The Genetics of Chronic Pain

NIH Pain Consortium Symposium 2014

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Spontaneous Pain

Ipsilateral Thermal Hyperalgesia

Contralateral Thermal Hyperalgesia

(see Nielsen et al. 2012)

(Lariviere et al. 2002)

(Mogil et al. 1995)
Approaches to Study the Genetics of Pain

1) Effect of gene sequence modifications
2) Gene expression changes in pain models
3) Other influences on genes and their expression
Monogenic vs. Polygenic

Rare disorder vs. Normal variability

(Diatchenko et al. 2005)

Figure 1. Distribution of a summary measure of pain sensitivity. A summary measure of pain sensitivity was derived from 16 individual pain measures, each standardized to unit normal deviates (z-scores) with a mean of 0 and
Association Studies

Of Qualitative Traits: i.e., Affected or unaffected

Test whether specific genotype frequencies (single-locus allele/SNP or multilocus haplotype) are significantly different between those affected and those unaffected by the disease or condition.

Of Quantitative Traits:
For e.g., Continuous numeric pain measures (VAS)
COMT: Zubieta et al., 2003

With pain measures:
Genetic basis for individual variations in pain perception and the development of a chronic pain condition

Luda Diatchenko1,4,8,9, Gary D. Slade2, Andrea G. Nackley1, Konakporn Bhalang3, Asgeir Sigurðsson1, Inna Belfer4,7, David Goldman6, Ke Xue4, Svetlana A. Shabalina5, Dmitry Shagin5, Mitchell B. Max7, Sergei S. Makarov8 and William Maixner1

Figure 1. Distribution of a summary measure of pain sensitivity. A summary measure of pain sensitivity was derived from 16 individual pain measures, each standardized to unit normal deviates (z-scores) with a mean of 0 and

Figure 3. Pain responsiveness categorized by three major COMT haplotype combinations. LPS: haplotype G_C_G_G, APS: haplotype A_T_C_A, HPS: haplotype A_C_C_G. The greater values reflect greater pain sensitivity. Each value represents the mean z-score with associated SEM.
Functional consequence of (synonymous) COMT polymorphisms: due to mRNA secondary structure

(Nackley et al. 2006)
Site of COMT action

- Brain areas, via opioid mechanisms?
- Spinal cord? via adrenergic receptor mechanisms?
- Prefrontal cortex?

- Multiple neurotransmitter systems affected: dopamine, adrenaline, noradrenaline
- Multiple possibilities for shared mechanisms with comorbid conditions
For COMT associations review and meta-analysis see Tammimaki and Mannisto (2012)

(Lacroix-Fralish and Mogil, 2009)
### Table 2  Pain related genes associated with neurotransmitter systems

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Neurotransmitter system affected</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>GCH1</td>
<td>Serotonin, dopamine, norepinephrine, epinephrine, nitric oxide (all via BH4)</td>
<td>↓ Sensitivity to experimental pain</td>
<td>11 71–74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Post-surgical pain (lumbar disectomy)</td>
<td></td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Serotonin</td>
<td>↑ Risk for CWP</td>
<td>75 76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Facilitation of experimental pain</td>
<td></td>
</tr>
<tr>
<td>ADRB2</td>
<td>Epinephrine</td>
<td>↑ Risk for CWP</td>
<td>77</td>
</tr>
<tr>
<td>HTR2A</td>
<td>Serotonin</td>
<td>↑ Risk for CWP</td>
<td>78 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Post-surgical pain</td>
<td></td>
</tr>
</tbody>
</table>

CWP, chronic widespread pain.

### Table 3  Pain related genes associated with ion channel function

<table>
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<tr>
<th>Gene name</th>
<th>Channel type affected</th>
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<tr>
<td>SCN9A</td>
<td>Voltage gated Na⁺ channels</td>
<td>↑ Chronic pain in mixed cohort (sciatica, osteoarthritis, pancreatitis, lumbar disectomy, and phantom limb)</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Sensitivity for experimental pain</td>
<td></td>
</tr>
<tr>
<td>KCNS1</td>
<td>Voltage gated K⁺ channels</td>
<td>↑ Chronic pain in 5 cohorts (sciatica, lumbar pain, amputation, phantom limb)</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Sensitivity for experimental pain</td>
<td></td>
</tr>
<tr>
<td>CACNA2D3</td>
<td>Voltage gated Ca²⁺ channels</td>
<td>↓ Sensitivity to thermal pain</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Chronic post-surgical pain (discogenic disease)</td>
<td></td>
</tr>
<tr>
<td>CACNG2</td>
<td>Voltage gated Ca²⁺ channels</td>
<td>↑ Chronic post-surgical pain (post-mastectomy)</td>
<td>90</td>
</tr>
</tbody>
</table>

(Young, Lariviere and Belfer, 2012)
• Analgesia
  
  – **COMT**: ↑ morphine (val158)
  
  – **MC1R**: ↓ lidocaine eff.; ↑ M6G eff.; ↑ desflurane requ (6.2 Vs. 5.2 vol%)
  
  – **OPRM1**: ↑ morphine postop, Ca pain (GG 118)

• Side effects
  
  – **CYP2D6**: ultrarapid metabolizers of codeine have ↑↑ SE
  
  – **ABCB1**: ↑ respiratory depression of fentanyl
  
  – **OPRM1**: A118G ↓ pupil constriction, resp depr
Concerns

- Reproducibility
- Specificity for type of pain
- Source of the candidate gene
Figure 2. Number of pain-relevant candidate gene association study findings in humans by phenotype (see online supplementary material for details). Genes with at least one positive association are shown in green; negative associations are shown in red.

(Mogil, TIGS 2012)
Modality Specificity of COMT Association? (Diatchenko et al. 2006)

- Of 16 pain measures, including:
  - threshold and tolerance to thermal stimuli
  - ischemic and mechanical stimuli and
  - temporal summation of heat pain
- Val^{158}Met associated with rate of temporal summation of heat pain
- LPS/APS/HPS haplotypes with thermal pain
- but possible dependence on variability of measures
(see also Segall et al. 2010; and Belfer et al. 2013 for sex differences)
COMT: Specificity for type of pain

Tammimaki and Mannisto, 2012

- Meta-analysis:
  - COMT associated only with
    - fibromyalgia or
    - chronic widespread pain
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↓ Post-surgical pain (lumbar discectomy) | 11  71–74 |
| SLC6A4    | Serotonin                      | ↑ Risk for CWP  
↑ Facilitation of experimental pain | 75  76    |
| ADRB2     | Epinephrine                    | ↑ Risk for CWP | 77        |
| HTR2A     | Serotonin                      | ↑ Risk for CWP  
↑ Post-surgical pain | 78  79    |

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↑ Sensitivity for experimental pain | 87        |
| KCNS1     | Voltage gated K$^+$ channels           | ↑ Chronic pain in 5 cohorts  
(sciatica, lumbar pain, amputation, phantom limb)  
↑ Sensitivity for experimental pain | 88        |
| CACNA2D3  | Voltage gated Ca$^{2+}$ channels       | ↓ Sensitivity to thermal pain  
↓ Chronic post-surgical pain (discogenic disease) | 89        |
| CACNG2    | Voltage gated Ca$^{2+}$ channels       | ↑ Chronic post-surgical pain  
(post-mastectomy) | 90        |

(Young, Lariviere and Belfer, 2012)
Figure 1. Scheme for objective selection of candidate genes relevant to chronic pain conditions. The initial list of candidates is prioritized on the basis of the number of times each gene appears in several different types of databases. The list is further narrowed to include only genes with more than 1 common variant in the human population under study, and further restricted to genes in which these common variations are likely to have functional effects on protein function or expression. The scheme incorporates ideas from several papers including Refs. 22,34,35.

Recommendations

• Need more big data studies
  – To look for convergent, entirely objective findings
  – Animal studies enough?

• Need more systematic meta-analyses

• Need to place a single gene’s results in the larger context (“Systems Neurogenetics”)
Table 1  Statistically significant QTLs of relevance to pain and analgesia in laboratory rodents

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Chromosome</th>
<th>LOD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Location&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Candidate gene(s)</th>
<th>Evidence&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute/tonic pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>2</td>
<td>5.9</td>
<td>30</td>
<td></td>
<td></td>
<td>(185)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>4.8</td>
<td>10</td>
<td></td>
<td></td>
<td>(185)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>5.8</td>
<td>50</td>
<td></td>
<td></td>
<td>(185)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4.4</td>
<td>30</td>
<td></td>
<td></td>
<td>(185)</td>
</tr>
<tr>
<td>Formalin</td>
<td>10</td>
<td>4.3</td>
<td>70</td>
<td></td>
<td></td>
<td>(186)</td>
</tr>
<tr>
<td>Hargreaves</td>
<td>7</td>
<td>6.3</td>
<td>50</td>
<td>Calca (54 cM)</td>
<td>Pharm., siRNA, gene expr.</td>
<td>(113)</td>
</tr>
<tr>
<td>Hot-plate</td>
<td>4</td>
<td>3.8 (♂ only)</td>
<td>71</td>
<td>Oprd1 (65 cM)</td>
<td>Pharm.</td>
<td>(187)</td>
</tr>
<tr>
<td>Tail withdrawal</td>
<td>4</td>
<td>3.6 (♂ only)</td>
<td>56</td>
<td>Oprd1 (65 cM)</td>
<td>Position</td>
<td>(123)</td>
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<tr>
<td></td>
<td>7</td>
<td>12.6</td>
<td>33</td>
<td>Trpc1 (44 cM)</td>
<td>Position</td>
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<tr>
<td></td>
<td>11</td>
<td>7.8</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autotomy</td>
<td>15</td>
<td>3.9</td>
<td>44</td>
<td></td>
<td></td>
<td>(188)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>3.0</td>
<td>44</td>
<td></td>
<td></td>
<td>(189)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>3.3 (♀ only)</td>
<td>32</td>
<td></td>
<td></td>
<td>(190)</td>
</tr>
<tr>
<td></td>
<td>2 (rat)</td>
<td>3.6</td>
<td>20</td>
<td></td>
<td></td>
<td>(191)</td>
</tr>
</tbody>
</table>

(Lacroix-Fralish and Mogil, 2009)
Genetic Relationships Among Neuropathic Pain Assays

- AUT: Chr 15 (+Chr 14)
- SNIVF: Chr 5
- PACOLD, PACVF, PNIVF, PNIHT: Chr ?
- PNI = Spin. N. Lig. (SNL)

(Young et al., 2014)
Systematic Meta-Analyses

• Migraine: Ligthart et al. 2011, others

• Disc degeneration: Eskola et al. 2012

• COMT: Tammimaki and Mannisto, 2012
  – Low to medium strength of findings…
  – Low COMT activity is not associated with migrainous headache or chronic musculoskeletal pain conditions
(Young, Lariviere and Belfer, 2012)
Need more critical reviews
Need to acknowledge specificity of pain type
Can use quantitative meta-analysis methods to determine mechanisms of comorbidity
The Larger Context:
What is the relative biological importance of the most popular genes being studied?

Figure 3. Popular candidate genes in pain genetic research. Studies of variants within these 10 genes outnumber studies of all other genes combined. Abbreviations: COMT, catechol-O-methyltransferase; GCH1, GTP cyclohydrolase 1; HLA, human lymphocyte antigen (major histocompatibility complex); HTR2A, serotonin receptor, 2A; IL1A,B, interleukin-1 receptor α or β; IL1RN, interleukin-1 receptor antagonist; OPRM1, μ-opioid receptor; SLC6A4, solute carrier family 6, member 4 (serotonin transporter); TRPV1, transient receptor potential cation channel, V1; TNF, tumor necrosis factor.
Thanks

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  – Harvard: Michael Costigan
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