



The Translational Value of Mouse Genetics

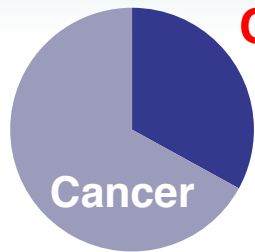
Jeffrey S. Mogil, Ph.D.



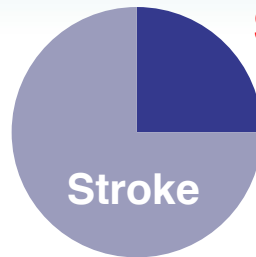
McGill

Dept. of Psychology and Centre for Research on Pain
McGill University, Montreal, QC

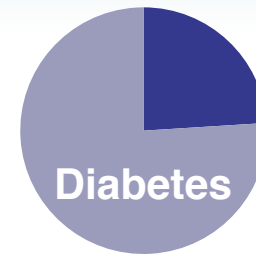
Variability in Chronic Pain Development



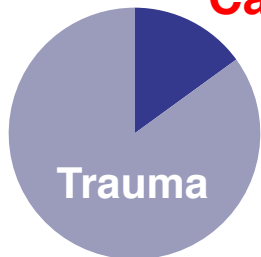
Cancer Pain



Shoulder Pain



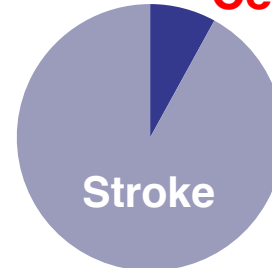
Painful Diabetic Neuropathy



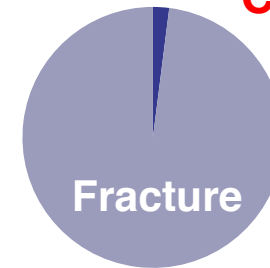
Causalgia



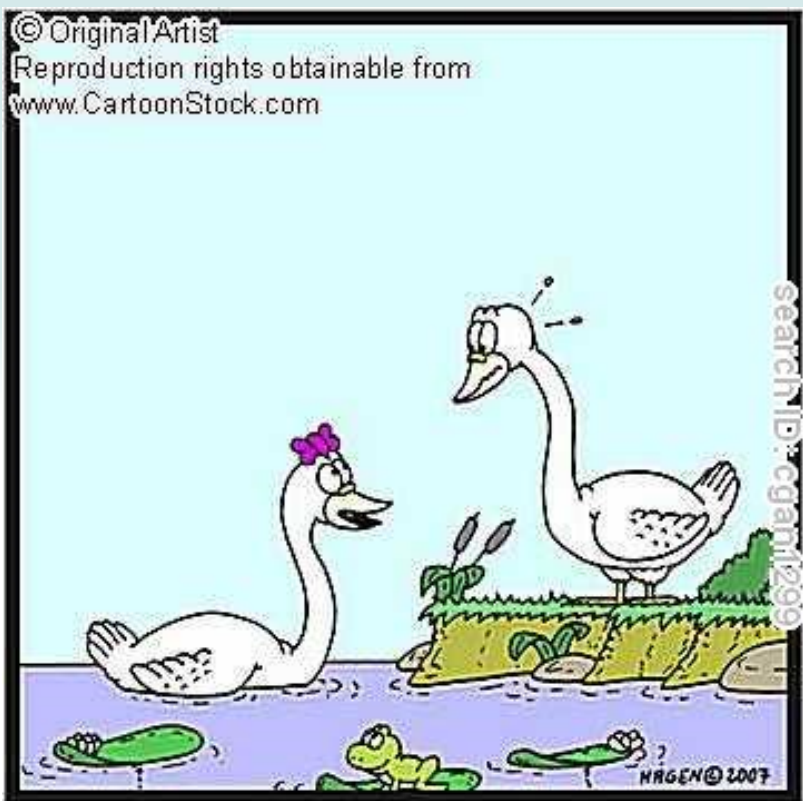
Post-Herpetic Neuralgia



Central Pain

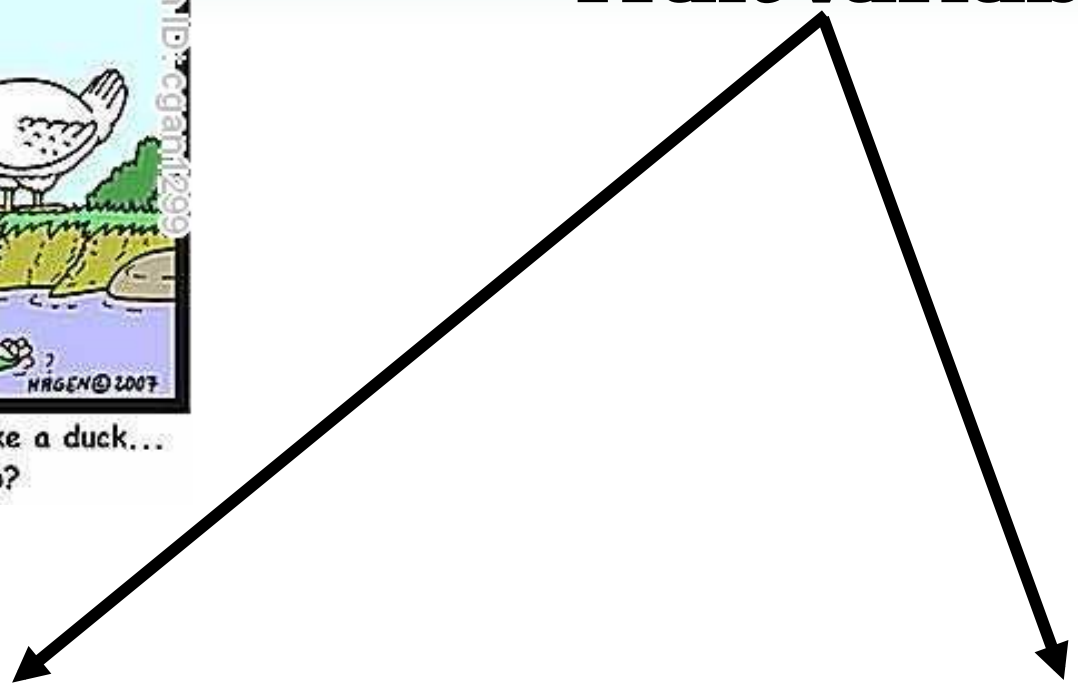


Complex Regional Pain Disorder



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Trait Variability



GENETIC VARIABILITY
("nature")

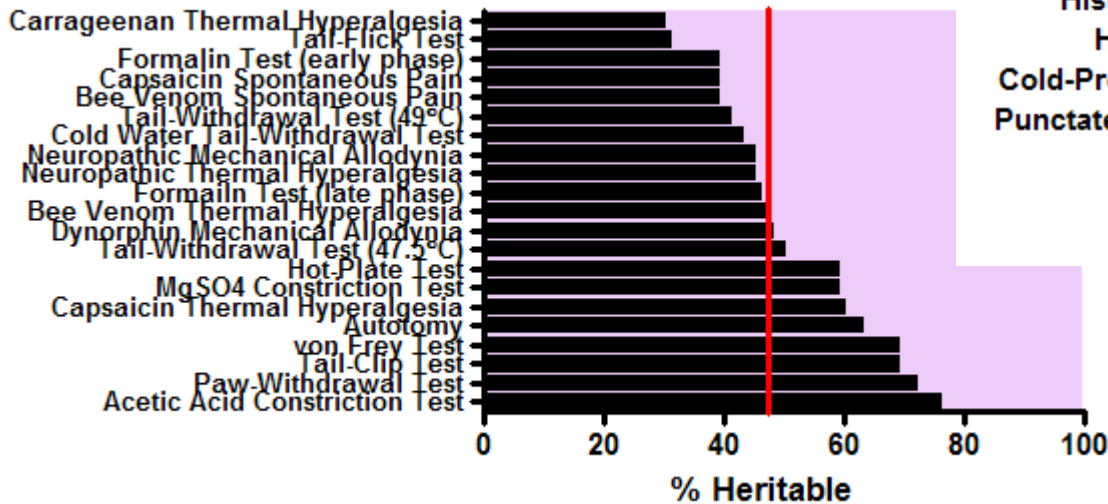
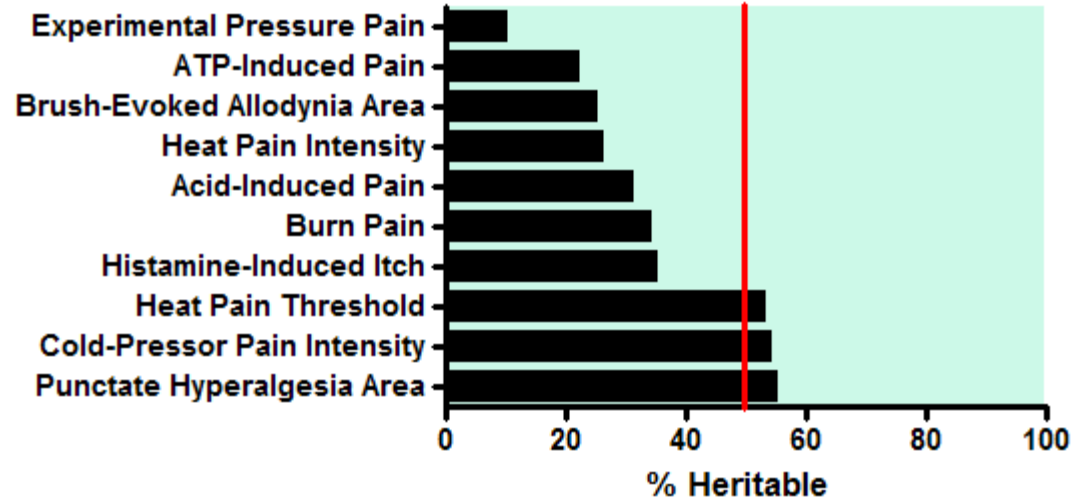
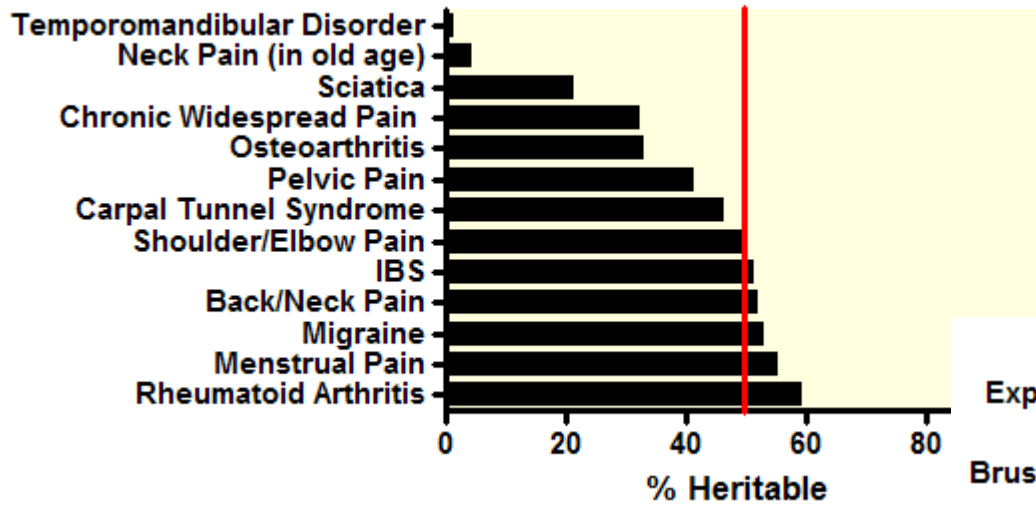


ENVIRONMENTAL VARIABILITY
("nurture")

“Heritability” of Pain-Related Traits



Heritability of Pain Traits



Three Modes of Translational Pain Genetics



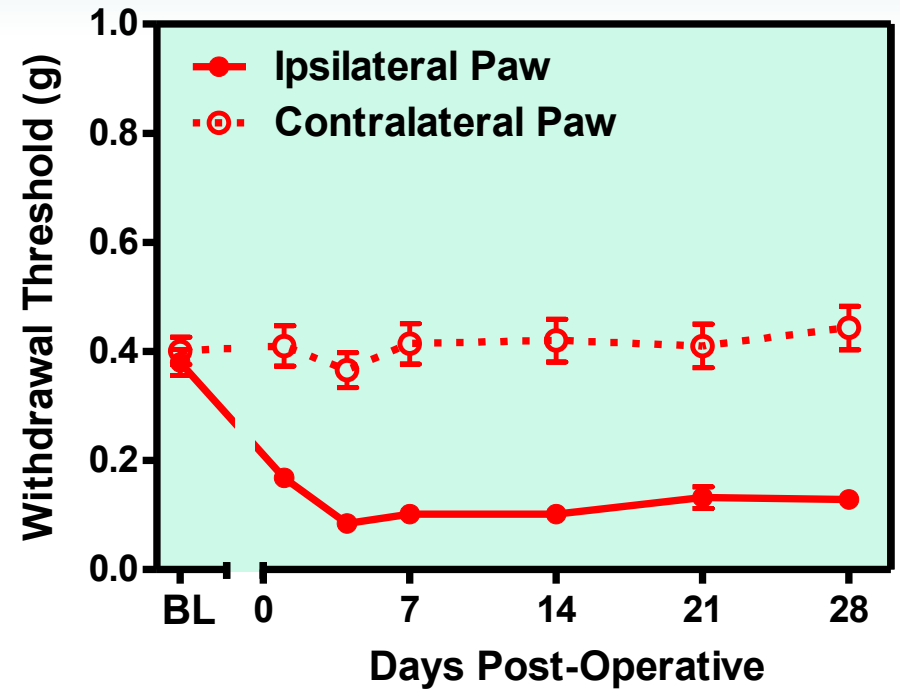
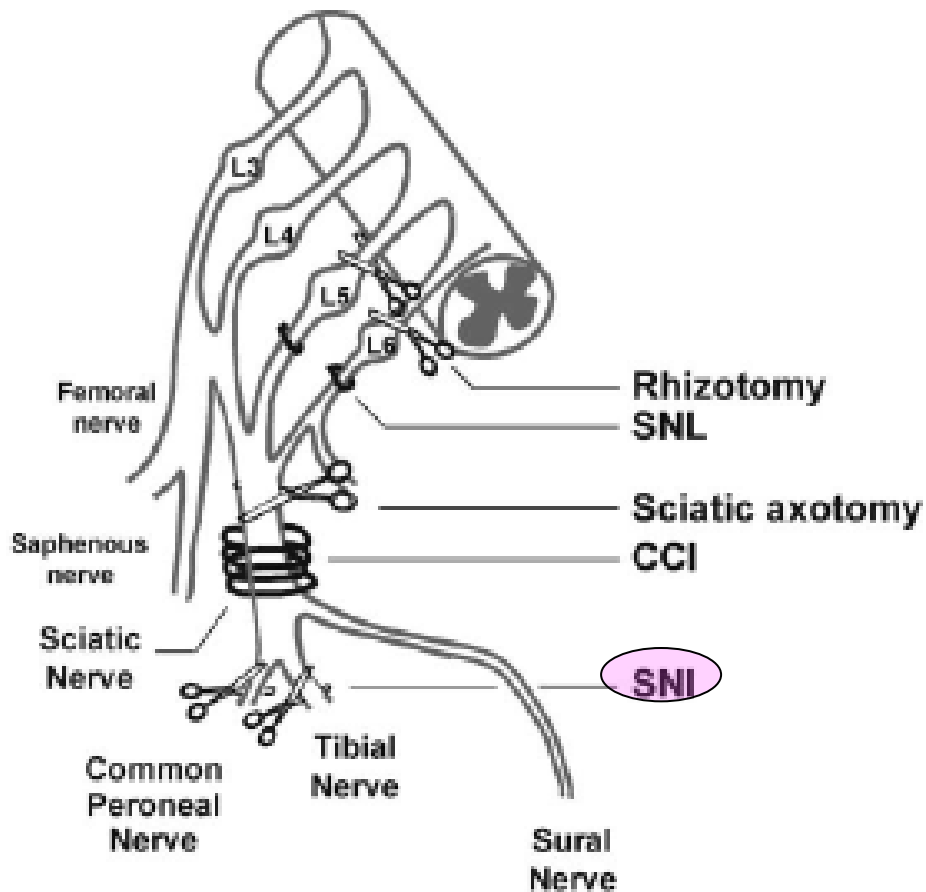
Three Modes of Translational Pain Genetics



***P2RX7* and Pain**

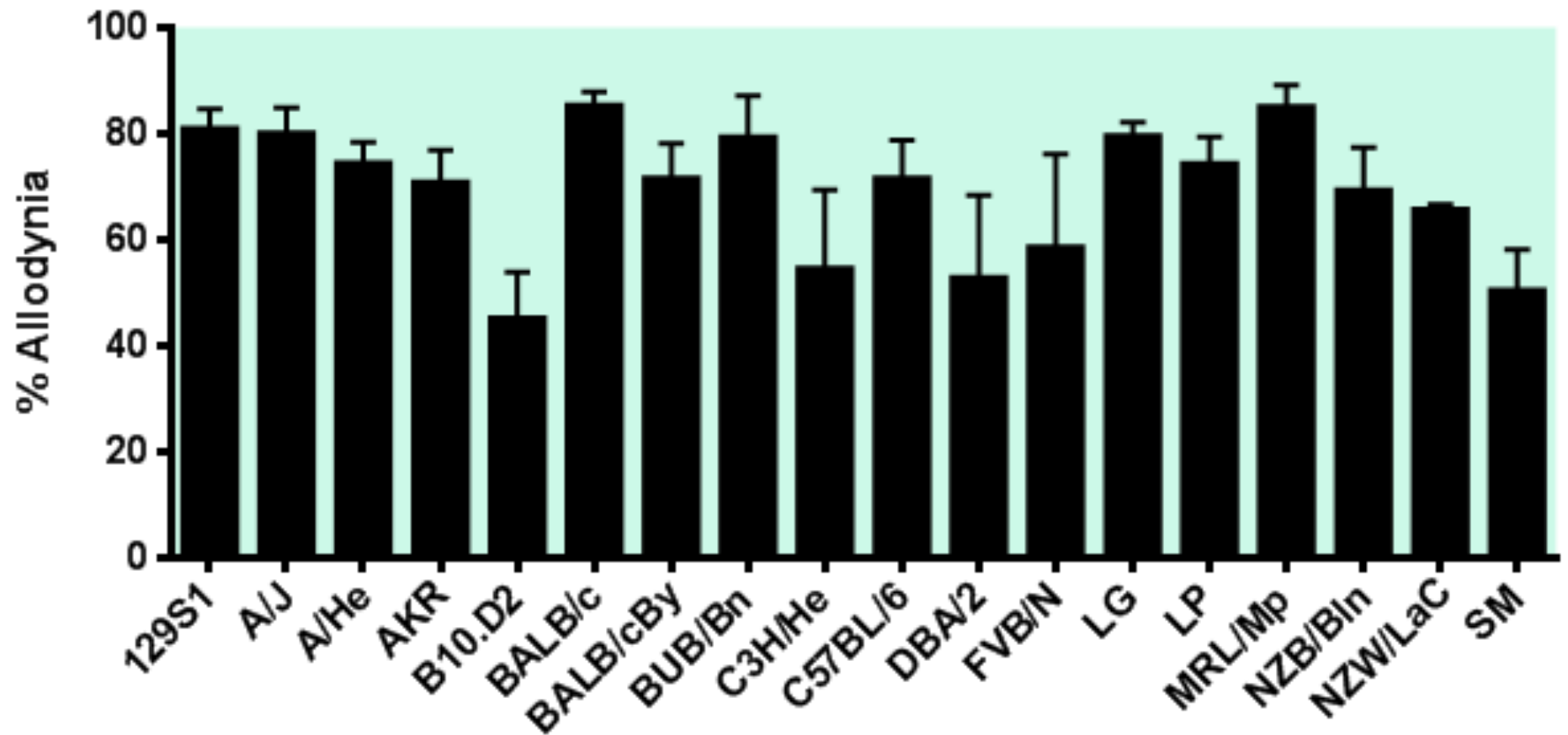


Haplotype Mapping of Mechanical Allodynia after Spared Nerve Injury



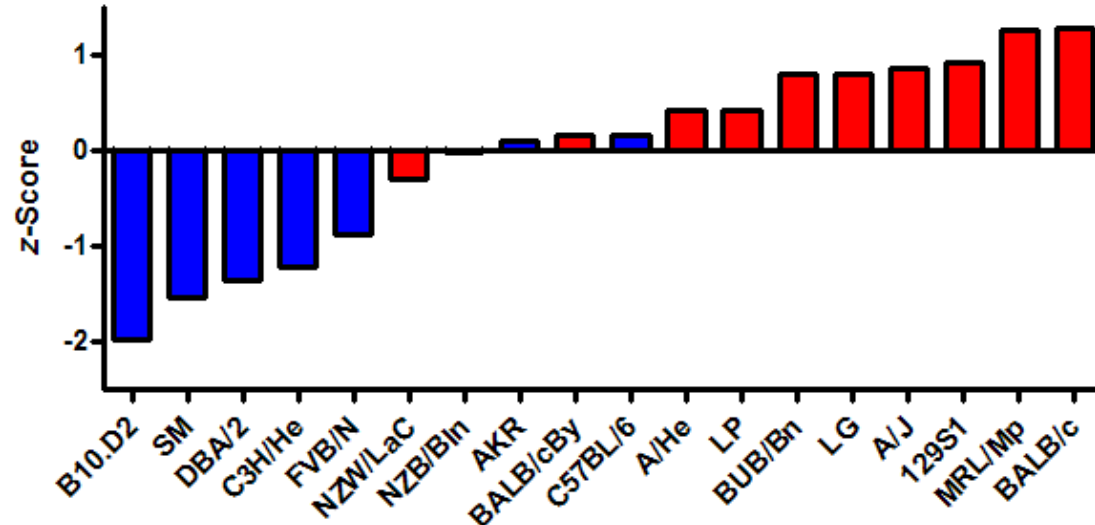
Sorge, Trang et al., *Nat. Med.*, 2012

Mechanical Allodynia in 18 Mouse Strains



Top 5 Haplotype Mapping Results

Gene	Chr.	Position	# SNPs	B10.D2	SM	D2	C3H	FVB	NZW	NZB	AKR	B/By	B6	A/He	LP	BUB	LG	A/J	129	MRL	B/c	Genetic Effect	ρ Value	
<i>P2rx7</i>	5	122.934	24	Blue	Blue	Blue	Blue	Blue	Red	Blue	Blue	Red	Blue	Red	Red	Red	Red	Red	Red	Red	Red	Red	0.49	0.00056
<i>Amtl</i>	7	112.997	114	Green	Blue	Blue	Blue	Green	Red	Red	Red	Red	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	0.52	0.0013
<i>Pttg1</i>	11	43.261	63	Green	Blue	Blue	Red	Red	Red	Red	Red	Red	Red	Red	Red	Blue	Red	Red	Red	Red	Red	Red	0.5	0.0019
<i>Kcnk2</i>	1	191.044	7	Blue	Blue	Blue	Red	Red	Red	Red	Red	Red	Blue	Red	Red	Red	Red	Red	Red	Red	Red	Red	0.41	0.0021
<i>Cln4-2</i>	7	6.610	44	Blue	Blue	Blue	Blue	Red	Red	Red	Green	Red	Blue	Red	Red	Red	Green	Red	Red	Red	Green	Red	0.53	0.0023

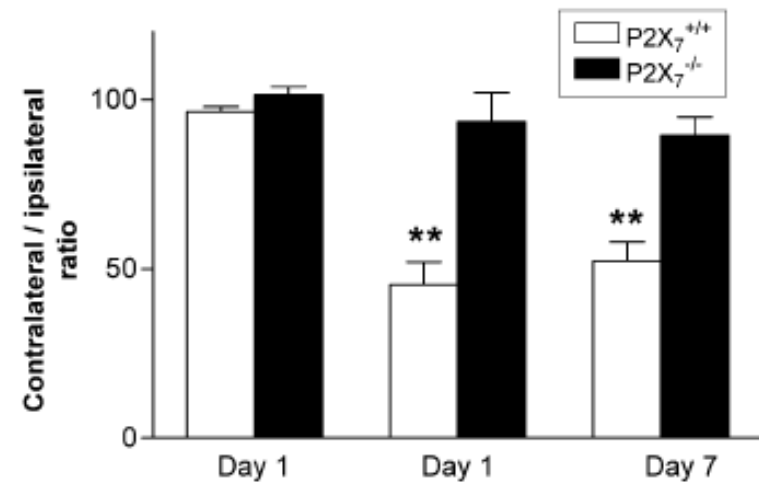
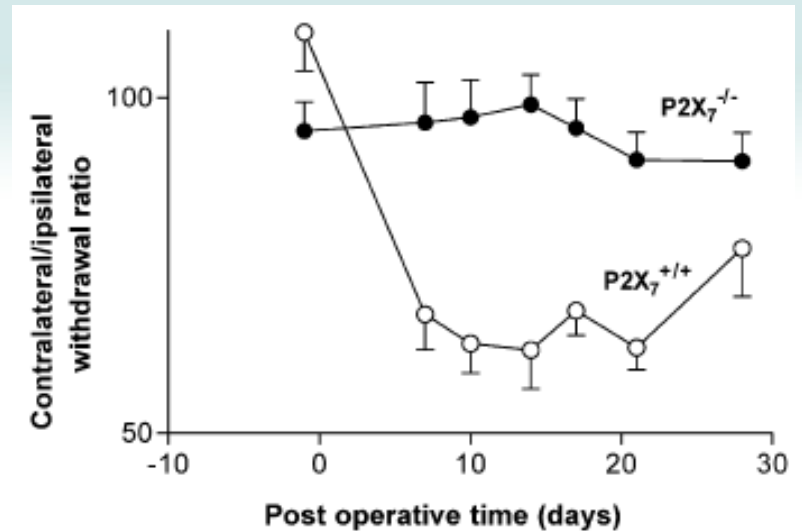
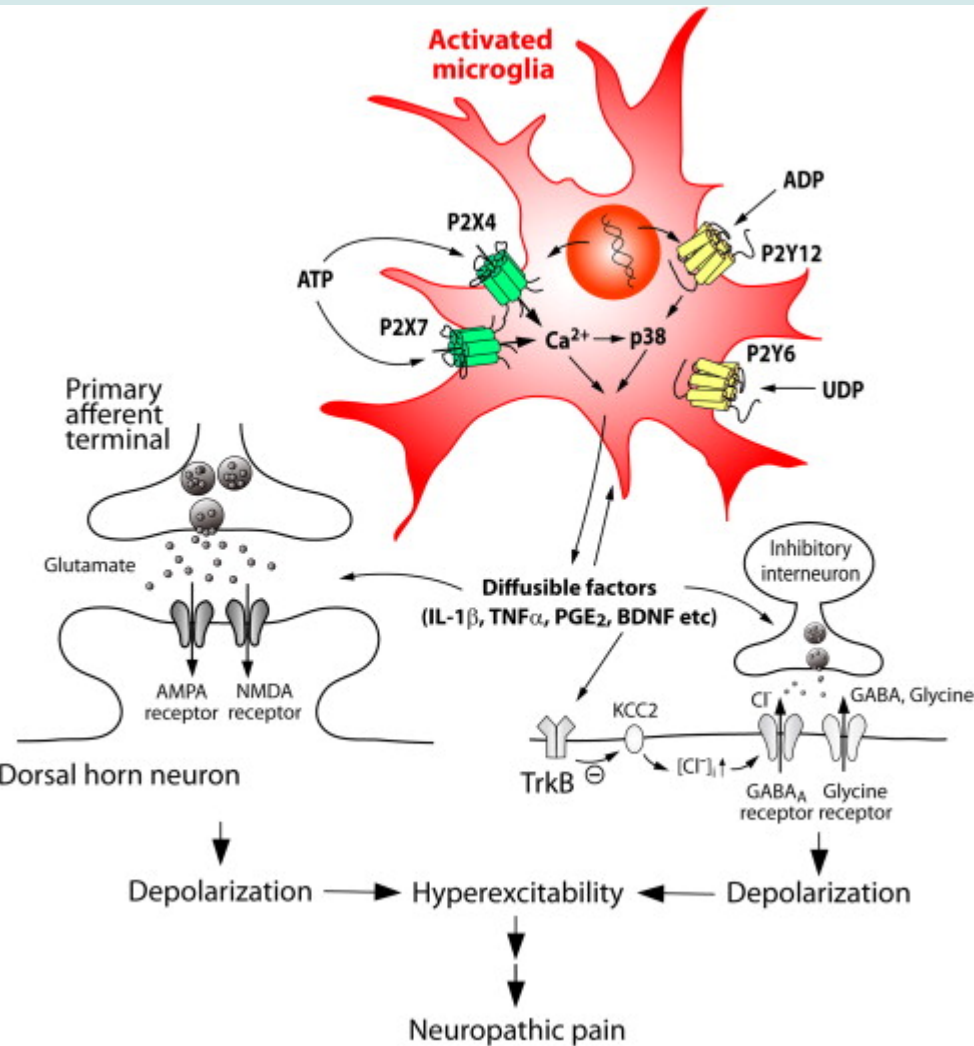


P2X7 and Pain

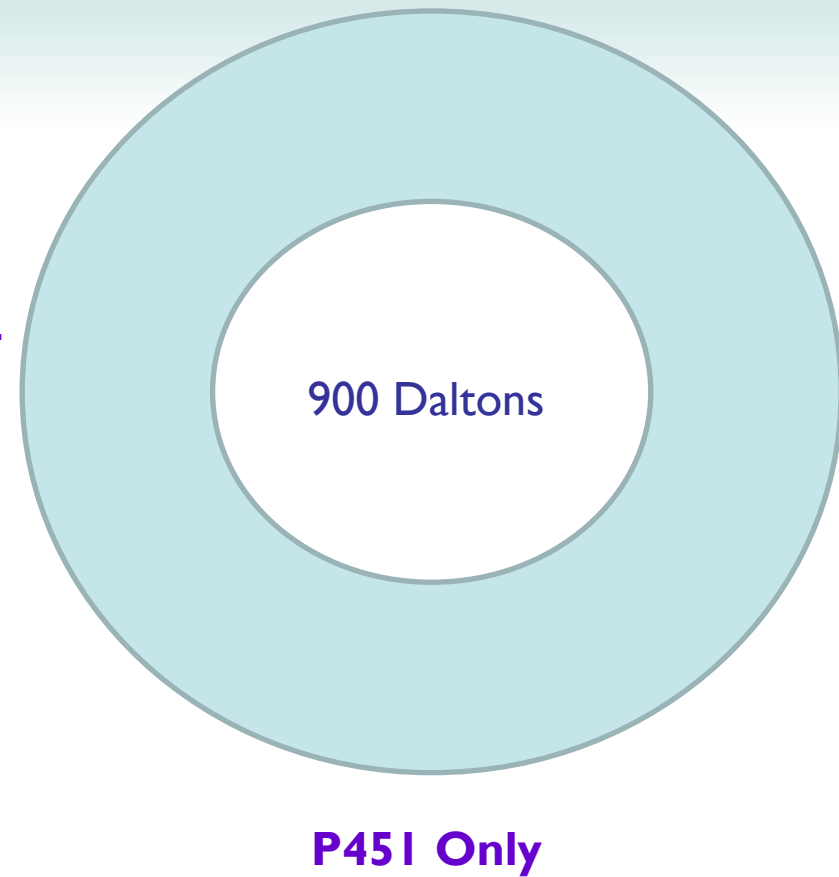
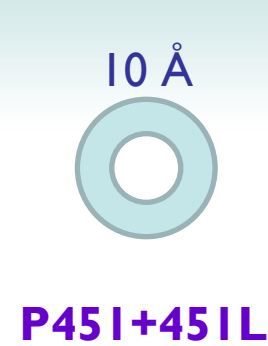
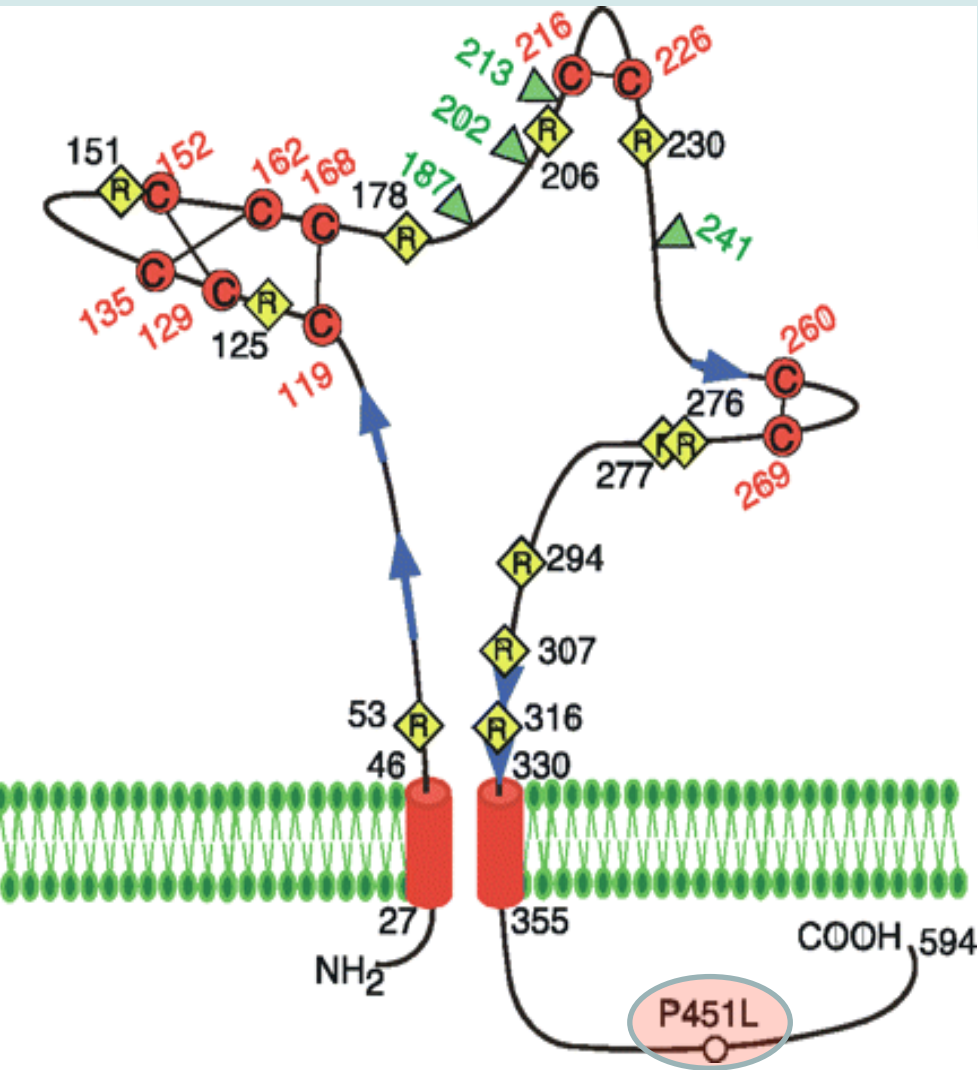
Pain 114 (2005) 386-396

Disruption of the P2X₇ purinoceptor gene abolishes chronic inflammatory and neuropathic pain

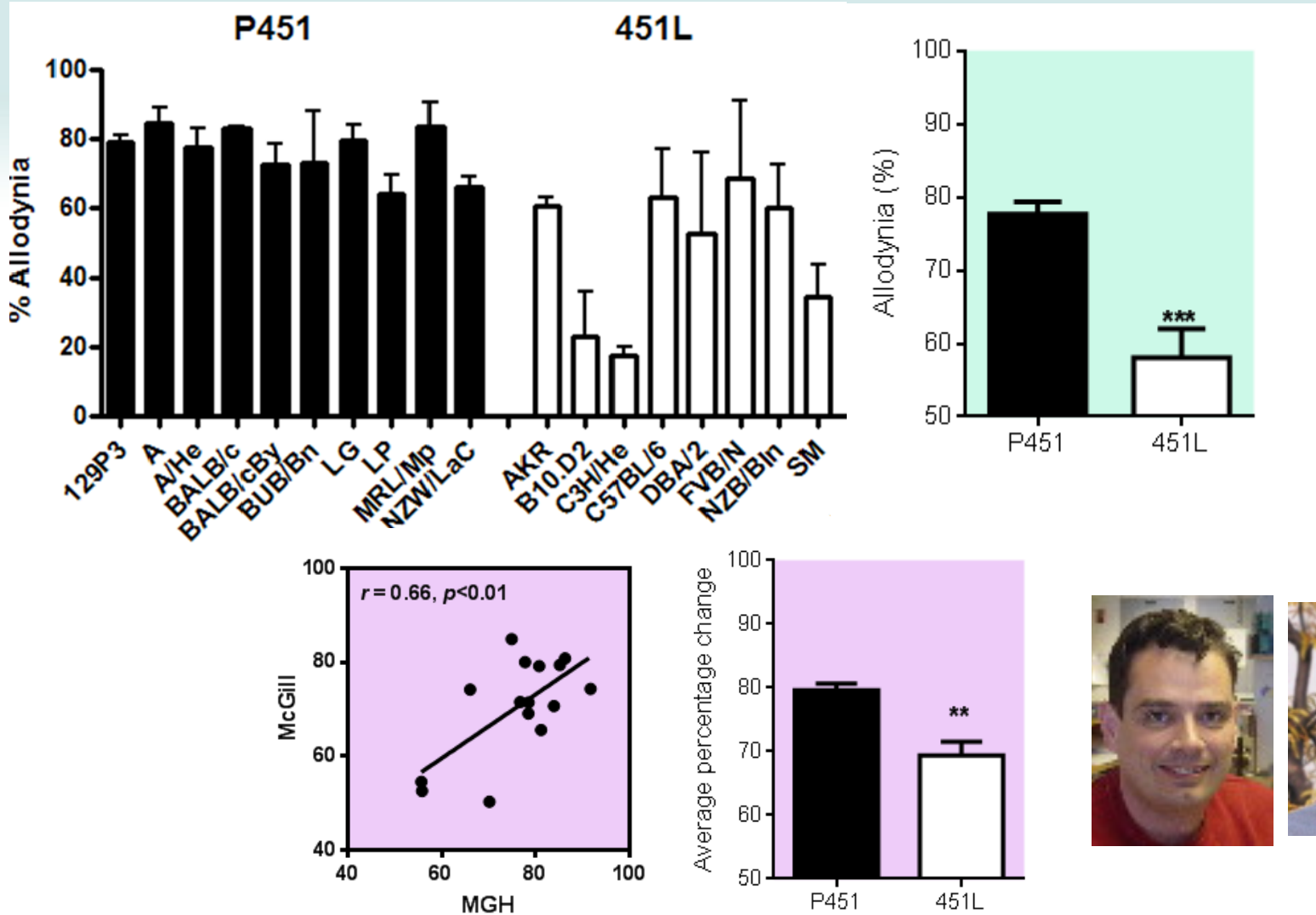
Iain P. Chessell^{a,*}, Jonathan P. Hatcher^a, Chas Bountra^a, Anton D. Michel^a, Jane P. Hughes^b



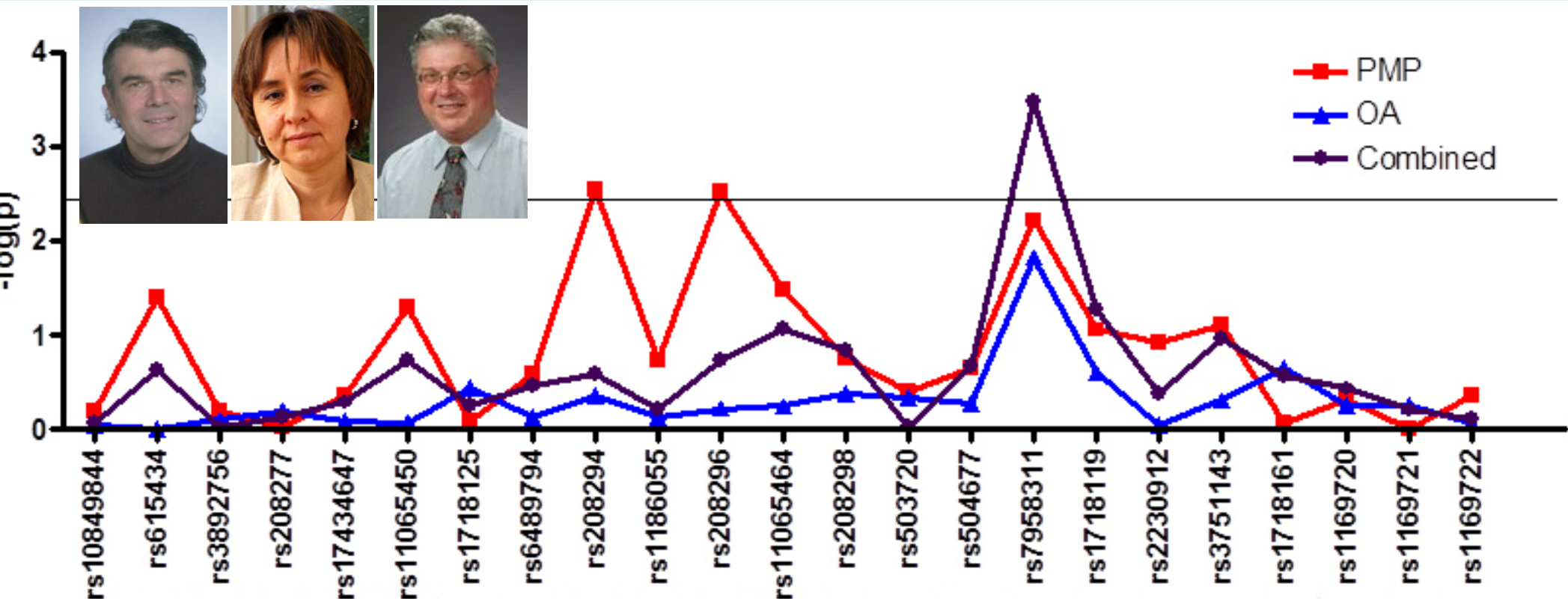
P451→L Genotype and the P2X7 “Pore”



Effect of P451 → L Variant



DNA Variants in *P2RX7* Affecting Pore Formation are Associated with Chronic Pain in Two Human Cohorts

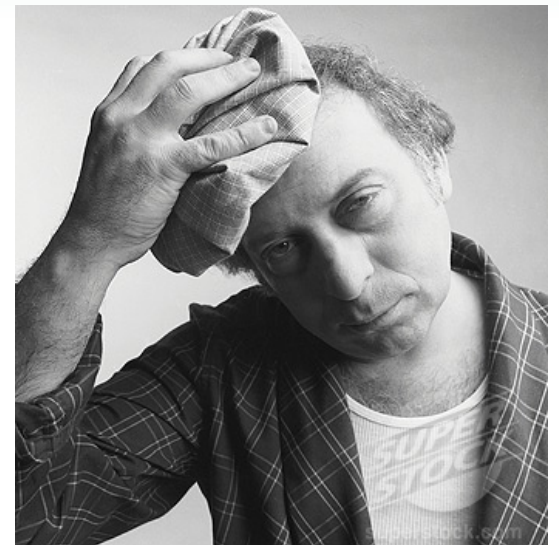


PMP = post-mastectomy pain
OA = osteoarthritis

Three Modes of Translational Pain Genetics

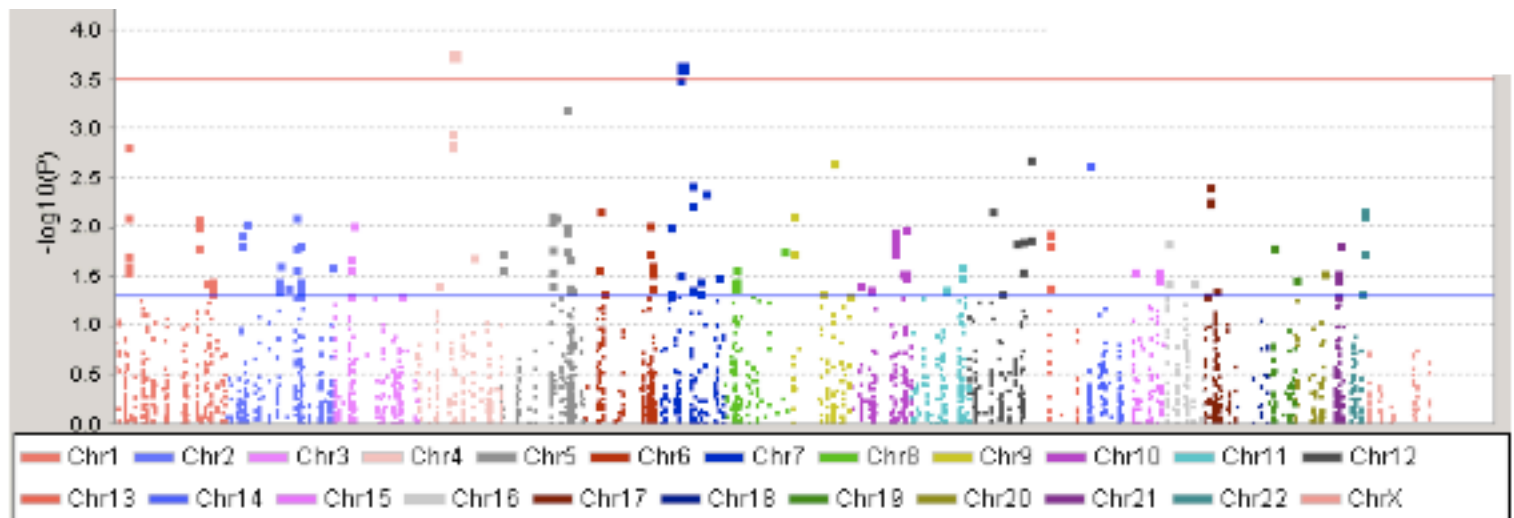


EREG/EGFR and Pain

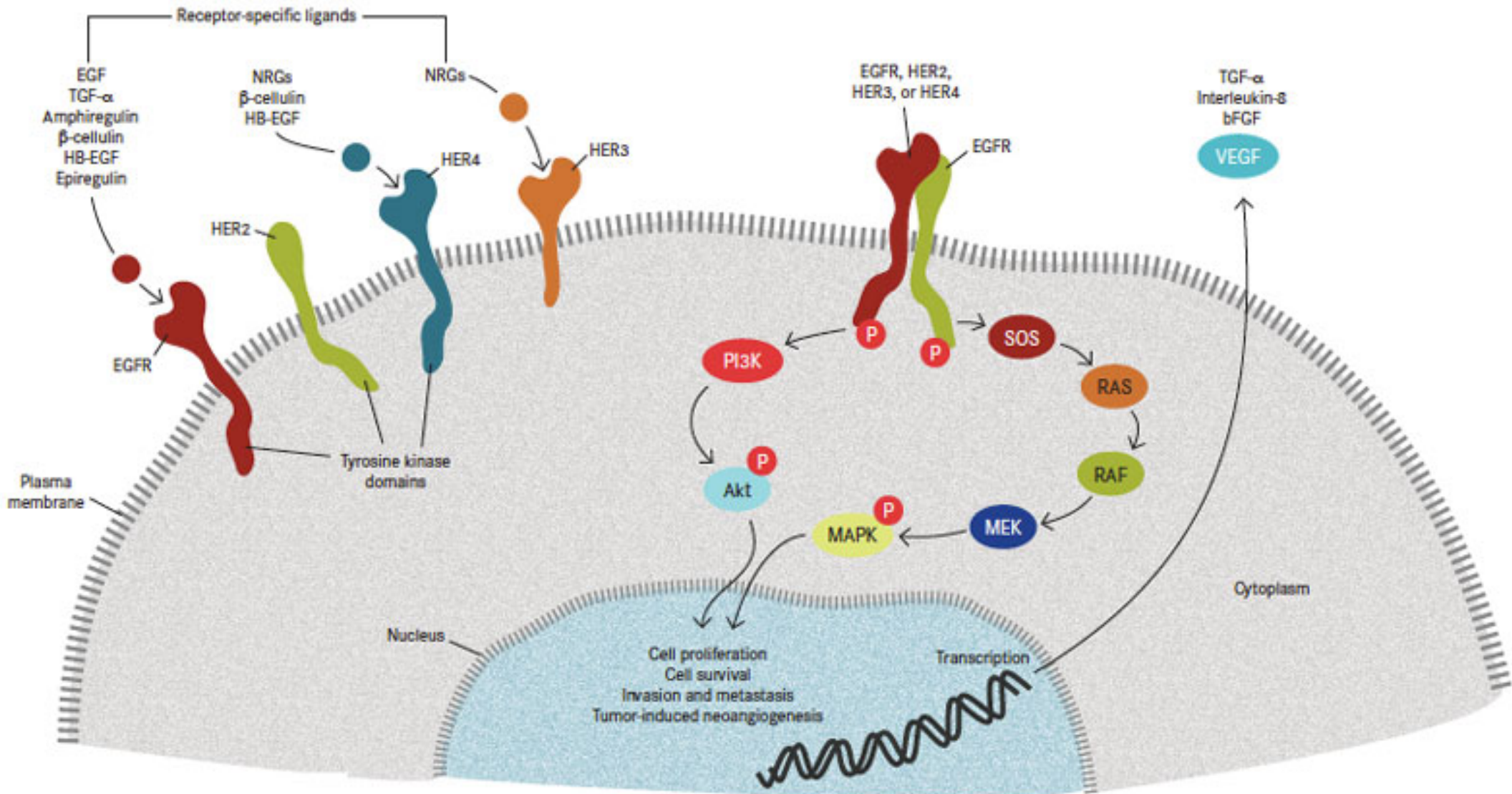


The OPPERA Study of Temporomandibular Disorder

CHR	SNP	GENE	Call Rate	MAF (W)	MAF (B)	OR	P
4	rs1563826	EREG	100.00%	0.21	0.51	0.41	0.00017
7	rs1140475	EGFR	100.00%	0.12	0.08	2.63	0.00023
5	rs2963155	NR3C1	99.87%	0.22	0.24	0.47	0.00063



Epiregulin (EREG) and EGFR



REDACTED

REDACTED

REDACTED

REDACTED

Three Modes of Translational Pain Genetics

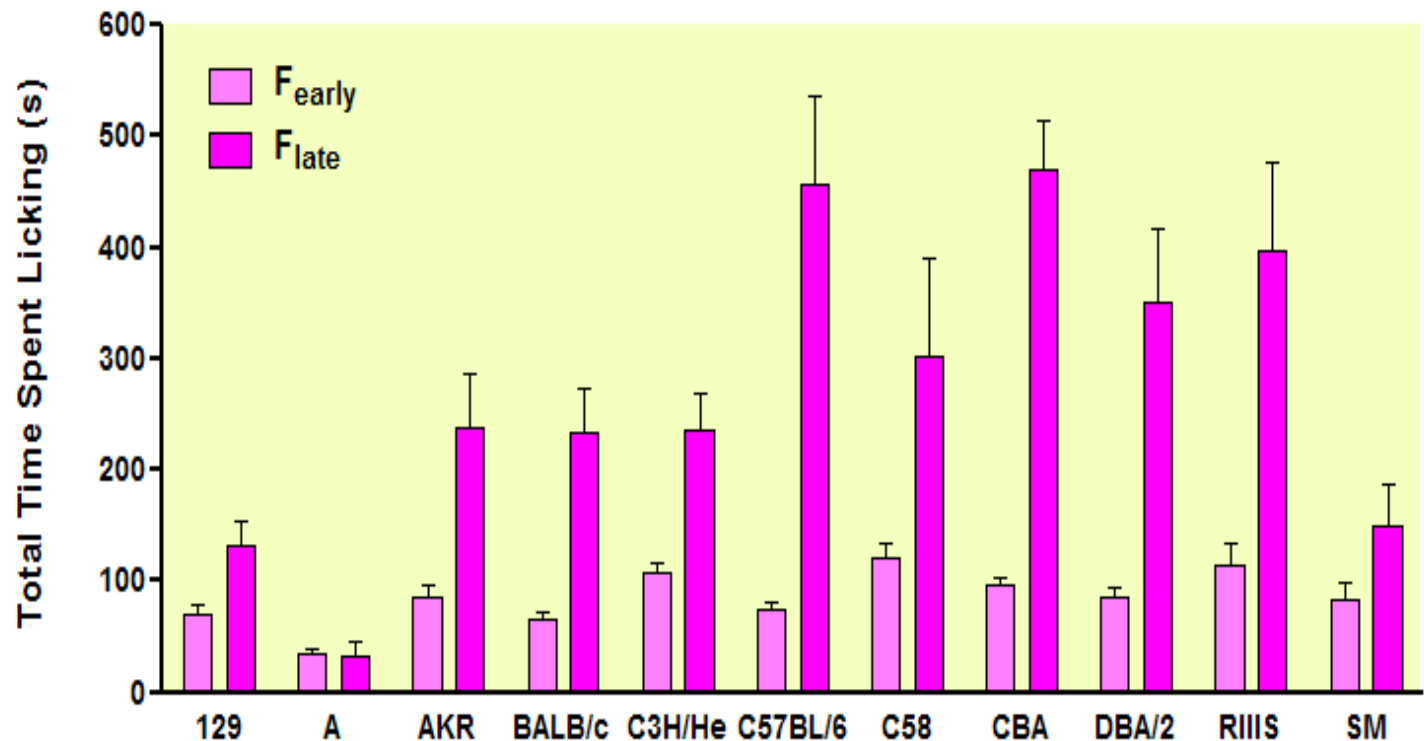
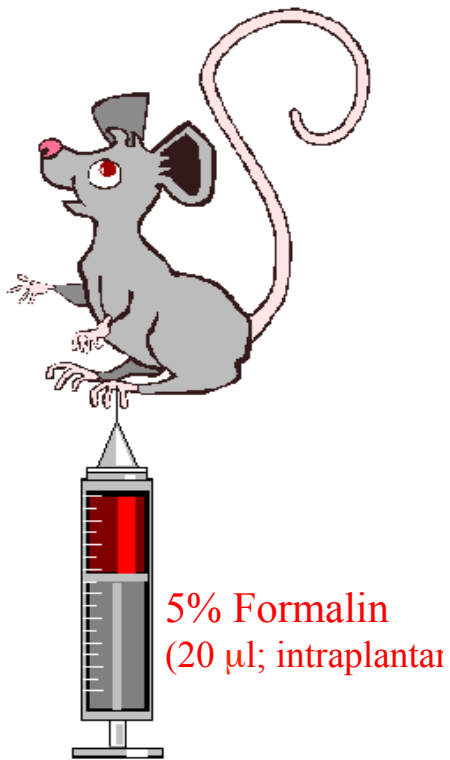


AVPR1A and Pain



Mapping a Formalin Test Gene

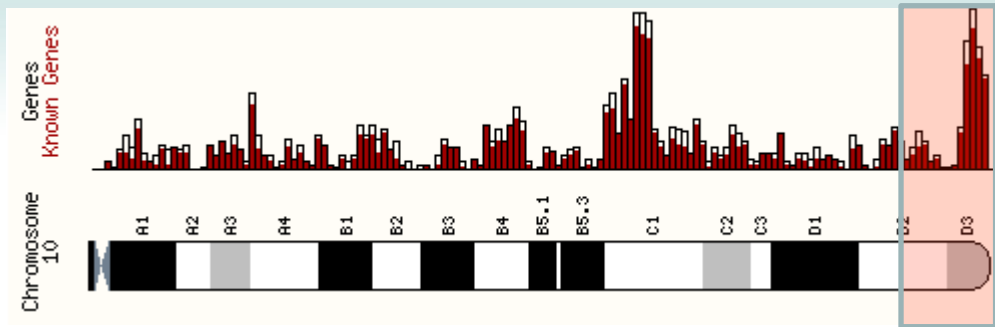
Step I. Contrasting formalin test phenotype between A/J and C57BL/6J (B6) strains.



Mogil et al., *Pain*, 1998

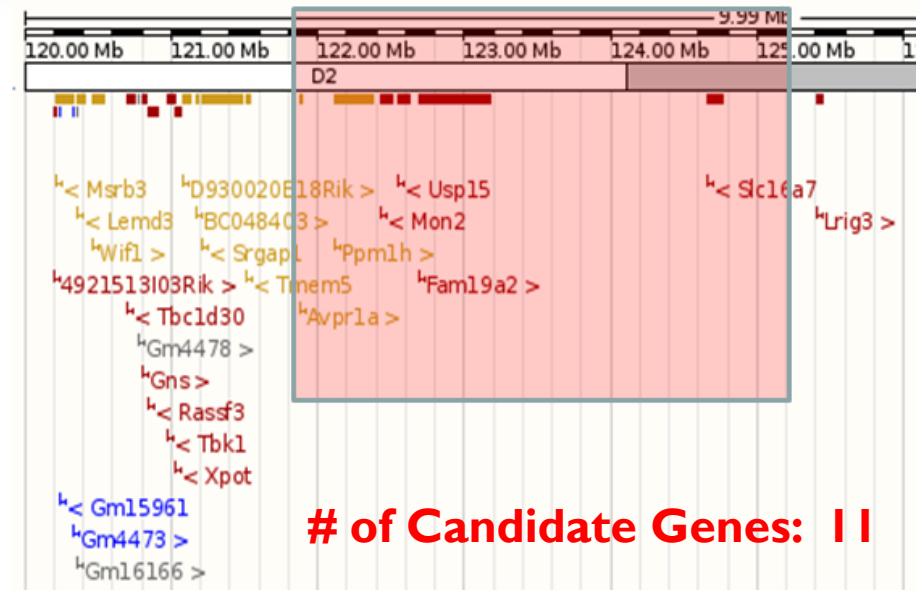
Mapping a Formalin Test Gene cont...

Step 2. (AxB6)_{F2} hybrid cross reveals linkage to a 19-Mb region of mouse chromosome 10.



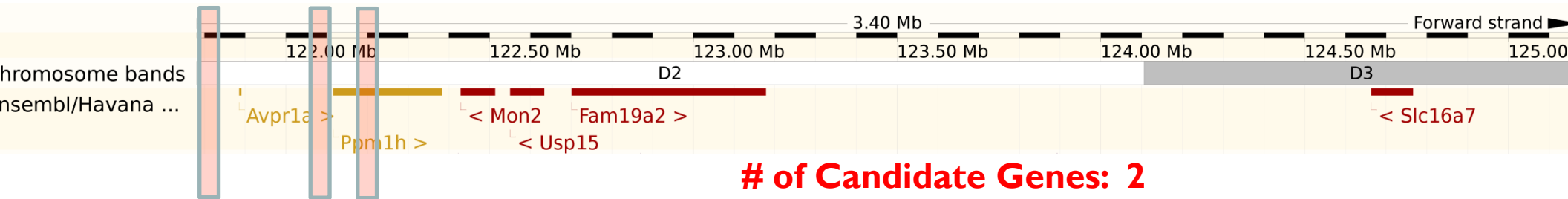
of Candidate Genes: 285

Step 3. Testing of AcB/BcA recombinant congenic strains and subcongenic strains derived from them localizes the gene to a 3.4-Mb region.



of Candidate Genes: 11

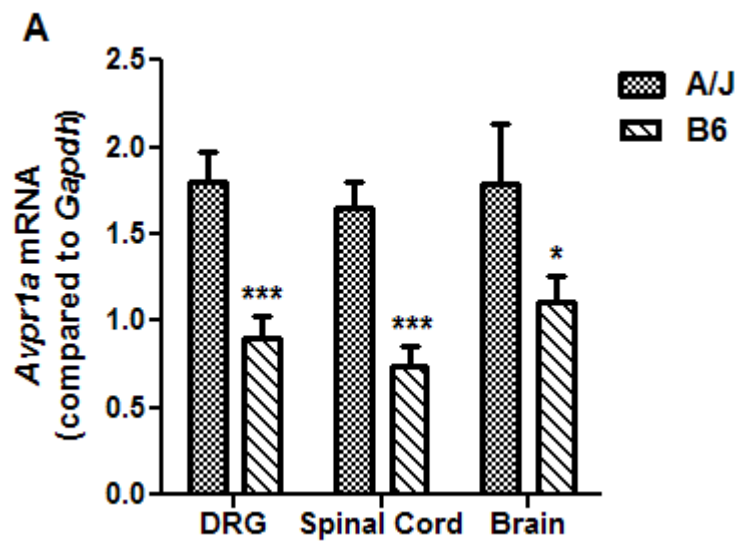
Step 4. Haplotype mapping using 16 inbred mouse strains localizes the gene to a 500-kb region.



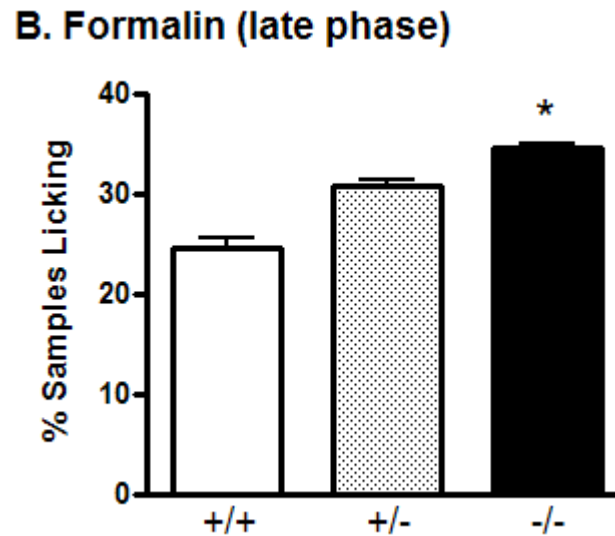
of Candidate Genes: 2

The Gene is *Avpr1a* (Vasopressin-1A Receptor)

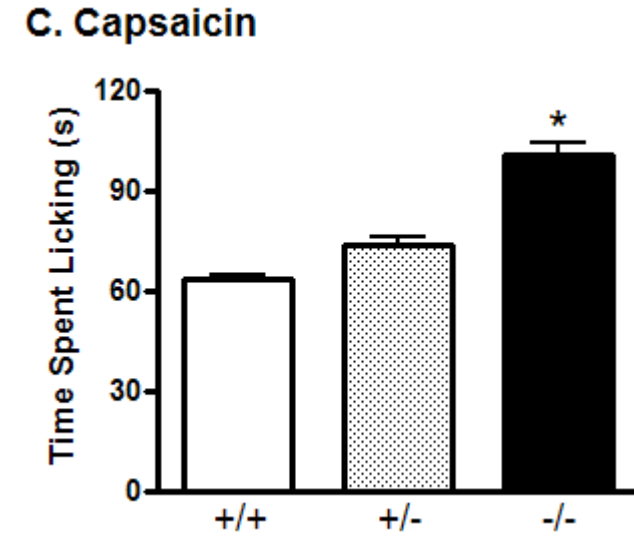
Strain-Dependent mRNA Expression



Knockout Mouse Phenotype

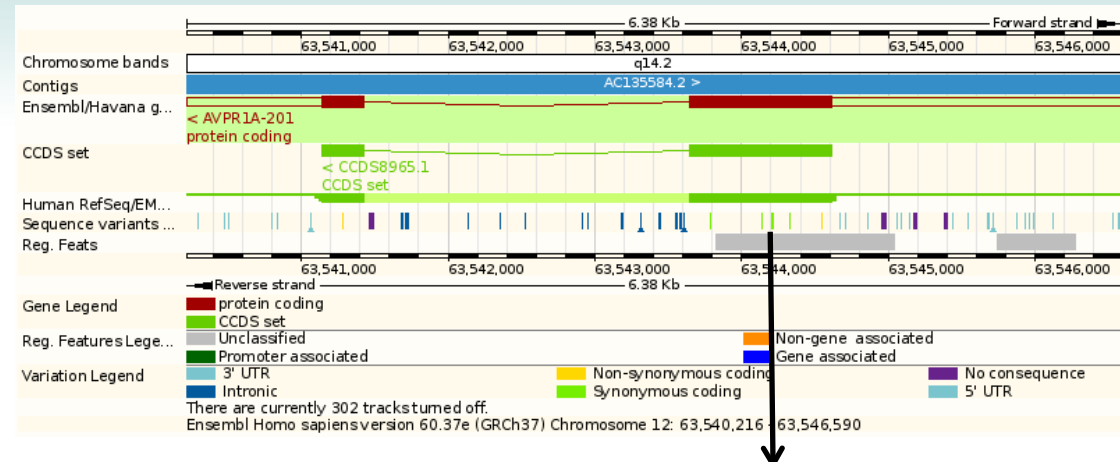


Generalizes to...



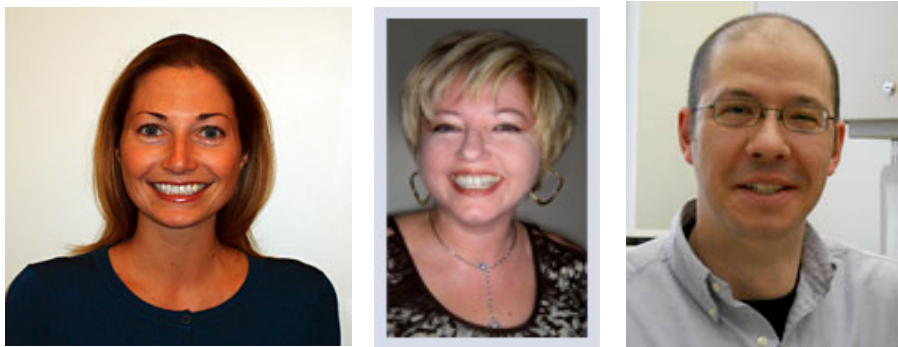
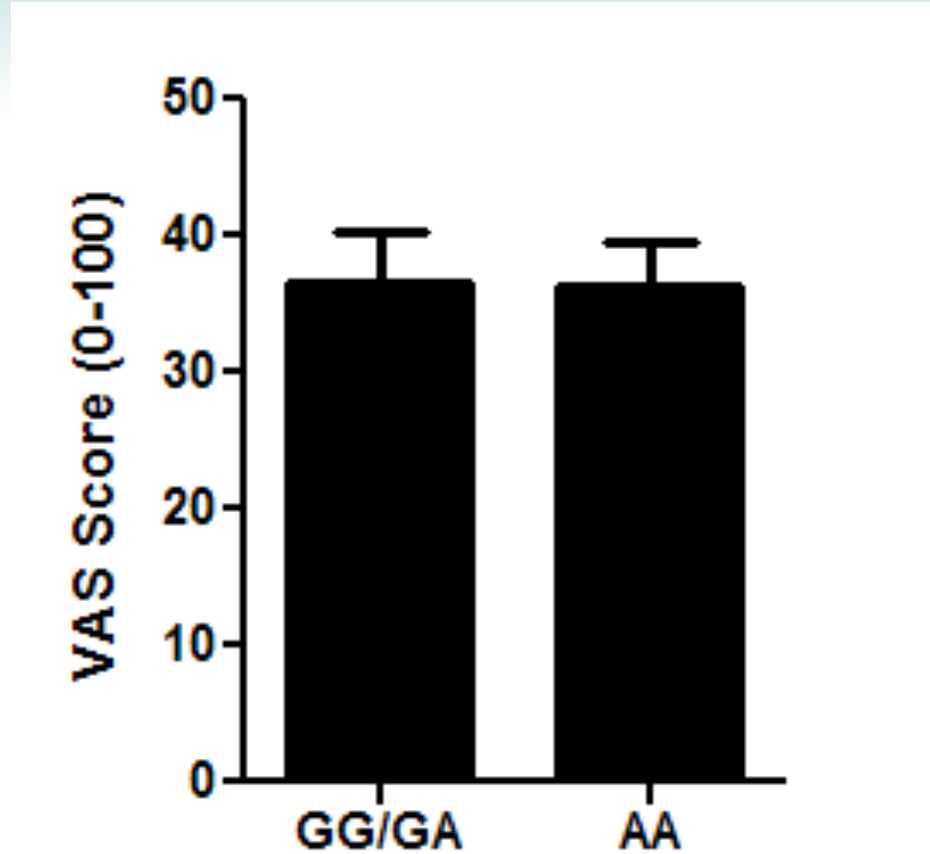
Mogil et al., *Nat. Neurosci.*, 2011

Association of *AVPR1A* Genotype to Capsaicin Pain in Humans



rs1077969

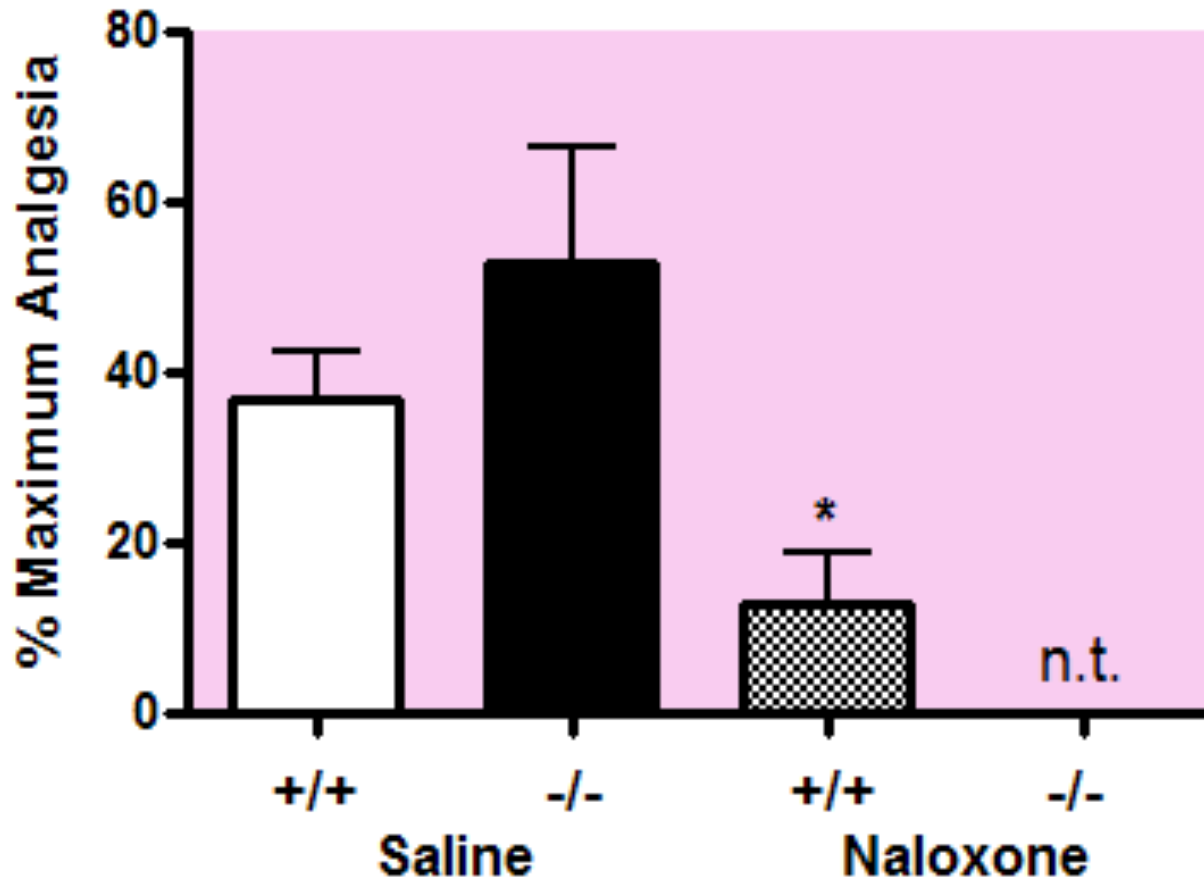
...AGGCCGACGCGAACATGCCGA...
A



**Life
Is
Complicated**



Male Vasopressin-1A Knockouts Can Not Engage Opioid Stress-Induced Analgesia



3-min forced swimming in 32°C water

Translational Genetics *Can* Work

MIT WORKS

There are Caveats...

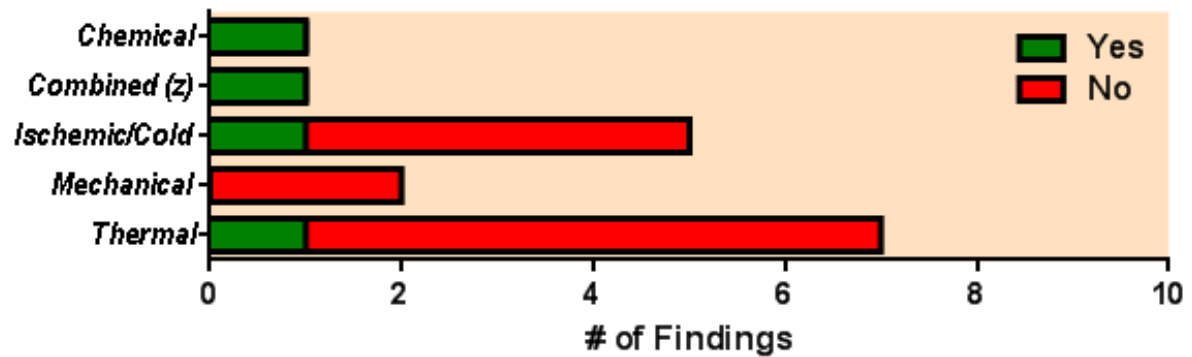
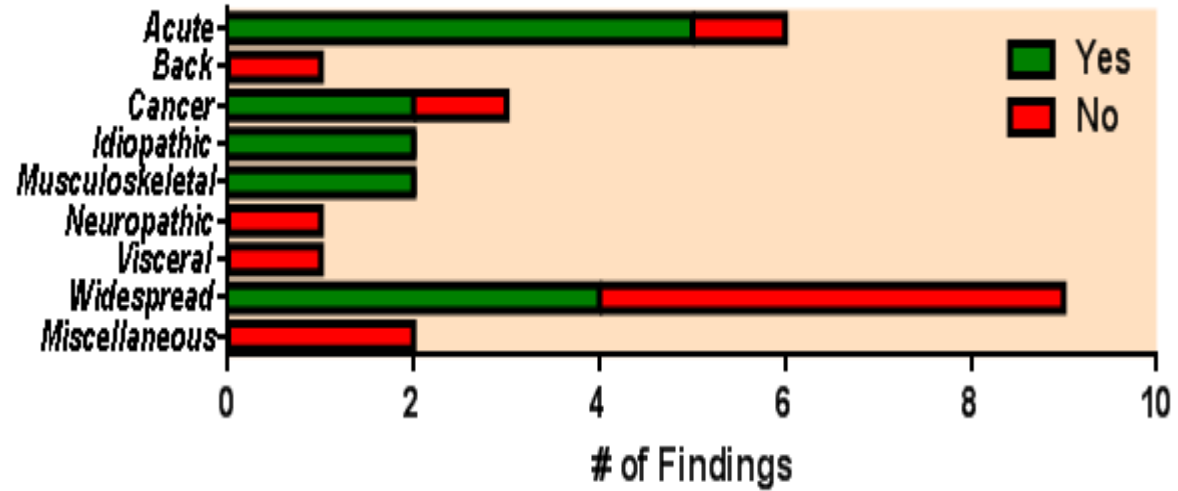
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U

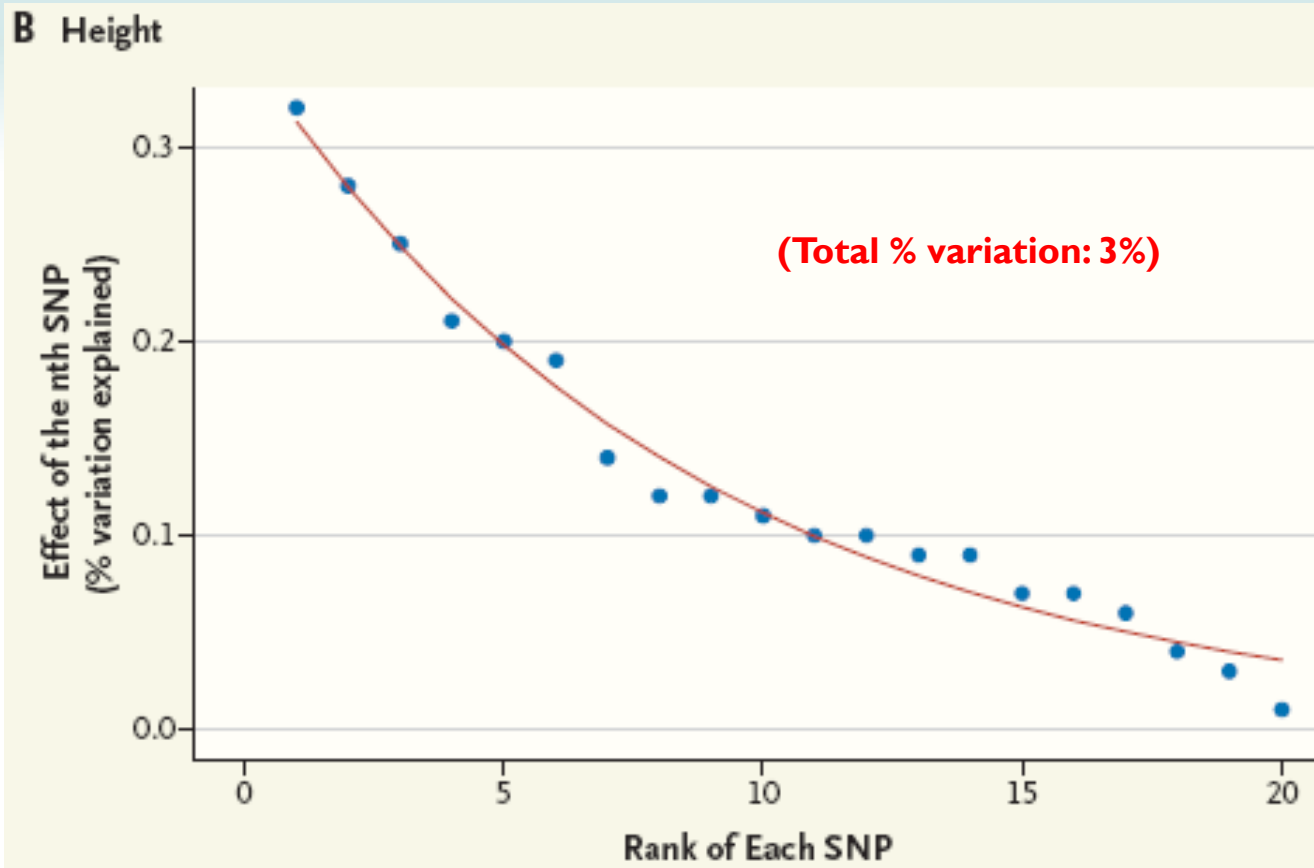
T

Poor Replicability

COMT



Limited Variance Explained



The File Drawer Problem



Is there *anything* that can be done about this?

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, their small individual effect size, and complicating interactions suggest, however, that the process will take quite some time, and that incorporation of genetic data into pain treatment and/or clinical trials is premature
- the genetic technique nonetheless has considerable heuristic value, especially as a guide to and refinement of drug development efforts

Thanks to...

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