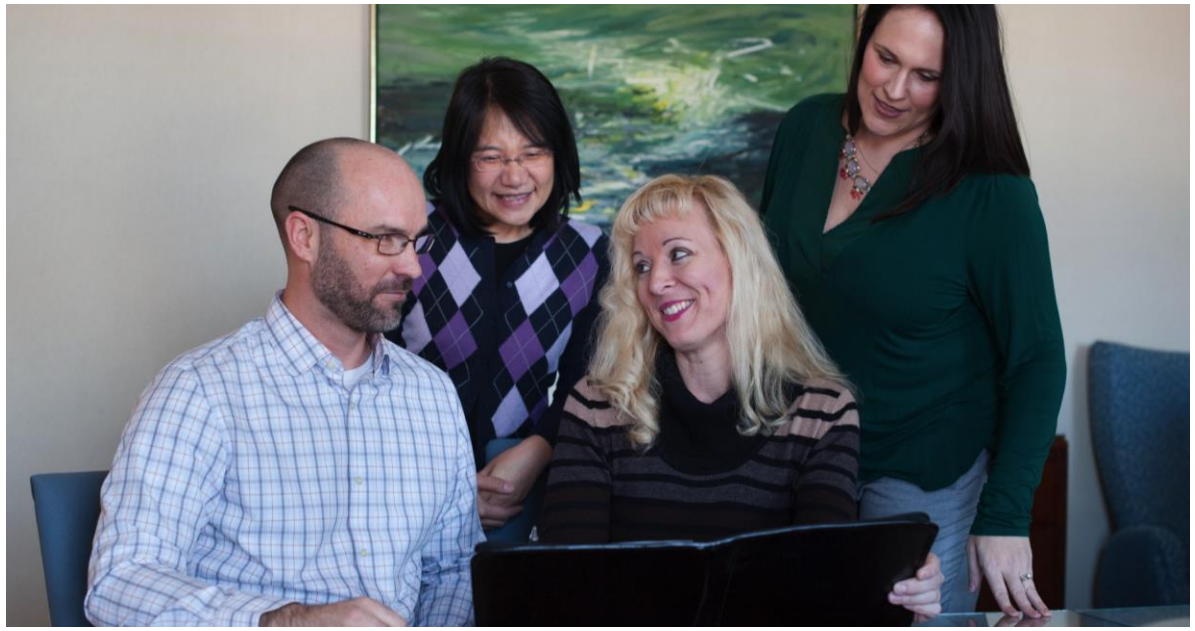
Transition from Acute to Chronic Pain: Using Somatosensory Testing and Genetics to Identify Who is at Risk



Background on Low Back Pain

- Low back pain is costly
- 2nd leading reason for healthcare visits
- Top 10 most expensive conditions

- Etiology
- Non-specific musculoskeletal condition

- Standard definitions for clinical research published in 2015 – Task Force on Research Standards for Chronic Low Back Pain (NIH)

Institute of Medicine. (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education and research.* Washington D.C.: The National Academies Press.

What do we know about LBP?

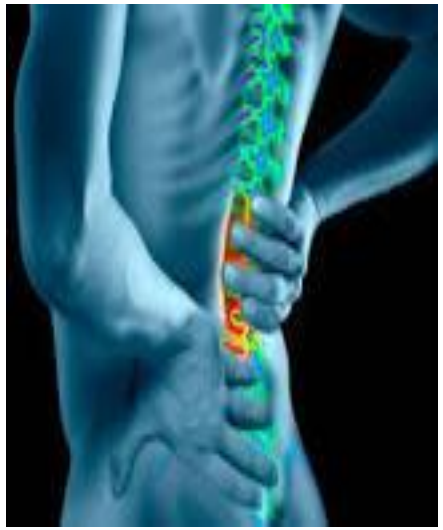
- Prior inception cohort designs
  - Approximately 60% of patients with an acute LBP episode will have resolution of pain within 6 weeks from onset of pain
  - Recurrent episodes are common
- Altered peripheral and central sensitivity in chronic low back pain
  - Individuals who develop chronic LBP develop central sensitization

Costa Lda C, Maher CG, McAuley JH, Hancock MJ, Herbert RD, Refshauge KM, Henschke N. Prognosis for patients with chronic low back pain: inception cohort study. *BMJ* 2009;339:b3829

Methods:

- After screening, informed consent and enrollment:

- Questionnaires
  - Demographics
  - BPI-SF/MPQ-SF
  - POMS
  - Kohn's Reactivity
  - Coping Questionnaire
  - Roland Morrison Disability Scale
  - Work history
- Blood draw
- Quantitative Sensory Testing



Findings

- Baseline analysis of 48 participants, of whom 19 went on to develop persistent low back pain and 29 resolved
- Persistent group was significantly older, less formal education, higher BMI, higher mean BPI-SF “least” pain score
- Persistent group had significantly higher thermal detection thresholds at the painful and remote sites as well as higher WUR at the remote site

Thermal detection

Table 3: Baseline Quantitative Sensory Testing Between Groups

	Persistent	Recovered	Total	P-Value	Normal
	N = 19	N = 29	N= 48		N = 69
Cold Detection Threshold (°C; Mean (SE))					
Remote site	26.31 (1.02)	28.63 (0.24)	27.71 (0.45)	0.0126*	28.66 (0.19)
Back	26.66 (0.94)	28.92 (0.22)	28.03 (0.42)	0.0131*	29.13 (0.14)
Warm Detection Threshold (°C; Mean (SE))					
Remote site	36.68 (0.68)	35.25 (0.26)	35.81 (0.32)	0.0448*	35.20 (0.22)
Back	36.67 (0.46)	34.95 (0.19)	35.63 (0.24)	0.0024*	34.76 (0.21)

Findings

- Comparison of 31 no-pain control participants and 31 participants with acute low back pain
- The acute low back pain group exhibited increased pain sensitivity to cold stimuli, mechanical stimuli, including mechanical temporal summation at both the painful back area and remote location
- Deep tissue specific peripheral sensitization was suggested due to significant differences in pressure pain threshold of the painful back area, but not the remote body site

Differential gene expression

- Three upregulated genes were *CCL2, PNOC*, and *CNR2*.
- Seven dysregulated genes were identified: *GCH1, CSF1, CALCA, PTGES, GDNF*, and *KCNQ2*.

- Upregulation of *PNOC* was significantly associated with mechanical sensitivity of the back region
- Dysregulation of *CALCA* and *GDNF* were significantly associated with cold pain threshold at the remote site
- *CSF1* was associated with wind-up ratio of the painful back region

Findings

- There were more African-American participants in the acute LBP group compared to the healthy no-pain control group ($p<0.01$).
- There were more participants in the acute LBP group earning an annual income less than $60,000 compared with the control group ($p<0.01$) and more participants were working full- or part-time in the control group compared to the acute LBP group ($p=0.01$).
- More participants in the control group had started college or were currently pursuing advanced education compared to the acute LBP group ($p<0.01$).

Somatosensory Changes in Acute LBP

- Compared to the no-pain control group, participants in the acute LBP group had lower threshold for cold at both the remote and back area ($p<0.05$ for both), meaning that pain was elicited at a higher temperature in the acute LBP group.
- The pressure pain threshold was significantly lower only in the back area of the acute LBP group compared to the control group ($p<0.01$) meaning that less pressure stimulus was required to elicit pain.

Table 3. Mean (ΔCq), mean Δ(ΔCq) and fold-change expression values of 10 differentially expressed genes in comparison between acute low back pain and healthy no-pain participants (**when GAPDH used for normalization**).

Genes	Acute low back pain (ΔCq)	No-pain controls (ΔCq)	Δ(ΔCq)	Fold-Change*	FDR
CCL2	10.367 (±1.593)	11.251 (±1.627)	-0.884 (±1.593)	1.845 (±0.331)	0.042
PNOC	9.694 (±1.060)	10.188 (±1.438)	-0.495 (±1.060)	1.409 (±0.480)	0.031
CNR2	6.840 (±0.944)	7.276 (±1.530)	-0.436 (±0.944)	1.353 (±0.520)	0.031
GCH1	4.735 (±0.855)	4.277 (±1.277)	0.458 (±0.855)	0.728 (±0.553)	0.011
CSF1	7.144 (±0.855)	6.636 (±1.109)	0.508 (±0.855)	0.703 (±0.553)	0.031
CALCA	11.451 (±1.04)	10.862 (±1.215)	0.589 (±1.040)	0.665 (±0.486)	0.031
PTGES	11.465 (±1.317)	10.490 (±1.594)	0.974 (±1.317)	0.509 (±0.401)	0.011
GDNF	12.674 (±1.472)	11.687 (±1.336)	0.986 (±1.472)	0.505 (±0.360)	0.033
KCNQ2	13.418 (±1.473)	12.409 (±1.216)	1.009 (±1.473)	0.497 (±0.360)	0.049
HTR2A	12.255 (±1.202)	11.048 (±1.356)	1.207 (±1.202)	0.433 (±0.435)	0.011

* Fold change: $2^{-\Delta(\Delta Cq)}$ where $\Delta(\Delta Cq) = \Delta Cq_{,LBP} - \Delta Cq_{,Normal}$, and FDR: False discovery rate.

Limitations

- Volunteers
- Blinding of assessors was not possible
- Sample did not match on all demographics such as race and education level
- Participants with acute episode had prior episodes of LBP

Conclusions

- This study was the first to report indications of selective peripheral and central sensitization in participants with acute LBP compared to normal controls

- These preliminary findings provide some evidence of potential candidate genetic markers that may influence pain signaling and inflammatory processes during the acute stage.

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