Overview of Genetics and Pain

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Conflict of Interest Disclosure

• Advisory Board- Quest Diagnostics, Purdue Pharma
• Speaker- Mundi Pharmaceuticals
• Honorarium - UPTODATE

Objectives

• Discuss the current state of pain genetics research
• Describe the role of genetics in pain assessment and management
• Discuss drug metabolism through CYP450 system and its effect on response to analgesics
• Utilize pharmacogenetic testing to assess for potential response to analgesics
Some basic definitions.....

• **Genotype** – combination of the two set of chromosomes at fertilization; an individual genetic constitution

• **Phenotype** – the outward appearance of the individual; part of genetic inheritance (predisposition) and influence of environment

• **Genomic Variation** - only use 5% genes to generate proteins; 1. Decipher population history 2. Track somatic changes 3. Predict response to therapy 4. Identify genes for complex disease

• **Allele** - different forms or DNA sequence of a gene

• **Genetic variations** - DNA sequence variants that are more common in populations; Single nucleotide polymorphisms account for 3 million differences between individual pairs; **significance** - influence risk for complex common diseases

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If it were only that easy....

• Science Daily News, Sept 9, 2011

**Gene That Controls Chronic Pain Identified**

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**Patient Profile**

• 62 y.o. Caucasian woman

• Postthoracotomy neuropathic pain
  • Constant severe burning pain left posterolateral surgical scar
  • Hyperalgesic along scar and dermatome

• Chronic low back pain, migraines

• PMH: COPD - Oxygen dependent/wheelchair bound
What's Genetics Have to do with Pain?

Genotype
- Over 350 genes in pain database
- Chronic Pain – multifactorial - polygenic and environmental
  - Variation implicated in pain development, characteristic, intensity, frequency, and analgesic responses
- Mechanisms
  - Neurotransmitter system
  - Sodium/potassium/calcium channels
  - Opioid metabolism

Mogil, 2012
### Table 1

<table>
<thead>
<tr>
<th>Gene Full name</th>
<th>Gene Name</th>
<th>Function</th>
<th>Pain effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT1</td>
<td>Catechol-O-Methyltransferase</td>
<td>Monooxygenase, require 3-OH substrates</td>
<td>Changes in effects of opioid agonists, variable response to pain</td>
</tr>
<tr>
<td>ABCB1</td>
<td>ATP-binding cassette, sub-family B (MDR/TAP), member 1</td>
<td>Drug transporter</td>
<td>Changes in metabolism of to analgesics/side effects</td>
</tr>
<tr>
<td>SCN9A</td>
<td>Sodium channel, voltage-gated type IX, α subunit</td>
<td>Voltage-gated Na+ channel</td>
<td>Increased chronic pain (mixed cohort); alteration pain perception; erythermalgia, paroxysmal extreme pain, congenital inability to experience pain</td>
</tr>
<tr>
<td>KCNS1</td>
<td>Potassium voltage-gated channel, delayed rectifier, subfamily S, member 1</td>
<td>Voltage-gated K+ channel</td>
<td>Increased risk neuropathic pain; sciatica, post-discectomy, amputation, phantom limb; experimental pain</td>
</tr>
<tr>
<td>HCN2</td>
<td>Hyperpolarization-activated cyclic nucleotide-gated channel 2</td>
<td>K+, Na+ channel</td>
<td>Inflammatory and neuropathic pain</td>
</tr>
<tr>
<td>TRPV1</td>
<td>Transient receptor potential cation channel, subfamily V, member 1</td>
<td>Non-selective calcium permeant cation channel</td>
<td>Thermal stimulation – neuropathic pain?</td>
</tr>
<tr>
<td>OPRM1</td>
<td>Opioid receptor mu</td>
<td>Receptor functions</td>
<td>Changes effects of opioid agonists</td>
</tr>
<tr>
<td>CYP450</td>
<td>Cytochrome P450</td>
<td>Catalyzes many reactive drug metabolism</td>
<td>Changes in metabolism of many reactive drugs</td>
</tr>
</tbody>
</table>

### Selected genes (variation) implicated in pain and response to analgesia

- **ABCB1**
  - ATP-binding cassette, sub-family B (MDR/TAP), member 1
  - Drug transporter
  - Moves drugs from intracellular to extracellular and CNS
  - Genetic polymorphisms may affect fentanyl, methadone, and morphine
  - May affect the clinical efficacy and safety

Jannetto & Bratanow, 2011
COMT
- Catechol-O-methyltransferase (COMT)\(^1\)
  - Modulate nociception
  - Has been associated with chronic widespread pain,
  - Influence on analgesic (opioid) efficacy
  - May affect efficacy/work in synergy OPMR1
  - Inconsistencies study replication, heterogeneity of studies with only weak associations\(^2\)
- Implications
  - Genetic testing may influence analgesic choice, more studies needed


HCN2
- Hyper-polarization activated cyclic nucleotide gated ion channel 2 (HCN2)
  - Associated with action potential firing
  - Affects Na\(^+\) and K\(^+\) channels- \(?\)pain intensity
- Implications
  - \(?\) Novel analgesics target these channels

Emery et al., 2011

SCN9A (NAV1.7)
- Sodium channel voltage gated type IX, alpha subunit (SCN9A)
  - Expressed in peripheral somatic and visceral sensory neurons
  - Loss or gain of function mutation pain perception – Mendelian inheritance pattern
  - Erythermalgia, Paroxysmal extreme pain disorder (PEPD), Congenital inability to experience pain (CIP)
- Implications
  - Development novel agents voltage gated sodium channel for neuropathic pain

Dib-Hajj et al., 2013
KCNS1

- Potassium voltage gated channel, delayed rectifier, subfamily s, member 1
  - Voltage gated K⁺ ion Channel
  - Variations possibly implicated in neuropathic pain
- Implications: Nerve injury could lead to increased risk neuropathic pain; sciatica, post-discectomy, amputation, phantom limb; experimental pain

Costigan et al., 2010

TRPV1

- Transient receptor potential cation channel, subfamily V, member 1 (TRPV1)
  - Function transduction painful thermal stimuli
  - Mouse model capsaicin effect for analgesia
    - Block the nociceptive sodium channels of TRPV1
- Implications
  - Analgesic target for therapy

Zakir, et al., 2012

OPMR1

- Opioid receptor mu (OPMR1)
  - Responsible opioid receptor function
  - Linked to opioid responsiveness
    - Caveat: Metaanalysis failed to find clinical relevance
    - ? May not have taken into account all SNPs of mu opioid receptor
- Implications
  - Identifying variants may affect therapy decisions

1Walter & Lötch, 2009,
Miscellaneous

- SNP identified (rs2952768 on chromosome 2q33.3-2q34)
  - Function unknown
  - Associated with sensitivity to opioids
  - Associated with liability to substance abuse

\*Nishizawa, et al., 2012

Cytochrome P450 (CYP450)

- Enzymes play role synthesis metabolism
- Five human CYPs that have been identified contributing most to drug metabolism
  - CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
- Implications
  - Testing for genetic variations may affect treatment decisions

De Gregori et al., 2010

Implications for nursing

- Excellent assessment of pain
  - Understand the potential for genetic etiology
- Ability to communicate with colleagues in other disciplines with basic understanding of possible contribution of genetic variation
- Treatment decisions based on pharmacogenetic testing
Patient Profile

- Developed chronic low back pain after work injury 30 years ago
- Developed severe post-thoracotomy pain after surgery and extensive hospitalization which included cardiopulmonary resuscitation and prolonged ventilatory support

Epigenetics

- Interaction between genes and environment
  - Affects gene expression – phenotype
  - Challenges use of individualized medicine based on genetic variation
    - Unquantifiable environmental effects

Role of epigenetic modification

- Transition from acute to chronic pain under epigenetic control
  - Immunologic response
  - Inflammatory cytokine expression
  - Glucocorticoid receptor function (pain sensitivity)
  - Pain regulatory genes downregulated
  - Opioid receptor regulation and function
  - Epigenetic alterations DNA methylation, histone acetylation, and RNA interference
Prevention Chronic Pain

- Epigenetic intervention
  - Possible medications interacting at level of epigenetic changes
    - Valproic acid – (histone deactylase inhibitor/DNA methylation)
    - Glucosamine (DNA methylation)
  - Multiple experimental modalities in process

Buchheit et al., 2012

Patient Profile

- Reports migraine headaches since childhood
- Reports family history of pain in ancestors and in children

Heritability

- Extended family study: any chronic pain about 16% and severe chronic pain 30%¹
- Twin studies
  - Low back/neck pain 35%²
  - Systematic review low back pain 21-67%³
  - Migraine and tension headaches 50%²
  - Irritable bowel syndrome 25%²
  - Neuropathic pain – assumed⁴
- Basic science models

¹Hocking et al., 2012 ²Nielsen et al., 2012 ³Ferreira et al, 2013 ⁴Mogil et al., 1999
Patient Profile

- Heritability- chronic pain consistent with studies, lack studies neuropathic pain
  - Migraine
  - Low back pain
**Implications for nursing**
- Explore family history
- May help with understanding of pain conditions
- Patient education
- Stay abreast of possible development of agents that may prevent evolution from acute to chronic pain

**Patient Profile**
- Multiple trials of analgesics in past
  - Side effects from codeine
  - Excessive somnolence from methadone
  - Inefficacy from fentanyl
  - Adverse effects from multiple tricyclic antidepressants
  - Adverse effects SNRIs

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**PHARMACOGENETIC TESTING**
Targets for Pain Management
Effect of Genetic variation

<table>
<thead>
<tr>
<th>Gene (with variant)</th>
<th>Analgesic affected</th>
<th>Consequence of variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1 Homozygous variants increased efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphin</td>
<td>Morphine</td>
<td>Homozygous variants increased efficacy</td>
</tr>
<tr>
<td>Poor metabolizers more adverse drug reactions, less efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine, oxycodone, tramadol</td>
<td></td>
</tr>
<tr>
<td>Poor metabolizers more adverse drug reactions, less efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT2B7</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Homozygous variants require lower doses; UGT2B7*2 variants less nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT</td>
<td>Morphin</td>
<td></td>
</tr>
<tr>
<td>Homozygous variants decrease in COMT activity; wild-type require higher doses than variant type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1</td>
<td>Morphin, M6G</td>
<td></td>
</tr>
<tr>
<td>Homozygous variants decreased efficacy; increased requirements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Jannetto & Bratanow, 2011

Pharmacogenetics

- How variations in genomes affect response to medications
- Term often used interchangeably with pharmacogenomics
- Genetic variation can influence efficacy/toxicity
- Pharmacogenetic testing
- Can assist with appropriate selection of medication and dosing
Selected analgesics – relevant genes

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Polymorphic Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A4, CYP3A5, ABCB1, OPRM1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP2B6, CYP3A4, CYP2D6, ABCB1</td>
</tr>
<tr>
<td>Morphine</td>
<td>ABCB1, COMT, UGT2B7, OPRM1</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6</td>
</tr>
</tbody>
</table>

See attached CYP-450 table for comprehensive table or www.drug-interactions.com

Adapted from Jannetto & Bratanow, 2011

CYP2D6

- CYP2D6 – 25% prescribed medications
  - Ex. Codeine metabolized by CYP2D6 to morphine
    - Poor metabolizers – little therapeutic effect
    - Ultra Rapid metabolizers – possible toxicity
  - Worldwide variation - examples
    - Ultra-metabolizers higher percentage in North Africa
    - Poor metabolizers – higher Europe

  Sistonen et al., 2007

CYP2C19

- CYP2C19 – 15% prescribed medications (includes some SSRIs, benzodiazepines)
  - Ex. Tricyclic antidepressants (also affected by CYP2D6)
    - Ultra-rapid metabolism may need alternative drug
    - Poor metabolizers may need lower dose

CYP3A4 and CYP3A5

- CYP3A enzymes metabolize >40% drugs
- Variations linked decreased enzyme activity
  - Increased drug levels
    - Ex. Fentanyl, hydrocodone, buprenorphine, methadone, clonazepam

Fine & Portenoy, 2007

CYP 2B6

- CYP 2B6 one of most polymorphic CYP genes (many variants)
  - Examples of drugs metabolized include efavirenz, bupropion, cyclophosphamide, ketamine, and methadone
- Implications for analgesia – methadone
  - May require dosing changes
    - NB – methadone metabolized through other pathways CYP3A4/5, CYP2D6

Zhanger & Kian, 2013

Pharmacogenomic testing

- Prediction of codeine toxicity in infants and mothers
  - Testing for CYP2D6 and ABCB1 able to predict 87% of infant and maternal CNS depression cases

Implications: Genetic markers can be used to improve outcomes of analgesic therapy (possibly beyond just predicting codeine toxicity)

Sistonin et al., 2012
Patient profile

• Testing indicated
  • Poor metabolizer CYP2C19 and CYP2D6
  • Variation of CYP3A4 variant showed decreased metabolism
• Medications rotated
  • Currently optimized on anticonvulsant, topical anesthetic, morphine

The Caveats

• Predicting response to analgesic therapy with testing one piece of puzzle
• Inability to predict precisely influence of genetic variations
• Challenges with medications such as methadone where multiple enzymes involved
• Cost of testing
  • Disparities in insurance coverage

Implications for nursing

• Excellent history and tracking of response/lack of response to analgesia
• Exploration of the possibility of pharmacogenetic testing if feasible
• Adjusting treatment plans
Future directions
- Identification of clinical relevance of pain genes
- Novel therapies for pain based on genetic variation
- Further refinement of pharmacogenetic testing
- Treatment algorithms based on pharmacogenetic results

So what does this all mean….
- Despite its delayed entry, pain genetics is now proceeding at a particularly rapid pace. As is not unusual in science, increasing knowledge has revealed the size of the problem to be far larger than anticipated. At the present time, I am not optimistic about pain geneticists explaining enough trait variance in clinical pain states or analgesic response to serve as a guide to individualized pain therapy any time soon. However, heuristic advances by pain geneticists are likely to accelerate and refine analgesic development efforts, leading ironically perhaps to new pain treatments for some rather than all.
  
  J. Mogil, 2012
References


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