Opioid Pharmacogenomics: More Than Metabolism

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GENOMICS AND SYSTEMS APPROACHES

“Next-generation pharmacogenomics to translate basic science to the clinic”

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Opioid Pharmacogenomics: Overview

- Pharmacokinetic-Metabolism
  - *CYP2D6* - codeine, oxycodone, tramadol
  - *CYP3A4/5* – fentanyl

- Pharmacodynamic Pharmacogenomics
  - *OPRM1*
    - Ethnicity: Caucasian, Chinese, Malay, Indian
  - Innate Immune Genes
    - Acute pain, cancer pain

- Can it be translated?

- Take Home Message
Opioids: Wide Interpatient Variability - Response & Dosage: Morphine

- **Post-Operative Pain**
  - PCA Morphine
  - $0.17 \pm 0.10$ mg/kg (40-fold range; n=3045)
    

- **Cancer Pain**
  - SC Morphine
  - $160 \pm 228$ mg (40-fold range 20-830) mg/24 hours [n=19]
    
    (Ashby et al J Pain Sympt Manage 14:157, 1997)

- **Pain (a subjective experience):**
  - An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

- **Multifactorial:** tolerance, hyperalgesia
Role of Genomic Factors in Interindividual Variability in Response to Opioids

- Pharmacokinetics
  - Metabolising enzymes, transporters
- Pharmacodynamics
  - Receptors/Targets & signalling pathways
- Candidate gene approach
CYP2D6: Highly Polymorphic Enzyme: EM/PM Phenotype Discovered 1976

**EM:** extensive metabolizers (~70-80%)

**UM:** ultrarapid metabolizers (~2-5%)

**IM:** intermediate metabolizers (~10%)

*41: 70%*

**PM:** Poor metabolizers (~5-10%)

Eichelbaum et al. 1978
Our results indicate that some people may, because of their inability to form morphine, be receiving a drug that is potentially inactive.
CYP2D6: The Codeine Story
Clinical Evidence

• Poor Metabolisers: ↓↓ Morphine
  - Healthy subjects: expt. pain- ↓ response
  - No study in clinical pain – but always written-no response in PMs

• Ultrarapid Metabolisers: ↑↑ Morphine
  - Adverse effects:
    • Respiratory depression-> death
    • FDA: Black box warning
CYP2D6: Oxycodone Story
Clinical Evidence

- Poor Metabolisers: ↓↓ Oxymorphone
  - Healthy subjects: experimental pain ↓ response
  - Clinical studies (post operative/cancer): ↔ dose, pain intensity, adverse effects; ↑ dose

- Ultrarapid Metabolisers: ↑↑↑ Oxymorphone
  - Healthy subjects: experimental pain ↑ response
  - Clinical studies (post operative/cancer): ↔ ↓ dose
CYP2D6 Polymorphism: Tramadol reduced effect in PMs

- Experimental pain
- 15 extensive (EM)
- 12 Poor metabolisers (PM)

Post Operative Surgical Patients PCA
- Nonresponder: insufficient analgesia without rescue analgesia
- 81% PM nonresponders
- 17% EM nonresponders (P=0.001)

URM: Respiratory depression

EPOS: European Pharmacogenetic Opioid Study

- 2294 cancer patients
- 17 Centres, 11 European Countries
- morphine (830), oxycodone (446), fentanyl (619) + … : Oral, SC, IV, TD
- Demographics, kidney & liver function
  - Symptoms: Pain, Cognition, Nausea, Tiredness, Respiration….
  - DNA

Trondheim (Norway)
Transdermal Fentanyl: EPOS

- 619 cancer patients
  - 63 (19-96) years; BMI 23 (9-24), ……
  - Patch Dose: 12.5 – 700 mcg/hour (56-fold range)
  - Plasma fentanyl: 16000-fold range (0.22-3572 nM)
  - Plasma norfentanyl: 2600-fold range (0.09-234 nM)

- Major Determinants of plasma fentanyl
  - Dose rate, sex, BMI, other drugs
  - *CYP3A4*22, *CYP3A5*3
  - ~50% of variability explained

Barrett et al Pharmacogen Genom 24, 185, 2014
Fentanyl Metabolic Ratio: 6000-fold

Norfentanyl
- major metabolite
- CYP3A4/5
  - \textit{CYP3A5}\textsuperscript{*1} carrier: \(P = 0.017\)
  - \textit{CYP3A4}\textsuperscript{*22} carrier: \(P = 0.029\)

\textbf{BUT}
- Combined contribution to variability 2%
- Only 14\% variability accounted for (GFR, drugs, BMI, albumin)

\textit{Barrett et al Pharmacogen Genom 24, 185, 2014}
Interindividual Variability in Response to Opioids: *It must be Pharmacodynamics*

- Mu receptor polymorphisms
- *Intracellular signalling proteins* polymorphisms
- Innate Immune system
Neuronal μ Receptor: Target

- Classical 7 TM
- G-protein coupled receptor

Mu Receptor Gene: OPRM1

- Chromosome 6 long arm
- > 3000 polymorphisms (1000 Genomes Project)
- 1395 MAF > 1%
- 2 common nonsynonymous SNPs
- 3 common synonymous coding variants
- Many splice variants

Levac et al Curr Opin Pharmacol 2, 76, 2002
**OPRM1**: μ Receptor

- **NonSynonymous SNP**
- **A118G (rs1799971)**
  - exon 1
  - Asn40→Asp
  - ↓ mRNA_protein
    - Loss of function
- **G variant allele:**
  - 12% Caucasians
  - 40% Asians

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Lötsch and Geisslinger, Trends in Molec Med 11, 82, 2005
Alfentanil Analgesia and Respiratory Depression: $OPRM1$ A118G

- Healthy subjects dosed with alfentanil
- G variant allele: reduces
  - analgesia- electrical stimulation (2-4-fold)
  - Respiratory depression (10-12 fold)

Oertel et al Pharmacogenetics & Genomics, 16, 625, 2006
Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment

Carmen Walter, Jörn Lötsch

“…. Despite initially promising results, available evidence of the clinical relevance of the OPRM1 118A>G polymorphism does not withhold a meta-analysis”

• Many Pain Types: Experimental, Cancer, Postoperative, Disease, Childbirth
• Many Opioids: morphine, fentanyl, alfentanil, methadone, M6G
• Low patient numbers: 8/24 studies > 100 subjects
• Ethnicity: mainly Caucasians
  • Forget it!
• 598 Chinese/ 230 Malay/133 Indian women
• Caesarean delivery - spinal anaesthesia
• IV patient controlled analgesia (PCA)
• Data collected on:
  - ethnicity, age, weight, surgery duration;
  - cumulative morphine use over 24 h post-op
  - VAS: post-op prior to morphine
  - genetics: *OPRM1*; G variant 34-44%
**OPRM1 A118G Variant: Increased Opioid Requirements - Postoperative Pain: Asians**

- 22%: PCA Morphine- hysterectomy  
  (Chou et al 2006)
- 20%: Epi Morphine/fentanyl- abdominal  
  (Hayashida et al 2008)
- 30% : PCA Morphine  
  (Sia et al 2013)
- 60%: PCA Morphine- knee arthroplasty  
  (Chou et al 2006)
- 60%: PCA Morphine- caesarian  
  (Sia et al 2008)
- 75%: PCA Morphine- caesarian  
  (Choo et al 2009)
- 30% (GG vs AA): PCA Morphine-hysterectomy  
  (Sia et al 2013)
- **Why?** Ethnicity:  G variant ~ 45%
Morphine activates neuroinflammation in a manner parallel to endotoxin

PNAS 109, 6325-6330, 2012

Xiaohui Wang\textsuperscript{a}, Lisa C. Loram\textsuperscript{b,c}, Khara Ramos\textsuperscript{b,c}, Armando J. de Jesus\textsuperscript{a}, Jacob Thomas\textsuperscript{d}, Kui Cheng\textsuperscript{a}, Anireddy Reddy\textsuperscript{b,c}, Andrew A. Somogyi\textsuperscript{d}, Mark R. Hutchinson\textsuperscript{a}, Linda R. Watkins\textsuperscript{b,c}, and Hang Yin\textsuperscript{a,c,f,1}

- Morphine binds to MD2 (an accessory protein of TLR4)
  - Ki = 4 $\mu$M
  - MD2-TLR4 oligomerization
  - TLR4 signaling activation

- Release of proinflammatory/neuroexcitatory cytokines (IL-1$\beta$, IL-6) -> increase pain sensitivity

- Similar mechanism to LPS (endotoxin)
Opioid Analgesia: controlled by $\mu$ Receptor \textit{(pro)} and TLR4 \textit{(con)} binding

Microglia: TLR4

Neurons: $\mu$ receptor + TLR4
Cytokines Genetics & Opioids

• **Cancer Patients:** Reyes-Gibby *et al* *(Cancer Epidemiol Biomarkers Prev 17, 3262, 200)*
  
  – *IL6* Promoter SNP: carriers associated with higher (~50%) morphine equivalent dosing requirements

• **Acute postoperative pain:**
  
  – *IL-1Ra* receptor antagonist gene tandem repeat associated with 100% higher morphine dose *(Candiotti et al Anesthesiol 114, 1162, 2011)*
Innate Immune Cellular Pathway Genes

- Cytokine Signalling: *IL1B, IL10, IL6, IL6R, ICE, TNF, TGFBI, CRP*
- Non-classical opioid signalling: *TLR4, TLR2, MD2, MYD88, BDNF*
- Classical Opioid Signalling: *OPRM1*

This analysis explains ~25% of opioid dependence.

Can it help explain (in part) the large interindividual variation in opioid drug dosage?

Gene mutations: ↑↓ opioid dosage
OPRM1 + Innate Immune Genes Contribute to Morphine Dosage: Postoperative Pain (1)

- 598 Chinese, 230 Malay & 133 Indian women
- Caesarean delivery under spinal anaesthesia
- OPRM1 A118G: 34% Chinese, 48% Malay, 44% Indian
- 24 hour postoperative morphine consumption PCA (mg)
  - Chinese: 4 ± 8 (0-40); Malay: 7 ± 10 (0-62); Indian: 12 ± 12 (0-55)
- VAS (>0) at time 0: Chinese 28/598; Malay 19/230; Indian 7/133
- Average 24 hr VAS Score:
  - Chinese (0-4); Malay (0-3); Indian (0-3)
- Mild-moderate pain phenotype

Alex Sia-Singapore
OPRM1 + Innate Immune Genes Contribute to Morphine Dosage: Postoperative Pain (2)

- ↑ morphine consumption: OPRM1, IL1B, TLR2, BDNF
- ↓ morphine consumption: IL6, TLR4, IL10
- Overall predictors of morphine consumption (pain post op, surgical duration, age, genetic)
  - Chinese: 4%
  - Malay: 5%
  - Indian: 22% (mainly genetic factors)
- Innate Immune markers play a role in morphine requirements in mild-moderate pain
## Singapore Study: Innate Immune Frequency Differences - Genetic Markers: Comparison to Caucasians

<table>
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<th>Gene</th>
<th>Chinese</th>
<th>Malay</th>
<th>Indian</th>
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<td>↓↓↓↓↓</td>
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<td>MYD88</td>
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<td>TNF</td>
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- ↔ = < 0.2
- ↓↓ = 0.2 - 1X
- ↑↑↓↓ = 1-2X
- ↑↑↑↓↓↓ = 2-5X
- ↑↑↑↑↓↓↓↓ = > 5X
Innate Immune Genetics and Opioids: Cancer Pain

- EPOS: 235 fentanyl patients- patches
  - good pain relief/no side effects
- Serum fentanyl conc determinants
- TLR4 het require higher serum fentanyl compared to homozygous wildtype
  - $P<0.009$ BUT 3% contribution to model $R^2$ (11% found)
Where to now?

• Exome – GWAS: human

Japanese Surgery Study groups
355: cosmetic jaw
112: major open abdominal

rs2952768
METTL21A: histone methyltransferase
CREB1: cAMP responsive element binding protein

Nishizawa et al Mol Psychiatr 19, 66, 2014
Where to now? *Epigenetics*

- Higher DNA methylation at *OPRM1* position + 126 in chronic pain patients (opioids vs no opioids)
- Weak relation to pain scores

*Doehring et al Pain 154, 15, 2013*
Avera Health: “Avera is unlocking the science behind pain management through our ability to select drugs that match each patient’s unique genetic characteristics”

All PK: \textit{CYP2D6} tests
Genetic & Non-Genetic Factors Influencing Response to Analgesics

Genetic Research Pitfalls
- Pain: difficult phenotype
- Population stratification
- Sample size: small
- Genes & SNPs: which
- Type 1/2 errors
- Statistical Analysis
- Publication bias
Take Home Messages

Opioid Pharmacogenomics

- Metabolism: *CYP2D6* – codeine, oxycodone, *tramadol*
- Pharmacodynamics: *OPRM1* - Asian
- Innate Immune: *IL6, IL1B, TLRs* - Ethnicity
- Patient-Psychology-Culture-Pain Type: Factors
- More than metabolism
- Not ready for general translation
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- **University of Adelaide**
Role of Glia in Pain Neuropathies
TETRAPARTITE SYNAPSE

Virus, diabetes…

DeLeo et al 2006