



# Genes Linked with Inflammatory Processes are Differentially Expressed in Patients with Chronic Heart Failure and Pain

Asa B. Smith, PhD, RN<sup>1</sup>; Susan G. Dorsey, PhD, RN, FAAN<sup>2</sup>; Evelina Mocci, PhD<sup>2</sup>; Miyeon Jung, PhD, RN, FAHA<sup>1</sup>; Susan J. Pressler, PhD, RN, FAHA, FAAN<sup>1</sup>  
1: School of Nursing, Indiana University; 2: School of Nursing, University of Maryland

## INTRODUCTION

- Chronic heart failure (HF) affects over 6 million adults in the United States
- Chronic pain is reported by up to 70% of patients with HF
- There are no guideline-directed therapies for pain in HF
- The mechanisms of pain in HF are poorly understood
- Gene expression analysis using mRNA sequencing can highlight mechanistic underpinnings of pain in HF

## AIM

- Identify candidate genes that are differentially expressed between patients with and without pain in HF

## METHODS

### Design

- Cross-sectional descriptive design
- Part of a parent randomized controlled trial (MEMOIR-HF)
- Primary sample:** 40 patients with HF: 20 with pain, 20 without pain. **Validation sample:** 24 patients with HF: 14 with pain, 10 without pain

### Measures

- Pain presence (yes/no) using Health Utilities Index Mark-3

### Analysis

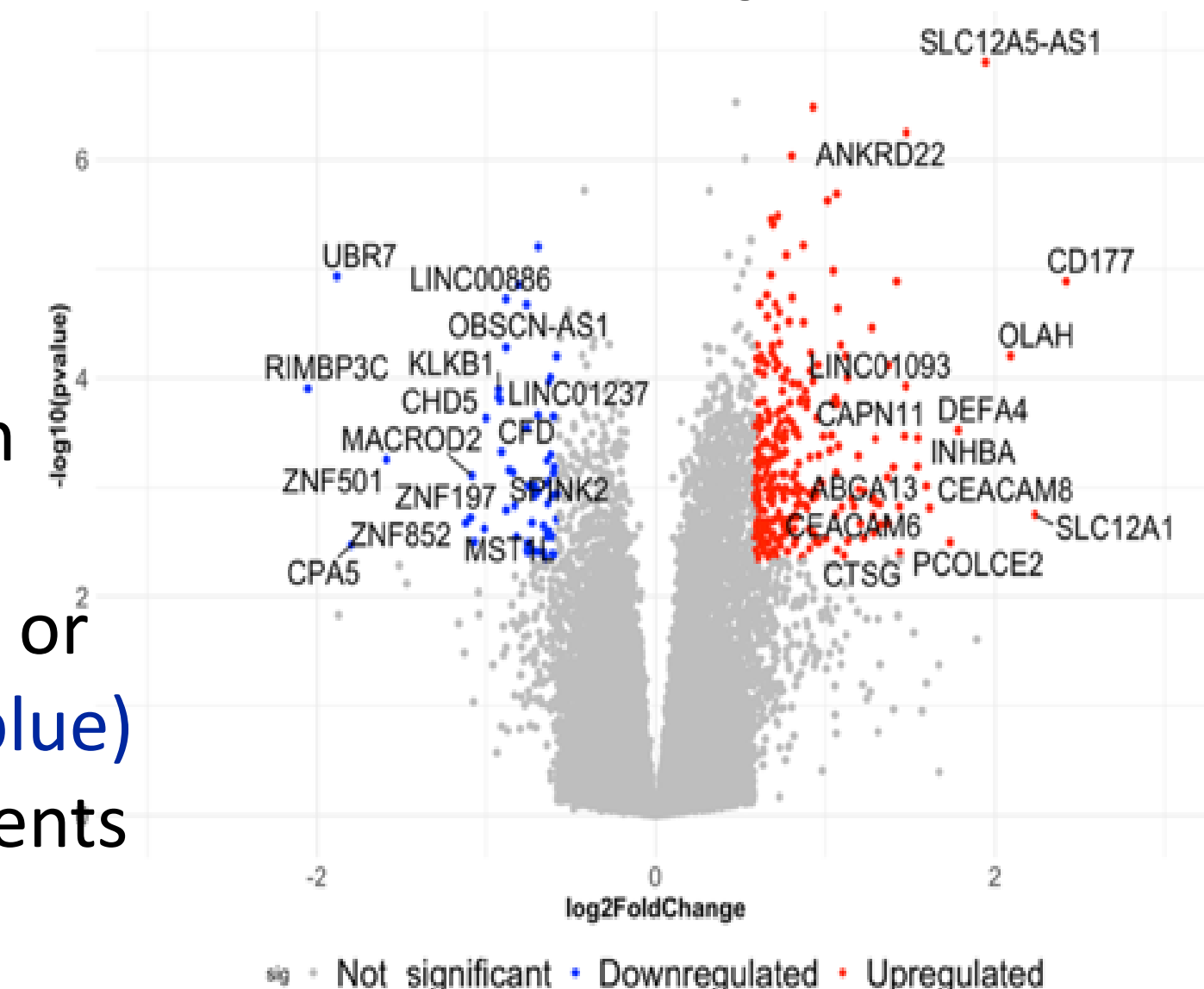
- t-tests and chi square for sample characteristics
- Differentially expressed genes (DEGs) were identified using DESeq2 after isolating and sequencing mRNA
- Potential pain mechanisms were identified by protein-protein interaction (PPI) network created based on the DEGs, and existing literature
- Validation of target genes using quantitative polymerase chain reaction (qPCR) in the validation sample

**Table 1 – Demographic and Clinical Characteristics**

Variable	Total Sample (n=40)	No pain (n=20)	Pain (n=20)	p-value
Age, years	64.55 ± 10.78	62.65 ± 13.87	66.45 ± 6.21	.274 <sup>a</sup>
Gender, n (%)				.741 <sup>b</sup>
Women	14 (35)	6 (30)	8 (40)	
Men	26 (65)	14 (70)	12 (60)	
Race, n (%)				.501 <sup>b</sup>
White	27 (67.50)	12 (60)	15 (75)	
Black	12 (30)	7 (35)	5 (25)	
More than one race	1 (2.50)	1 (5)	0	
NYHA Class				.185 <sup>b</sup>
I	9 (22.50)	7 (35)	2 (10)	
II	17 (42.50)	8 (40)	9 (45)	
III	14 (35)	5 (25)	9 (45)	
LVEF, %	42.56 ± 13.58	43.05 ± 14.04	42.08 ± 13.44	.824 <sup>a</sup>
Comorbid conditions, n (%)				
Arthritis	8 (20)	2 (10)	6 (30)	.235 <sup>b</sup>
Atrial fibrillation	12 (30)	5 (25)	7 (35)	.731 <sup>b</sup>
Coronary artery disease	14 (35)	6 (30)	8 (40)	.741 <sup>b</sup>
CABG	7 (17.50)	2 (10)	5 (25)	.407 <sup>b</sup>
Depression	4 (10)	0	4 (20)	.106 <sup>b</sup>
Diabetes	14 (35)	8 (40)	6 (30)	.741 <sup>b</sup>
Hyperlipidemia	29 (72.50)	15 (75)	14 (70)	<.999 <sup>b</sup>
Hypertension	28 (70)	16 (80)	12 (60)	.301 <sup>b</sup>
Myocardial infarction	7 (17.50)	3 (15)	4 (20)	<.999 <sup>b</sup>
Stroke	3 (7.50)	2 (10)	1 (5)	<.999 <sup>b</sup>
Ventricular arrhythmia	11 (27.5)	5 (25)	6 (30)	<.999 <sup>b</sup>
Depressive symptoms, PHQ-8	4.23 ± 5.05	3.95 ± 5.82	4.50 ± 4.27	.735 <sup>a</sup>
Quality of life, LHFQ	16.4 ± 17.35	15.85 ± 18.09	16.95 ± 17.02	.844 <sup>a</sup>
Mobility, Timed Up and Go	8.74 ± 1.96	8.65 ± 1.81	8.84 ± 2.14	.765 <sup>a</sup>

NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; CABG: coronary artery bypass graft; PHQ-8: Patient Health Questionnaire; LHFQ: Living with Heart Failure Questionnaire

**Figure 1 – Volcano Plot for Differentially Expressed Genes**

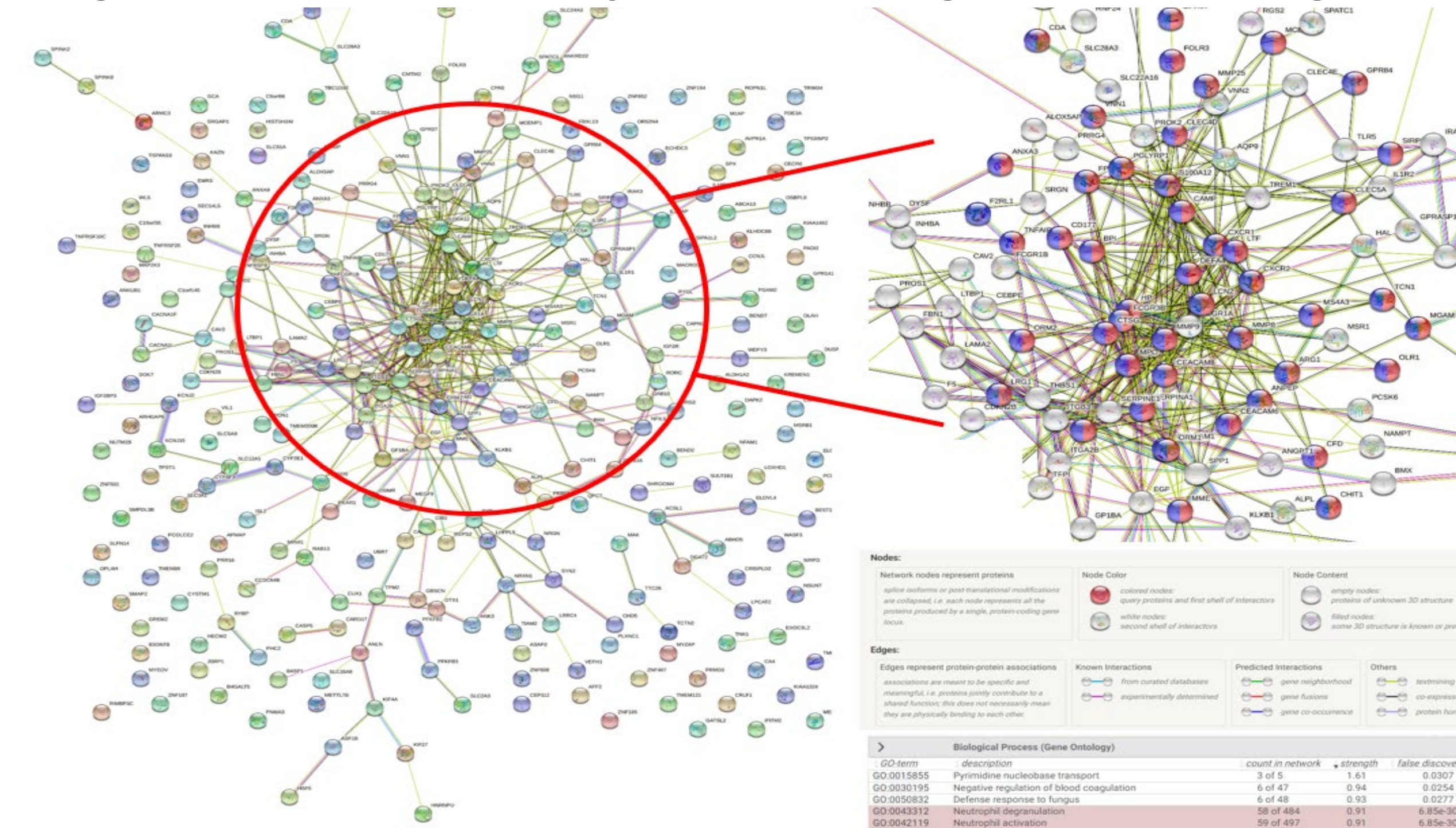


- 334 DEGs were identified
- 57 DEGs among patients with pain were either upregulated (red) or downregulated (blue) compared to patients with pain (fig. 1)

## RESULTS

- DEGS visualized as a network with 288 nodes and 497 edges
- Core cluster of over 15 DEGs within the PPI network (fig. 2)
- DEGs in the PPI network part of neutrophil activation and degranulation pathways (fig. 2)

**Figure 2 – PPI network analysis emphasizing core network of genes**



- Seven genes were identified from the PPI network (table 2)
- Of the seven, three genes were validated in a second sample of 24 patients (table 2)

**Table 2 – Log Fold Change in Gene Expression**

Gene Name (Code)	Primary (n=40)			Validation (N=24)	
	LFC	p-value	padj	LFC	p-value
Cathepsin G (CTSG)	1.44	4.02E-03	4.74E-02	1.29	4.91E-01
Neutrophil Defensin 3 (DEFA3)	1.43	1.51E-02	8.95E-02	1.30	5.64E-01
Lipocalin-2 (LCN2)	1.28	1.26E-03	2.84E-02	0.96	4.96E-01
Lactotransferrin (LTF)	1.33	2.20E-03	3.63E-02	0.77	5.32E-01
Matrix metalloproteinase 8 (MMP8)	1.37	2.14E-03	3.60E-02	1.80	2.14E-01
Matrix metalloproteinase 9 (MMP9)	1.42	1.30E-05	7.01E-03	0.78	2.66E-01
Proprotein convertase subtilisin/kexin type 9 (PCSK9)	2.95	1.45E-02	NA	0.98	9.19E-01

LFC: log fold change; qPCR: quantitative polymerase chain reaction

## DISCUSSION

- Three DEGs identified and validated between patients with and without pain
- The identified genes are known to be associated with inflammatory and cardiovascular disease pathways
- Limitations were a single item pain measure and a small sample sizes
- Research with robust pain measures while controlling for covariates is needed

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