Postoperative Pain: Nature vs Nurture

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A tale of two patients

TAH

- 39 yrs 72kg
- **GA:** Propofol, desflurane, relaxant, paracetamol, paracoxib, fentanyl (2ug/kg+2ug/kg/hr) [=1.21ng/ml]
- **PACU** pain 10/10
  - 15 mg morphine iv
- **Day1** PCA 40mg morphine
  - Rest pain 4/10

TAH

- 52 yrs 73kg
- **GA:** Propofol, desflurane, relaxant, paracetamol, paracoxib, fentanyl (2ug/kg+2ug/kg/hr) [=0.95ng/ml]
- **PACU** pain 0/10
  - 0 mg morphine iv
- **Day1** PCA 12mg morphine
  - Rest pain 2/10
Can we predict this?
In search of the Holy Grail of personalised medicine...
Methods of pre-operative pain prediction

• Demographics
  – Type of surgery, age, gender, redheads...

• Psychological
  – Anxiety-depression
  – Catastrophising

• Pain Physiology (Quantitative sensory testing)
  – Individual endogenous pain control systems
  – Response to exogenous opioids
    • Cold/heat
    • Electricity
    • Pressure
  – Pain & fentanyl dose-response
Prediction of severe pain (VAS$>7$) in PACU

Preoperative prediction of severe postoperative pain

“Despite extensive resources used on patient-controlled analgesia, spinal drug delivery methods, co-analgesics, multimodal analgesia, guidelines for acute pain management, and implementation of acute pain services, the results, in terms of an improved outcome after major surgery, seem unexpectedly modest.”
Failure to get the Holy Grail...
Nature & Nurture
Let's look into the details of the machine.
Epigenesis

Nature

Nurture
Processes required for analgesia
Nature

= Genes
The Pain Pathway

Pain Matrix

Modulation
Central: BDNF, OPRD1/K1/M1, CNR1, GABRs, TNF, PLA2
Peripheral: IL1/6/12/18, COX-2, NTRK1, NGF, GDNF, TNF, LIF, CCL2, CNR2
Microglia: TLR2/4, P2RX4/7, CCL2, CX3CR1, BDNF

Transduction
Heat: TRPV1/2/3/4, P2XR3
Cold: TRPM8, TRPA1
Damage: P2RX3, P2RY, BDKRB1/2, Htr3A, ACCNs...
Mechanical: TRPV4, TRPC/P, ACCN1/2

Conduction
Na+ channels: SCN10A, SCN11A (nociceptor-specific)
SCN1,3,8A, SCN9A,
K+ channels: KCNQ, other K+ channel genes

Synaptic Transmission
Neurotransmitter receptors: NR1,2, GRIA1-4, GRIC1-3, NK1R
Ca2+ channels: CACNA1A-S, CACNA2D1
“Let's hurt some mice…”

The Mutant Mouse Database (~400 SNPs)


http://paingeneticslab.ca/4105/06_02_pain_genetics_database.asp
What is the relative contribution of genetics to pain sensitivity?

“Let’s hurt some twins…”

- 22%-55% Norbury
  - Heat, cold, acid, ATP
- 26% to 60% Neilsen


Laws of genetics # 1

Rare genes can have big effects...

Clinically useless, but scientifically important – the path to new drugs

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**Table 2. Heritable Pain Conditions.**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Affected</th>
<th>Cell Loss</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSAN-1</td>
<td>Autosomal dominant mis-sense mutations in serine palmitoyltransferase long chain base subunit 1 (SPTLC1)</td>
<td>Apoptotic cell loss of sensory and other neurons</td>
<td>Pain and heat loss</td>
<td>[70]</td>
</tr>
<tr>
<td>HSAN-2</td>
<td>Miss-sense mutations in the protein kinase PRKNW1</td>
<td>Developing sensory cell loss</td>
<td>Developing loss of all sensation</td>
<td>[71]</td>
</tr>
<tr>
<td>HSAN-3 (Familial dysautonomia)</td>
<td>Splicing deficit in IkkAP protein</td>
<td>Failure in sensory neuron development</td>
<td>Pain-free phenotype</td>
<td>[72]</td>
</tr>
<tr>
<td>HSAN-4 (CIPA)</td>
<td>Loss of functional NGF receptor TrkA</td>
<td>Loss of most small diameter sensory neurons</td>
<td>Congenital insensitivity to pain</td>
<td>[1]</td>
</tr>
<tr>
<td>Mutilated foot rat</td>
<td>δ subunit of the (Cct4 ) gene</td>
<td>Loss of nociceptors</td>
<td>Ulceration and loss of pain sensitivity</td>
<td>[73]</td>
</tr>
<tr>
<td>Erythermalgia</td>
<td>Point mutations in sodium channel Na_{v}1.7 – increased excitability</td>
<td>No cell loss</td>
<td>Chronic inflammation</td>
<td>[9]</td>
</tr>
<tr>
<td>Paroxysmal extreme pain (familial rectal pain)</td>
<td>Point mutations in Na_{v}1.7 - loss of inactivation</td>
<td>No cell loss</td>
<td>Mechanically induced extreme pain</td>
<td>[8]</td>
</tr>
<tr>
<td>Insensitivity to pain</td>
<td>Miss-sense mutations in Na_{v}1.7</td>
<td>No cell loss</td>
<td>Complete insensitivity to acute pain</td>
<td>[7]</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pgen.1000086.t002
The Tale of 3 Sodium Channels

- \( \text{Na}_v 1.9 \) (SCN11A)
  - controlled by inflammatory mediators and controls thresholds

- \( \text{Na}_v 1.8 \) (SCN10A)
  - Specific for nociception/thresholds/cold

- \( \text{Na}_v 1.7 \) (SCN9A)
  - Delayed inactivation = bursting
    - *Loss-of-function mutants* = normal (pain-free) human [but dead mice]
    - *Gain-of-function mutants* = erythromyalgia & acute paroxysmal pain

Waxman S. Polymorphisms in ion channel genes: emerging roles in pain. Brain 2010: 133; 2514–2518
Laws of genetics # 2

Common genes have small effects...

- **Pain sensitivity**
  - COMT haplotypes and TM Pain
  - Chronic pain propensity (OPRM1, Beta-2)

- **PD responses to analgesics**
  - OPRM1

- **Analgesic PK**
  - P450 (CYP2D6, also CYP3A4/5, UDG)
    - Codeine & Tramadol
  - ABCB1 (ATP-binding cassette = drug efflux)
OPRM1: A118G

- AA=5.9 vs GG=9.4 mg morphine

**Table 1** Recent studies of *OPRM1* gene SNPs and opiate neuraxial analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>SNP</th>
<th>Number of subjects</th>
<th>Study cohort</th>
<th>Opiate studied</th>
<th>Measured outcomes</th>
<th>Observed associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sia <em>et al.</em> [15*]</td>
<td>A118G</td>
<td>588</td>
<td>Chinese Singaporean women undergoing elective cesarean term delivery</td>
<td>Intrathecal morphine</td>
<td>1) Pain scores 2) 24 h postoperative IV morphine requirement 3) Nausea</td>
<td>Pain scores and IV morphine requirement lowest in AA group; postoperative nausea highest in AA group</td>
</tr>
<tr>
<td>Hayashida <em>et al.</em> [16]</td>
<td>A118G</td>
<td>138</td>
<td>Japanese men and women undergoing abdominal aortic surgery</td>
<td>Epidural fentanyl or morphine</td>
<td>24 h postoperative opioid requirement (systemic fentanyl equivalent)</td>
<td>The GG group required significantly more 24 h opiates than the AG and AA groups</td>
</tr>
<tr>
<td>Landau <em>et al.</em> [17]</td>
<td>A118G</td>
<td>224</td>
<td>Nulliparous women laboring at full term</td>
<td>Continuous spinal–epidural analgesia using intrathecal fentanyl</td>
<td>ED50 related to intrathecal fentanyl dose with respect to labor analgesia</td>
<td>Reduced intrathecal fentanyl ED50 in G allele carriers</td>
</tr>
</tbody>
</table>

In Summary - Bad News…

“*To date, almost every genetic association with common human nociception has been disputed*…”

“The study of pain-related SNPs in the human has proved problematic, due to the tendency of different data sets to yield conflicting conclusions; in many cases, a finding from one has been contradicted by those from others”
1. Look at other parts of the DNA...

2. Look at combinations of common pain-related genes...

3. Look in more detail at nurture...
Combos: the clinical usefulness?

$P = 0.003\quad KCNJ6=G/G$ or $ABCB1=C/C$

AUC-ROC = 68\% \quad (P<0.0001)$

Sensitivity = 74\% (PCA>0.58mg/hr)
Specificity = 60\%

NPV [Predict “Minimal-pain”] = 80\%
PPV [Predict “Severe-pain”] = 50\%

Misclassify = 35\%
Nurture = Top Down = Environment
The Machinery of Nurture = Epigenesis

...the environment makes the genes whisper or shout...
Epigenetics ≈ development

Royal jelly turns off DNA methylation – stops young bees turning into a worker bees

The Mechanisms of Epigenetics

- Histone acetylation = activates gene expression
- DNA-CpG methylation = silences genes
- RNAi

*Phenotypic plasticity and the epigenetics of human disease*
Andrew P. Feinberg *Nature*; 447(24) 2007 doi:10.1038/nature05919

*Review: Epigenetics in pain and analgesia: An imminent research field*
Bladder Pain. ”These genes act as transcriptional repressors, mediate gene silencing and inhibit cell differentiation by methylating the lysine residue 27 of histone H3 (H3K27me3). By contrast, inflammatory stimuli are strong inducers of the lysine (K)-specific demethylase 6B, an enzyme demethylating H3K27me3. In addition, the human polycomb group protein EZH2 (Enhancer of Zeste homolog 2) was shown to control CpG methylation by direct interaction with DNA methyltransferases”

PKPD: HDACI and CYP3A4
Epigenetics and Pain: Studies #2

- Chronic opioids $\uparrow \mu$-receptor gene methylation

- Prescription opioid analgesics rapidly change the human brain.

Right Amygdala 3% ↓ .... Hypothalamus 4% ↑
Possible epigenetic treatments

• Subarachnnoid RNAi
  – Anti-NMDA
  – TRPV1 ..... (5days-6 months analgesia)

• Histone deacetylase inhibitors (HDACI) \(\rightarrow\)
  \(\uparrow\)expression of:
  – CYP3A4, mGlu2, & \(\mu\)-opioid receptors
  – Valproate
  – No tolerance
Conclusions / Speculations

1. Clinical/Psych testing \( \cong \) predicting rugby results.

2. Combinations of common pain-related genes might change the expected odds:
   - i.e. 25% severe pain \( \rightarrow \) 70% severe pain
   OR
   - i.e. 25% severe pain \( \rightarrow \) 10% severe pain

3. Epigenetics... ? more important than genetics

4. What do we do with this information?
Le Rêve

Picasso
The modern definition of epigenetics is information heritable during cell division other than the DNA sequence itself.

Developmental processes are regulated largely by epigenetics, because different cell types maintain their fate during cell division even though their DNA sequences are essentially the same.