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Transcriptomics of Anterior Shoulder Instability: Differences in Gene Expression in the Blood of Patients with and without Significant Glenoid Bone Loss

Joseph W. Galvin[1], DO, Patrick Rooney[1], MD, Alec Egan[1], MD, John M. Tokish[2], MD, Jason A. Grassbaugh[1], MD, Brendan Masini[1], MD, Katherine E. Free[3], BS, Marit K. Bastian[3], BS, Laurel H. Gillette[3], MS, Zachary T. Colburn[3], PhD, MBA, MS

[1]Department of Orthopaedic Surgery, Madigan Army Medical Center, Tacoma, Washington, U.S.A.

[2]Department of Orthopaedic Surgery, Mayo Clinic-Arizona, Scottsdale, Arizona, U.S.A.

[3]Department of Clinical Investigation, Madigan Army Medical Center, Tacoma, Washington, U.S.A.

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I (and/or my co-authors) have something to disclose.

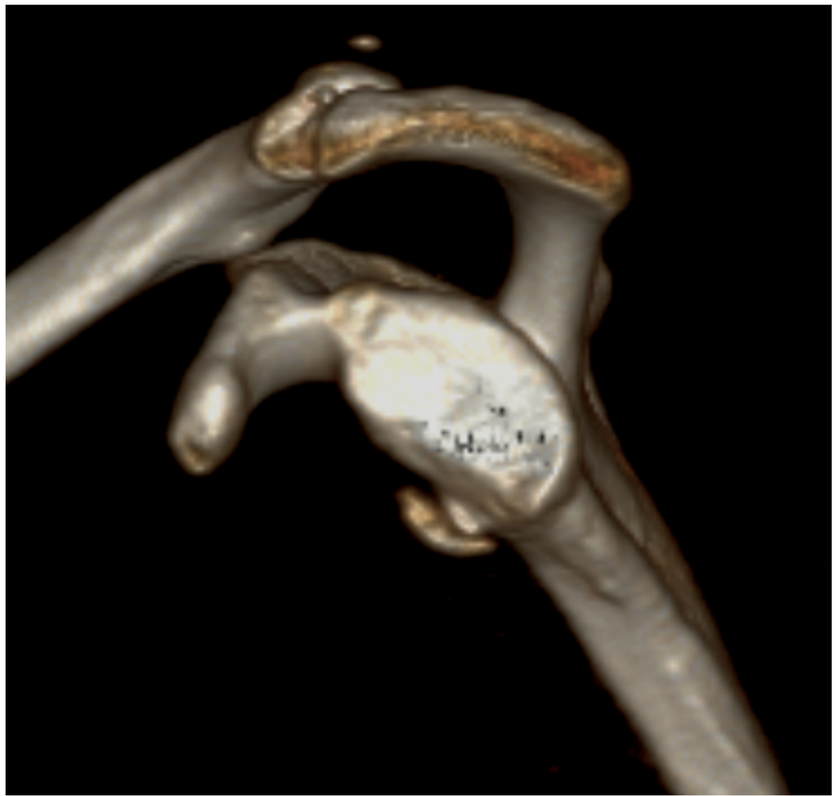
Detailed disclosure information is available via:

AAOS Orthopaedic Disclosure Program on the AAOS website at http://www.aaos.org/disclosure

Provisional Patent. DHA-MAMC 23-05-US01-PRI: 63/462,611 filed 28 Apr 2023, “System and Method for Assessing a Risk of Bone Loss in a Patient” by Galvin, LTC Joseph W. (MAMC-Army); Colburn, Dr. Zachary T. (MAMC)

Background

- Anterior shoulder instability is common in young adults, especially in the military population and contact athletes
- Mechanical factors contributing to anterior instability are well established
- Limited information exists regarding the pathobiology associated with anterior shoulder instability and bone loss



Purpose

- Compare gene expression differences in the blood and tissue of young patients with anterior shoulder instability with and without significant glenoid bone loss

- Identify novel blood transcriptomic biomarkers for the reliable delineation of glenoid bone loss

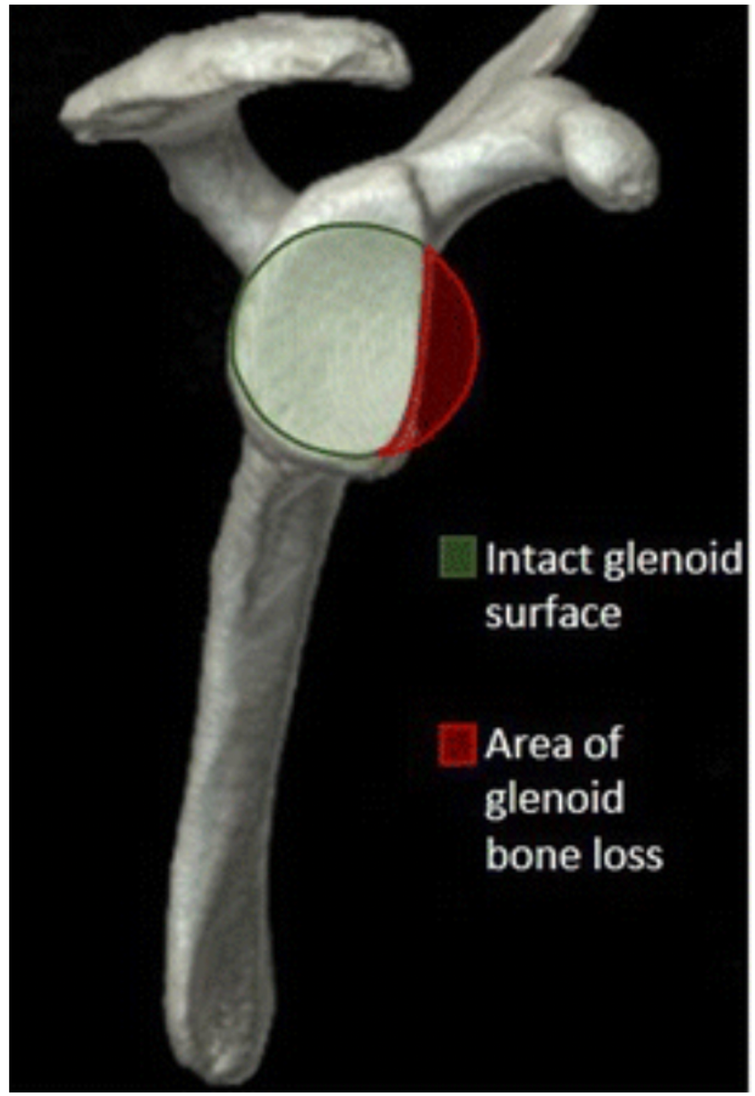
Methods

- Prospective evaluation at a single institution

- **Inclusion criteria**
  - Patients undergoing arthroscopic or open shoulder stabilization for unidirectional anterior shoulder instability

- **Exclusion criteria**
  - Collagen disorders
  - Posterior, Multidirectional, or functional shoulder instability (FSI)

- Glenoid bone loss was determined using CT 3-D reconstructions and the validated PICO method



Methods: RNA Isolation and Gene Expression

- Blood specimens and shoulder anterior capsular specimens obtained at the time of surgery were compared between patients with **significant GBL (≥10%) N=10, and without (<10% GBL) N=7**

- RNA was extracted and a 277-gene panel was utilized to quantify gene expression on an nCounter

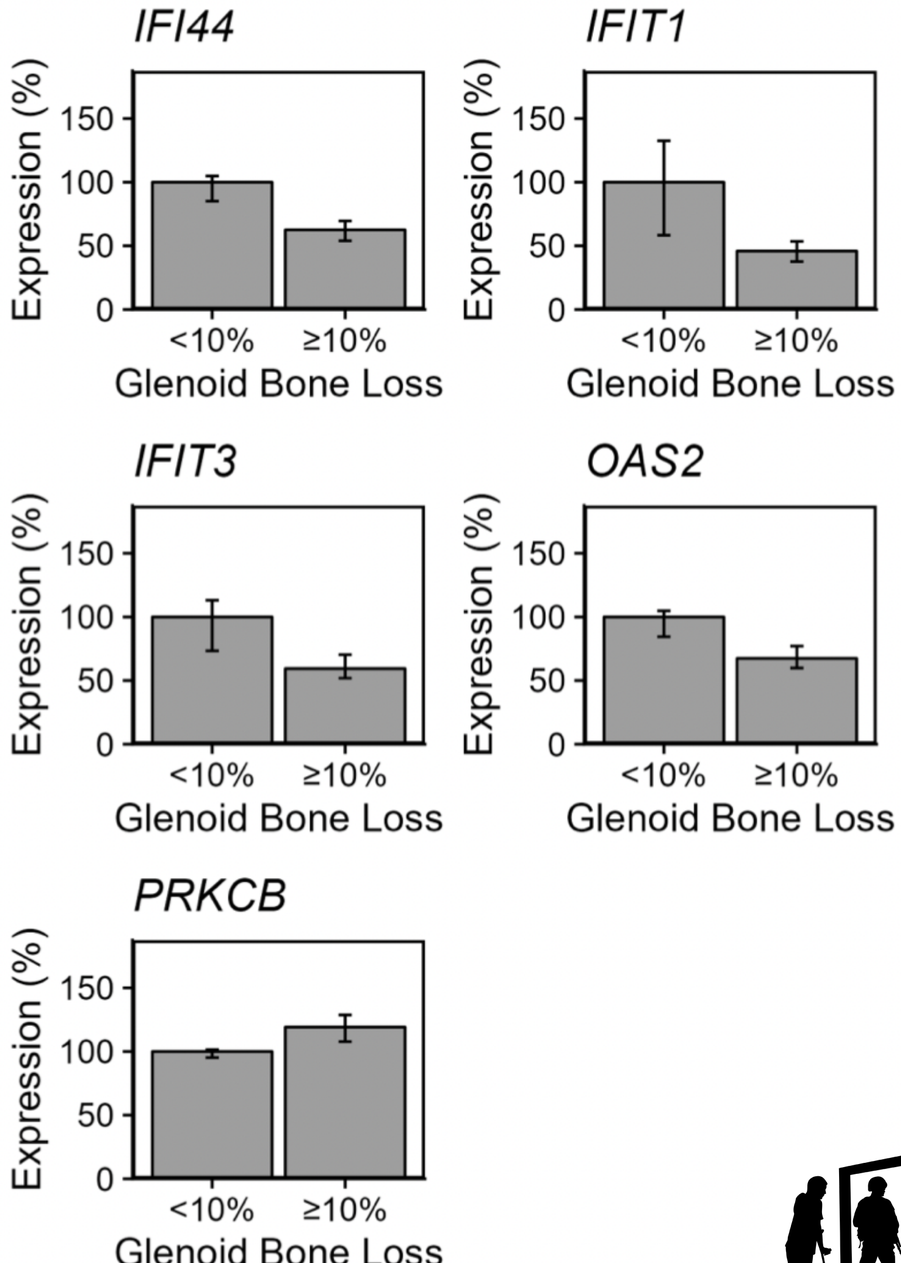
Demographics

	<10% GBL (N=7)	≥10% GBL (N=10)	p-value
Mean age, years (SD)	29 (21-41)	24 (20-29)	0.56
Sex (Male: Female)	6:1	10:0	0.41
Laterality (Right: Left)	2:5	5:5	0.62
Mean % Glenoid Bone Loss (range)	2.3% (0-8)	16.4% (10-25)	**0.001**
Hill Sachs Length (mm), (range)	17 (14-18)	21 (15-27)	**0.03**
On track: Off track	7:0	1:9	**0.001**
Number of Dislocations (range)	3 (1-12)	53 (1-100)	0.05
Surgery Performed, (n)			0.04
Arthroscopic Bankart Repair	5	1	
Arthroscopic Bankart + Remplissage	2	4	
Open Latarjet	0	5	

Results

Differential Gene Analysis: Peripheral blood

Gene	logFC	p-value	q-value (adjusted p-value)	P-value Wilcoxon Rank sum
IFIT1	-1.24	0.000013	0.003	**0.003**
CCL3	-2.32	0.00013	0.008	0.07
FGFR2	-27.67	0.00016	0.008	0.315
IFI44	-0.95	0.00011	0.008	**0.014**
IFIT3	-0.86	0.0001	0.008	**0.010**
PRKCB	0.28	0.00019	0.008	**0.005**
CXCL10	-24.17	0.0003	0.012	0.315
NOD1	-1.51	0.0004	0.015	0.055
OAS2	-0.59	0.0006	0.019	**0.001**

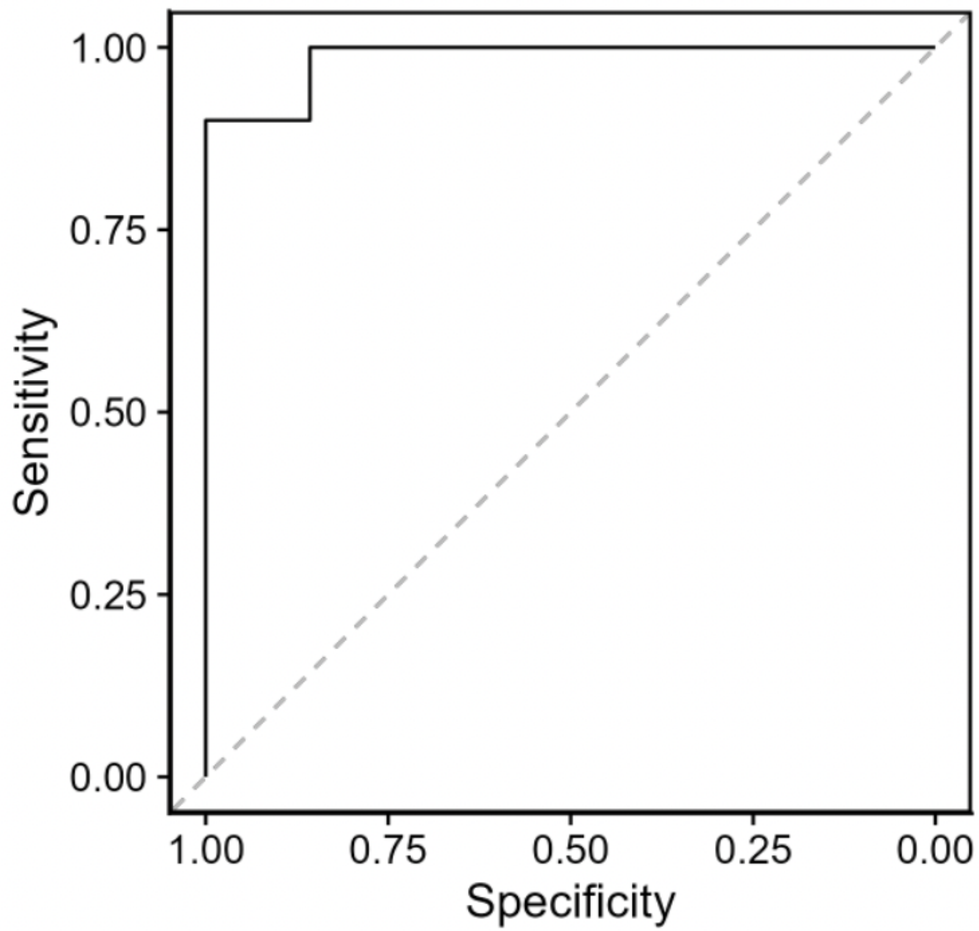


Transcriptomic Classifier to Predict Severity of Glenoid Bone Loss

- Developed predictive model using 5 differentially expressed genes in the blood

- Accuracy of 88%
- Sensitivity 0.90
- Specificity 0.86

Receiver Operating Characteristic (ROC) Curve



Discussion – Genes of Interest

- **IFIT1**
  - Overexpressed in patients with <10% glenoid bone loss
  - IFIT1 regulates Wnt/B-Catenin signaling
  - Critical to bone homeostasis

- **PRKCB**
  - Overexpressed in patients with >10% GBL
  - Identified as a potential targeting in treatment of Ewing Sarcoma
  - Hypothesized to be upregulated in rapid bone turnover

Limitations

- Small sample size
- No control group (i.e., patients without instability)
- Did not account for bipolar bone loss
- The log fold change is relatively small for the 5 genes expressed. Further studies will be required to confirm these findings.

Conclusion

- There are significant gene expression differences in the blood of anterior shoulder instability patients with and without significant GBL

- Differential expression of 5 genes allowed development of an accurate predictive model and transcriptomic biomarker to predict severity of GBL

- This novel blood transcriptomic data may assist in tracking GBL and injury progression in patients with recurrent anterior shoulder instability

- **May lead to a biomarker which can improve current prognostic treatment algorithms for the outcomes of arthroscopic Bankart repair**

- Larger prospective studies are needed to confirm these findings