



The Nature & Nurture of Pain

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The Two “Genetics”



1. “Genetics” as the study of biology on the level of the gene.
 - genetics à la Watson & Crick
 - defining the molecular “building blocks” of pain
2. “Genetics” as the study of variability, of inherited individual differences.
 - genetics à la Gregor Mendel



www.paingeneticslab.com

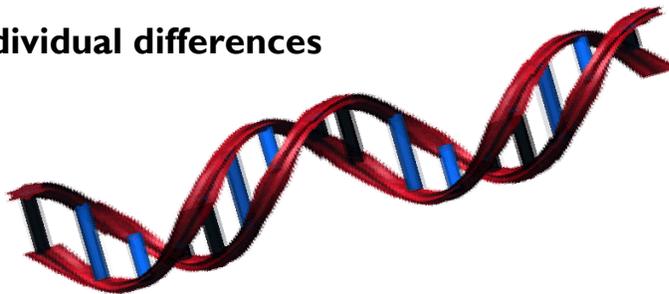


Why Do Genetics?

1) identifying new targets for drug development

- an *unbiased* target discovery approach
- a way to do biology without drugs/antibodies

2) explaining individual differences



Current Genetic Techniques

Technique	Molecule	Advantages	Disadvantages
<i>In rodents:</i>			
Transgenics	DNA	• simplicity	• interpretation difficult • single-gene focus
QTL Mapping	DNA	• causality • multigenic	• time-consuming • not guaranteed to work • blind to environment
Microarray	mRNA	• multigenic • genes or environment	• no causality • genes or environment?
Knockdown	mRNA	• simplicity	• hard to interpret null effects • single-gene focus
<i>In humans:</i>			
Linkage	DNA	• doable in humans!	• single-gene traits only
Association	DNA		• hard to replicate
Microarray	mRNA		• limited to available tissues
Deep Sequencing	DNA		• very expensive

PainGenesdb Selector

Total Genes: 203

Search by: Cellular Process

Gene: **Bdrb1**
 Year: 1997
 Papers: 6
 Receptor: **+**
 Hypersensitivity: **-**
 Analgesia: **+**
 Common Name: **bradykinin receptor, beta 1**

Protein Acronym: **BR1**
 Addition Acronym: **Kain B1**
 Entrez Gene: **188**
 Chrom: **11**
 Position: **79,003,265**
 XQ Type: **Conventional**
 Tissue: **Whole Body**
 Cellular Process: **Cell signalling**
 Function: **G-protein coupled receptor**
 Subfunction: **Neuroinhibitor**

Gene	ProteinName	CommonName	ProteinAcronym	AdditionAcronym	CellularProcess	Function	Subfunction	Receptor	Hypersens	Analgesia
Opm1	opioid receptor, mu	mu receptor	MOR		Cell signalling	G-protein coupled receptor	Opioid	+	-	-
Kcnj5	potassium inwardly-rectifying channel, subfamily J, member 5		Kir2.4	OR2.4	Cell signalling	Channel	Potassium channel	+	+	-
Bdrb1	bradykinin receptor, beta 1		BR1	Kain B1	Cell signalling	G-protein coupled receptor	Neuroinhibitor	-	-	+

Project: Pain Genes Database | Created for: **Jeffrey S. Mogil, Ph.D.**, Dept. of Psychology and Centre for Research on Pain, McGill University
 Financial Support by: **The Louise Edwards Foundation** | Created by: **Jean B. Leduc**, **Substans in Motion** © 2006-2007 514-485-9287

“Pain Genes” Knockout Mice with a Pain Phenotype

Total Genes: 322
 Total Papers: 755



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“If it were not for the great variability among individuals medicine might as well be a science and not an art.”

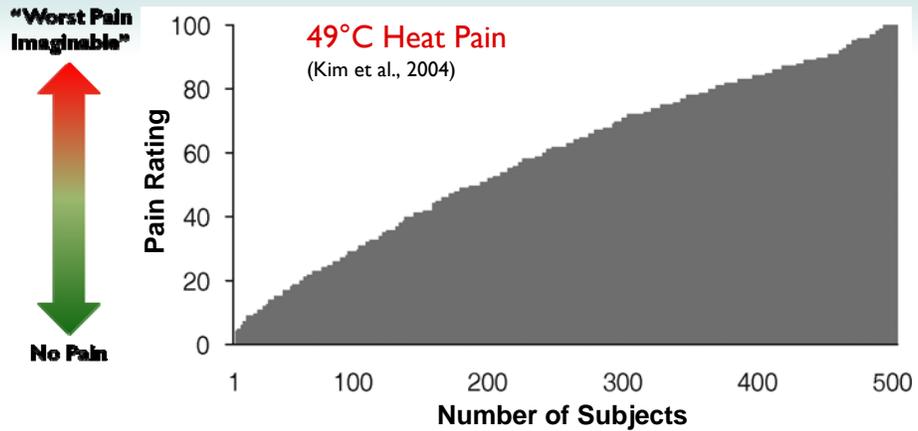


-Sir William Osler, 1892

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Variability in Human Pain Sensitivity: Experimental



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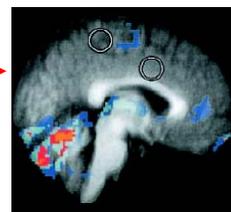
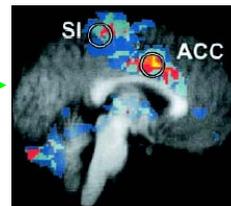
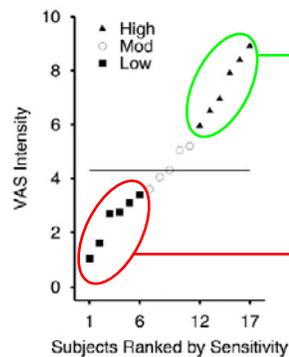


Is Variability in Human Pain Sensitivity *Real*?

Neural correlates of interindividual differences in the subjective experience of pain

Proc. Natl. Acad. Sci. USA,
100:8538, 2003

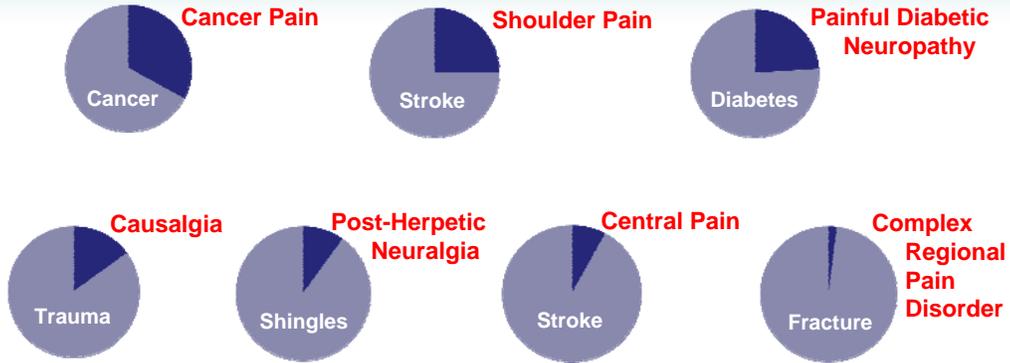
Robert C. Coghill^{1,2*}, John G. McHaffie^{1*}, and Ye-Fen Yen³



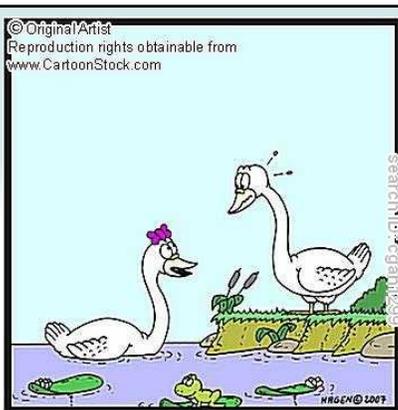
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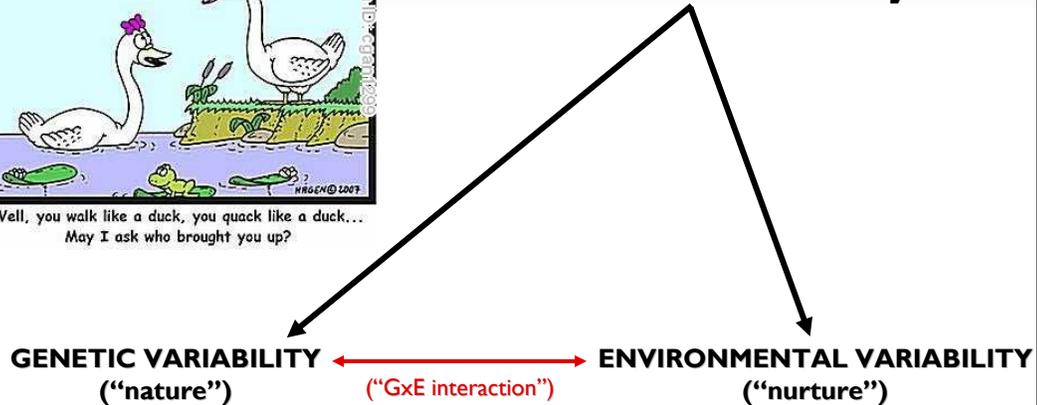
Variability in Human Pain Sensitivity: Clinical



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Trait Variability



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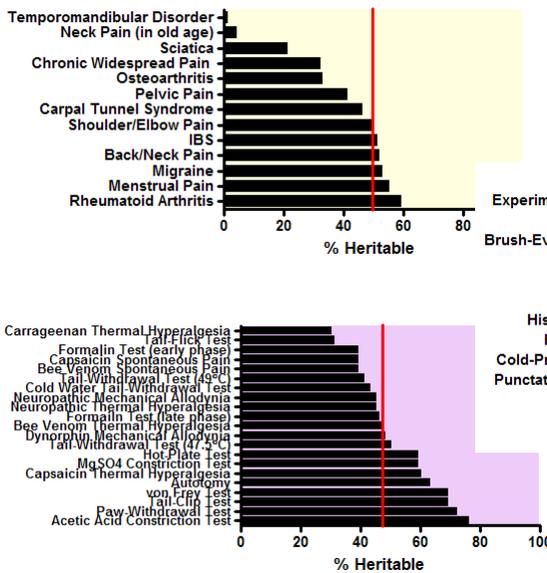


Estimating Heritability

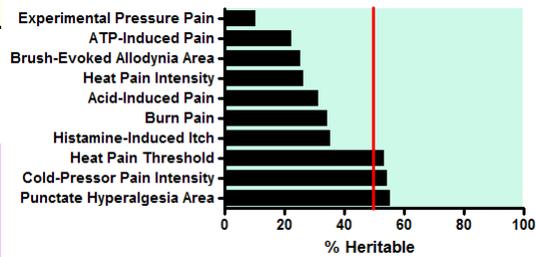
$$V_{\text{Trait}} = V_{\text{Genetic}} + V_{\text{Environmental}}$$



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Heritability of Pain Traits

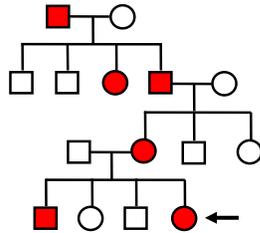


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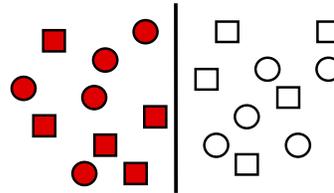


Finding "Pain Variability Genes"

Linkage Mapping



Association Studies



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Genes Responsible for Monogenic Pain Disorders



"The Human Pincushion"
 (congenital insensitivity
 to pain with anhidrosis;
 HSN Type IV)

HSN Type I	9q22.1	<i>SPTLC1</i>	sphingolipid synthesis
HSN Type II	12p13	<i>HSN2</i>	(function unknown)
HSN Type III	9p31	<i>IKBKAP</i>	transcription factor
HSN Type IV	1q21	<i>NTRK1</i>	neurotrophin receptor
HSN Type V	1p13.1	<i>NGFB</i>	neurotrophin
"	2q24	<i>SCN9A</i>	sodium (Na _v 1.7) channel
FEPS	8q12	<i>TRPA1</i>	cation (TRPA1) channel
PE	2q24	<i>SCN9A</i>	sodium (Na _v 1.7) channel
PEPD	2q24	<i>SCN9A</i>	sodium (Na _v 1.7) channel
FHM Type I	19p13	<i>CACNA1A1</i>	calcium channel subunit
FHM Type II	1q21	<i>ATP1A2</i>	ion pump subunit
FHM Type III	2q24	<i>SCN1A</i>	sodium (Na _v 1.1) channel

FEPS: familial episodic pain syndrome; HSN: hereditary sensory neuropathy;
 PE: primary erythromelalgia; PEPD: paroxysmal extreme pain disorder; FHM: familial hereditary migraine



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Genes Reported to be Associated with Pain States

ADRB2	temporomandibular disorder	Diatchenko, 2006
CACNG2	chronic postoperative pain	Nissenbaum, 2010
COMT	experimental pain	Zubieta, 2003; Diatchenko, 2005/6; Kim, 2006
	temporomandibular disorder	Diatchenko, 2005
	fibromyalgia	Gursoy, 2003
ESR1	TMJ osteoarthritis	Kang, 2007
FAAH	experimental pain	Kim, 2006
GCH1	low back pain	Tegeger, 2006
	experimental pain	Tegeger, 2006; Kim, 2007
HLA (many)	CRPS	Kemler, 1999; Mailis, 1994; van Hilten, 2000
	postherpetic neuralgia	Sato, 2002
HTR2A	fibromyalgia	Bondy, 1998
	irritable bowel syndrome	Pata, 2004
HTT	temporomandibular disorder	Herken, 2001; Cohen, 2002
IL1	low back pain	Solovieva, 2004
IL1RN	low back pain	Solovieva, 2004; Foster, 2004
	vulvar vestibulitis	Jeremias, 2000
IL6	sciatica	Noponen-Hietala, 2005
	rheumatoid arthritis	Oen, 2005
IL10	pelvic pain	Shoskes, 2002
KCNS1	experimental pain, lumbar root pain	Costigan, 2010
MAOB	postoperative pain	Sery, 2006
MC1R	experimental pain	Mogil, 2005
	vulvar vestibulitis	Foster, 2004
OPRD	experimental pain	Kim, 2004
OPRM	experimental pain	Fillingim, 2005
	chronic, non-cancer pain	Janicki, 2006
SCN9A	osteoarthritis, sciatica, postamputation pain	Reimann, 2010
SLC6A4	fibromyalgia	Offenbaecher, 1999
TRPA1	experimental pain	Kim, 2006
TRPV1	experimental pain	Kim, 2004



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The Problem with Association Studies...

NATURE | Vol 447 | 7 June 2007

nature

Replicating genotype-phenotype associations

NCI-NHGRI Working Group on Replication
 in Association Studies

"...So far, comprehensive reviews of the published literature, most of which reports work based on the candidate-gene approach, have demonstrated a plethora of questionable genotype-phenotype associations, replication of which has often failed in independent studies."

Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Medicine | www.plosmedicine.org

0696

August 2005 | Volume 2 | Issue 8 | e124



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What About Human Pain Genetics?

- COMT:**
- val158met associated with pain (Zubieta et al., 2003)
 - a haplotype associated with pain, but not val158met (Diatchenko et al., 2005)
 - no association with neuropathic pain (Armero et al., 2005)
 - no association with post-operative pain (Kim et al., 2006)
 - val158met associated with fibromyalgia (Cohen et al., 2009)
 - no association with chronic pain (Hocking et al., 2010)
 - a different haplotype associated with low back pain (Dai et al., 2010)
- MC1R:**
- variants associated with decreased pain sensitivity (Mogil et al., 2005)
 - variants associated with increased pain sensitivity (Liem et al., 2005)
- GCHI:**
- a haplotype associated with pain (Tegeeder et al., 2006)
 - a haplotype associated with pain, but only after sensitization (Tegeeder et al., 2008)
 - no association with post-operative pain (Kim et al., 2007)
 - a haplotype associated only with capsaicin pain (Campbell et al., 2009)
 - a haplotype delays cancer pain (Campbell et al., 2009)

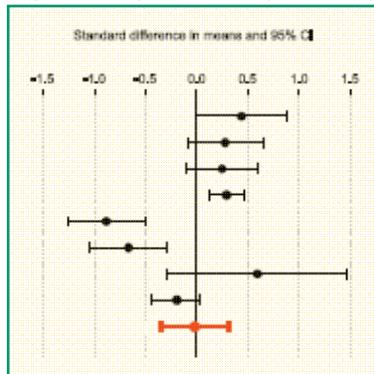


A Meta-Analysis of *OPRM1* and Pain

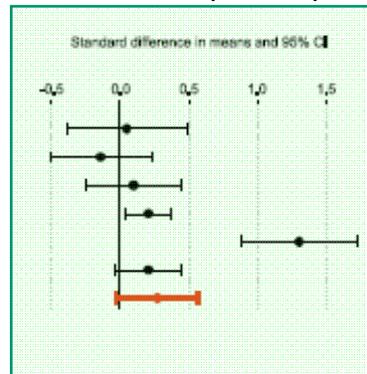
Meta-analysis of the relevance of the *OPRM1* 118A>G genetic variant for pain treatment

Carmen Walter, Jörn Lötsch*

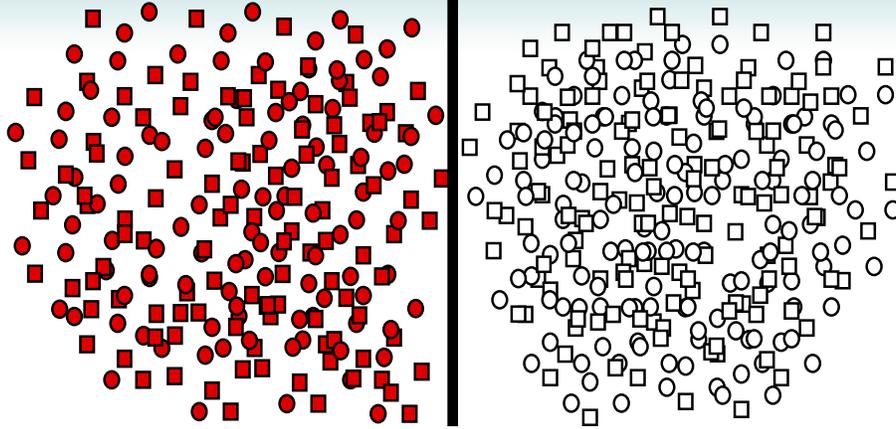
Opioid Requirements (G vs. AA)



Pain Scores (G vs. AA)



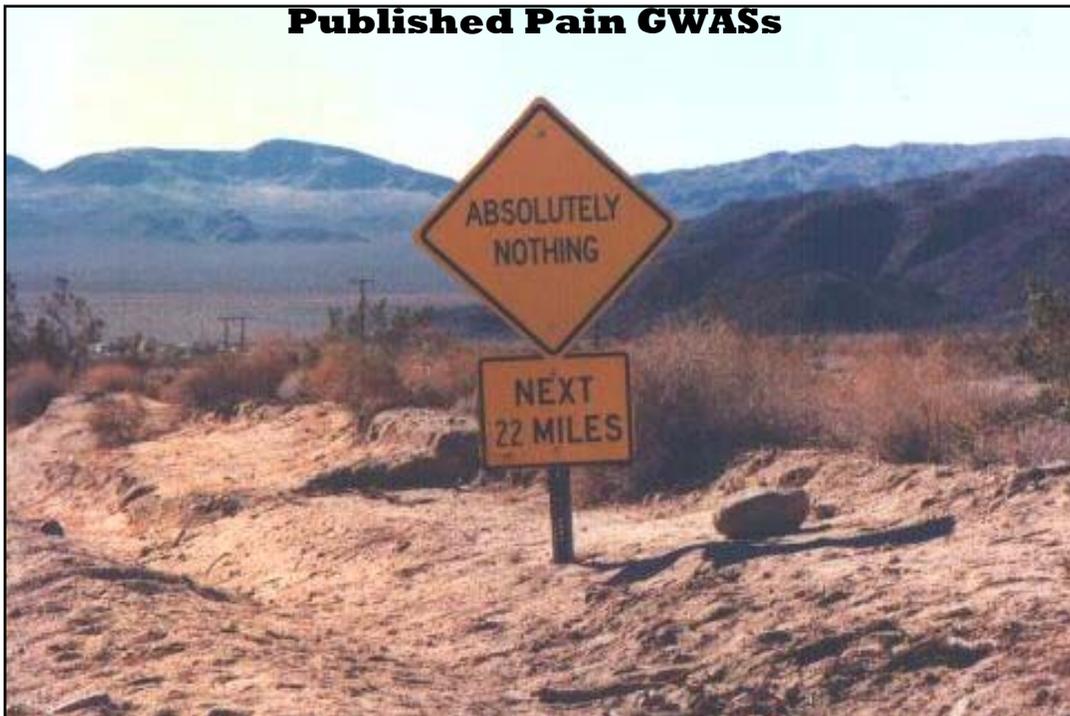
Genome-Wide Association Studies (GWAS)



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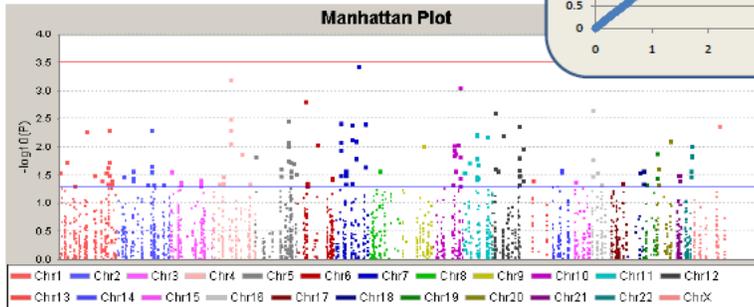
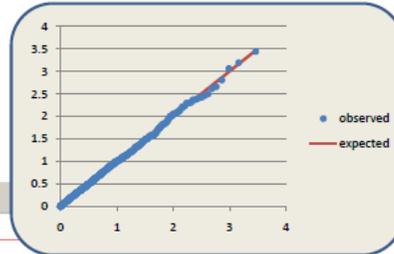
Published Pain GWASs



The Closest Approximation in Pain: The **OPPERA** Study (W. Maixner, PI)

177 TMD cases vs 1443 controls

CHR	SNP	GENE	Call Rate	MAF (W)	MAF (B)	OR	P
7	rs728273	IFRD1	99.57%	0.41	0.69	0.64	0.00036
4	rs1563826	EREG	100.00%	0.21	0.51	0.60	0.00063
10	rs12415832	GRK5	99.88%	0.021	0.051	2.54	0.00086



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Do GWASs “Work”?

YES

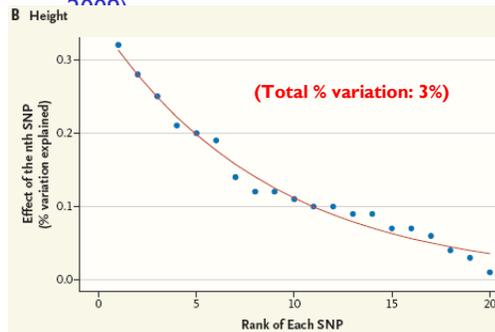
[J.N. Hirschhorn \(N. Engl. J. Med., 2009\)](#)

...in 2005, two friends and well-known geneticists, Francis Collins and Thomas Gelehrter, made a public bet: Gelehrter predicted that no more than three new common variants would be reproducibly associated with common diseases by the time the American Society of Human Genetics (ASHG) held its meeting in the autumn of 2008. During the past 2 years, however, genomewide association studies have identified more than 250 genetic loci in which common genetic variants occur that are reproducibly associated with polygenic traits... Collins was the clear winner, by a margin of more than 200 new associated variants.

“The main goal of these studies is not prediction of individual risk but rather discovery of biological pathways underlying polygenic diseases and traits.”

NO

[D.B. Goldstein \(N. Engl. J. Med., 2009\)](#)



“If common variants are responsible...most genes are “height genes” or “type 2 diabetes genes”...in pointing at everything, genetics would point at nothing.”



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But wait...

- what about *APOE*?
- what about *BRCA1* and *BRCA2*?
- what about *CFH* and macular degeneration?
- what about hearing loss genes?

**Q. Is chronic pain more like type-2 diabetes,
or more like macular degeneration?**



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The Future: Genome-Wide Resequencing

- if the common disease-common variant hypothesis is wrong, and the common disease-rare variant hypothesis is correct, then the solution is to find the rare variants
- this can be done by sequencing many people with the disease, at great (but decreasing; the "\$1000 genome") cost
- the truth is...pain is not "important" enough to spend the money (!)

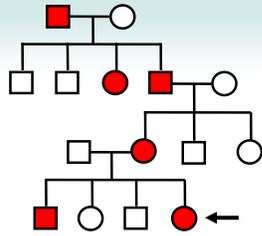


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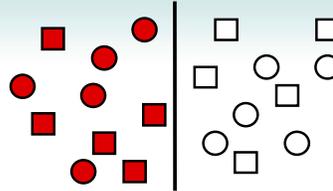


Finding "Pain Variability Genes"

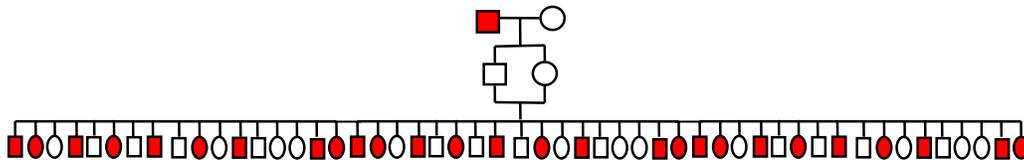
Linkage Mapping



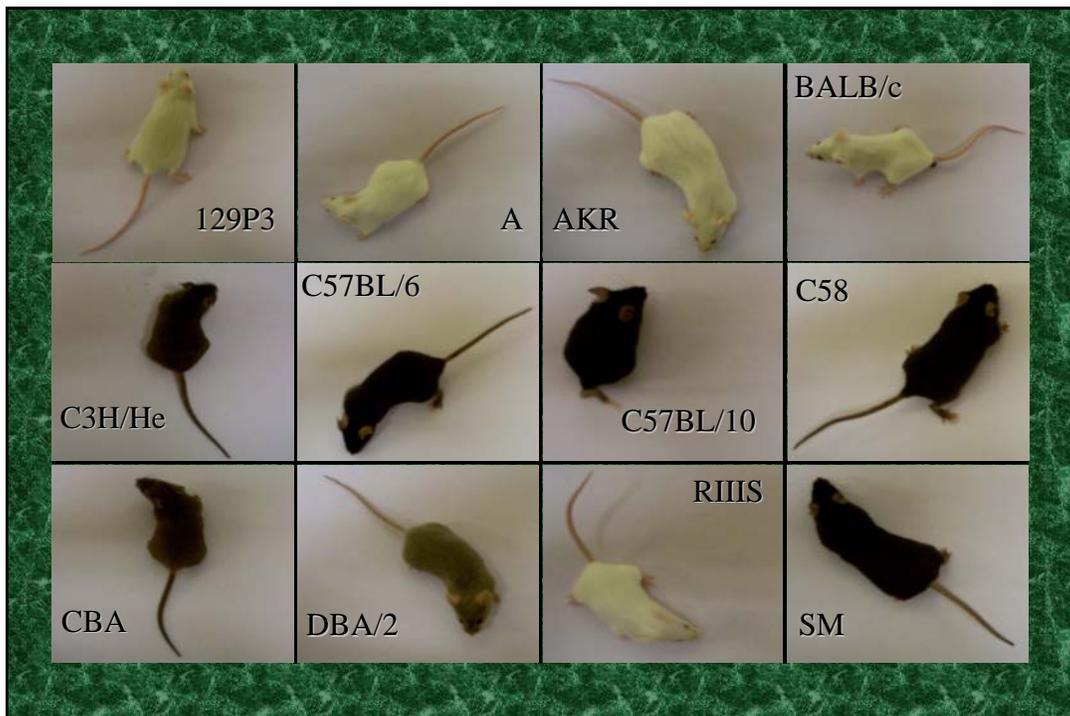
Association Studies



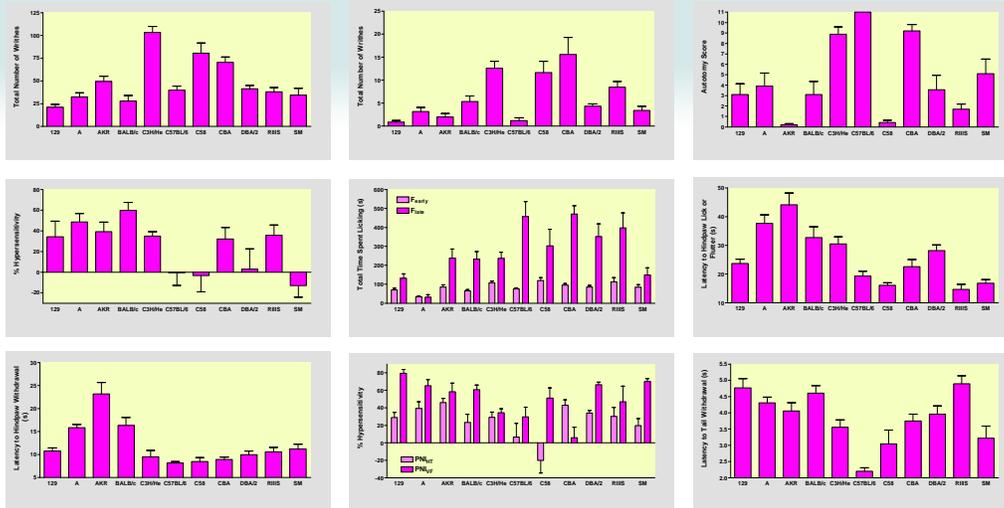
Experimental Crosses (Linkage Mapping)



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Strain Differences in Pain Sensitivity



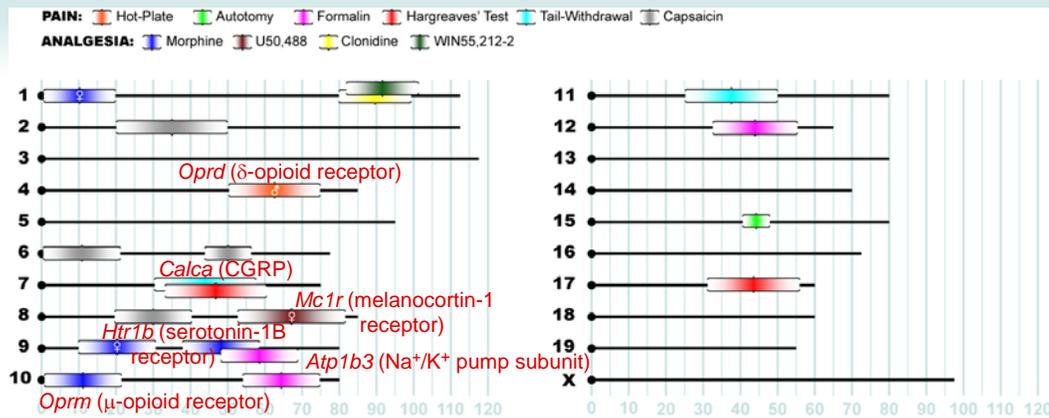
Mogil et al., *Pain*, 1999



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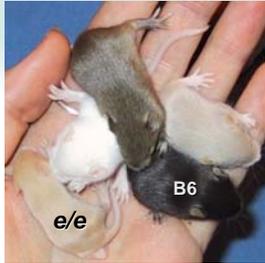
Published Pain-Relevant Genomic Linkages (Quantitative Trait Loci)



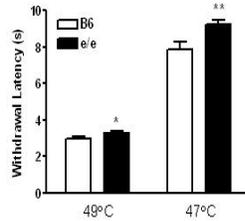
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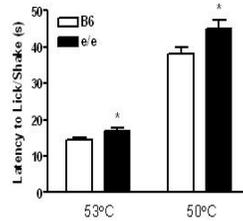
MC1R (melanocortin-1 receptor) and Pain: Mice and Humans



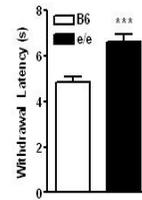
a. Tail-Withdrawal Test



b. Hot-Plate Test



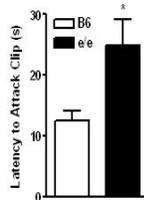
c. Paw-Withdrawal Test



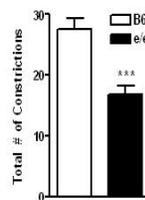
2+ Variants

0/1 Variants

d. Tail-Clip Test



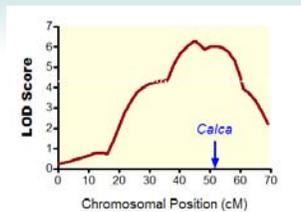
e. Abdominal Constriction Test



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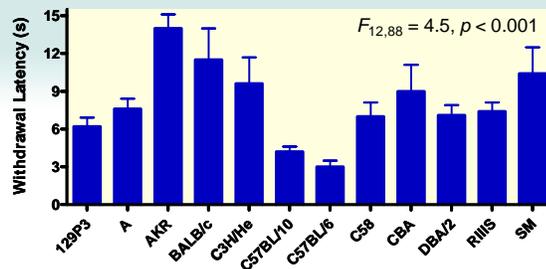


Calca (CGRP) and Thermal Pain: Mice and Humans



B. 12 inbred mouse strains

Mogil et al., PNAS, 2006



1246 cases and controls with RC4 (thermal sensitivity) factor score

OPPERA Study
(in preparation)

CHR	SNP	GENE	Call Rate	MAF (W)	MAF (B)	BETA	P
11	rs1553005	CALCA	99.81%	0.31	0.34	0.13	0.00055
4	rs1024323	GRK4	100.00%	0.38	0.59	-0.12	0.00074
3	rs2236953	CACNA2D2	99.32%	0.13	0.03	-0.18	0.00096

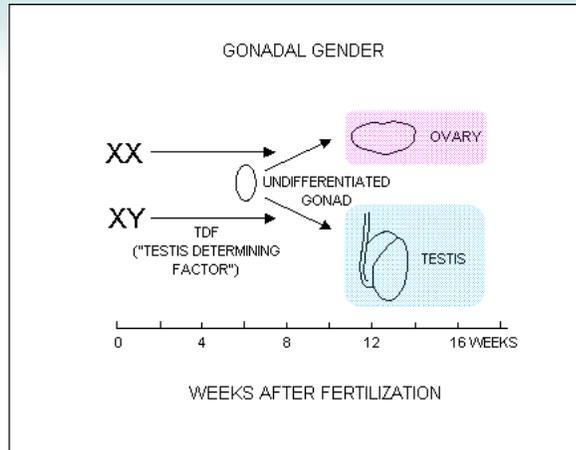
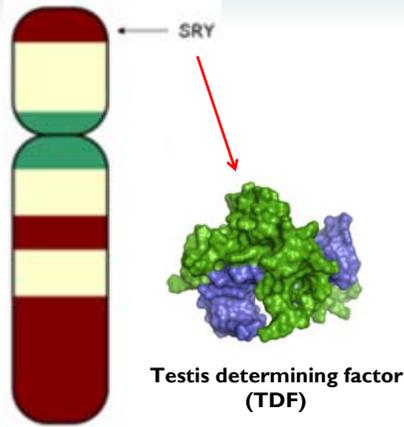


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One Other Gene We *Know* is Involved in Pain

Chromosome Y



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Qualitative Sex Differences in Pain Mechanisms

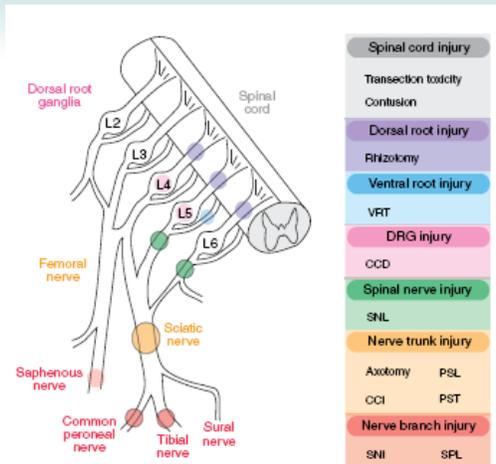


Mis



Mers

Strain Survey (31 Strains!) of Neuropathic Mechanical Allodynia



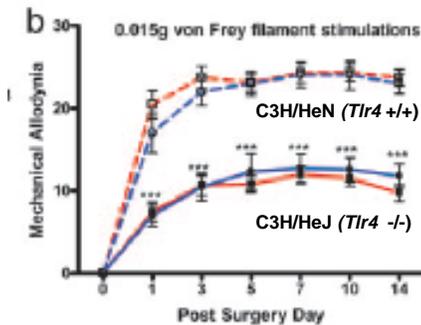
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Sex-Specific Effect of *Tlr4* (Toll-like receptor 4) Genetic Dysfunction on Mechanical Allodynia

PNAS The CNS role of Toll-like receptor 4 in innate
 neuroimmunity and painful neuropathy

Flobert Y. Tanga^{1,2}, Nancy Nuttle-McMenemy^{1,4}, and Joyce A. DeLeo^{1,2,5}



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Male-Specific and Testosterone-Dependent Involvement of *Spinal*/TLR4 in Chronic Pain



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Conclusions

- variability in pain sensitivity, susceptibility to developing chronic pain disorders, and analgesic response is robust in humans and rodents
- slowly but surely, pain-relevant genes are being identified and confirmed in mice and humans
- the large total number of pain-relevant genes suggests, however, that the process will take quite some time, and that incorporation of genetic data into pain treatment is premature
- the genetic technique nonetheless has considerable heuristic value, especially as a guide to and refinement of drug development efforts (e.g., TLR4)



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Thanks to...

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+ 80 McGill Undergraduates



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