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)

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

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

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

* 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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