Differentially Expressed Genes

Transformed data was utilized for exploratory data analysis, such as clustering analysis and PCA, as well as for identifying differentially expressed genes (DEGs) using the limma-trend method. However, both DESeq2 and limma-voom use the original read count data, not the transformed data. For normalized expression data, filters were applied to remove genes expressed at low levels across all samples. The presence of extremely large numbers in the dataset is assessed using kurtosis, and a log2 transformation is enforced if the mean kurtosis is larger than 50.

Pathway analyses in iDEP utilize fold-change values of all

genes, calculated through either limma or DESeq2, distinguishing this approach from the DEG2 enrichment analysis that exclusively employs gene lists of DEGs.[18]

Drug Gene Enrichments

Biclustering analysis was performed using the BCCC method with the QUBIC R packages, aiming to identify genes correlated within subsets of samples. This approach is particularly advantageous for datasets with a substantial sample size (N > 15) and involving more than two sample groups. The analysis focused on the top 1,000 most variable genes, resulting in the discovery of 14 clusters, with Cluster 1 standing out, comprising 230 genes correlated across 67 samples.

Subsequent pathway enrichment analysis within Cluster 1 was conducted using Drug.GeneSetDB. Enrichment p-values were calculated through a one-sided hypergeometric test, adjusted for multiple testing using the Benjamini-Hochberg procedure, and converted to false discovery rates (FDRs). FDR values indicate the likelihood of observing enrichment by chance, with larger pathways tending to have smaller FDRs due to increased statistical power. Fold enrichment, representing the percentage of genes in the list belonging to a pathway divided by the corresponding percentage in the background, serves as a measure of effect size, indicating the overrepresentation of genes in a specific pathway. The background genes are derived from the original gene list, filtered based on a low threshold in RNA-seq. Post-analysis, pathways are filtered based on a stringent FDR cutoff of 0.05, and the top 10 significant pathways are presented for further exploration.[18]

dpGSEA Python app was used for the re-analysis of adenosine's role and other potential drug-gene associations. dpGSEA utilizes transcriptomic signatures derived from drug-perturbed cell lines in the Connectivity Map Project (CMAP) and the Library of Integrated Network-based Cellular Signatures (LINCS) projects at the Broad Institute.[19] dpGSEA generates annotated gene sets. These gene sets are structured into proto-matrices based on gene signature cutoffs, determined by the ranked top fold change or statistical significance.[19]

Results

A total number of 58,825 genes in 67 samples were studied. Of these, 25,575 genes passed the filter, and 25,438 were converted to Ensembl gene IDs in the database. The remaining 137 genes were kept in the data using their original IDs. There were 33 case samples and 34 control samples.

Genes with minimal counts per million (CPM) were retained if they exhibited at least 0.5 CPM in a single library, and the criterion for inclusion was set at one library. For transforming counts data for clustering and PCA, the EdgeR transformation method was employed, utilizing the formula log2 (CPM + 4), where a pseudo count (c) of 4 was added to address low count variability. Additionally, missing values were handled by imputing them with the gene median.

The densitigram was generated using specific settings, including the filtration of genes with minimal counts per million (CPM) set at 0.5, ensuring they are present in at least one library. The transformation of count data for clustering and principal component analysis (PCA) was achieved using the EdgeR method with log2 transformation (log2 (CPM+c)), where the pseudo count (c) was set to 4. This transformation accounts for variability in low-count genes. The effects of data transformation can be seen to be minor based on the density plots [Figure 1].

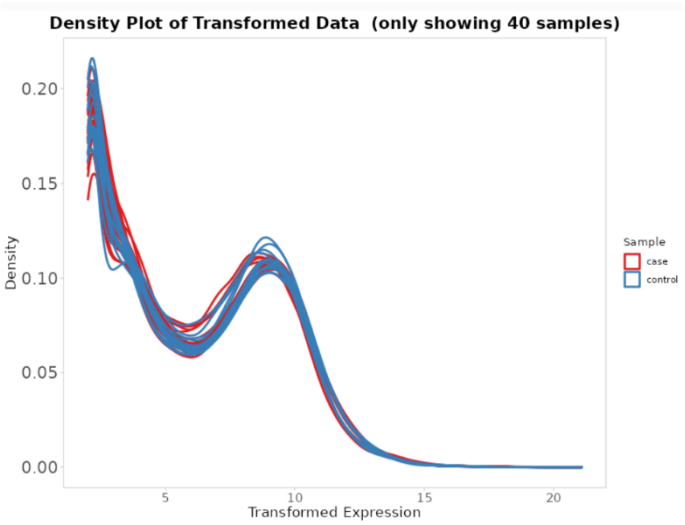

Figure 1. Density diagram showing variability transformation of genes

In the analysis conducted using the DESeq2 method with a FDR cutoff of 0.1 and a minimum fold-change threshold of 2, the threshold-based Wald test results revealed significant differences in gene expression between the case and control groups. Specifically, 1,036 genes were identified as upregulated, while 378 genes were found to be downregulated in the case-control comparison [Figure 2].

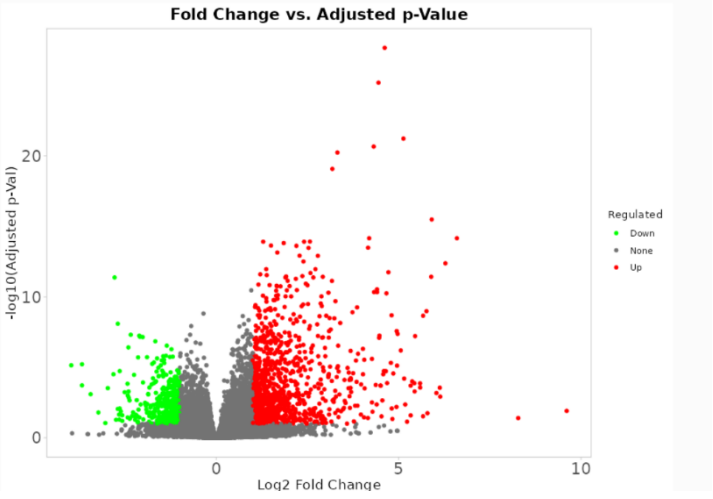

Figure 2. Volcano plot of gene expression levels

The investigation focused on the GO Biological Process pathway database with a significance cutoff of 0.1 for FDR. Conversely, upregulated pathways encompass the regulation of skeletal muscle adaptation, the transition between fast and slow fibers, skeletal myofibril assembly, the regulation of skeletal muscle fiber development, skeletal muscle thin filament assembly, and the positive regulation of skeletal muscle fiber development. Downregulated pathways include the detoxification of copper ions, the stress response to copper ion, microglial cell-mediated cytotoxicity, the regulation of microglial cell-mediated cytotoxicity, and the regulation of microvillus length [Figure 3].

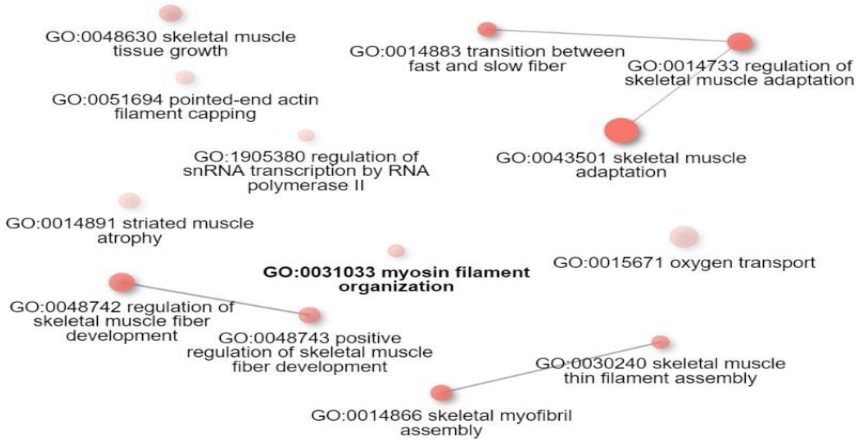

Figure 3. GO biological pathways enrichment results

In this study, biclustering analysis employing the BCCC method, biclust, and QUBIC R packages was harnessed to uncover subsets of correlated genes, emphasizing the importance of a large sample size (N > 15) and multiple sample groups. Focusing on the 1,000 most variable genes, Cluster 1, comprising 230 genes correlated across 67 samples, was subjected to enrichment analysis. Notably, the study utilized this biclustering approach for drug repurposing, particularly leveraging the Drug Gene Set Database (Drug GeneSetDB). The enriched pathways within Cluster 1 included medications as well as those associated with STITCH 3'-phosphoadenosine 5'-phosphosulfate [Table 2].

Table 2. Results of Drug Gene Set Database enrichment

Adjusted *P* Value	Fold	Pathway
2.46E-2	11	STITCH 3'-phosphoadenosine 5'-phosphosulfate(CID000010214)
2.46E-2	11	STITCH 3'-phosphoadenosine 5'-phosphosulfate(CID100000990)
2.46E-2	11.2	STITCH adenosine 3',5'-diphosphate(CID000159296)
2.49E-2	10.3	STITCH 3'-phosphoadenosine 5'-phosphate(CID100000073)

The analysis of adenosine using dpGSEA revealed a striking enrichment score of 7.49E-13, signifying a significant impact on transcriptomic signatures. The enrichment score P-value of 0.049 shows the statistical significance of these findings. Furthermore, adenosine demonstrated a target compatibility score of 0.668, suggesting substantial compatibility with specific target genes. The associated P-value of 0.048 reinforces the statistical relevance of this compatibility [Figure 4].

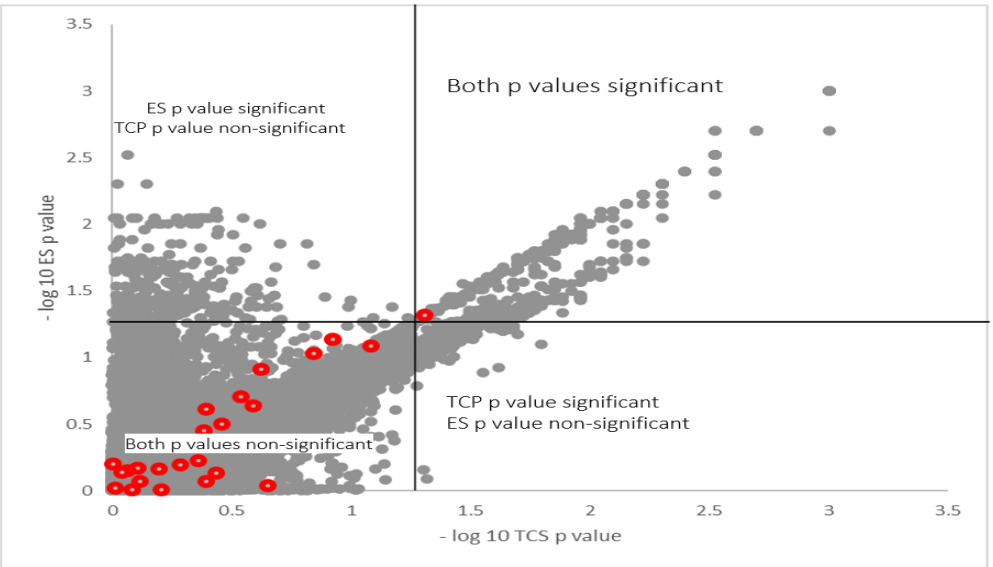

Figure 4. Diagram of target compatibility score (TCS) P-value and enrichment score (ES) P-value; The red bubbles represent adenosine derivates and gray ones are other medications

Discussion

In the study, analysis of gene expression profiles in adhesive capsulitis revealed 1,036 upregulated and 378 downregulated genes, implicating pathways related to skeletal muscle adaptation and identifying adenosine and its derivatives as potential therapeutic targets, with further significance observed in the association with adenosine. A1 adenosine receptors (A1AR), in particular, regulate bone resorption, impacting bone density and preventing bone loss.[20] Additionally, adenosine receptor stimulation has complex effects on the release of pro-inflammatory cytokines in rheumatoid arthritis (RA), depending on selective receptor engagement.[21] Exogenous adenosine and its metabolite inosine have demonstrated anti-inflammatory effects in synoviocytes of osteoarthritis (OA) and RA.[22] Adenosine exerts an indirect role in joint protection by modulating the pro-inflammatory NF-kB molecular signaling in immune cells, contributing to joint health.[23] Intra-articular injection of adenosine has been studied for its potential benefits in managing OA. Research suggests that such injections, often in liposomal form, may reduce cartilage damage in established murine and rat models of OA.[24] The combination of intra-articular adenosine, lidocaine, and magnesium (ALM) has been investigated for its efficacy, showing superiority over other treatments in reducing postoperative systemic and joint inflammation.[25] Moreover, the intra-articular administration of selective adenosine receptor agonists, such as A2A and A3 receptor agonists, has shown promise in preventing the development of OA.[26] Acting through A1AR plays an important role in the tubuloglomerular feedback (TGF) mechanism within the kidney, as evidenced by the complete abolition of TGF responses in mice with a targeted deletion of the A1AR coding sequence. In a similar study,[27] polymyalgia rheumatica (PMR), affecting elderly individuals, primarily involves large tendons and muscles around the hips and shoulders. Despite corticosteroids being the main treatment, IL-6 inhibitors are effective alternatives. This study explores elevated adenosine levels in old tenocytes, demonstrating increased IL-6 production, suggesting a potential age-dependent inflammatory response in PMR. Levels of equilibrative nucleoside transporter 1 (ENT1), or the transporter of the adenosine, remain consistent between young and old tenocytes,[27] necessitating further research on adenosine metabolism in aged tendons and its implications for PMR's age association.

Conclusion

The study relies on the analysis of existing Gene Expression Omnibus datasets, which limits the availability of specific patient demographics and clinical details that could provide a more nuanced understanding of AC variations. Additionally, the Bioinformatics analysis lacks experimental validation. The identified genes and pathways require further confirmation through wet-lab experiments to establish their functional relevance in AC. Although differentially expressed genes were identified, their direct causative role in AC remains to be established. The study does not explore the mechanistic aspects of how these genes contribute to the pathogenesis of the condition. While adenosine is identified as a potential therapeutic target, the study does not investigate the specific mechanisms of action or potential side effects of interventions targeting the adenosine pathway, which warrants further investigation. In the study, analysis of gene expression profiles in adhesive capsulitis revealed 1,036 upregulated and 378 downregulated genes, implicating pathways related to skeletal muscle adaptation

and identifying adenosine and its derivatives as potential therapeutic targets.

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Authors Contribution:

Y.S. and M.D. conceptualized and supervised the study, with T.A. and S.U. curating data and performing bioinformatics analyses, supported by S.M.M.A.. A.N., M.Z., and S.S. reviewed datasets and edited the manuscript, while K.A. provided resources and L.T. validated results. All authors (Y.S., T.A., A.N., K.A., S.U., S.M.M.A., M.Z., L.T., S.S., M.D.) approved the final manuscript.

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Yashar Shahbaz MD [1]
Taimoor Ali MBBS [2]
Atieh Nouralishahi MD [3]
Kazem Ansari MD [4]
Salwa Usman MD [5]
Syed Mohammad Mohtashim Ali MD[6]
Mohammad Zarenezhad MD [7]
Lohrasb Taheri MD [8]
Shahram Shafa MD [9]
Mansoor Deilami MD [10]

1 Orthopedic Research Center, Shahid Kamyab Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
2 Department of orthopaedic surgery, Dow University of health sciences, civil hospital, karachi, Pakistan
3 Sub-Department of Operations and Analytics, Department of Management, Faculty of Environment, Science and Economy, University of Exeter Exeter, UK
4 Shahid Sadoughi University of Medical Sciences, Yazd, Iran
5 Department of Family Medicine, Hamdard Health, Chicago, IL United States
6 Department of Orthopaedic surgery, Children's health Ireland hospital, Dublin, Ireland
7 Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran
8 Department of Surgery, School of Medicine, Peymanie Hospital, Jahrom University of Medical Sciences, Iran
9 Department of Orthopedics, School of Medicine, Peymanie Hospital, Jahrom University of Medical Sciences, Iran
10 Department of Anesthesiology and Critical Care, School of Medicine, 5th Azar Hospital, Sayyad Shirazi Hospital, Golestan University of Medical Sciences, Golestan, Iran

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