Genetic and Non-Genetic Risk Factors for Development of Chronic Pain

Roger B. Fillingim, Ph.D.
University of Florida, and North Florida/South Georgia VA Health System

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Overview

• Conceptual & methodological considerations
  • Non-genetic risk factors for chronic pain
  • Genetic risk factors for chronic pain
  • Conceptual model and future directions
What Kind of Chronic Pain?

- Post-operative chronic pain
- Other iatrogenic chronic pain (chemotherapy-induced)
- Disease associated (e.g. PHN, DPN)
- Post-Traumatic
- Insidious
What Kind of Chronic Pain (part 2)?

- Neuropathic
- Musculoskeletal
- Visceral

(I’ll use examples of Back Pain, CWP, TMD, post-surgical pain)
Types of Risk Factors

**Dispositional**
- Genetics
- Demographics
  - age, sex, race
- Personality
- Depression

**Situational**
- Stress
- Mood/Coping
- Transient biological processes

**Exposures**
- Trauma/Injury
  - surgery, MVA, infection
- Stressors/Occupation
- Smoking/Diet
Methodologic Considerations

• Sample Sizes
  – Incidence rates, allele frequencies

• Base rate problems
  – Frequency of exposure/risk factor variables
  – Frequency of pain in general population

• Follow-up period

• Risk Factors: mechanisms or markers?
Overview

- Conceptual & methodological considerations
- **Non-genetic risk factors for chronic pain**
- Genetic risk factors for chronic pain
- Conceptual model and future directions
"I'm the one with the medical degree, I'll determine if your back is bothering you, or not..."
1. Psychosocial variables associated with reported onset of back and neck pain and transition from acute to chronic pain disability. (Level A evidence)

2. Psychosocial variables generally have more impact than biomedical or biomechanical factors on back pain disability. (Level A)

3. Cognitive factors (attitudes, cognitive style, fear avoidance beliefs) (Level A)

4. Self-perceived poor health (Level A)

5. Depression, anxiety, negative emotions (Level A)

6. Personality and traits (Level C)

7. Sexual and/or physical abuse (Level D)

8. Psychosocial factors as risk factors for long-term pain and disability. (Level A)

Level A: evidence from two or more good-quality prospective studies
Level C: inconclusive data
Level D: no studies available meeting criteria
## Occupational Factors and Risk for Low Back Pain (Linton, et al, 2001)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Job Satisfaction</td>
<td>Strong Evidence (13/14 studies)</td>
</tr>
<tr>
<td>Monotonous Work</td>
<td>Strong Evidence (4/6 studies)</td>
</tr>
<tr>
<td>Work Relations</td>
<td>Strong Evidence (5/6 studies)</td>
</tr>
<tr>
<td>Perceived Demands</td>
<td>Strong Evidence (3/3 studies)</td>
</tr>
<tr>
<td>Control</td>
<td>Moderate Evidence (2/2)</td>
</tr>
<tr>
<td>Work Pace</td>
<td>Moderate Evidence (2/3)</td>
</tr>
<tr>
<td>Occupational Stress</td>
<td>Strong Evidence (3/3 studies)</td>
</tr>
<tr>
<td>Perceived Ability to Work</td>
<td>Strong Evidence (3/3 studies)</td>
</tr>
<tr>
<td>Belief that Work is Dangerous</td>
<td>Moderate Evidence (2/2)</td>
</tr>
</tbody>
</table>
Spinal Mechanical Load and Risk for Low Back Pain (Bakker, et al, 2009)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy Physical Work</td>
<td>Conflicting Evidence</td>
</tr>
<tr>
<td>Standing/Walking at Work</td>
<td>Strong Evidence for no association</td>
</tr>
<tr>
<td>Sitting at Work</td>
<td>Strong Evidence for no association</td>
</tr>
<tr>
<td>Whole Body Vibration at Work</td>
<td>Conflicting Evidence</td>
</tr>
<tr>
<td>Bending/Twisting at Work</td>
<td>Conflicting Evidence</td>
</tr>
<tr>
<td>Nursing Tasks</td>
<td>Conflicting Evidence</td>
</tr>
<tr>
<td>Leisure Sport/Exercise</td>
<td>Strong Evidence for no association</td>
</tr>
<tr>
<td>Leisure Activities</td>
<td>Conflicting Evidence</td>
</tr>
</tbody>
</table>
# Risk Factors for Chronic Widespread Pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific Risks</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Demographics           | Gender and older age (in kids)  
Gender (in adults)  
Davies, et al, 2009  
Davies, et al, 2009 |
| Childhood Events       | Financial difficulties  
Maternal death  
Institutional Care  
Multiple somatic symptoms | Jones, et al, 2007; 2009 |
| HPA Axis Function      | Low Morning Cortisol  
High Evening Cortisol  
| Psychological Distress | Depression                                                                 | Mikkelson, et al, 2008;  
| Pain Sensitivity       | Tender Point Count (but not PPT)                                              | Gupta, et al, 2007 |

Odds Ratio

- Female Gender
- Other Pains
- Parents' Education
- Somatization
- Life Satisfaction
Psychological Risk Factors for TMD
(Slade, et al, 2007)

Individuals scoring in the upper tertile of depression (A) and somatization (C) and the lower tertile of confidence (B) showed significantly higher incidence of new onset TMD. This finding is independent of COMT haplotype.
Pain Sensitivity as a Risk Factor for TMD
(Slade, et al, 2007)

Individuals scoring in the upper tertile of pain sensitivity showed significantly higher incidence of new onset TMD. The pain phenotype score was a composite index of 13 different measures of pain sensitivity, across three stimulus modalities (heat, pressure, ischemic).
**Chronic Post-Operative Pain**
(Kehlet, Jensen, & Woolf, 2006)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Estimated incidence of chronic pain</th>
<th>Estimated chronic severe (disabling) pain (&gt;5 out of score of 10)</th>
<th>US surgical volumes (1000s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30-50%</td>
<td>5-10%</td>
<td>159 (lower limb only)</td>
</tr>
<tr>
<td>Breast surgery (lumpectomy and mastectomy)</td>
<td>20-30%</td>
<td>5-10%</td>
<td>479</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>30-40%</td>
<td>10%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>10%</td>
<td>2-4%</td>
<td>609</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>30-50%</td>
<td>5-10%</td>
<td>598</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>10%</td>
<td>4%</td>
<td>220</td>
</tr>
</tbody>
</table>

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

**Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures**
78 (52%) patients reported chronic pain after thoracotomy.

Retrospectively, a greater proportion of patients with chronic pain reported moderate to severe acute pain. Also, trend toward younger age in the pain group.

**Table 2**

<table>
<thead>
<tr>
<th>Years post-operatively</th>
<th>Patients with CPTP</th>
<th>%</th>
<th>Years post-operatively</th>
<th>Patients with CPTP</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–1.0</td>
<td>19/31</td>
<td>61</td>
<td>0.5–1.5</td>
<td>30/52</td>
<td>58</td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>11/21</td>
<td>52</td>
<td>1.5–2.5</td>
<td>30/55</td>
<td>55</td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>10/26</td>
<td>38</td>
<td>2.0–2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>20/29</td>
<td>69</td>
<td>2.5–3.0</td>
<td>18/41</td>
<td>44</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>10/22</td>
<td>45</td>
<td>3.0–3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>8/19</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>78/149</td>
<td>52</td>
<td>Total</td>
<td>78/149</td>
<td>52</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>CPTP (n = 78)</th>
<th>No CPTP (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No acute pain</td>
<td>12 (15%)</td>
<td>27 (38%)</td>
</tr>
<tr>
<td>Mild acute pain</td>
<td>13 (17%)</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>Moderate acute pain</td>
<td>23 (29%)</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>Severe acute pain</td>
<td>30 (38%)</td>
<td>12 (17%)</td>
</tr>
</tbody>
</table>
Gender and Post-Thoracotomy Pain
(Ochroch, et al, 2006)

Women (right bar) reported more acute pain than men (left bar)
Gender and Post-Thoracotomy Pain
(Ochroch, et al, 2006)

Women (right bar) reported more long-term pain than men (left bar)
Acute Post-Op Pain in Patients Reporting Post-Thoracotomy Pain at 48 Weeks
(Gottschalk, et al, 2008)

Acute pain was greater post-op days 4 and 5 among patients who reported pain at 48 weeks. Also, patients with pain at 48 weeks were younger than those with no pain.
Reduced Endogenous Pain Modulation as a Risk Factor for Chronic Post-Thoracotomy Pain
(Yarnitsky, et al, 2008)

DNIC predicted development of chronic pain (pain rating > 20) 7 months after thoracotomy

Table 3
Reduced model based on only DNIC and acute pain as predictors of chronic pain

<table>
<thead>
<tr>
<th>Term</th>
<th>Chi-square</th>
<th>p</th>
<th>Odds ratio</th>
<th>OR lower 95% CI</th>
<th>OR upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.47</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNIC</td>
<td>9.20</td>
<td>0.0024</td>
<td>0.52</td>
<td>0.33</td>
<td>0.77</td>
</tr>
<tr>
<td>Acute pain</td>
<td>9.20</td>
<td>0.0024</td>
<td>1.80</td>
<td>1.28</td>
<td>2.77</td>
</tr>
</tbody>
</table>

The odds ratios are based on changes of 10 U for both DNIC and acute pain, i.e., 10-point changes on scales ranging from −100 to 100 and 0 to 100, respectively.

Fig. 2. Logistic regression probability plot relating DNIC to the probability of development of chronic pain.
Chronic Post-Mastectomy Pain
(Poleshuck, et al, 2006)

48.4% women reported surgery-related pain at 3-month follow-up

<table>
<thead>
<tr>
<th>Table 3. Logistic Regression Model for Presence of Chronic Pain Following Breast Cancer Surgery (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK FACTOR VARIABLE</strong></td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Breast cancer history</td>
</tr>
<tr>
<td>Radiation therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Linear Regression Model for Intensity of Chronic Pain Following Breast Cancer Surgery (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK FACTOR VARIABLE</strong></td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Breast cancer history</td>
</tr>
<tr>
<td>Preoperative breast pain</td>
</tr>
<tr>
<td>Surgery type</td>
</tr>
<tr>
<td>Cancer status</td>
</tr>
<tr>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Marital status</td>
</tr>
<tr>
<td>Clinically meaningful acute pain</td>
</tr>
</tbody>
</table>
## Predictors of Chronic Postoperative Pain

(Hinrichs-Rocker, et al, 2008)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Younger Age</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Depression</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Psychic Vulnerability (Neuroticism)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Stress</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Late Return to Work</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table

<table>
<thead>
<tr>
<th></th>
<th>Hernia</th>
<th>Thoracotomy</th>
<th>Cholecystectomy</th>
<th>Breast surgery</th>
<th>Spine surgery</th>
<th>Knee surgery</th>
<th>Other surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td># Studies</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td># Patients/study</td>
<td>44-5506</td>
<td>30-1348</td>
<td>100-186</td>
<td>93-569</td>
<td>17-257</td>
<td>77-860</td>
<td>22-848</td>
</tr>
<tr>
<td>Incidences of chronic pain (%)</td>
<td>9-46</td>
<td>20-57</td>
<td>13-26</td>
<td>17-52</td>
<td>30-70</td>
<td>13-23</td>
<td>16-49</td>
</tr>
</tbody>
</table>
Overview

- Conceptual & methodological considerations
- Non-genetic risk factors for chronic pain
- Genetic risk factors for chronic pain
- Conceptual model and future directions
You have recessive jeans for plumbing.
Advantages of Genetic Markers as Risk Factors

• No chicken and egg problem
• Highly reliable
• May reveal pathophysiology
• Can indicate new biological treatment targets
## Heritability of Clinical Pain Conditions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pain Condition</th>
<th>Study Design</th>
<th>Heritability Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fejer et al, 2006; MacGregor et al, 2004</td>
<td>Neck Pain</td>
<td>Twin Studies</td>
<td>.36 - .58</td>
</tr>
<tr>
<td>Hestbaek et al, 2004; MacGregor et al, 2004</td>
<td>Low Back Pain</td>
<td>Twin Studies</td>
<td>.40 - .68</td>
</tr>
<tr>
<td>Kato et al, 2006</td>
<td>Widespread Pain</td>
<td>Twin Studies</td>
<td>.48 - .54</td>
</tr>
<tr>
<td>Zondervan, et al 2005</td>
<td>Pelvic Pain</td>
<td>Twin Study</td>
<td>.41</td>
</tr>
<tr>
<td>Hakim, et al, 2002</td>
<td>Carpal Tunnel</td>
<td>Twin Study</td>
<td>.46</td>
</tr>
</tbody>
</table>
Catechol-O-methyl-transferase Gene (COMT) and Pain Sensitivity?

• COMT metabolizes catecholamines

• Common met^{158}val SNP of COMT: met/met have low COMT activity; val/val have high COMT activity

• Val/val genotype was associated with higher pain-related mu-opioid receptor binding and reduced pain response to hypertonic saline; met/met was associated with lower binding (Zubieta, et al, 2003)
COMT Haplotype and TMD Incidence
(Diatchenko, et al, 2005)

A
Membrane bound form
rs2097903 rs6269 rs4633 rs4818 (val/met) rs4680
A-61%, G-39%
G-43%, A-57%
T-50%, C-50%
G-42%, C-58%
A-50%, G-50%
A-59%, G-41%

Soluble form

B
D’s are in the range from
0.28 to 0.35
D’s are in the range from
0.04 to 0.11
D’s are in the range from
1.00 to 0.94
haploblock 1 haploblock 2 haploblock 3

C
Haplotype Sequence Frequency, %
LPS APS HPS
G--C--------- -- G--G 36.5
A--T--------- -- C--A 48.7
A--C--------- -- C--G 10.7
G--C--------- -- C--G 1.2
A--T--------- -- G--G 1.0
A--C--------- -- G--G 1.0
G--C--------- -- C--A 0.7
COMT Haplotype and TMD Incidence
(Diatchenko, et al, 2005)

Individuals with at least one low pain sensitive (LPS) haplotype were at lower risk for development of TMD compared to those with no LPS haplotypes.
Haplotypes constructed from 4 *COMT* SNPs: rs6269, rs4633, rs4818, rs4680
COMT Haplotypes and FIQ Scores Mexican and Spanish FM Patients (Vargas-Alarcon, et al, 2007)
Combined Influences of COMT and Catastrophizing on Shoulder Pain (George, et al, 2008)

- 58 (24 F, 34 M) patients with chronic shoulder pain, undergoing arthroscopic surgery

- Pre-operative testing
  - Psychological questionnaires (catastrophizing)
  - Psychophysical testing
  - Buccal swab for DNA (COMT diplotypes from Diatchenko, et al, 2005)

- Arthroscopic surgery
- Post-operative testing (3-5 months later)
Combined Influences of Pain Catastrophizing and COMT Haplotype

**Pre-Operative Pain**

- LPS and Low PCS (n = 24)
- LPS and High PCS (n = 10)
- APS/HPS and Low PCS (n = 16)
- APS/HPS and High PCS (n = 8)

**Post-Operative Pain**

- LPS and Low PCS (n = 20)
- LPS and High PCS (n = 8)
- APS/HPS and Low PCS (n = 13)
- APS/HPS and High PCS (n = 6)
Replication in DOMS Model of Shoulder Pain (George, et al, 2008)

- 63 (35 F, 28 M) healthy young (age=20.9) participants

- Delayed Onset Muscle Soreness Protocol with Kin-Com isokinetic dynamometer
  - Assessed VAS ongoing pain 24, 48, 72 hours later
  - Assessed VAS pain in response to 4 kg/cm² pressure to rotator cuff tendon insertion

- Psychological questionnaires (catastrophizing)

- Buccal swab for DNA (COMT diplotypes from Diatchenko, et al, 2005)
Catastrophizing and COMT in Experimental Shoulder Pain

VAS Rating (0-100)

* APS/HPS+Hi PCS group > other groups, p < .05
Is the mu-Opioid Receptor Gene (OPRM1) Associated with Baseline Pain Sensitivity?

• Uhl (1999) suggested OPRM1 was a strong candidate for a “pain gene”

• The A118G variant mu receptor shows greater binding affinity for beta-endorphin (Bond, et al, 1998)

• We studied baseline pain sensitivity in 167 (96 F, 71 M) individuals and determined A118G genotype using PCR
**OPRM1 A118G Genotype and Pressure Pain Thresholds among Females and Males**

- **Trapezius**
  - Male: AA (67 F, 55 M) vs. AG/GG (24 F, 12 M)
  - Female: AA (67 F, 55 M) vs. AG/GG (24 F, 12 M)

- **Masseter**
  - Male: AA (67 F, 55 M) vs. AG/GG (24 F, 12 M)
  - Female: AA (67 F, 55 M) vs. AG/GG (24 F, 12 M)

- **Ulna**
  - Male: AA (67 F, 55 M) vs. AG/GG (24 F, 12 M)
  - Female: AA (67 F, 55 M) vs. AG/GG (24 F, 12 M)

* Sex X genotype interaction, p’s = .09
* Genotype effect, all p’s < .05 for males
OPRM1 A118G Genotype and Pain Responses in a Second Cohort

all p's > .05
But, this was a multi-ethnic cohort…

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African American</strong></td>
<td>75 (92.6%)</td>
<td>6 (7.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Hispanic-Whites</strong></td>
<td>57 (72.2%)</td>
<td>21 (26.6%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td><strong>Non-Hispanic Whites</strong></td>
<td>63 (71.6%)</td>
<td>24 (27.3%)</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

p < .05
OPRM1 A118G Genotype and Pain Responses Across Ethnic Groups

African American
Hispanic
White

* Significant genotype effect
OPRM1 and Foot Ulcer Pain in Diabetics
(Cheng, et al, 2009)
Carriers of the 118G allele had lower serum levels of IL-6 and higher self-reported general health compared to AA carriers.
GTP Cyclohydrolase Gene (GCH1)  
(Tegeder, et al, 2006)

• Enzyme involved in production of 6(R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4).

• BH4 is a key cofactor in the synthesis of several pain neuromodulators including catecholamines, serotonin and nitric oxide, and BH4 induces pain hypersensitivity.

• GTP cyclohydrolase and BH4 were increased after nerve injury and inhibition of GTP cyclohydrolase reduced neuropathic & inflammatory pain in rats.
GTP Cyclohydrolase Gene (*GCH1*)
(Tegeder, et al, 2006)

A pain protective haplotype of *GCH1* was associated with reduced frequency of leg pain after discectomy (B) and with lower sensitivity to experimental pain in 2 cohorts (C)
GTP Cyclohydrolase Gene (**GCH1**) (Tegeder, et al, 2008)

The pain protective haplotype of **GCH1** was associated with reduced hyperalgesia following a freeze lesion and following capsaicin application.

![Graph showing pain thresholds](image)
Three of the SNPs identified by Tegeder, et al were significantly associated with pain ratings following application of topical capsaicin. The linear combination of SNPs accounted for 35% of the variance in pain ratings.
Association of IL6 With Low Back Pain

- A haplotype (GGGA) constructed from 4 SNPs was more frequent in patients with discogenic sciatica compared to controls (Noponen-Hietala, et al, 2005)

- Patients with GGGA haplotype reported more days with back/leg pain and more sick days over a three-year follow-up (Karppinen, et al, 2008)
Overview

• Conceptual & methodological considerations

• Non-genetic risk factors for chronic pain

• Genetic risk factors for chronic pain

• Conceptual model and future directions
Painful Temporomandibular Disorders

High Psychological Distress

- Mood
- Anxiety
- Depression
- Stress Response
- Somatization

High State of Pain Amplification

- Tissue Injury
- Blood Pressure
- Impaired Pain Regulatory Systems
- Pro-inflammatory State

Environmental Contribution

- GAD65
- MAO
- Serotonin receptor
- Cannabinoid receptors
- NMDA
- CREB1
- Dopamine receptors
- Adrenergic receptors
- GR
- Serotonin transporter
- CACNA1A
- DREAM
- POMC
- NET
- Opioid receptors
- BDNF
- NGF
- Prodynorphin
- Interleukins

Diatchenko, et al, 2005
Orofacial Pain: Prospective Evaluation and Risk Assessment

Central Hypothesis: Pain amplification and psychological factors, both of which are influenced by genetic variants and environmental events, represent causal influences for TMD onset and persistence.

Funded by NIDCR-U01DE017018
Chronic Pain Disorders

- Altered Pain Processing
- Psychological Processes
- Biological Processes

Genetic Factors

Effect Modifiers (e.g., sex, age, race)

Environmental Exposures
Summary

• Multiple non-genetic factors predict future onset of chronic pain (demographics, psychosocial)

• Likely genetic risk factors include genes encoding proteins involved in response to injury (e.g. IL6, GCH1) and central pain modulation (e.g. COMT, OPRM1)

• Genetic and non-genetic risk factors interact

• Implications for trial design include:
  – sample size considerations (allele frequency)
  – choice of patient population
  – phenotypic measures (QST, psychosocial factors)
Thank You