Pharmacogenetics & Obstetric Anesthesia

GENETICS AND PAIN

SAOA, Lausanne 2010

Ruth Landau, MD
Virginia and Prentice Bloedel Professor
Director of Obstetric Anesthesia & Clinical Genetics Research
Department of Anesthesiology & Pain Medicine
rulandau@u.washington.edu
Pharmacogenetics

Overview
- Pharmacogenetics
- Polymorphisms (SNPs)

Candidate genes
- CYP2D6
- COMT gene
- μ-opioid receptor

Labor and post-Cesarean analgesia
Human Genome Project

Nature, Feb 2001
Science/Nature April 2003

Human genome contains:
- 3.1647 Bio nucleotide bases (A, C, T, G)
- ~ 30’000 genes (2968 on \(X^1\); 231 on \(X^Y\))
- Average gene ~ 3’000 bases (+ 2.4 Mio)
- Unknown function for 50% of genes...
- Identical sequences in 99.9% of individuals
- Variation 1/1000 nucleotides
Polymorphisms
(poly=several; morph=forms)

✓ Naturally occurring mutations (>1%)
✓ May change amino acid sequence
✓ May change function (phenotype)
✓ Important ethnic variability

Single Nucleotide Polymorphism (SNP)
- Homozygote wild-type (AA)
- Heterozygote wild-type/variant (AG)
- Homozygote variant (mutant) (GG)
Figure 2 The home page of PharmGKB provides a straightforward schema for understanding pharmacogenomics. After drugs are delivered, PKs and PDs both involve sets of genes and lead to both efficacious and toxic effects. Variation in response can be related to the PK and PD genes by studying their variations in the human population. All data in the PharmGKB are indexed as being relevant to PK, PD, clinical outcomes (CO), genetic variation (GN), or functional assays at the molecular and cellular level (FN).
Polymorphisms: enzymes & receptors

Genetic Polymorphism
Drug METABOLISM (degradation)

Genetic polymorphism
Drug SENSITIVITY (efficacy)

Genetically regulated heterogeneity in drug effects
(polygenic drug response)

#1

#2

#3

<table>
<thead>
<tr>
<th></th>
<th>Efficacy (%)</th>
<th>Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A wt/wt</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>B wt/v</td>
<td>85</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>C v/v</td>
<td>95</td>
<td>&gt;80</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>&gt;80</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>&gt;80</td>
</tr>
</tbody>
</table>
Cytochrome P450

**CYP2D6 polymorphism**

- **UM**: Ultrarapid metabolizers (2-5%)
- **EM**: Extensive metabolizers (95-97%)
- **IM**: Intermediate metabolizers (2-5%)
- **PM**: Poor metabolizers (2-5%)

**Metabolized by CYP2D6**

- **Tricyclic antidepressants**
  - Amitriptyline
  - Desipramine
  - Imipramine
  - Nortriptiline
  - Clomipramine
  - Maprotiline
  - Desmethycitalopram

- **Neuroleptics**
  - Clozapine
  - Haloperidol
  - Methotrimeprazine
  - Chlorpromazine
  - Olanzarine
  - Perphenazine
  - Risperidone
  - Thiioridazine
  - Bufuralol
  - Bupranolol

- **SSRI agents or similar agents**
  - Fluvoxamine
  - Fluoxetine
  - Sertraline
  - Paroxetin
  - Venlafaxine
  - Mitrazapine
  - Mianserine

- **Miscellaneous**
  - Captopril
  - Ondasenetrone
  - Ritonavir
  - Dexfenfluramine
  - Debrisoquin
  - Methoxyamphetamine
  - Tropisetrone

- **Beta blockers**
  - Metoprolol
  - Timolol
  - Propranolol
  - Alpenolol

- **Antiarrhythmics**
  - Nimodipine
  - Flecainide
  - Mexiletine
  - Amiodarone
  - Propafenone
  - Quinidine
  - Encainide
  - Sparteine

- **Analgesics**
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Dextromethorphan
  - Tramadol
  - Dihydrocodeine
  - Ethylmophine
Molecular genetics of CYP2D6: clinical relevance with focus on psychototropic drugs.

Bertilsson, Br J Clin Pharmacol 2002

Doses of nortriptyline to be used

- 500
- 100–150
- 10–20 mg

'Normal dose'
Codeine intoxication associated with ultrarapid CYP2D6 metabolism.  

Gasche, NEJM 2004
Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0.2.2 ng/mL. The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later analysed for morphine by GC-MS, which found a morphine concentration of 87 ng/mL was the typical range of milk concentrations after repeated maternal codeine is 1.9–20.5 ng/mL at doses of 60 mg every 6 h.

<table>
<thead>
<tr>
<th>Action</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid codeine when breastfeeding use paracetamol or non-steroidal anti-inflammatory drugs</td>
<td>Avoids potential neonatal toxicity</td>
<td>Potential uncontrolled maternal pain</td>
</tr>
<tr>
<td>Avoid high-dose codeine (240 mg daily) for more than a few days</td>
<td>Minimises potential neonatal toxicity</td>
<td>Suboptimal maternal pain control</td>
</tr>
<tr>
<td>Avoid breastfeeding when taking codeine</td>
<td>Avoids potential neonatal toxicity</td>
<td>Dose may still be too high a dose for ultra-rapid metabolisers</td>
</tr>
<tr>
<td>Inform and monitor mother and baby for signs of opioid toxicity</td>
<td>Ability to intervene early and prevent serious toxicity</td>
<td>Loss of the benefits of breastfeeding</td>
</tr>
<tr>
<td>Genotype mother for CYP2D6</td>
<td>Predicts mothers at risk of producing excess of morphine</td>
<td>Parental anxiety and false positive identification of toxicity</td>
</tr>
</tbody>
</table>

Table: Clinical strategies to manage breastfeeding while on codeine

Polymorphism of CYP2D6 can be life threatening for some breastfed babies. Given that the frequency of CYP2D6 ultra-rapid metaboliser genotypes ranges from 1% in Finland and Denmark to 10% in Greece and Portugal, and 29% in Ethiopia, this polymorphism is clinically important. Several strategies can be considered...
COMT Val158Met genotype affects $\mu$-opioid neurotransmitter responses to a pain stressor

Zubieta, Science 2003

Cathechol-$O$-methyltransferase Val158Met gene
Met158: ↓↓↓ 3-4x enzyme activity of COMT
Modulates dopaminergic neurotransmission

Volunteers Met/ Met:
Less pain tolerance ...
Increased regional density of $\mu$-OR

influences human experience of pain
The Val158Met polymorphism of the human COMT gene may influence morphine requirements in cancer pain patients

Rakvag, Pain 2005

<table>
<thead>
<tr>
<th></th>
<th>Val/ Val (n=44)</th>
<th>Val/ Met (n=96)</th>
<th>Met/ Met (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine dose (mg/24 h)*</td>
<td>155 (160)</td>
<td>117 (100)</td>
<td>95 (99)</td>
</tr>
<tr>
<td>Morphine serum (nmol/ l)</td>
<td>119 (199)</td>
<td>86 (88)</td>
<td>78 (72)</td>
</tr>
<tr>
<td>M6G serum (nmol/ l)</td>
<td>711 (992)</td>
<td>506 (493)</td>
<td>410 (484)</td>
</tr>
<tr>
<td>M3G serum (nmol/ l)</td>
<td>3809 (4436)</td>
<td>2812 (2209)</td>
<td>2536 (2707)</td>
</tr>
</tbody>
</table>

All numbers are mean (SD).
* $P=0.03$ for differences between Val/ Val and Met/ Met genotype groups. ($P=0.06$ for diff in M6G; $P=0.14$ for diff in M3G; $P=0.85$ for diff in morphine).

Increase in regional density of μOR according to genotype could improve the efficacy of morphine in individuals Met158Met ...
A118G SNP of OPRM1 (μ-OR gene)

↑ 3-fold the binding affinity and potency of β-endorphins

Bond, PNAS 1998
Ethnicity and genetic variability of $\mu$-OR

<table>
<thead>
<tr>
<th>ETHNICITY</th>
<th>n</th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-Amer</td>
<td>195</td>
<td>91%</td>
<td>9%</td>
<td>0.5%</td>
<td>1</td>
</tr>
<tr>
<td>Europ-Amer</td>
<td>161</td>
<td>70%</td>
<td>29%</td>
<td>1%</td>
<td>1</td>
</tr>
<tr>
<td>Indian (controls)</td>
<td>117</td>
<td>29%</td>
<td>47%</td>
<td>24%</td>
<td>2</td>
</tr>
<tr>
<td>Malay (controls)</td>
<td>131</td>
<td>28%</td>
<td>55%</td>
<td>18%</td>
<td>2</td>
</tr>
<tr>
<td>Chinese (controls)</td>
<td>156</td>
<td>37%</td>
<td>52%</td>
<td>11%</td>
<td>2</td>
</tr>
<tr>
<td>Mixed Europ-Amer</td>
<td>181</td>
<td>67%</td>
<td>29%</td>
<td>4%</td>
<td>3</td>
</tr>
</tbody>
</table>

3) Landau et al, *Anesthesiology* 2004
ED50 IT fentanyl with G118 allele:

17.7μg (13.4–21.9)  
Ratio 1.5 (p=0.0091)

ED50 IT fentanyl with G118 allele:

13.2μg (5.7–20.5)  
Ratio 2.1 (p=0.002)
Effect of $\mu$-OR A118G polymorphism on ED50 of epidural sufentanil for labor analgesia

Capogna et al, in press IJOA

ED50 epidural sufentanil ---> VAS<10 @30min
A118 (group A, n=31) = 23.5$\mu$g (95% CI 22-24.3)
A118G + G118 (Group G, n=23) = 21.5$\mu$g (95% CI 20.8-22.3) ($p=0.002$).
Ratio 1.09 (95% CI: 1.04-1.1)
Observational study of the effect of μ-opioid receptor genetic polymorphism on intrathecal opioid labor analgesia and post-cesarean delivery analgesia

C.A. Wong, a R.J. McCarthy, a J. Blouin, b,1 R. Landau b

a Northwestern University Feinberg School of Medicine, Chicago, IL, USA; b University of Geneva, Geneva, Switzerland


Table 1  Labor study: subject and analgesia characteristics

<table>
<thead>
<tr>
<th></th>
<th>Labor analgesia</th>
<th>Postoperative analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>group A (n=144)</td>
<td>group G (n=46)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>30</td>
<td>32</td>
<td>0.43</td>
</tr>
<tr>
<td>(28, 34)</td>
<td>(30, 34)</td>
<td></td>
</tr>
<tr>
<td>Stated ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>111 (77)</td>
<td>30 (65)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (8)</td>
<td>1 (2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (3)</td>
<td>7 (15)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 (12)</td>
<td>8 (17)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>1.0</td>
</tr>
<tr>
<td>(26, 33)</td>
<td>(26, 32)</td>
<td></td>
</tr>
</tbody>
</table>

Data reported as median (interquartile range) or number (%).
Fig. 1 Kaplan-Meier survival curves of duration of intrathecal fentanyl analgesia. The median duration of intrathecal fentanyl labor analgesia in group A was 70 min (95% CI 62 – 78) compared to 63 min in group G (95% CI 50 – 76) (P=0.54, log-rank test).
N=104

Spinal anesthesia = bup 12mg, fentanyl 15µg, morphine 150µg

Primary outcome = supplemental acetaminophen/hydrocodone

Table 3  Post-cesarean analgesia study: outcomes

<table>
<thead>
<tr>
<th></th>
<th>group A (n=78)</th>
<th>group G (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS at 1st rescue analgesia request (mm)</td>
<td>26 (0, 47)</td>
<td>40 (0, 60)</td>
<td>0.15</td>
</tr>
<tr>
<td>Time to 1st rescue analgesia (h)</td>
<td>22 (12, 24)</td>
<td>22 (15, 24)</td>
<td>0.84</td>
</tr>
<tr>
<td>Rescue analgesia requested within 24 h</td>
<td>46 (59%)</td>
<td>17 (68%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4%)</td>
<td>1 (4%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33 (42%)</td>
<td>3 (12%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Satisfaction with analgesia (VAS, mm)</td>
<td>90 (78, 98)</td>
<td>90 (75, 95)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Data reported as median (interquartile range) or number (percent of total).
A118G Single Nucleotide Polymorphism of Human μ-Opioid Receptor Gene Influences Pain Perception and Patient-controlled Intravenous Morphine Consumption after Intrathecal Morphine for Postcesarean Analgesia

Alex T. Sia, M.D.,* Yvonne Lim, M.D.,† Eileen C. P. Lim, B.Sc.,‡ Rachelle W. C. Goh, S.R.N.,§ Hai Yang Law, Ph.D.,|| Ruth Landau, M.D.,# Yik-ying Teo, Ph.D.,** Ene Choo Tan, Ph.D.††

<table>
<thead>
<tr>
<th>AA, n = 271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Paying class, private:subsidized</td>
</tr>
<tr>
<td>Prev C-sec, 0:&lt;1</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
</tr>
<tr>
<td>Total morphine, mg</td>
</tr>
<tr>
<td>Total VAS</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) unless otherwise indicated.

* Statistically significant difference found between the three groups.

AA = wild-type homozygous; AG = variant heterozygous; GG = variant homozygous; delivery; VAS = 0–100 visual analog scale.
Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment

Carmen Walter, Jörn Lötsch

 automated Docent

pharmazentrum frankfurt/ZAFES, Institute for Clinical Pharmacology, Goethe University, Theodor Stern Kai 7, D-60590 Frankfurt am Main, Germany

![PAIN® 146 (2009) 270-275](image)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Setting</th>
<th>Std diff in means</th>
<th>Standard error</th>
<th>Variance</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-value</th>
<th>p-value</th>
<th>118G carriers</th>
<th>Wt type</th>
<th>Relative weight</th>
<th>Std diff in means and 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou 2006</td>
<td>Post-OP</td>
<td>0.439</td>
<td>0.227</td>
<td>0.551</td>
<td>-0.008</td>
<td>0.883</td>
<td>1.933</td>
<td>0.053</td>
<td>37</td>
<td>43</td>
<td></td>
<td>-1.5 &lt; 0.0 &lt; 0.5</td>
<td>12.21</td>
</tr>
<tr>
<td>Chou 2006 a</td>
<td>Post-OP</td>
<td>0.282</td>
<td>0.189</td>
<td>0.036</td>
<td>-0.008</td>
<td>0.652</td>
<td>1.496</td>
<td>0.135</td>
<td>46</td>
<td>74</td>
<td></td>
<td>-1.0 &lt; 0.0 &lt; 0.5</td>
<td>12.41</td>
</tr>
<tr>
<td>Reyes-Gibbs 2007</td>
<td>Chronic</td>
<td>0.290</td>
<td>0.175</td>
<td>0.031</td>
<td>-0.003</td>
<td>0.582</td>
<td>1.427</td>
<td>0.133</td>
<td>41</td>
<td>106</td>
<td></td>
<td>-0.5 &lt; 0.0 &lt; 0.5</td>
<td>10.77</td>
</tr>
<tr>
<td>Sie 2008</td>
<td>Post-OP</td>
<td>0.294</td>
<td>0.083</td>
<td>0.007</td>
<td>0.131</td>
<td>0.458</td>
<td>3.532</td>
<td>0.000</td>
<td>314</td>
<td>271</td>
<td></td>
<td>-1.0 &lt; 0.0 &lt; 0.5</td>
<td>12.90</td>
</tr>
<tr>
<td>Hayashiida 2008</td>
<td>Post-OP</td>
<td>-0.877</td>
<td>0.194</td>
<td>0.037</td>
<td>-1.257</td>
<td>-0.498</td>
<td>-4.532</td>
<td>0.000</td>
<td>97</td>
<td>41</td>
<td></td>
<td>-1.0 &lt; 0.0 &lt; 0.5</td>
<td>12.77</td>
</tr>
<tr>
<td>Landon 2008</td>
<td>Laboring women</td>
<td>-0.861</td>
<td>0.182</td>
<td>0.037</td>
<td>-1.038</td>
<td>-0.284</td>
<td>-3.435</td>
<td>0.001</td>
<td>39</td>
<td>102</td>
<td></td>
<td>-0.5 &lt; 0.0 &lt; 0.5</td>
<td>11.40</td>
</tr>
<tr>
<td>Hühne 2009</td>
<td>Post-OP</td>
<td>0.593</td>
<td>0.490</td>
<td>0.203</td>
<td>-0.289</td>
<td>1.476</td>
<td>1.317</td>
<td>0.188</td>
<td>12</td>
<td>49</td>
<td></td>
<td>0.5 &lt; 0.0 &lt; 0.5</td>
<td>11.22</td>
</tr>
<tr>
<td>Lötsch 2009</td>
<td>Chronic</td>
<td>-0.193</td>
<td>0.122</td>
<td>0.015</td>
<td>-0.432</td>
<td>0.046</td>
<td>-1.581</td>
<td>0.114</td>
<td>91</td>
<td>299</td>
<td></td>
<td>0.5 &lt; 0.0 &lt; 0.5</td>
<td>11.47</td>
</tr>
</tbody>
</table>

**Group random effects**

-0.015 ± 0.028 ± 0.285 ± 0.315 ± 0.099 ± 0.229 ± 0.677 ± 1.065

**Fig. 1.** Association of the OPRM1 118A>G polymorphism with opioid requirements of pain patients in various clinical settings. Meta-analysis indicates no significant association of the N40D μ-opioid receptor variant. Statistics and Forest plots of the standardized differences in means between groups (top: 118AG/GG versus 118AA, bottom: 118GG versus 118AA/AG) with 95% confidence intervals are shown for each study. The relative weight that each study was given in the meta-analysis is indicated by a bar chart at the right side of the first Forest plot. The second Forest plot at the right side of the figure indicates, for each study, the meta-analysis result that would have been obtained when that particular study had not been included.
WHERE DO WE GO FROM HERE?!
Pain and analgesia
✓ Pain sensitivity
✓ Analgesic efficacy

Table 1. SNPs Suggested To Affect Human Pain Sensitivity.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Mutation</th>
<th>Phenotype</th>
<th>Example Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCH1</td>
<td>GTP cyclohydrolase</td>
<td>Multiple SNPs</td>
<td>Partial analgesia</td>
<td>[35]</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
<td>Multiple SNPs</td>
<td>Increased/diminished pain sensitivity</td>
<td>(26,58,65,66)</td>
</tr>
<tr>
<td>DPRO1</td>
<td>Opioid receptor µ1</td>
<td>Multiple SNPs</td>
<td>Decreased pain sensitivity</td>
<td>[32,53]</td>
</tr>
<tr>
<td>OPRD1</td>
<td>Opioid receptor δ1</td>
<td>Multiple SNPs</td>
<td>Increased pain sensitivity</td>
<td>[67]</td>
</tr>
<tr>
<td>MCIR</td>
<td>Melanocortin 1 receptor</td>
<td>Loss of function SNPs</td>
<td>Partial analgesia</td>
<td>[39,68]</td>
</tr>
<tr>
<td>TRPA1</td>
<td>TRP alpha receptor A1</td>
<td>Transient receptor potential A1</td>
<td>Partial analgesia</td>
<td>[56]</td>
</tr>
<tr>
<td>TRPV1</td>
<td>TRP Vanilloid receptor V1</td>
<td>SNIP</td>
<td>Decreased pain sensitivity</td>
<td>[67,69]</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Cytochrome P450 2D6</td>
<td>Multiple SNPs</td>
<td>Partial analgesia</td>
<td>[59]</td>
</tr>
<tr>
<td>ABCB1</td>
<td>ATP-binding cassette, B1</td>
<td>SNP</td>
<td>Increased analgesic efficacy</td>
<td>[61]</td>
</tr>
<tr>
<td>FAAH</td>
<td>Fatty acid amide hydrolase</td>
<td>Multiple SNPs</td>
<td>Increased pain sensitivity</td>
<td>[38]</td>
</tr>
</tbody>
</table>

**Pain Matrix**

- **BRAIN**
  - Central: BDNF, OPRD1, H3/MA1, CNR1, GABRs, TNF, PLA2
  - Peripheral: L1, L2/3, COX-2, NTRK1, NGF, GDNF, TNF, LIF, CCL2, CNR2
  - Microglia: TLR2/4, P2RX4/7, CCL2, CXCR1, BDNF

- **Modulation**
  - Transduction: TRPV1, 2/3/4, P2XR3; Cold: TRPM8, TRPA1
  - Damage: P2RX3, P2RX1, BDKRB1, Htr3A, ACCNs...
  - Mechanical: TRPV1, TRPV1, 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, GRIK1-5, NR1R
  - Ca²⁺ channels: CACNA1A, CACNA2D1

**Basic wiring and defined genes involved in the pain phenotype**
Pain perception & modulation
- Complex multifactorial phenomenon
- Complex phenotype - modalities
- Polygenic

Analgesia
- Complex response - Polygenic
- Multimodal analgesia - Poly/ polygenic

A splash of cold water into the face of gene fever within the pain field. It appears that any plan to incorporate genotyping information into clinical pain practice is premature.