

# The Genetics of Chronic Pain

*NIH Pain Consortium Symposium 2014*

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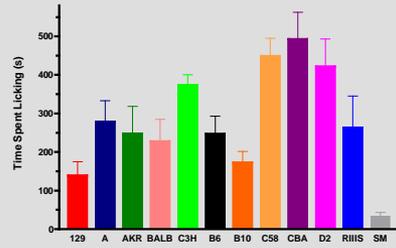


(see Nielsen et al. 2012)

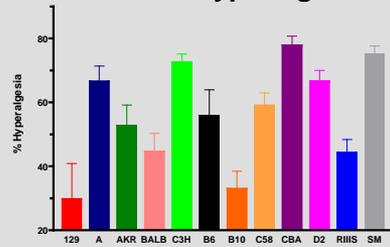


(Lariviere et al. 2002)

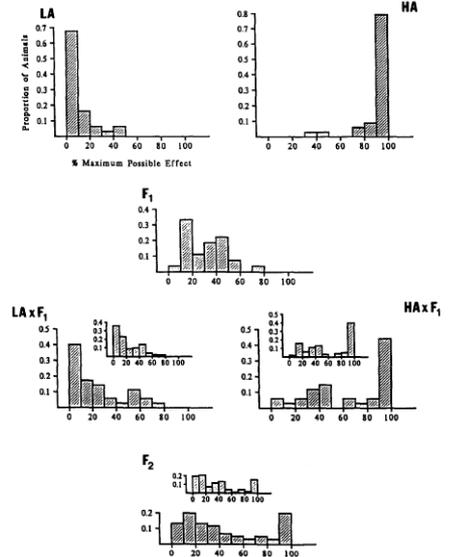
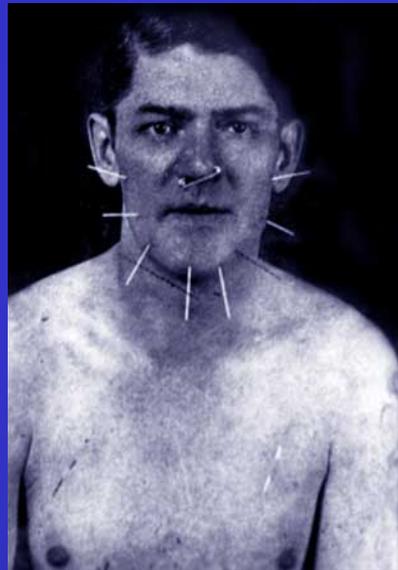
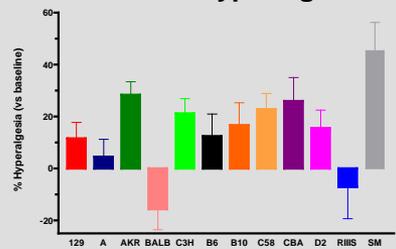
### Spontaneous Pain



### Ipsilateral Thermal Hyperalgesia



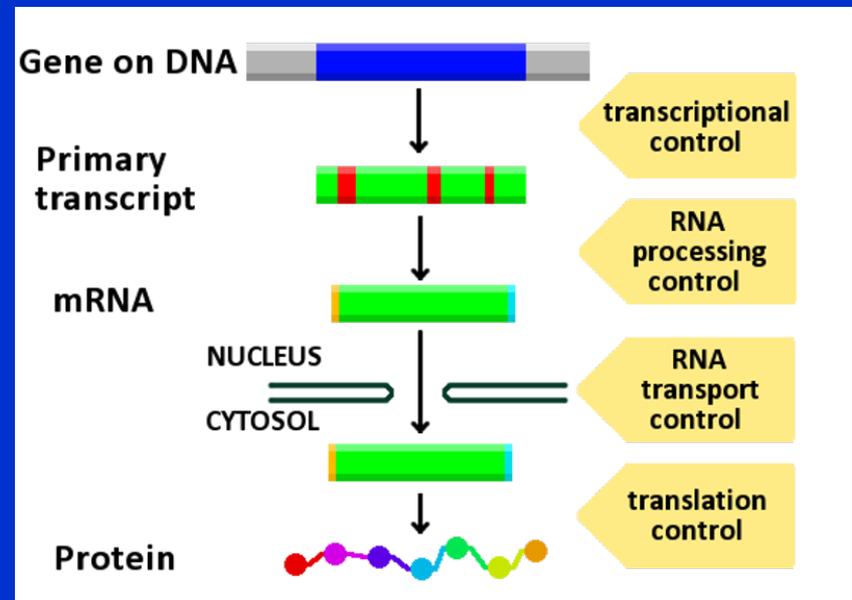
### Contralateral Thermal Hyperalgesia



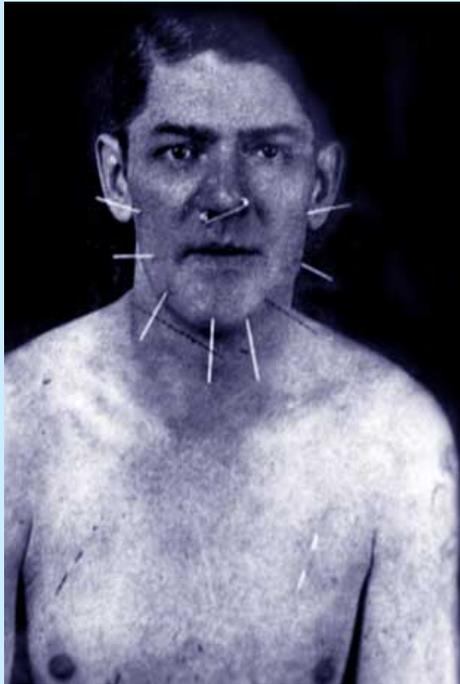
(Mogil et al. 1995)

# Approaches to Study the Genetics of Pain

- 1) Effect of gene sequence modifications
- 2) Gene expression changes in pain models
- 3) Other influences on genes and their expression



Rare disorder



Vs.

Normal variability

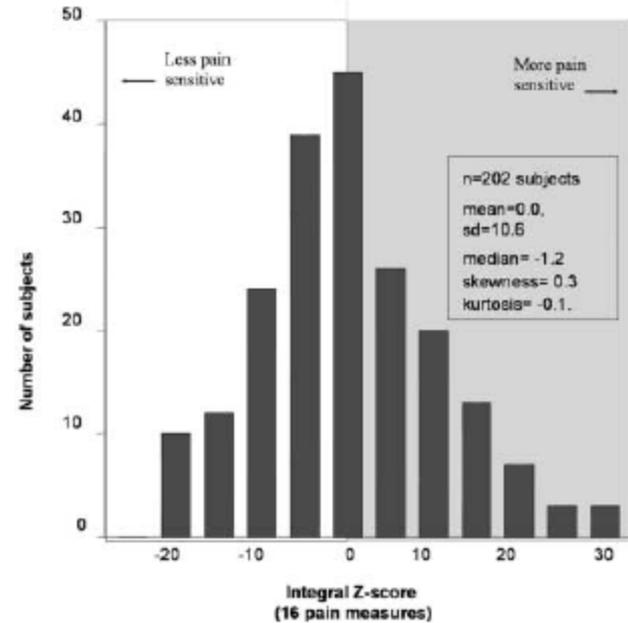


Figure 1. Distribution of a summary measure of pain sensitivity. A summary measure of pain sensitivity was derived from 16 individual pain measures, each standardized to unit normal deviates (z-scores) with a mean of 0 and

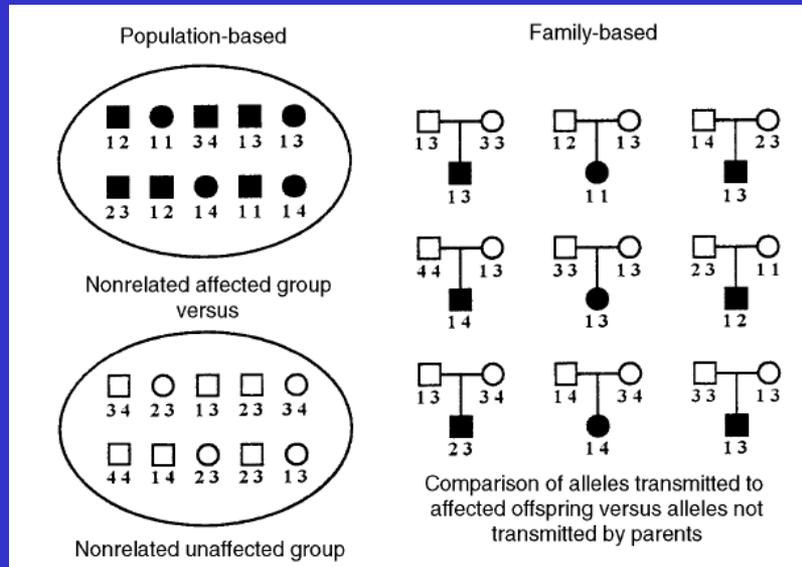
(Diatchenko et al. 2005)

Monogenic

Vs.

Polygenic

# Association Studies



## Of Qualitative Traits:

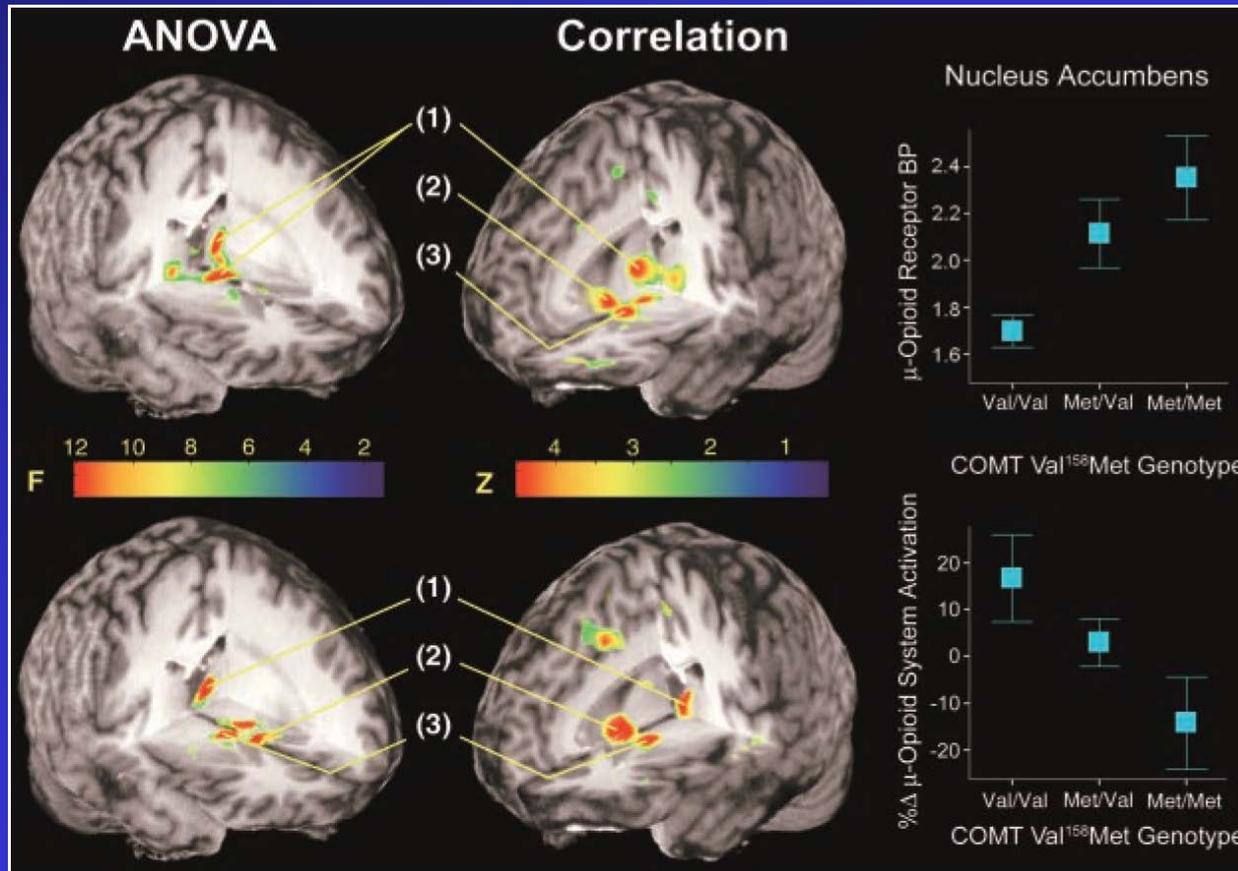
i.e., Affected or unaffected

Test whether specific genotype frequencies (single-locus allele/SNP or multilocus haplotype) are significantly different between those affected and those unaffected by the disease or condition.

## Of Quantitative Traits:

For e.g., Continuous numeric pain measures (VAS)

# COMT: Zubieta et al., 2003



With pain measures:

# Genetic basis for individual variations in pain perception and the development of a chronic pain condition

Luda Diatchenko<sup>1,8,\*</sup>, Gary D. Slade<sup>2</sup>, Andrea G. Nackley<sup>1</sup>, Konakporn Bhalang<sup>3</sup>, Asgeir Sigurdsson<sup>1</sup>, Inna Belfer<sup>4,7</sup>, David Goldman<sup>4</sup>, Ke Xu<sup>4</sup>, Svetlana A. Shabalina<sup>5</sup>, Dmitry Shagin<sup>6</sup>, Mitchell B. Max<sup>7</sup>, Sergei S. Makarov<sup>8</sup> and William Maixner<sup>1</sup>

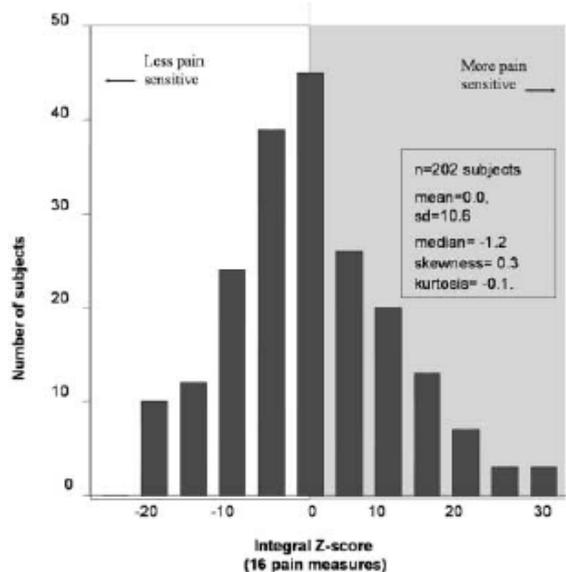
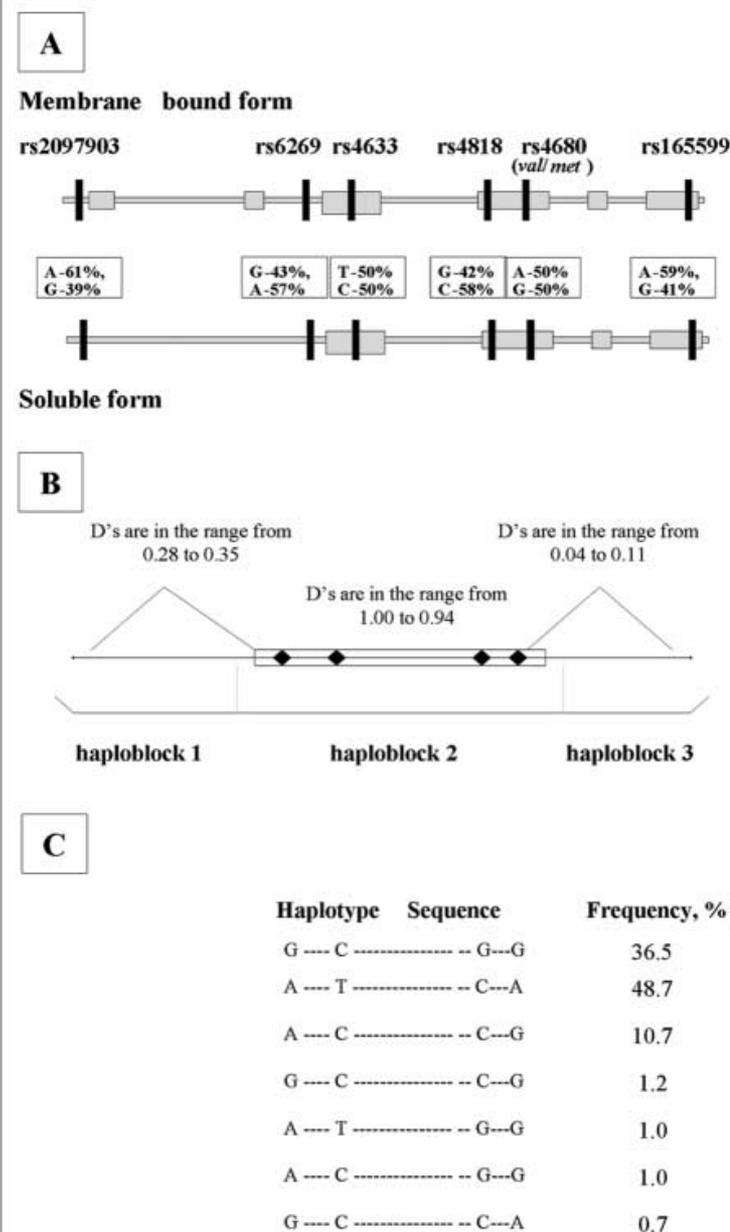
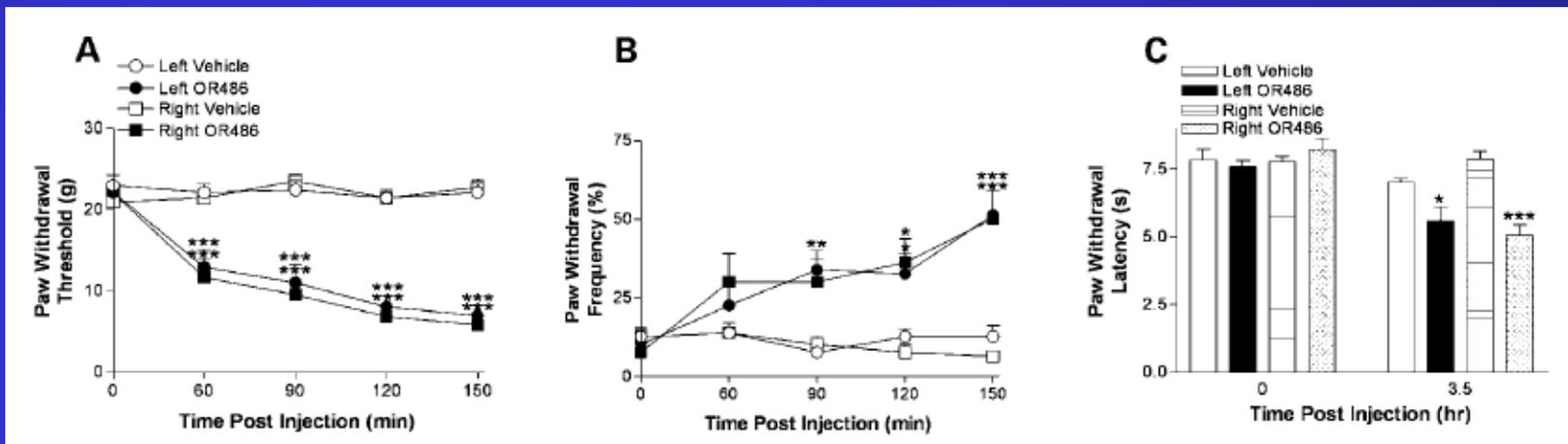
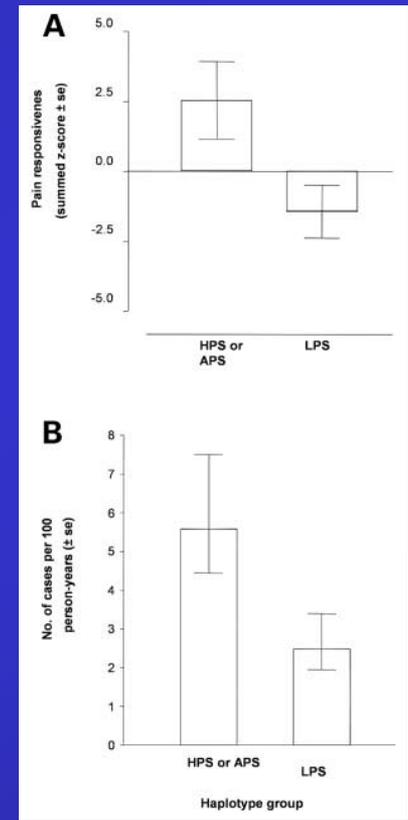
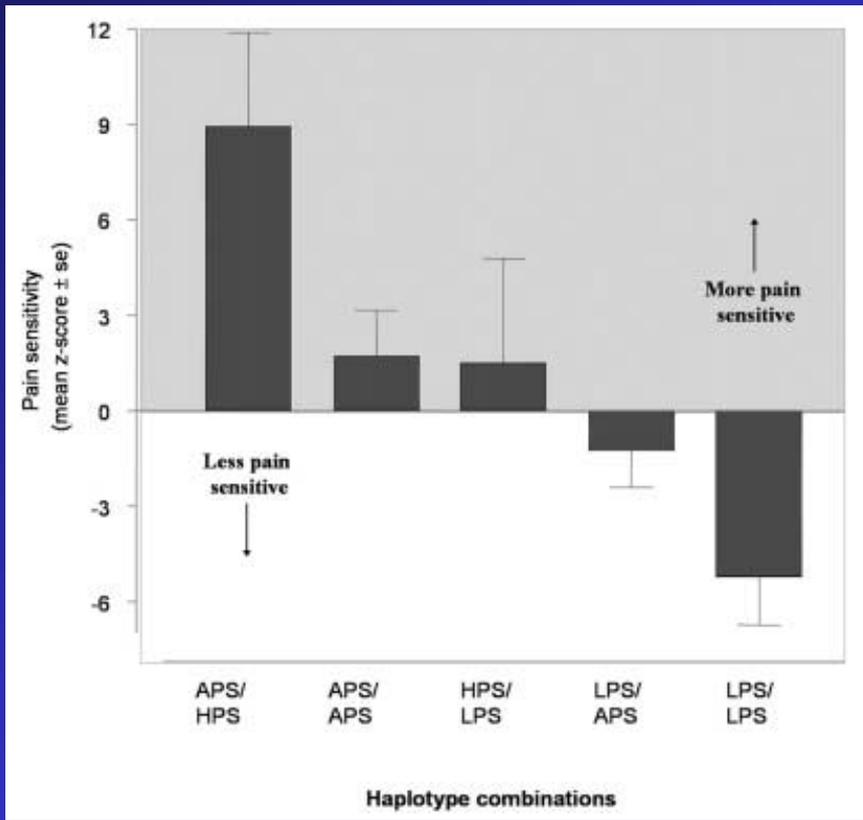


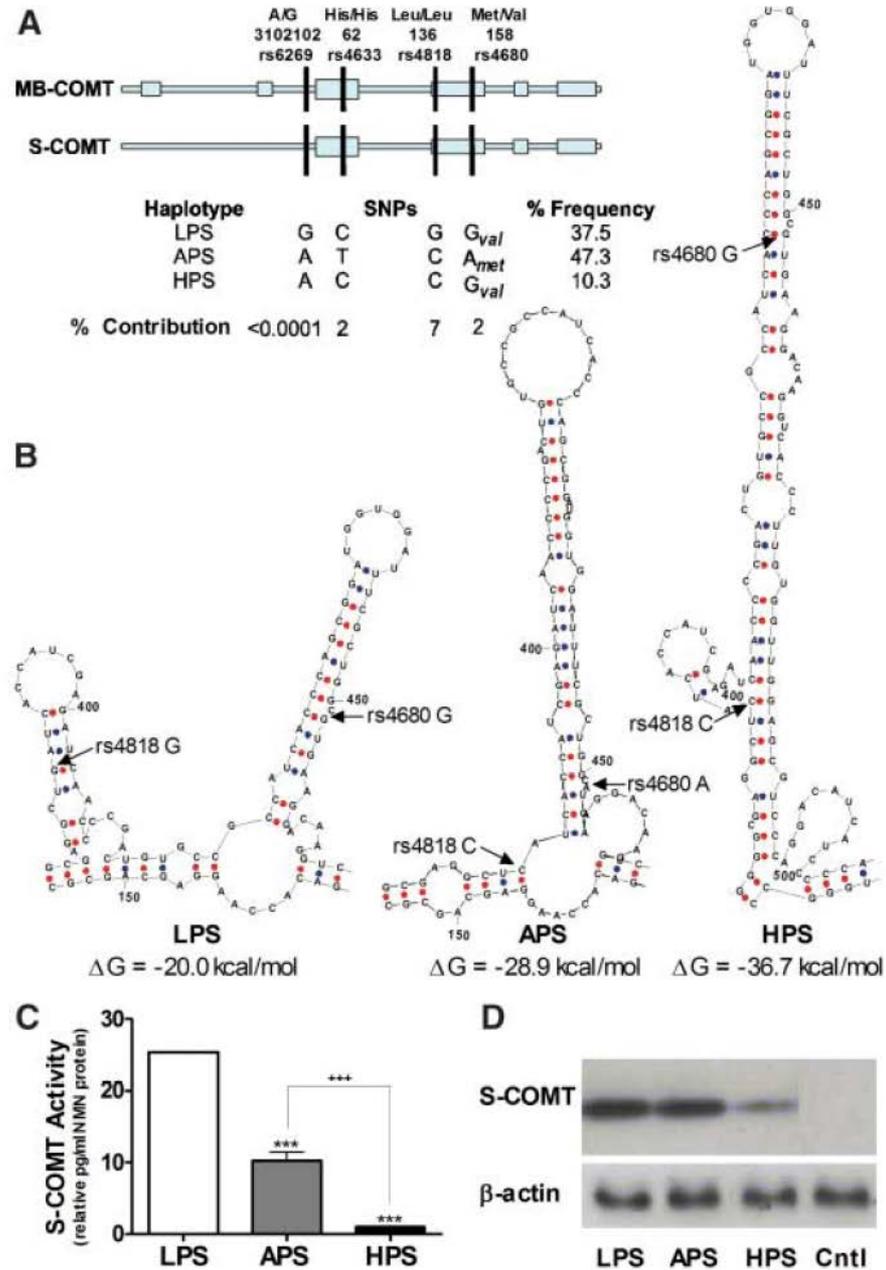
Figure 1. Distribution of a summary measure of pain sensitivity. A summary measure of pain sensitivity was derived from 16 individual pain measures, each standardized to unit normal deviates (z-scores) with a mean of 0 and

Figure 3. Pain responsiveness categorized by three major *COMT* haplotype combinations. LPS: haplotype G\_C\_G\_G, APS: haplotype A\_T\_C\_A, HPS: haplotype A\_C\_C\_G. The greater values reflect greater pain sensitivity. Each value represents the mean z-score with associated SEM.





# Functional consequence of (synonymous) COMT polymorphisms: due to mRNA secondary structure



(Nackley et al. 2006)



## Site of COMT action

- Brain areas, via opioid mechanisms?
- Spinal cord? via adrenergic receptor mechanisms?
- Prefrontal cortex?
  
- Multiple neurotransmitter systems affected: dopamine, adrenaline, noradrenaline
- Multiple possibilities for shared mechanisms with comorbid conditions

**Table 3 Genes (excluding HLA) associated with clinical and experimental pain states<sup>a</sup> and analgesia in humans. Only positive findings are referenced.**

Phenotype	Gene	Protein	Reference
Angina			
	<i>ADRA2C</i>	Adrenergic receptor, $\alpha 2C$	(207)
	<i>ADRB2</i>	Adrenergic receptor, $\beta 2$	(207)
	<i>NOS3</i>	Nitric oxide synthase, endothelial	(208)
Arthritis pain			
	<i>ESR1</i>	Estrogen receptor, alpha	(209)
	<i>IL6</i>	Interleukin-6	(210)
Back pain			
	<i>GCHI</i>	GTP cyclohydrolase 1	(93)
	<i>IL1A/B</i>	Interleukin-1 ( $\alpha$ and $\beta$ )	(211)
	<i>IL1RN</i>	Interleukin-1 receptor antagonist	(211)
	<i>IL6</i>	Interleukin-6	(212)
Burning mouth syndrome			
	<i>IL1B</i>	Interleukin-1 $\beta$	(213)
Experimental pain			
	<i>COMT</i>	Catechol-O-methyltransferase	(115, 162–163)
	<i>FAAH</i>	Fatty acid amide hydrolase	(214)
	<i>GCHI</i>	GTP cyclohydrolase 1	(93, 170)
	<i>MC1R</i>	Melanocortin-1 receptor	(63)
	<i>OPRD1</i>	Opioid receptor, delta 1	(105, 214)
	<i>OPRM1</i>	Opioid receptor, mu 1	(215, 216)
	<i>TRPA1</i>	Transient receptor potential, A1	(214)
	<i>TRPV1</i>	Transient receptor potential, V1	(10, 214)
Fibromyalgia			
	<i>COMT</i>	Catechol-O-methyltransferase	(167)
	<i>HTR2A</i>	Serotonin receptor, 2A	(217)
	<i>SLC6A4</i>	Serotonin transporter	(155)
Headache/migraine			
	Many (see references for reviews)		

For COMT associations review and meta-analysis see Tammimaki and Mannisto (2012)

(Lacroix-Fralish and Mogil, 2009)

Table 3 (Continued)			
Phenotype	Gene	Protein	Reference
Irritable bowel syndrome			
	<i>IL10</i>	Interleukin-10	
	<i>HTR2A</i>	Serotonin receptor, 2A	
	<i>SLC6A4</i>	Serotonin transporter	
	<i>TNFA</i>	Tumor necrosis factor, $\alpha$	
Non-steroidal anti-inflammatory drug analgesia			
	<i>PTGS2</i>	Cyclooxygenase-2	
Opioid analgesia			
	<i>COMT</i>	Catechol-O-methyltransferase	
	<i>CYP2D6</i>	Cytochrome P450 2D6	
	<i>MC1R</i>	Melanocortin-1 receptor	
	<i>OPRM1</i>	Opioid receptor, mu 1	
Pelvic pain			
	<i>IL10</i>	Interleukin-10	(231)
Postoperative pain			
	<i>MAOB</i>	Monoamine oxidase B	(232)
Temporomandibular disorder			
	<i>ADRB2</i>	$\beta 2$ -adrenergic receptor	(233)
	<i>COMT</i>	Catechol-O-methyltransferase	(115)
	<i>SLC6A4</i>	Serotonin transporter	(156, 234)
Vulvar vestibulitis			
	<i>IL1B</i>	Interleukin-1 $\beta$	(235)
	<i>IL1RN</i>	Interleukin-1 receptor antagonist	(159)
	<i>MC1R</i>	Melanocortin-1 receptor	(159)

**Table 2** Pain related genes associated with neurotransmitter systems

Gene name	Neurotransmitter system affected	Phenotype	References
<i>GCH1</i>	Serotonin, dopamine, norepinephrine, epinephrine, nitric oxide (all via BH4)	↓ Sensitivity to experimental pain ↓ Post-surgical pain (lumbar discectomy)	11 71–74
<i>SLC6A4</i>	Serotonin	↑ Risk for CWP ↑ Facilitation of experimental pain	75 76
<i>ADRB2</i>	Epinephrine	↑ Risk for CWP	77
<i>HTR2A</i>	Serotonin	↑ Risk for CWP ↑ Post-surgical pain	78 79

CWP, chronic widespread pain.

**Table 3** Pain related genes associated with ion channel function

Gene name	Channel type affected	Phenotype	References
<i>SCN9A</i>	Voltage gated Na <sup>+</sup> channels	↑ Chronic pain in mixed cohort (sciatica, osteoarthritis, pancreatitis, lumbar discectomy, and phantom limb) ↑ Sensitivity for experimental pain	87
<i>KCNS1</i>	Voltage gated K <sup>+</sup> channels	↑ Chronic pain in 5 cohorts (sciatica, lumbar pain, amputation, phantom limb) ↑ Sensitivity for experimental pain	88
<i>CACNA2D3</i>	Voltage gated Ca <sup>2+</sup> channels	↓ Sensitivity to thermal pain ↓ Chronic post-surgical pain (discogenic disease)	89
<i>CACNG2</i>	Voltage gated Ca <sup>2+</sup> channels	↑ Chronic post-surgical pain (post-mastectomy)	90

(Young, Lariviere and Belfer, 2012)



- Analgesia

- *COMT*: ↑ morphine (val158)

- *MC1R*: ↓ lidocaine eff.; ↑ M6G eff.; ↑ desflurane requ (6.2 Vs. 5.2 vol%)

- *OPRM1*: ↑ morphine postop, Ca pain (GG 118)

- Side effects

- *CYP2D6*: ultrarapid metabolizers of codeine have ↑↑ SE

- *ABCB1*: ↑ respiratory depression of fentanyl

- *OPRM1*: A118G ↓ pupil constriction, resp depr



# Concerns

- Reproducibility
- Specificity for type of pain
- Source of the candidate gene

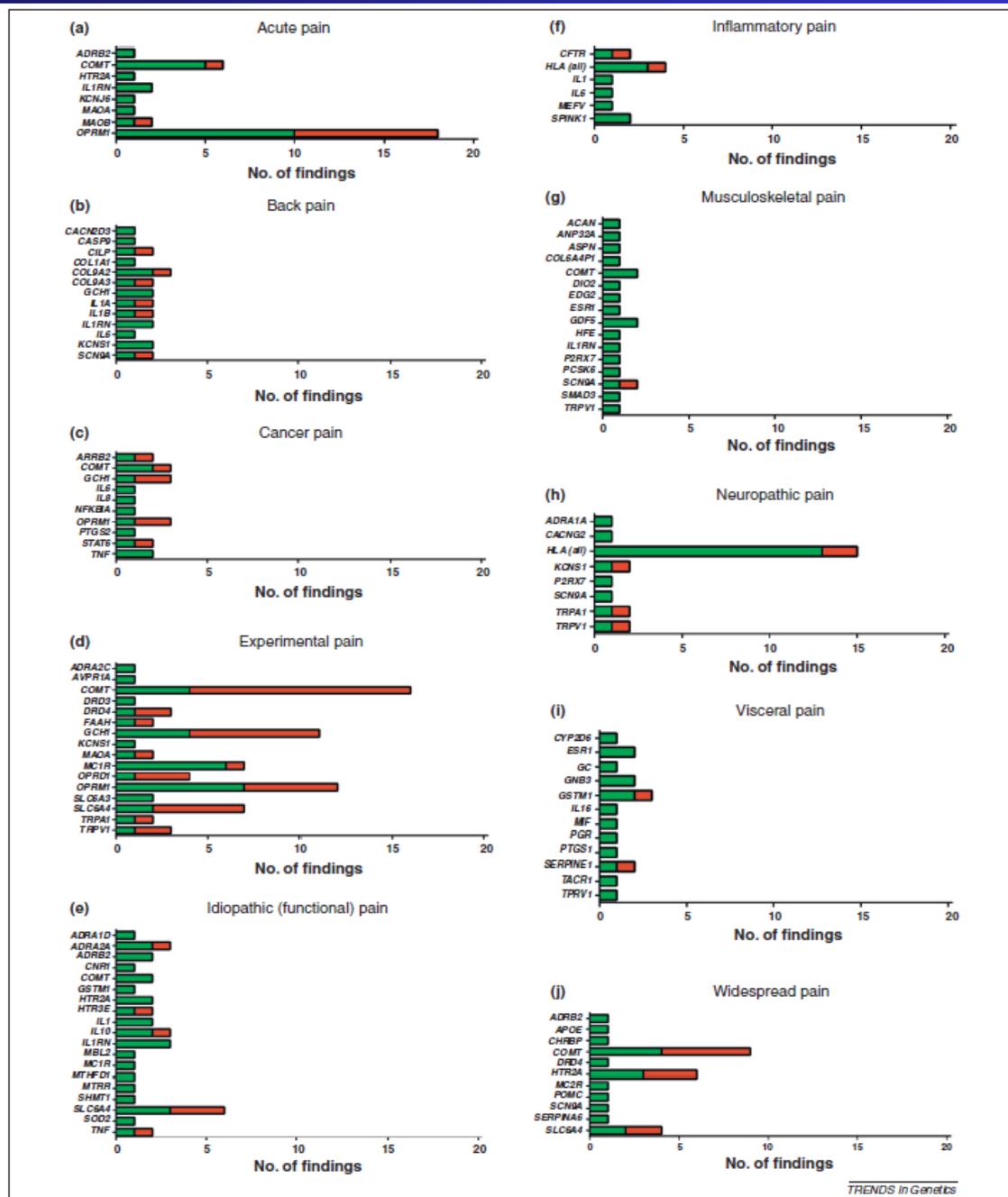


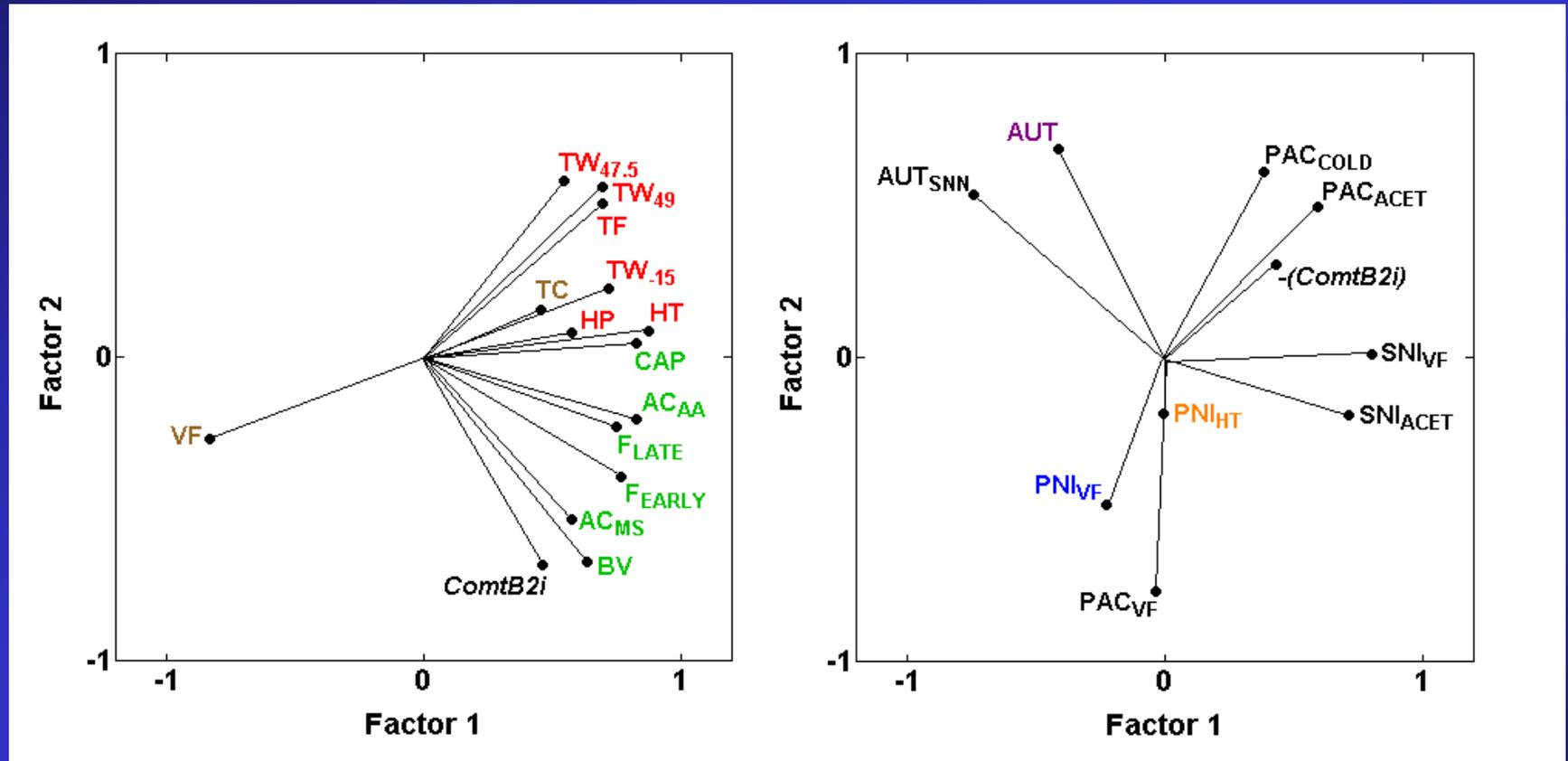
Figure 2. Number of pain-relevant candidate gene association study findings in humans by phenotype (see online supplementary material for details). Genes with at least one positive association are shown in green; negative associations are shown in red.

# Modality Specificity of COMT

## Association? (Diatchenko et al. 2006)

- Of 16 pain measures, including:
  - threshold and tolerance to thermal stimuli
  - ischemic and mechanical stimuli and
  - temporal summation of heat pain
- Val<sup>158</sup>Met associated with rate of **temporal summation of heat pain**
- LPS/APS/HPS haplotypes with **thermal pain**
- but possible dependence on variability of measures

(see also Segall et al. 2010;  
and Belfer et al. 2013 for sex differences)



(Young et al., Heritability of Nociception IV, *PAIN*, 2014)



# COMT: Specificity for type of pain

Tammimaki and Mannisto, 2012

- Meta-analysis:
  - COMT associated only with
    - fibromyalgia or
    - chronic widespread pain

**Table 2** Pain related genes associated with neurotransmitter systems

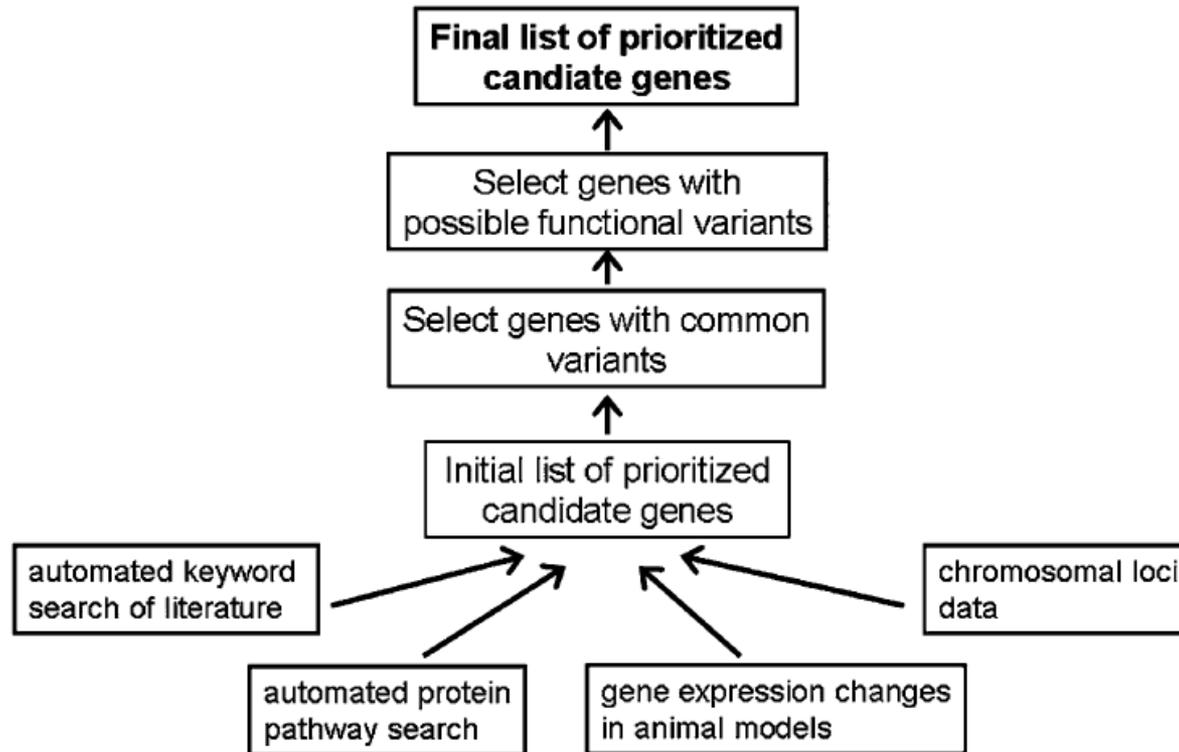
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(Young, Lariviere and Belfer, 2012)



**Figure 1.** *Scheme for objective selection of candidate genes relevant to chronic pain conditions. The initial list of candidates is prioritized on the basis of the number of times each gene appears in several different types of databases. The list is further narrowed to include only genes with more than 1 common variant in the human population under study, and further restricted to genes in which these common variations are likely to have functional effects on protein function or expression. The scheme incorporates ideas from several papers including Refs. 22,34,35.*

from J. A. Strong (2007) Genetics of Pain: Lessons for Future Studies. *Int Anesthesiol Clin* 45:13-25.



# Recommendations

- Need more big data studies
  - To look for convergent, entirely objective findings
  - Animal studies enough?
- Need more systematic meta-analyses
- Need to place a single gene's results in the larger context (“Systems Neurogenetics”)

**Table 1** Statistically significant QTLs of relevance to pain and analgesia in laboratory rodents

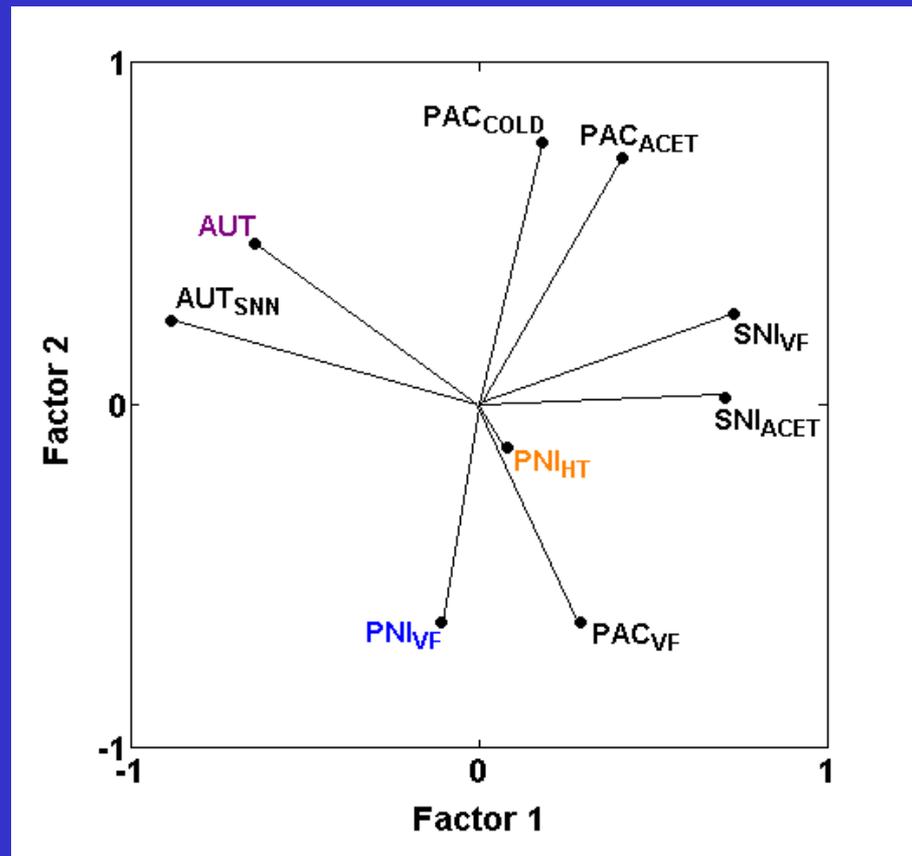
Phenotype	Chromosome	LOD <sup>a</sup>	Location <sup>b</sup>	Candidate gene(s)	Evidence <sup>c</sup>	Reference
<i>Acute/tonic pain</i>						
Capsaicin	2	5.9	30			(185)
	7	4.8	10			(185)
	7	5.8	50			(185)
	8	4.4	30			(185)
Formalin	10	4.3	70			(186)
Hargreaves	7	6.3	50	<i>Calca</i> (54 cM)	Pharm., siRNA, gene expr.	(113)
Hot-plate	4	3.8 (♂ only)	71	<i>Oprd1</i> (65 cM)	Pharm.	(187)
Tail withdrawal	4	3.6 (♂ only)	56	<i>Oprd1</i> (65 cM)	Position	(123)
	7	12.6	33	<i>Trpv1</i> (44 cM)	Position	(123)
	11	7.8	46			(123)
<i>Chronic pain</i>						
Autotomy	15	3.9	44			(188)
	15	3.0	44			(189)
	15	3.3 (♀ only)	32			(190)
	2 (rat)	3.6	20			(191)

(Lacroix-Fralish and Mogil, 2009)

# Genetic Relationships Among Neuropathic Pain Assays

AUT: Chr 15  
(+Chr 14)

PAC<sub>COLD</sub>,  
PAC<sub>VF</sub>,  
PNI<sub>VF</sub>,  
PNI<sub>HT</sub>: Chr ?



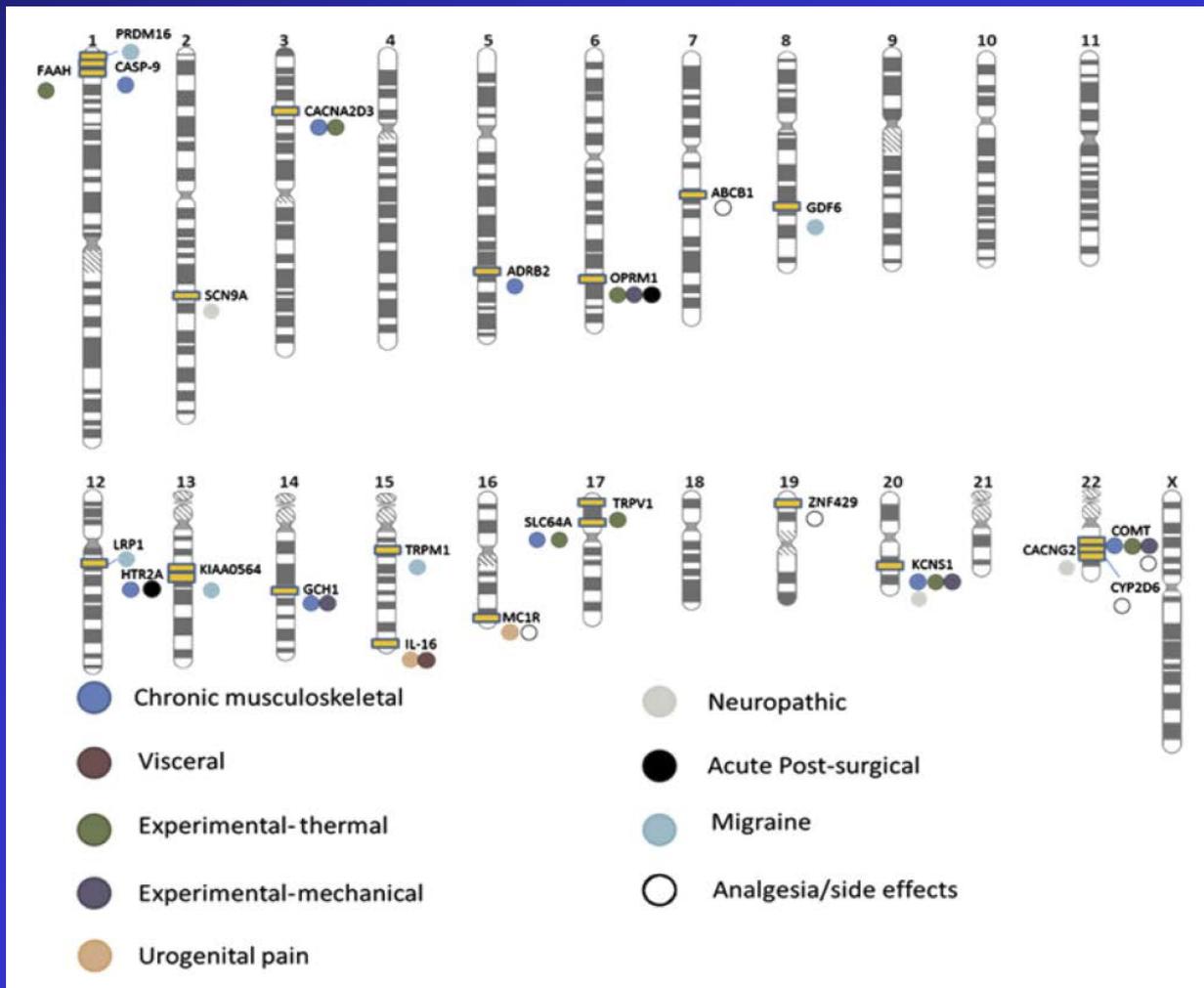
SNI<sub>VF</sub>: Chr 5

(Young et al., 2014)

PNI = Spin. N. Lig. (SNL)

# Systematic Meta-Analyses

- Migraine: Ligthart et al. 2011, others
- Disc degeneration: Eskola et al. 2012
- COMT: Tammimaki and Mannisto, 2012
  - Low to medium strength of findings...
  - Low COMT activity is not associated with migrainous headache or **chronic musculoskeletal pain** conditions



(Young, Lariviere and Belfer, 2012)



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[www.elsevier.com/locate/pain](http://www.elsevier.com/locate/pain)

Patterns of pain: Meta-analysis of microarray studies of pain

Michael L. LaCroix-Fralish<sup>a,1</sup>, Jean-Sebastien Austin<sup>a</sup>, Felix Y. Zheng<sup>b</sup>, Daniel J. Levitin<sup>a</sup>, Jeffrey S. Mogil<sup>a,c,\*</sup>

*Submitted to the Annals of Applied Statistics*

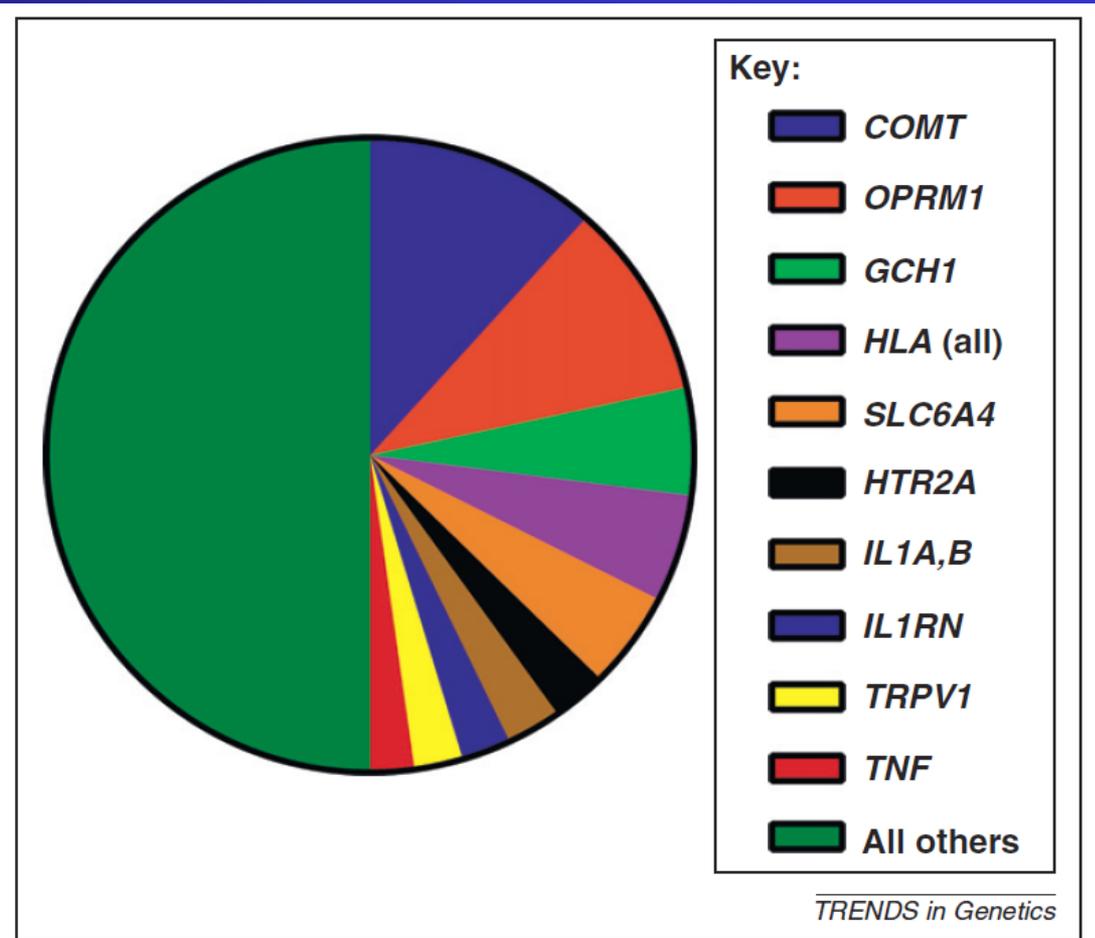
## IMPUTATION OF TRUNCATED P-VALUES FOR META-ANALYSIS METHODS AND ITS GENOMIC APPLICATION

BY SHAOWU TANG, YING DING, ETIENNE SIBILLE, JEFFREY S. MOGIL, WILLIAM R.  
LARIVIERE, AND GEORGE C. TSENG

- Need more critical reviews
- Need to acknowledge specificity of pain type
- Can use quantitative meta-analysis methods to determine mechanisms of comorbidity

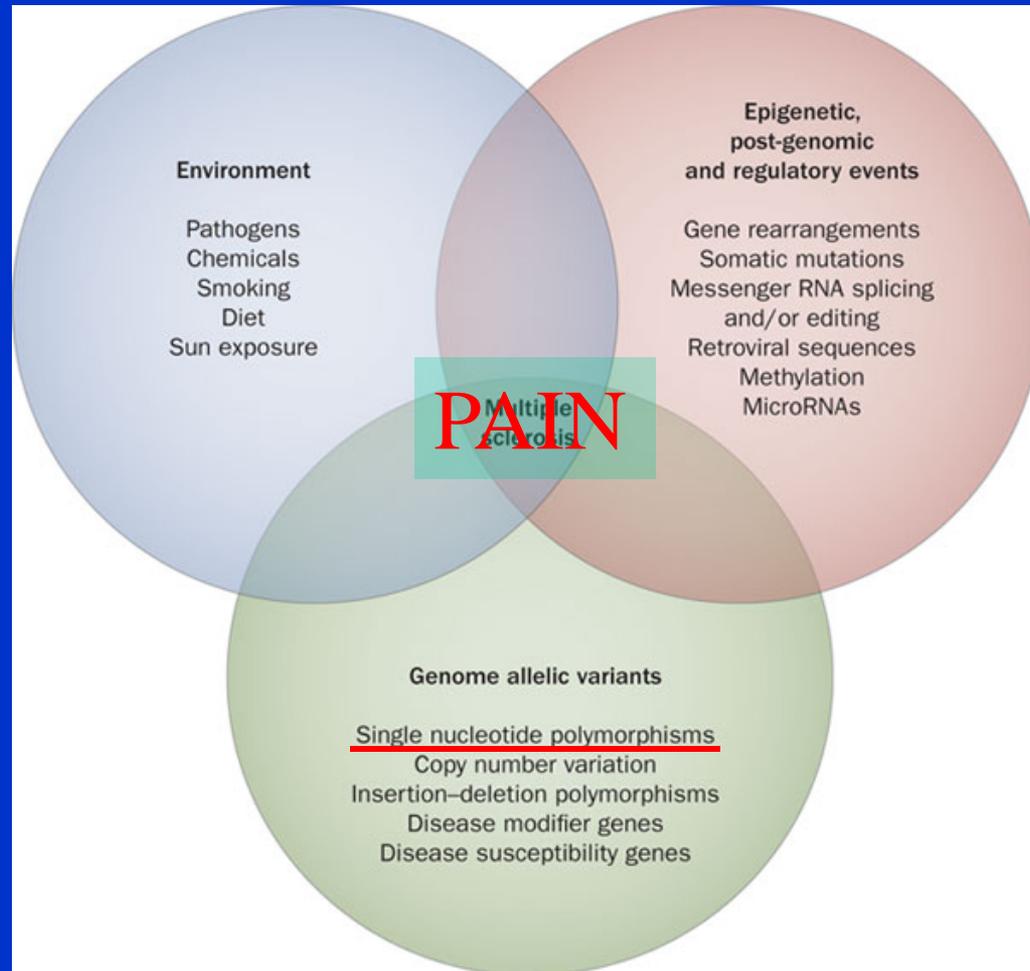
# The Larger Context:

What is the relative biological importance of the most popular genes being studied?



**Figure 3.** Popular candidate genes in pain genetic research. Studies of variants within these 10 genes outnumber studies of all other genes combined. Abbreviations: *COMT*, catechol-*O*-methyltransferase; *GCH1*, GTP cyclohydrolase 1; *HLA*, human lymphocyte antigen (major histocompatibility complex); *HTR2A*, serotonin receptor, 2A; *IL1A,B*, interleukin-1 receptor  $\alpha$  or  $\beta$ ; *IL1RN*, interleukin-1 receptor antagonist; *OPRM1*,  $\mu$ -opioid receptor; *SLC6A4*, solute carrier family 6, member 4 (serotonin transporter); *TRPV1*, transient receptor potential cation channel, V1; *TNF*, tumor necrosis factor.

(Mogil, TIGS 2012)



# Thanks

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- People
  - Pittsburgh: Inna Belfer, Erin Young
  - McGill: Jeff Mogil, Luda Diatchenko
  - Harvard: Michael Costigan
  - Jax: Elissa Chesler

