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## **Comments**

Medical student Nancy Lee participated in this study as part of the Senior Scholars research program at the University of Massachusetts Medical School.





# Expression of *ITGB8* in Epicardial Adipose Tissue is Highly and Directly Correlated with the Severity of Coronary Atherosclerosis

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## Background

**Obesity and its associated cardiovascular diseases have reached epidemic proportions.** Prior studies suggest that in those with increased visceral adiposity, immune cells in visceral adipose tissue (VAT) establish chronic local inflammation that results in ectopic lipid deposition in peripheral organs and insulin resistance.

**Epicardial adipose tissue (EAT) has been advanced as a possible direct link between obesity and cardiovascular disease.** In patients with coronary artery disease (CAD), EAT has been shown to express increased levels of inflammatory cytokines.

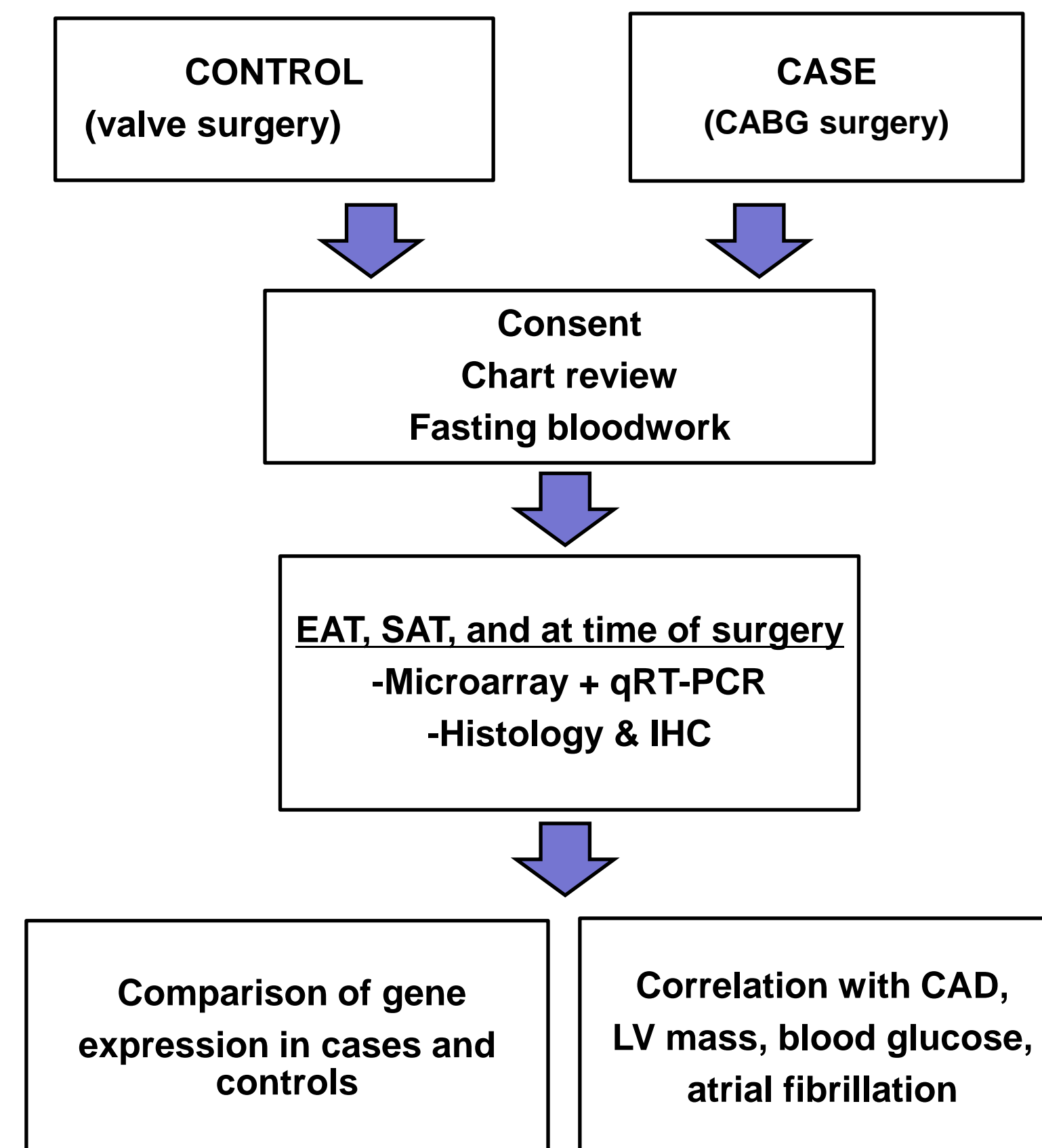
**What is not currently understood is whether or not inflammatory gene expression influences the development of atherosclerosis or is a compensatory response to established disease.**

## Objectives

The purpose of this study was to determine:

- Whether there are differences in gene expression between EAT and subcutaneous adipose tissue (SAT)
- If gene expression in EAT of patients *with* and *without* CAD differs
- If there is a difference, whether these differentially expressed genes participate in the inflammatory pathways.

## Methods

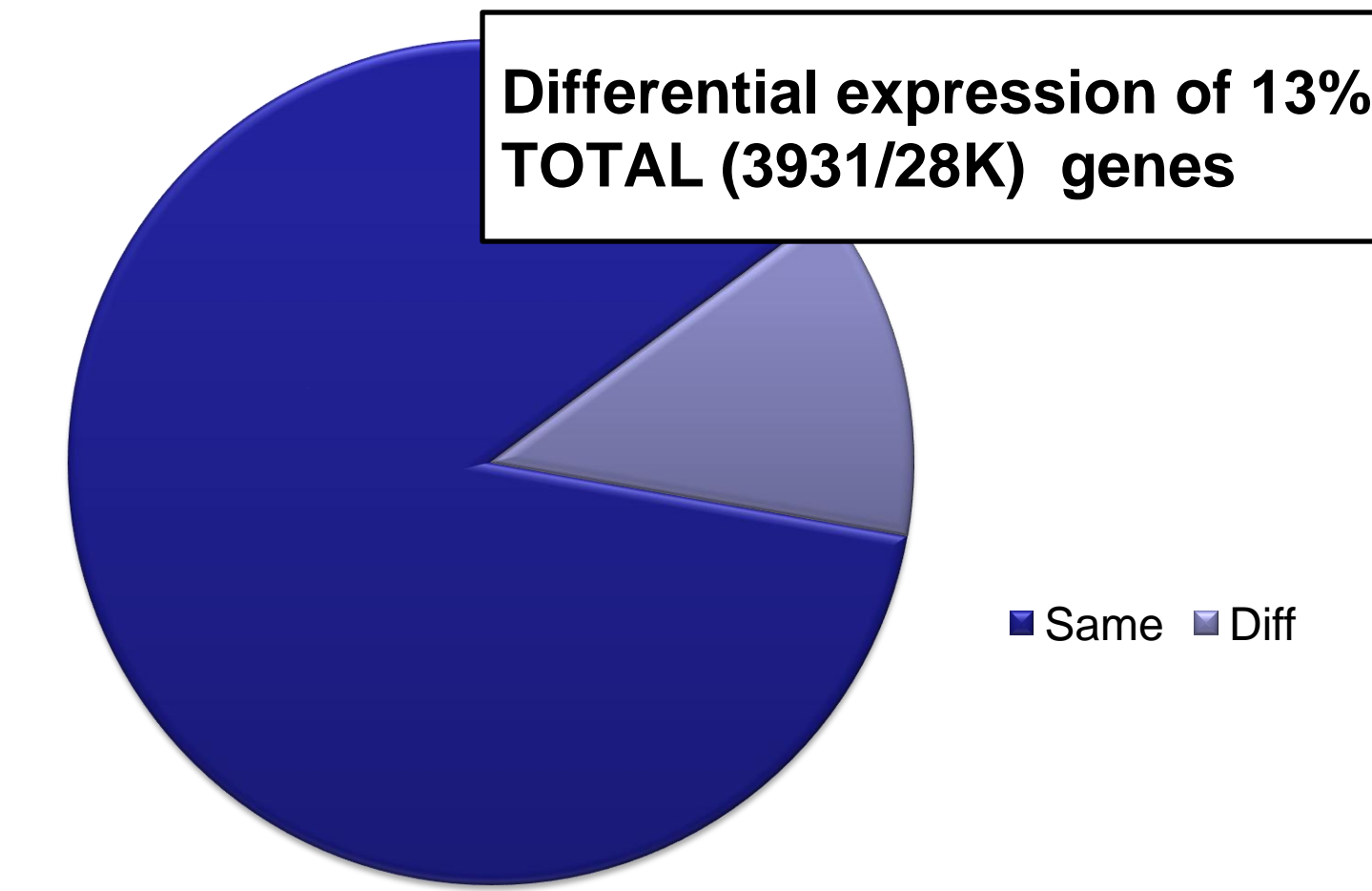


- Informed consent obtained from **controls (pts without CAD)** and **cases (pts with CAD)** scheduled for elective cardiothoracic surgery.
- 500 mg EAT and SAT collected at the time of surgery, fixed for microscopy and frozen for RNA extraction.
- RNA was hybridized to Affymetrix Human Gene 1.0 ST chips.
- Genes w/ FC>3 in EAT vs. SAT were identified.

- Gensini scores for participants determined through review of cardiac catheterization data.
- Probe intensities for these resultant genes were then correlated with the severity of atherosclerosis in each patient as determined by the Gensini score.

## Results

### Is Subcutaneous Fat Different than Epicardial Fat?



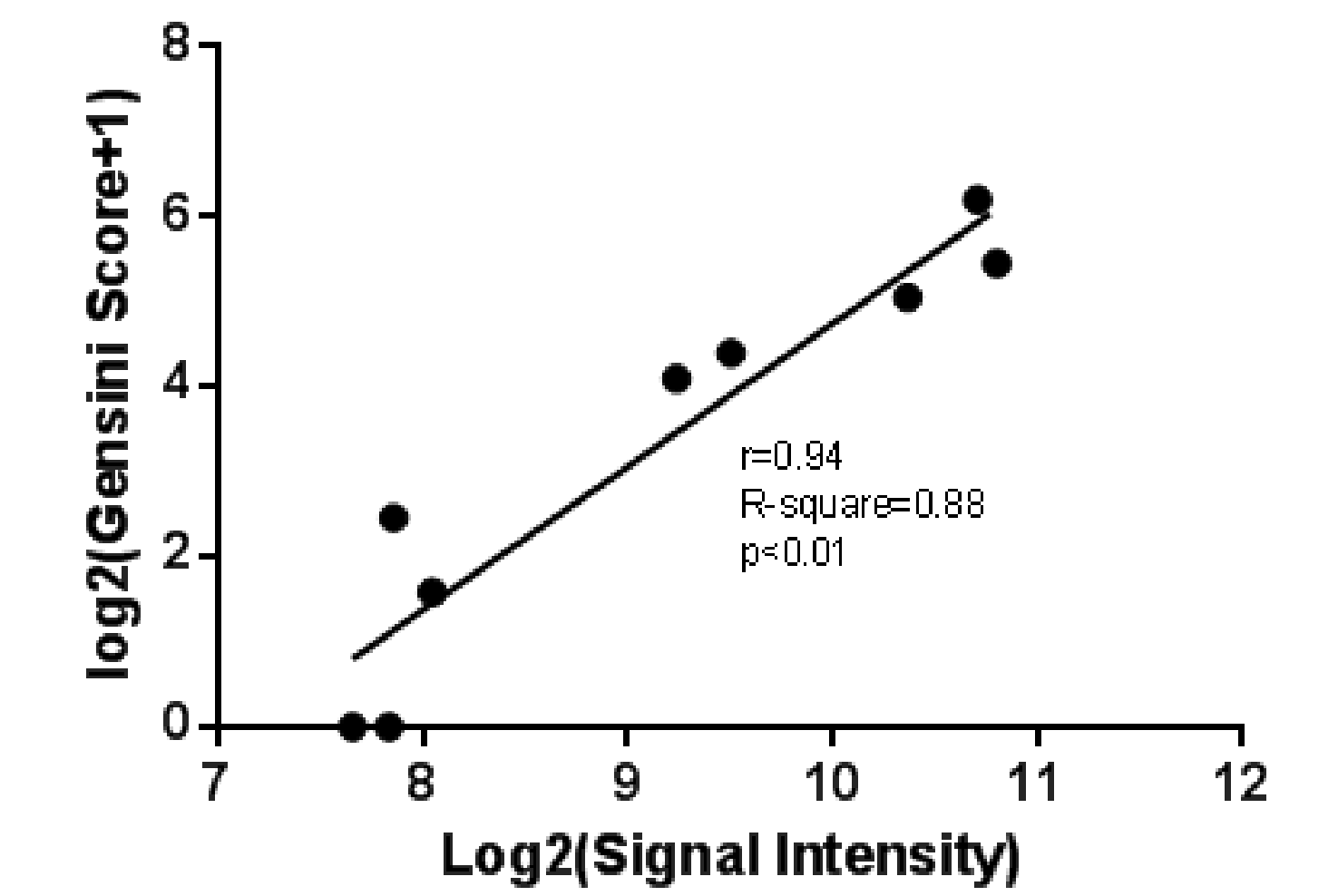
Of these, 35 genes differentially expressed in EAT vs SAT by FC>3 and p<0.05

| Name   | Symbol   | EAT     | SAT    | FC    | P     |
|--|----------|---------|--------|-------|-------|
| integrin 1 (glycoprotein Ib/IIb)   | ITGB1    | 1004.07 | 24.08  | 41.69 | 0.000 |
| polyoma virus and herpes simplex 1 (autosomal recessive)-like 1                  | POPL1    | 1004.04 | 49.59  | 20.24 | 0.000 |
| chemokine (C-C motif) ligand 21  | CCL21    | 1153.91 | 171.44 | 6.73  | 0.000 |
| transcription factor 21  | TF21     | 451.14  | 114.81 | 3.93  | 0.000 |
| 1 box 20   | 1BX20    | 583.09  | 111.56 | 5.23  | 0.000 |
| hepatoglycin III/hepatoglycin-related protein                                    | HPR3/HPR | 284.38  | 103.14 | 2.75  | 0.000 |
| uropodin 1B  | UROP1B   | 219.55  | 47.12  | 4.66  | 0.000 |
| claudin 1  | CLDN1    | 444.40  | 99.67  | 4.46  | 0.000 |
| serpin peptidase inhibitor, clade A (alpha-1 antitrypsin, antitrypsin, member 3) | SERP1A3  | 309.53  | 67.94  | 4.57  | 0.000 |
| sodium channel, voltage-gated, type VII, alpha                                   | SCN7A    | 278.58  | 66.15  | 4.21  | 0.001 |
| cystical leukotriene receptor 2  | CYSLTR2  | 349.11  | 83.38  | 4.19  | 0.001 |
| myotubularin 1   | MMRN1    | 324.32  | 74.13  | 4.37  | 0.001 |
| complement component 7   | C7       | 358.49  | 89.26  | 4.01  | 0.001 |
| cashin 19 type 2   | CASH19   | 233.90  | 57.61  | 4.05  | 0.001 |
| immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu     | IGJ      | 547.50  | 136.92 | 3.99  | 0.001 |
| leucocyte leukotriene oxidase-related protein                                    | LORP1    | 238.20  | 59.91  | 3.98  | 0.001 |
| low density lipoprotein-related protein 2  | LRP2     | 188.17  | 47.71  | 3.97  | 0.001 |
| prostaglandin 4  | PTG4     | 207.18  | 52.11  | 3.97  | 0.001 |
| indoleamine N-methyltransferase  | INMT     | 304.75  | 76.20  | 3.99  | 0.001 |
| integrin, beta 8   | ITGB8    | 243.03  | 61.21  | 3.97  | 0.001 |
| arachidonate 15-lipoxygenase   | ALOX15   | 232.20  | 58.51  | 3.97  | 0.001 |
| paenotropin  | PTN      | 237.68  | 59.40  | 3.99  | 0.001 |
| transglutaminase 4   | TGM4     | 206.40  | 52.31  | 3.94  | 0.001 |
| transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)  | TGM2     | 1216.83 | 308.91 | 3.93  | 0.000 |
| cathepsin B  | CTSB     | 104.13  | 26.41  | 3.94  | 0.001 |
| heparin 1  | HPC1     | 201.04  | 50.73  | 3.96  | 0.001 |
| collagen type VI alpha 6   | COL6A6   | 489.59  | 123.52 | 3.97  | 0.001 |
| prostaglandin G/H synthase 2 (GcIIa, strain)                                     | PTGDS    | 119.40  | 29.81  | 4.00  | 0.000 |
| butyrylcholinesterase  | BChE     | 66.38   | 16.55  | 3.99  | 0.001 |
| FBI murine osteosarcoma viral oncogene homolog B                                 | FOSB     | 51.11   | 12.81  | 3.98  | 0.000 |
| hydroxysteroid (17-beta) dehydrogenase 13  | HSD17B13 | 110.11  | 27.69  | 3.98  | 0.000 |
| chemokine (C-C motif) ligand 14  | CCL14    | 170.04  | 42.73  | 3.98  | 0.001 |
| osteopontin releasing hormone binding protein                                    | OPORP    | 100.00  | 25.00  | 4.00  | 0.000 |
| neuropilin 1 receptor Y1   | NP1YR    | 38.00   | 9.50   | 4.00  | 0.000 |
| heparinase   | HPS1     | 200.00  | 50.00  | 4.00  | 0.000 |

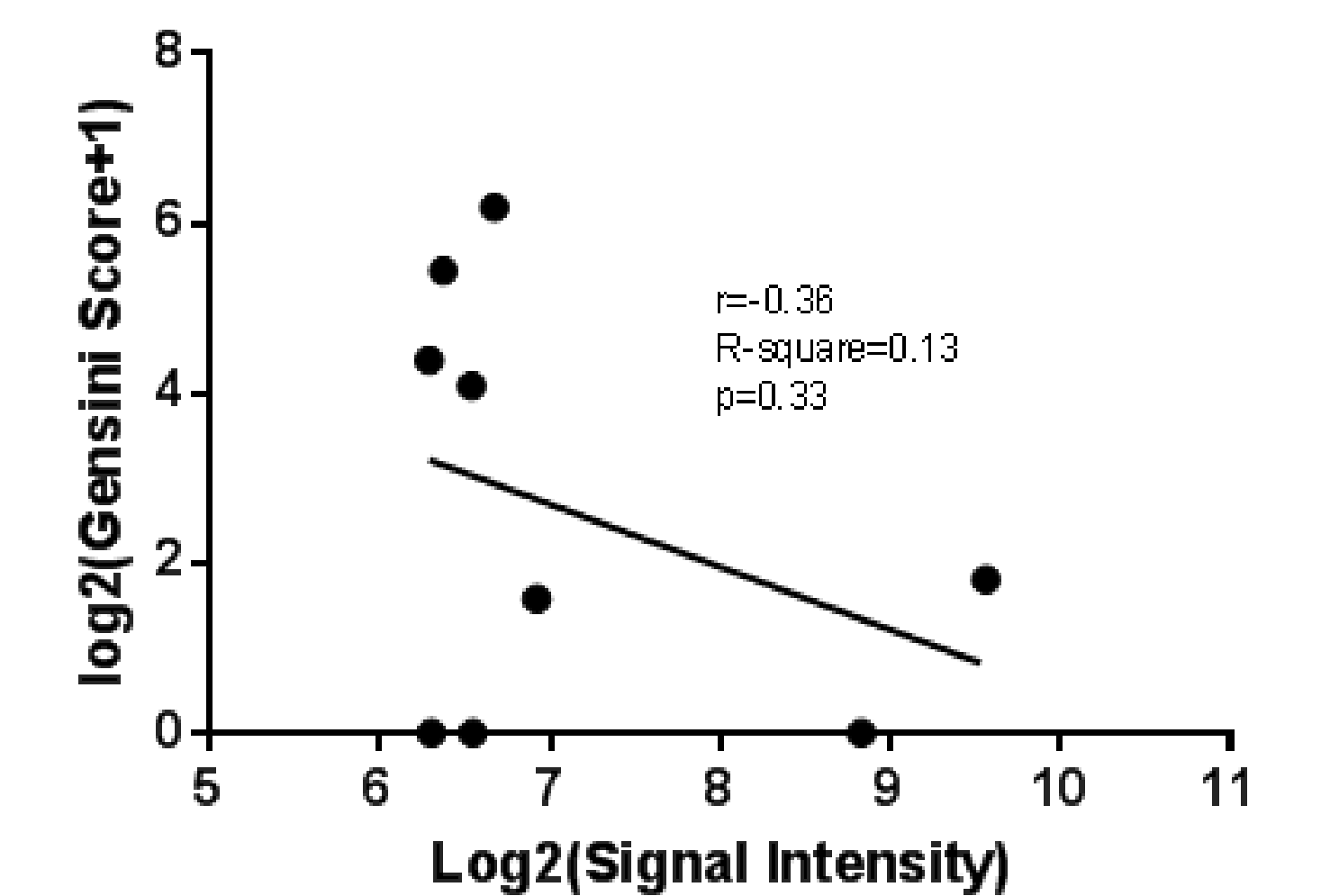
| Gene     | r-value | p-value |
|----------|---------|---------|
| ITGB8    | 0.94    | 0.0001  |
| CYSLTR2  | 0.77    | 0.0147  |
| ALOX15   | 0.76    | 0.0184  |
| COL6A6   | 0.75    | 0.0194  |
| MMRN1    | 0.75    | 0.0199  |
| LRP2     | 0.74    | 0.0232  |
| HPR      | 0.72    | 0.0278  |
| CRHBP    | 0.70    | 0.0374  |
| IGJ      | 0.69    | 0.0386  |
| UCP1     | 0.68    | 0.0436  |
| C7       | 0.67    | 0.047   |
| TCF21    | -0.71   | 0.0314  |
| TNFRSF1A | -0.73   | 0.0263  |
| TGM2     | -0.80   | 0.009   |

Of the 35, 14 are correlated with CAD severity measured by Gensini score

Correlation of Epicardial Adipose Expression of *ITGB8* and Severity of CAD



Correlation of Subcutaneous Adipose Expression of *ITGB8* and Severity of CAD



Of the 14 genes correlated with CAD severity, EAT expression of *ITGB8* had the strongest positive correlation. Importantly, this relationship did not persist in SAT, suggesting it was an effect specific to EAT.

## Conclusion

Expression of *ITGB8* was found to be directly correlated with CAD severity. **Integrin  $\alpha\beta 8$  (*ITGB8*)** has been previously shown to be expressed by fibroblasts and functions to activate immune-modulating TGF $\beta$ . TGF $\beta$  signaling has also been correlated with advanced atherosclerosis. We speculate that EAT expression of *ITGB8* may have pro-inflammatory effects, possibly through activation of TGF $\beta$ , and stimulating recruitment of dendritic cells or T cells to secondary lymphoid organs in EAT. Whether or not this is the case is a goal of future studies.

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