

# Comparing Sex-Based Transcriptomic Differences to Patient-Matched Reported Outcomes in Femoroacetabular Impingement Syndrome

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**Disclosures:** Authors have no relevant disclosures.

**INTRODUCTION:** Femoroacetabular Impingement Syndrome (FAIS) results from anatomical abnormalities at the interface of the femur and acetabulum, leading to increased pain and limited range of motion of the affected hip. Untreated FAIS has been implicated in development of labral tears, chondral injury, and consequent early-onset hip osteoarthritis. Recent studies have demonstrated that females with FAIS experience worse pain and functional mobility, compared to males, in addition to delayed recovery after hip arthroscopic surgery [1]. While such variance has been theoretically attributed to contrasting biomechanics and hip morphology, the underlying molecular basis has largely been undefined [2]. And so, in this study, we aimed to identify potential gene targets that could be implicated in such sex-specific differences in FAIS-associated pain, in addition to comparing individual gene expression with patient-reported outcomes (PROs).

**METHODS:** Preoperative, hip-specific PROs—the Hip Disability and Osteoarthritis Outcome Score (HOOS) and Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC)—were collected from seven patients (3M, 4F; average age: 31.43 years), who were undergoing hip arthroscopy for FAIS. Intraoperatively, hip synovium tissue was obtained that were subsequently mechanically and enzymatically digested into single-cell suspensions. After SYTOX Blue staining, live, SYTOX Blue negative cells were then isolated via fluorescence-activated cell sorting (FACS) and submitted for single-cell RNA sequencing (scRNA-seq) utilizing 10x Genomics Chromium GEM-X Single Cell 3' Reagent Kits v4. Raw sequencing data was processed using Cell Ranger (version 9.0.2), and Seurat (version 5) was used for data integration and downstream analysis. Differential gene expression analysis was performed between male and female samples using DESeq2, and genes with adjusted p-values < 0.05 and |log<sub>2</sub> fold change| ≥ 0.32 were considered biologically relevant. Separately, individual PROs were aggregated between male and female patients and compared using Welch's t-tests. Additionally, Pearson r correlations and simple linear regression models were utilized to evaluate the associations between average gene expression and PROs. This study was approved by the Institutional Review Board. All data are presented in the form of mean ± SE.

**RESULTS SECTION:** Males had higher preoperative HOOS Sports and Recreation scores than females (50.0 ± 3.6 vs. 28.7 ± 2.1, p = 0.01 (Figure 1A-B)). There were no differences in other HOOS sub-scores and WOMAC scores (Figure 1A-B). Single-cell transcriptomic profiling of hip synovial tissue captured a total of 39,322 cells (16,253 male and 23,069 female). Using canonical gene markers, we identified six distinct cell types, including fibroblasts (PDGFRα, CD55), pericytes (RGS5, ACTA2), endothelial cells (CD34, PECAM1), macrophages (PTPRC, MRC1), T-cells (CD3E), and a fibroadipogenic progenitor (FAP)-like population (PDGFRA, CD34) that we termed hip progenitor cells (HPCs) (Figure 2A). Given the unique role of fibroblasts in promoting nerve sensitization in chronic pain states, we further examined the differential gene expression of fibroblasts between males and females, which revealed two particular pain-mediating genes of interest: FAM155A, upregulated in females, log<sub>2</sub>FC = 0.97, p ≤ 0.01; and SOCS1, upregulated in males, log<sub>2</sub>FC = 1.02, p ≤ 0.01 (Figure 2B-C). Lastly, FAM155A was found to be most correlated with HOOS (Symptoms), r = 0.32, p = 0.48, whereas SOCS1 was found to be most correlated with HOOS (Sports & Rec), r = 0.54, p = 0.21.

**DISCUSSION:** In this study, we reveal two genes with known pain-mediating properties that are differentially expressed in males and females with FAIS: FAM155A, upregulated in females, is a core structural subunit of the NALCN sodium leak channel complex; which has been shown to contribute to neuronal sensitization and the development of inflammatory and neuropathic pain; whereas SOCS1, upregulated in males, has a protective role in suppressing maladaptive inflammatory cytokine signaling. While these genes are only loosely correlated with PROs, we are limited by our small sample size, and future investigation is warranted to explore the potential mechanistic role of these genes in the context of FAIS-associated pain, in addition to observing how differential expression of these genes might also affect recovery trajectories after hip arthroscopy.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Female patients with FAIS typically experience more pain and worse quality of life than their male counterparts. This is the first study to our knowledge that explores transcriptomic level sex-based differences in FAIS patients, while suggesting associations to baseline PROs.

**REFERENCES:** [1] Joseph, R., Pan, X., Cenkus, K., Brown, L., Ellis, T., & Di Stasi, S. (2016). Sex Differences in Self-Reported Hip Function Up to 2 Years After Arthroscopic Surgery for Femoroacetabular Impingement. *The American journal of sports medicine*, 44(1), 54–59. <https://doi.org/10.1177/0363546515610535> [2] Brown-Taylor, L., Schroeder, B., Lewis, C. L., Perry, J., Hewett, T. E., Ryan, J., & Di Stasi, S. (2020). Sex-specific sagittal and frontal plane gait mechanics in persons post-hip arthroscopy for femoroacetabular impingement syndrome. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*, 38(11), 2443–2453. <https://doi.org/10.1002/jor.24680>

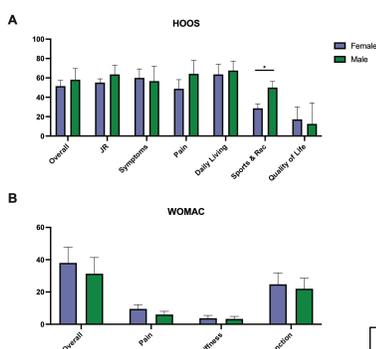


Figure 1. (A) Average HOOS scores between female and males. (B) Average WOMAC scores between female and males. \*p<0.05

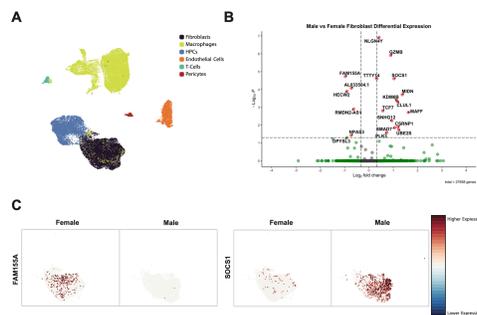


Figure 2. (A). UMAP distribution of cell types within sequenced hip synovial tissue. (B) Volcano plot of differentially expressed genes between male and female fibroblasts. (C) Differential expression of FAM155A and SOCS1 in male and female fibroblasts.

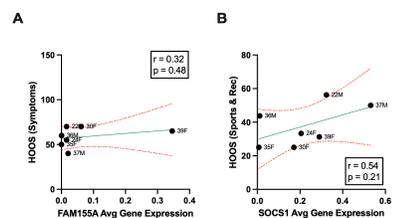


Figure 3. (A) Correlation of HOOS (Symptoms) and FAM155A average gene expression in fibroblasts. (B) Correlation of HOOS (Sports & Rec) and SOCS1 average gene expression in fibroblasts. Plots include 95% CI (red) and best-fit lines from linear regression models (green).