Genetic and Non-Genetic Risk Factors for Development of Chronic Pain

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Overview

- **Conceptual & methodological considerations**
- Non-genetic risk factors for chronic pain
- Genetic risk factors for chronic pain
- Conceptual model and future directions

What Kind of Chronic Pain?

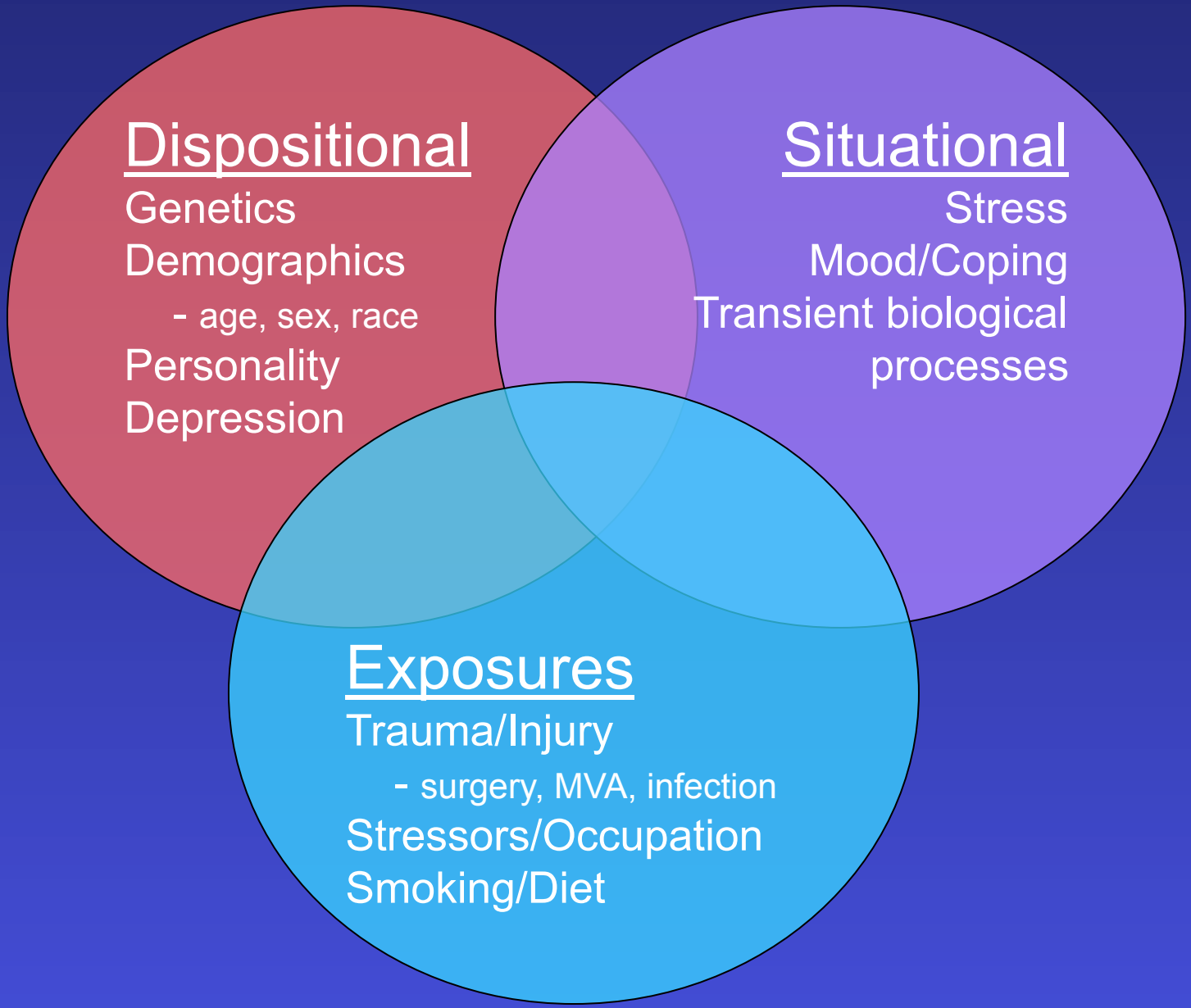
- Post-operative chronic pain
- Other iatrogenic chronic pain (chemotherapy-induced)
- Disease associated (e.g. PHN, DPN)
- Post-Traumatic
- Insidious

What Kind of Chronic Pain (part 2)?

- Neuropathic
- Musculoskeletal
- Visceral

(I'll use examples of Back Pain, CWP, TMD, post-surgical pain)

Types of Risk Factors



Methodologic Considerations

- Sample Sizes
  - Incidence rates, allele frequencies
- Base rate problems
  - Frequency of exposure/risk factor variables
  - Frequency of pain in general population
- Follow-up period
- Risk Factors: mechanisms or markers?

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"I'M THE ONE WITH THE MEDICAL DEGREE, I'LL DETERMINE IF YOUR BACK IS BOTHERING YOU, OR NOT..."

Psychological Factors and Risk for Low Back Pain (Linton, 2000)

1. Psychosocial variables associated with reported onset of back and neck pain and transition from acute to chronic pain disability. (Level A evidence)
2. Psychosocial variables generally have more impact than biomedical or biomechanical factors on back pain disability. (Level A)
3. Cognitive factors (attitudes, cognitive style, fear avoidance beliefs) (Level A)
4. Self-perceived poor health (Level A)
5. Depression, anxiety, negative emotions (Level A)
6. Personality and traits (Level C)
7. Sexual and/or physical abuse (Level D)
8. Psychosocial factors as risk factors for long-term pain and disability. (Level A)

Level A: evidence from two or more good-quality prospective studies
Level C: inconclusive data
Level D: no studies available meeting criteria

Occupational Factors and Risk for Low Back Pain (Linton, et al, 2001)

Factor	Evidence
Job Satisfaction	Strong Evidence (13/14 studies)
Monotonous Work	Strong Evidence (4/6 studies)
Work Relations	Strong Evidence (5/6 studies)
Perceived Demands	Strong Evidence (3/3 studies)
Control	Moderate Evidence (2/2)
Work Pace	Moderate Evidence (2/3)
Occupational Stress	Strong Evidence (3/3 studies)
Perceived Ability to Work	Strong Evidence (3/3 studies)
Belief that Work is Dangerous	Moderate Evidence (2/2)

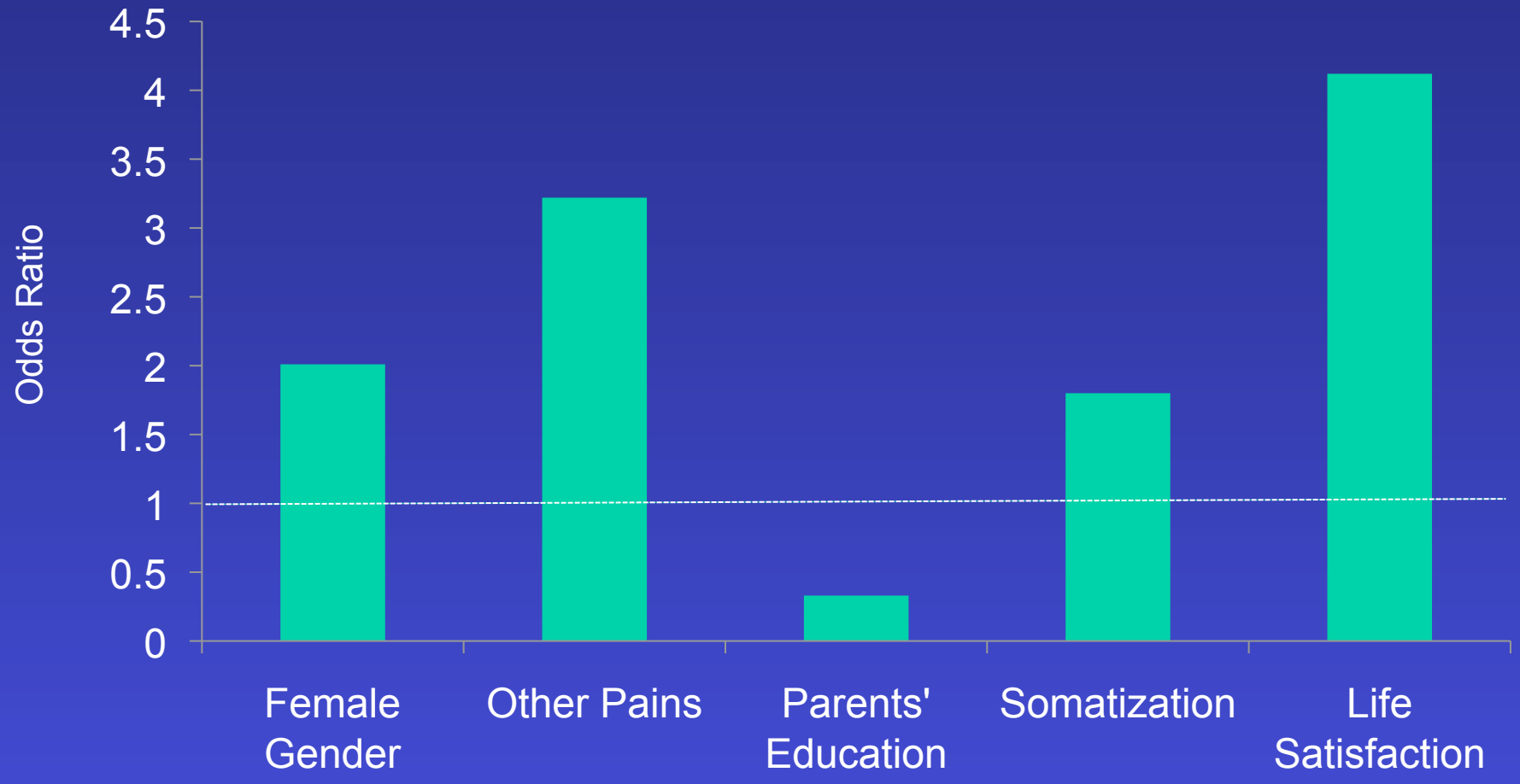
Spinal Mechanical Load and Risk for Low Back Pain (Bakker, et al, 2009)

Factor	Evidence
Heavy Physical Work	Conflicting Evidence
Standing/Walking at Work	Strong Evidence for no association
Sitting at Work	Strong Evidence for no association
Whole Body Vibration at Work	Conflicting Evidence
Bending/Twisting at Work	Conflicting Evidence
Nursing Tasks	Conflicting Evidence
Leisure Sport/Exercise	Strong Evidence for no association
Leisure Activities	Conflicting Evidence

Risk Factors for Chronic Widespread Pain

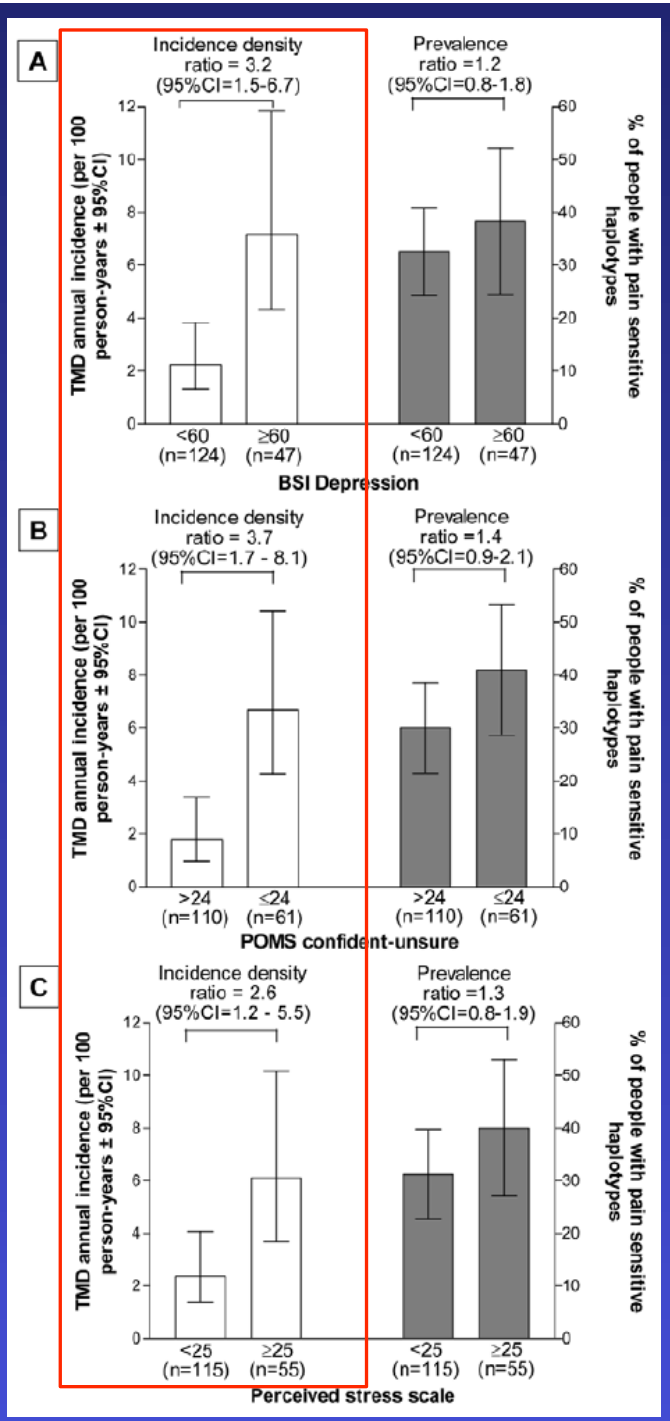
Category	Specific Risks	Reference
Demographics	Gender and older age (in kids) Gender (in adults) SES (mediated by psych factors)	Mikkelson, et al, 2008 Davies, et al, 2009 Davies, et al, 2009
Childhood Events	Financial difficulties Maternal death Institutional Care Multiple somatic symptoms	Jones, et al, 2007; 2009
HPA Axis Function	Low Morning Cortisol High Evening Cortisol High post-dex. cortisol	McBeth, et al, 2007
Psychological Distress	Depression	Mikkelson, et al, 2008; McBeth, et al, 2007
Pain Sensitivity	Tender Point Count (but not PPT)	Gupta, et al, 2007

Risk Factors for Temporomandibular Disorders in Adolescents (LeResche, et al, 2007)



Psychological Risk Factors for TMD
(Slade, et al, 2007)

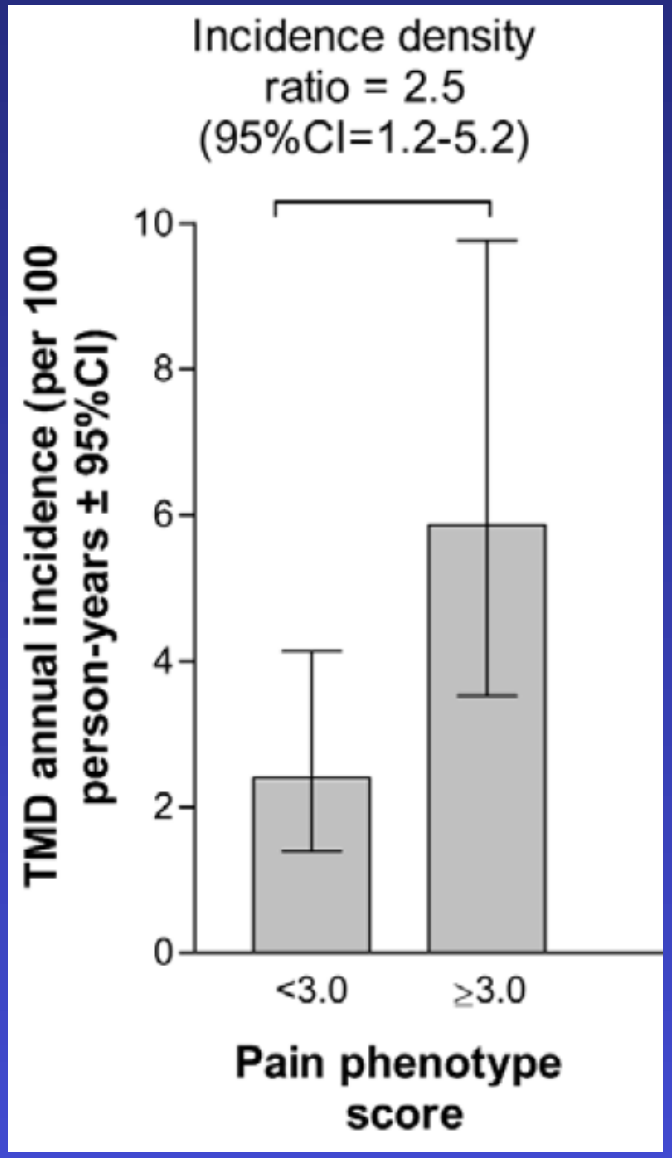
Individuals scoring in the upper tertile of depression (A) and somatization (C) and the lower tertile of confidence (B) showed significantly higher incidence of new onset TMD. This finding is independent of COMT haplotype.



Pain Sensitivity as a Risk Factor for TMD

(Slade, et al, 2007)

Individuals scoring in the upper tertile of pain sensitivity showed significantly higher incidence of new onset TMD. The pain phenotype score was a composite index of 13 different measures of pain sensitivity, across three stimulus modalities (heat, pressure, ischemic).



Chronic Post-Operative Pain
(Kehlet, Jensen, & Woolf, 2006)

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation[2]	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)[3]	20–30%	5–10%	479
Thoracotomy[4-7]	30–40%	10%	Unknown
Inguinal hernia repair[8-10]	10%	2–4%	609
Coronary artery bypass surgery[11-13]	30–50%	5–10%	598
Caesarean section[14]	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures*

Post-Thoracotomy Pain
(Pluijms, et al, 2006)

78 (52%) patients reported chronic pain after thoracotomy.

Retrospectively, a greater proportion of patients with chronic pain reported moderate to severe acute pain. Also, trend toward younger age in the pain group.

Table 2

Incidence of chronic post-thoracotomy pain (CPTP) as a function of the length of time post-surgery, expressed in 6 or 12 month intervals.

Years post-operatively	Patients with CPTP	%	Years post-operatively	Patients with CPTP	%
0.5–1.0	19/31	61	0.5–1.5	30/52	58
1.0–1.5	11/21	52			
1.5–2.0	10/26	38	1.5–2.5	30/55	55
2.0–2.5	20/29	69			
2.5–3.0	10/22	45	2.5–3.5	18/41	44
3.0–3.5	8/19	42			
Total	78/149	52	Total	78/149	52

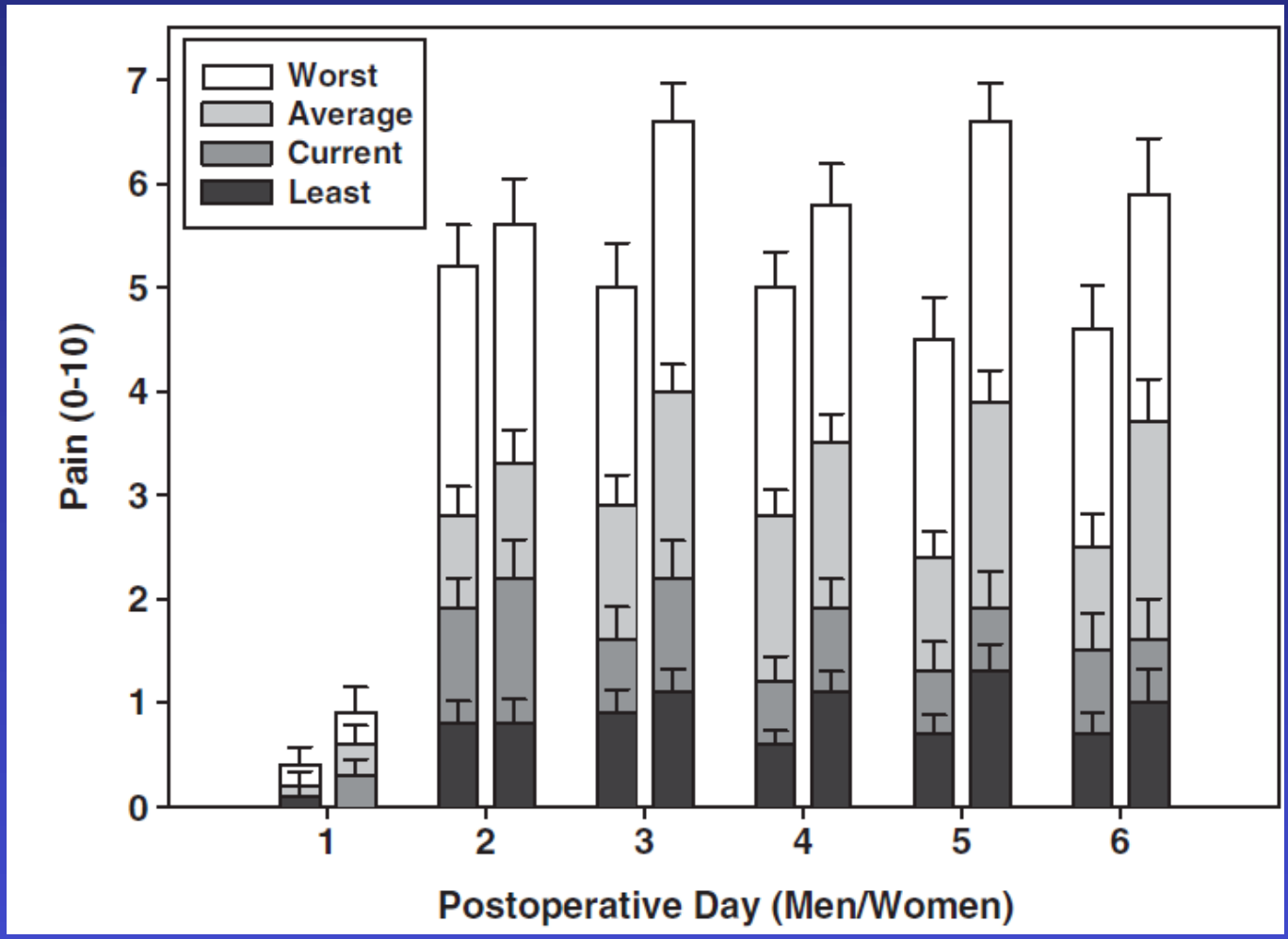
Table 3

Relationship between severity of acute post-operative pain and presence of chronic post-thoracotomy pain (CPTP).

	CPTP ($n = 78$)	No CPTP ($n = 71$)
No acute pain	12 (15%)	27 (38%)
Mild acute pain	13 (17%)	16 (23%)
Moderate acute pain	23 (29%)	16 (23%)
Severe acute pain	30 (38%)	12 (17%)

Gender and Post-Thoracotomy Pain

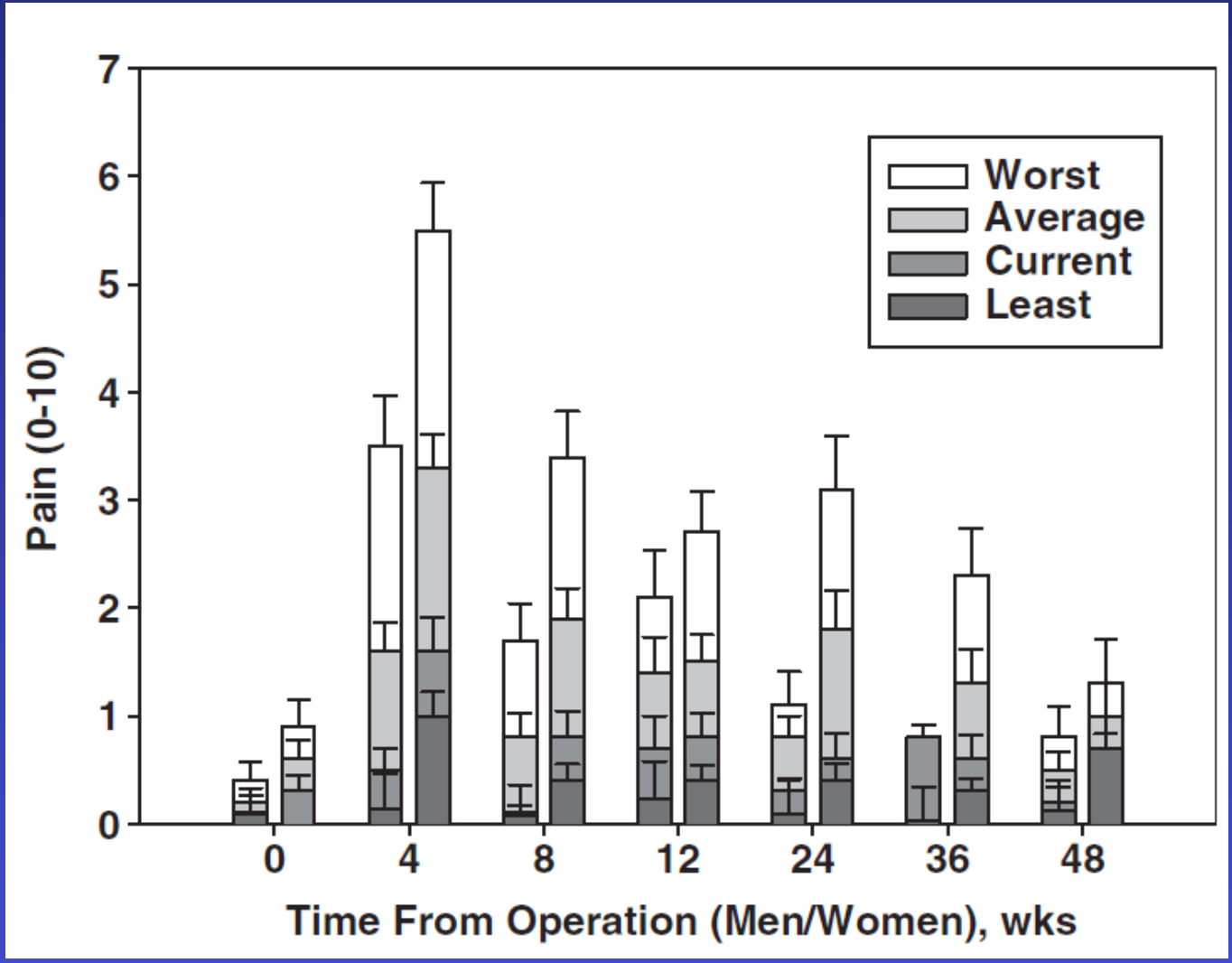
(Ochroch, et al, 2006)



Women (right bar) reported more acute pain than men (left bar)

Gender and Post-Thoracotomy Pain

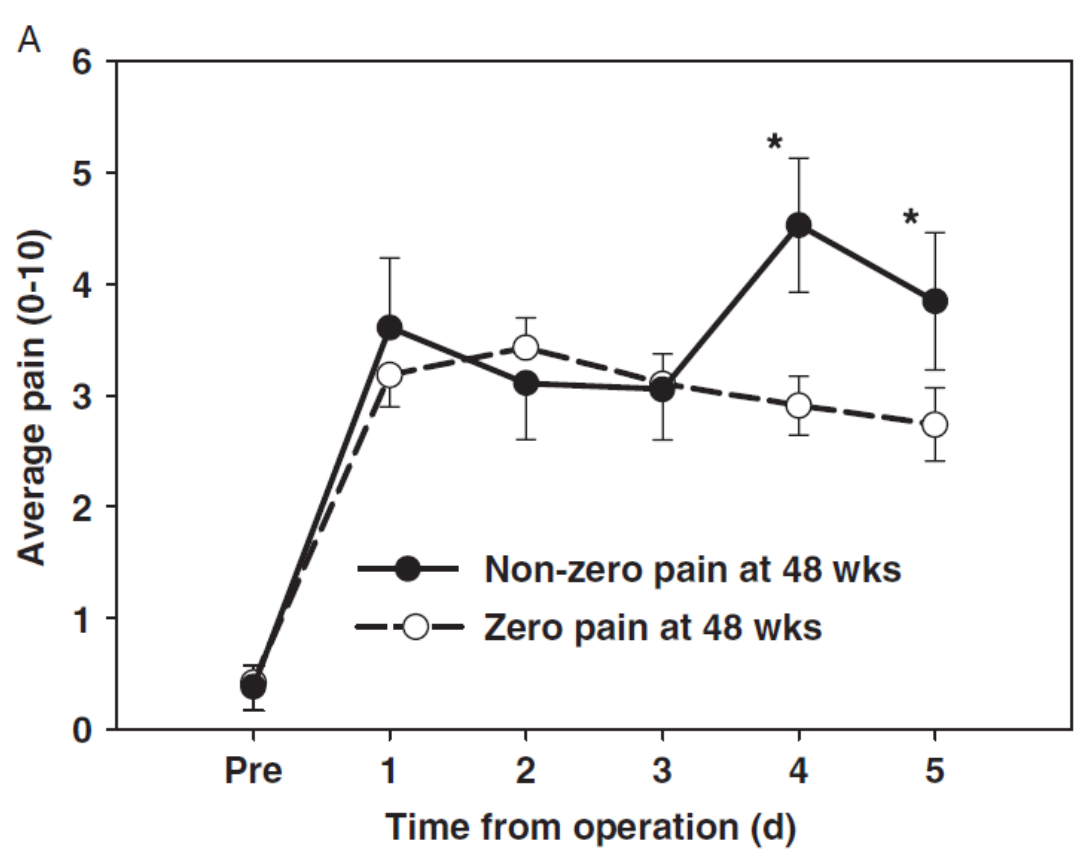
(Ochroch, et al, 2006)



Women (right bar) reported more long-term pain than men (left bar)

Acute Post-Op Pain in Patients Reporting Post-Thoracotomy Pain at 48 Weeks

(Gottschalk, et al, 2008)



Acute pain was greater post-op days 4 and 5 among patients who reported pain at 48 weeks. Also, patients with pain at 48 weeks were younger than those with no pain.

Reduced Endogenous Pain Modulation as a Risk Factor for Chronic Post-Thoracotomy Pain (Yarnitsky, et al, 2008)

DNIC predicted development of chronic pain (pain rating > 20) 7 months after thoracotomy

Table 3
Reduced model based on only DNIC and acute pain as predictors of chronic pain

Term	Chi-square	*p*	Odds ratio	OR lower 95% CI	OR upper 95% CI
Intercept	2.47	0.12			
DNIC	9.20	0.0024	0.52	0.33	0.77
Acute pain	9.20	0.0024	1.80	1.28	2.77

The odds ratios are based on changes of 10 U for both DNIC and acute pain, i.e., 10-point changes on scales ranging from −100 to 100 and 0 to 100, respectively.

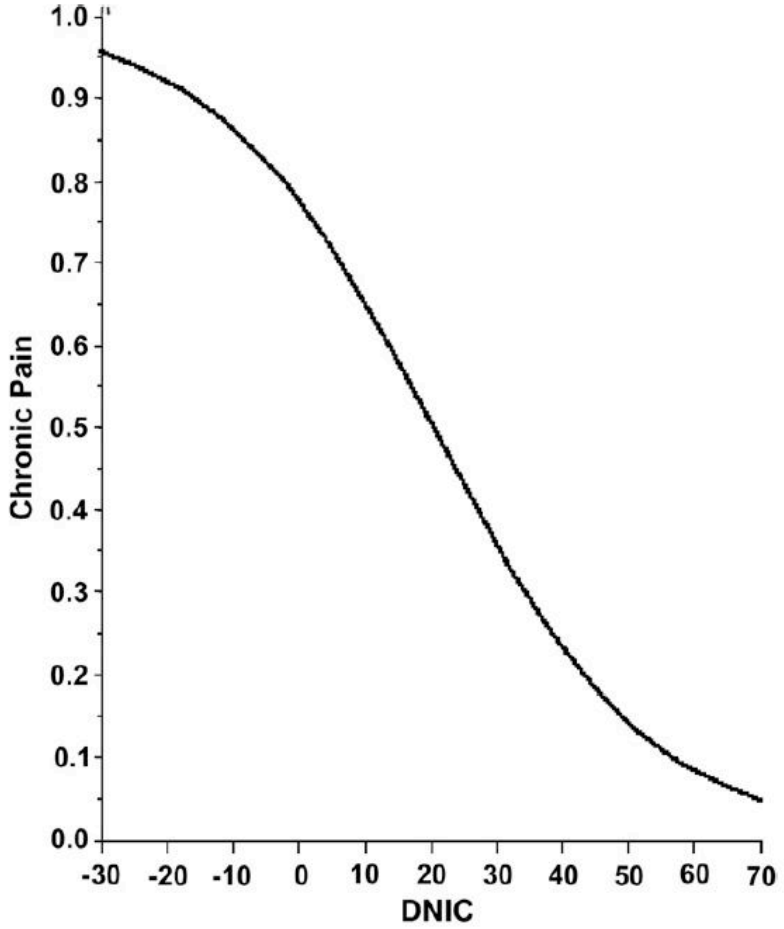


Fig. 2. Logistic regression probability plot relating DNIC to the probability of development of chronic pain.

Chronic Post-Mastectomy Pain

(Poleshuck, et al, 2006)

Table 3. Logistic Regression Model for Presence of Chronic Pain Following Breast Cancer Surgery (n = 93)

Risk Factor Variab	95% Confidence Interval
Age (yrs)	0.91–0.99
Breast cancer history	0.17–1.55
Preoperative breast pain	0.28–2.54
Surgery type	0.87–9.14
Cancer status	0.28–3.54
Radiation therapy	0.84–7.76
Marital status	0.68–5.55
Clinically meaningful acu	0.85–7.76

Table 4. Linear Regression Model for Intensity of Chronic Pain Following Breast Cancer Surgery (n = 93)

Risk Factor Variable	B	Standard Error	Beta*	P
Age (yrs)	.00	.01	.03	.79
Breast cancer history	−.44	.31	−.13	.17
Preoperative breast pain	.17	.33	.06	.60
Surgery type	.68	.34	.24	.047
Cancer status	−.16	.37	−.05	.67
Radiation therapy	.91	.32	.31	.005
Marital status	.22	.30	.07	.46
Clinically meaningful acute pain	.82	.29	.28	.007

48.4% women reported surgery-related pain at 3-month follow-up

Predictors of Chronic Postoperative Pain

(Hinrichs-Rocker, et al, 2008)

	Hernia	Thoracotomy	Cholecystectomy	Breast surgery	Spine surgery	Knee surgery	Other surgeries
# Studies	11	8	5	8	8	3	5
# Patients/study	44–5506	30–1348	100–186	93–569	17–257	77–860	22–848
Incidences of chronic pain (%)	9–46	20–57	13–26	17–52	30–70	13–23	16–49

Factor	Yes	No
Female Sex	5	18
Younger Age	17	18
Anxiety	5	6
Depression	**8**	**6**
Psychic Vulnerability (Neuroticism)	**4**	**1**
Stress	**3**	**1**
Late Return to Work	**3**	**0**

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- **Genetic risk factors for chronic pain**
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You have recessive jeans for plumbing.
DNA 101
search ID: dre0653
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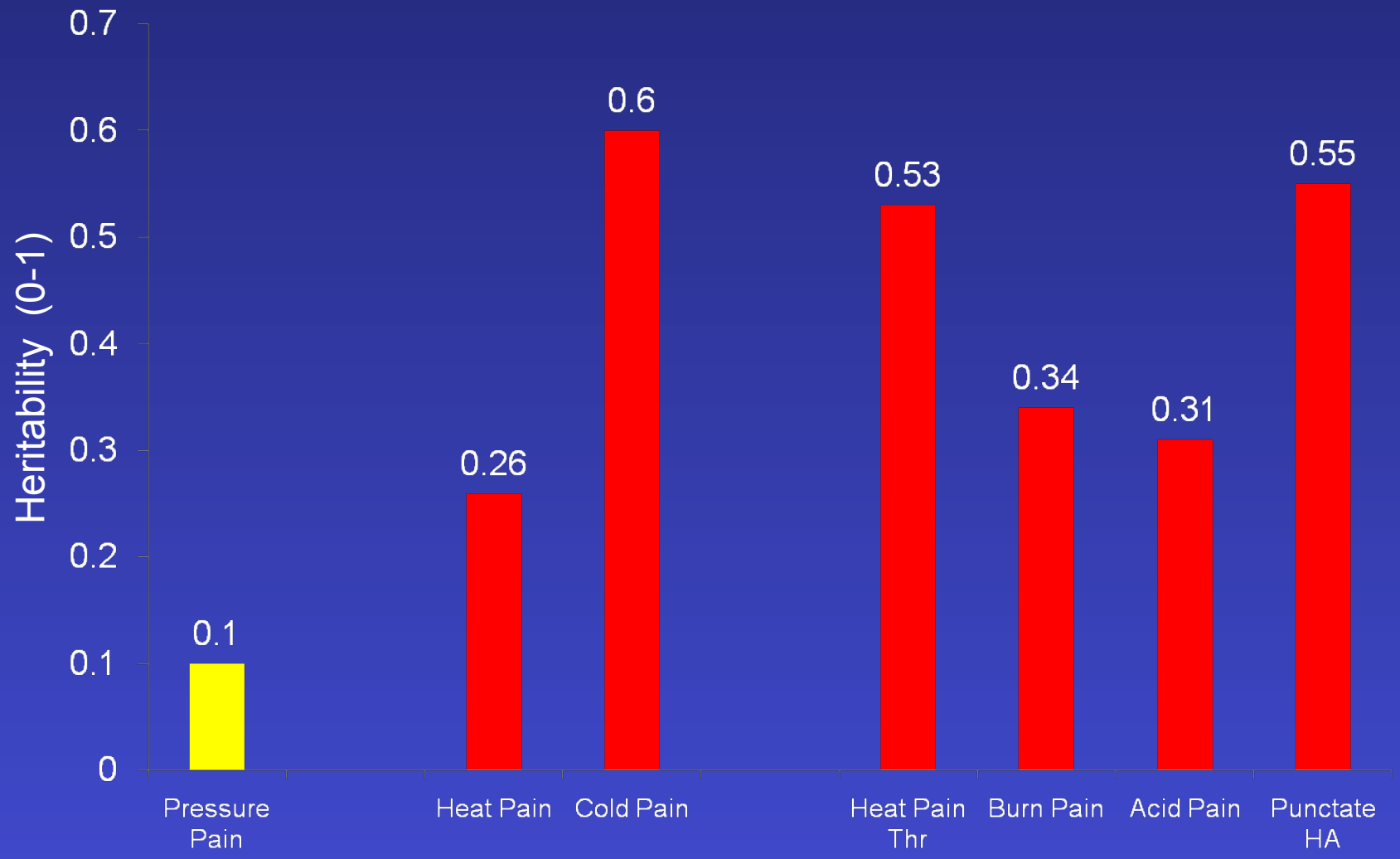
Advantages of Genetic Markers as Risk Factors

- No chicken and egg problem
- Highly reliable
- May reveal pathophysiology
- Can indicate new biological treatment targets

Heritability of Clinical Pain Conditions

Reference	Pain Condition	Study Design	Heritability Estimate
Mulder, et al 2003; Nyholt, et al 2004	Migraine	Twin Studies	.34 - .57
Fejer et al, 2006; MacGregor et al, 2004	Neck Pain	Twin Studies	.36 - .58
Hestbaek et al, 2004; MacGregor et al, 2004	Low Back Pain	Twin Studies	.40 - .68
Kato et al, 2006	Widespread Pain	Twin Studies	.48 - .54
Zondervan, et al 2005	Pelvic Pain	Twin Study	.41
Hakim, et al, 2002	Carpal Tunnel	Twin Study	.46

Heritability of Experimental Pain Measures

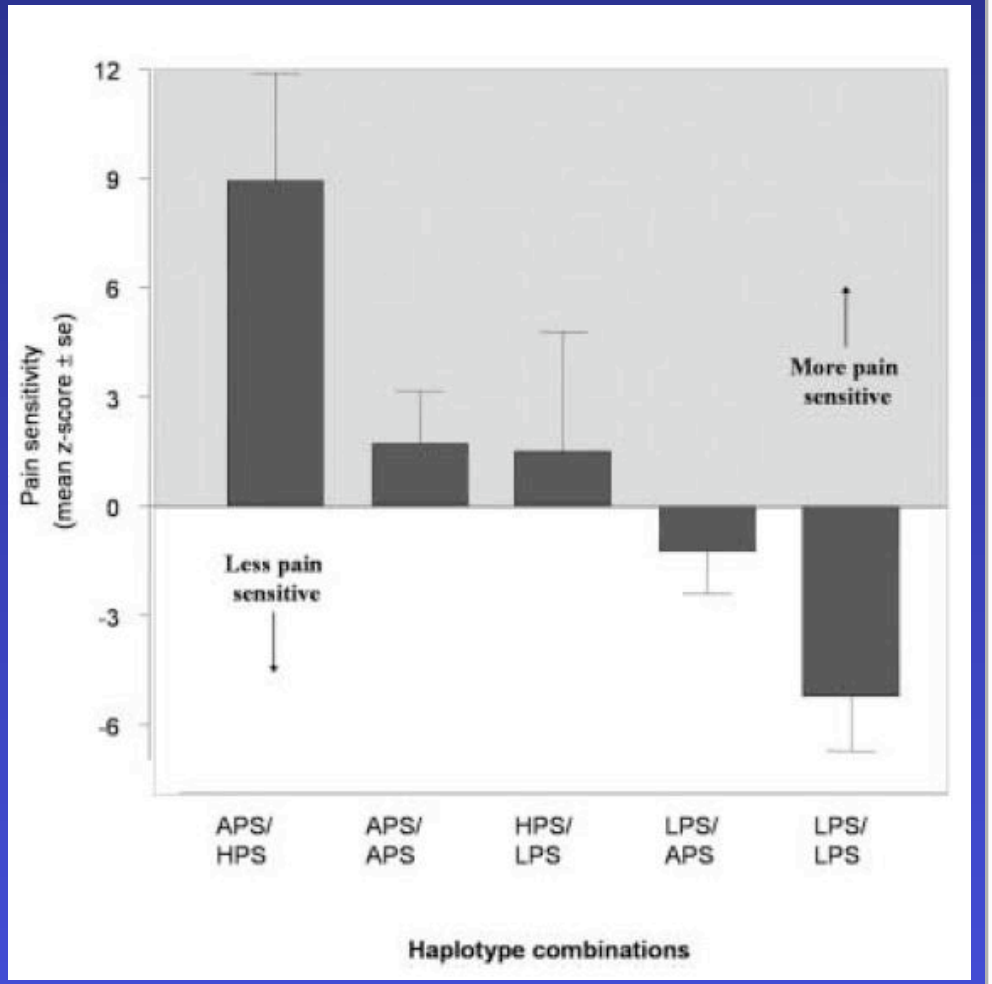


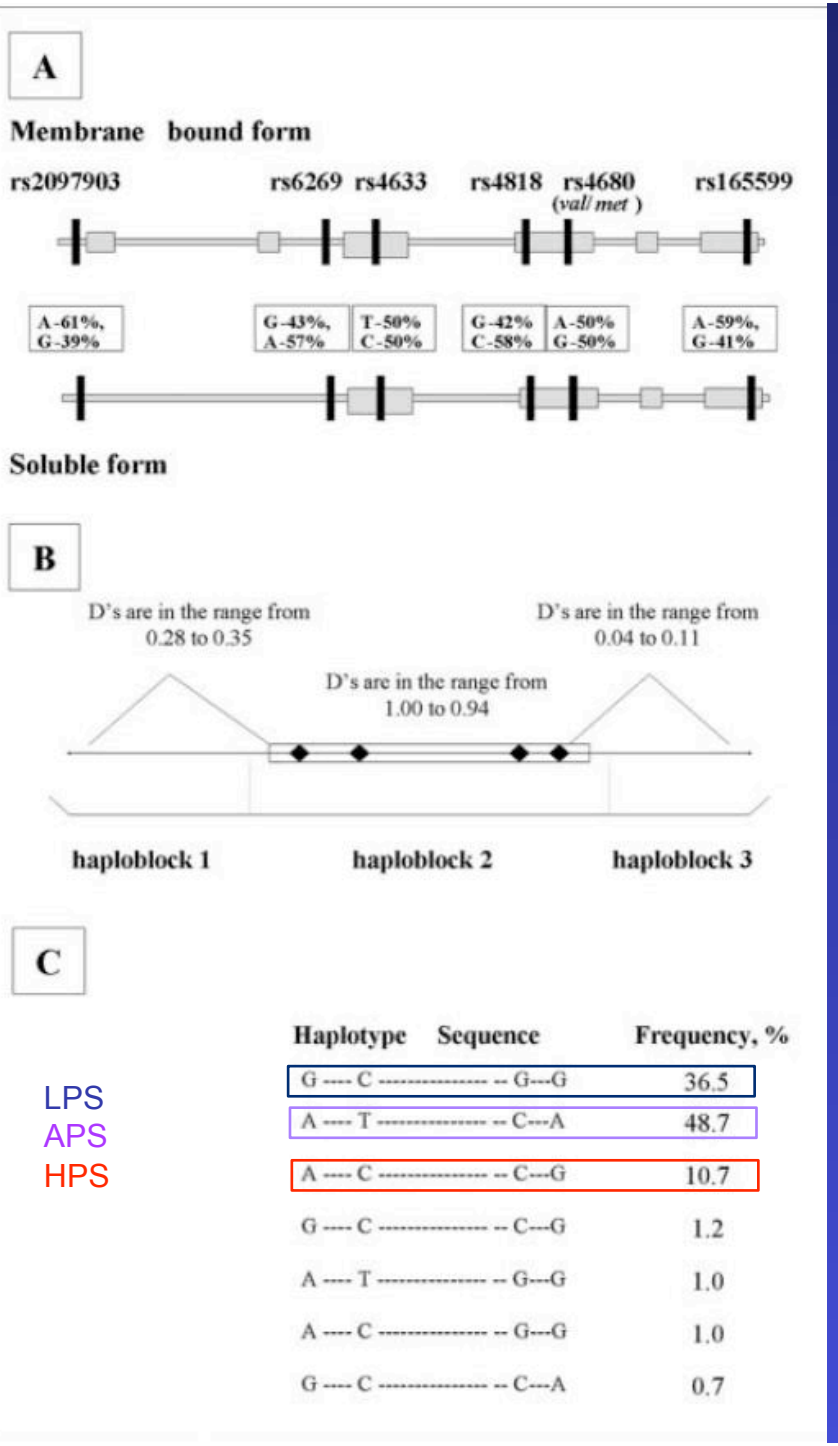
Catechol-*O*-methyl-transferase Gene *(COMT)* and Pain Sensitivity?

- COMT metabolizes catecholamines
- Common *met*^{158}*val* SNP of *COMT*: *met/met* have low COMT activity; *val/val* have high COMT activity
- *Val/val* genotype was associated with higher pain-related mu-opioid receptor binding and reduced pain response to hypertonic saline; *met/met* was associated with lower binding (Zubieta, et al, 2003)

COMT Haplotype and TMD Incidence

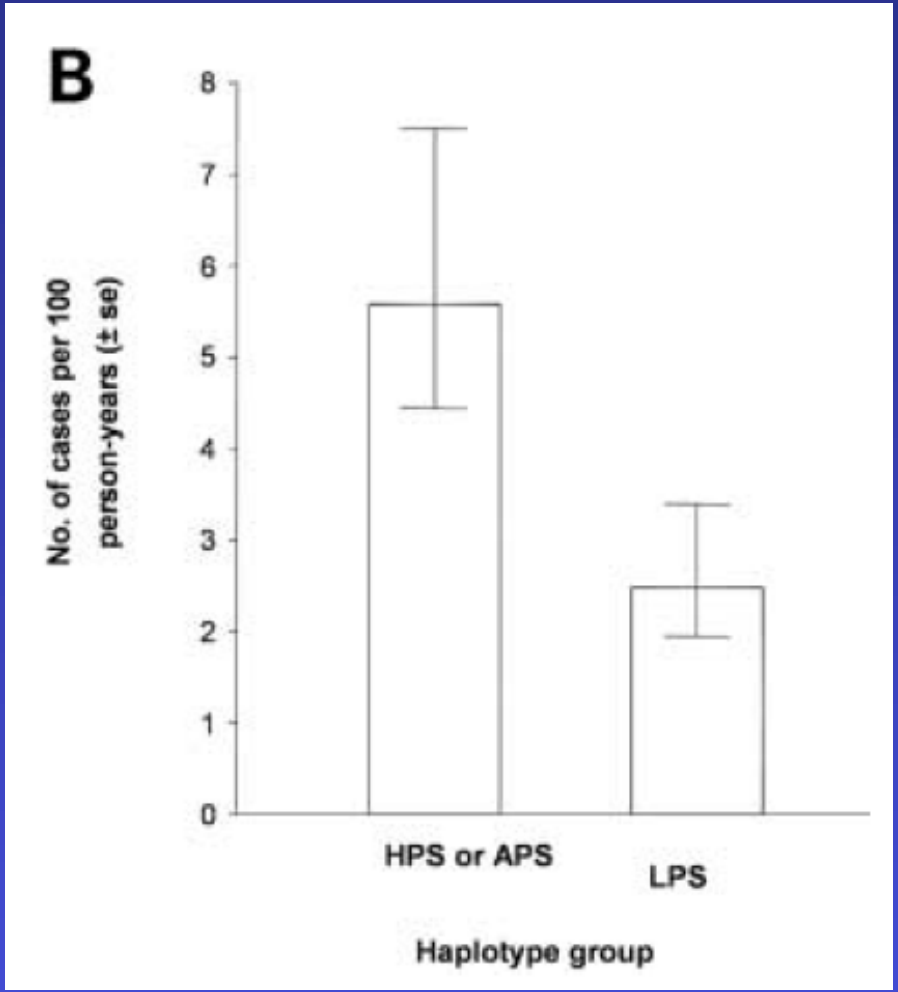
(Diatchenko, et al, 2005)



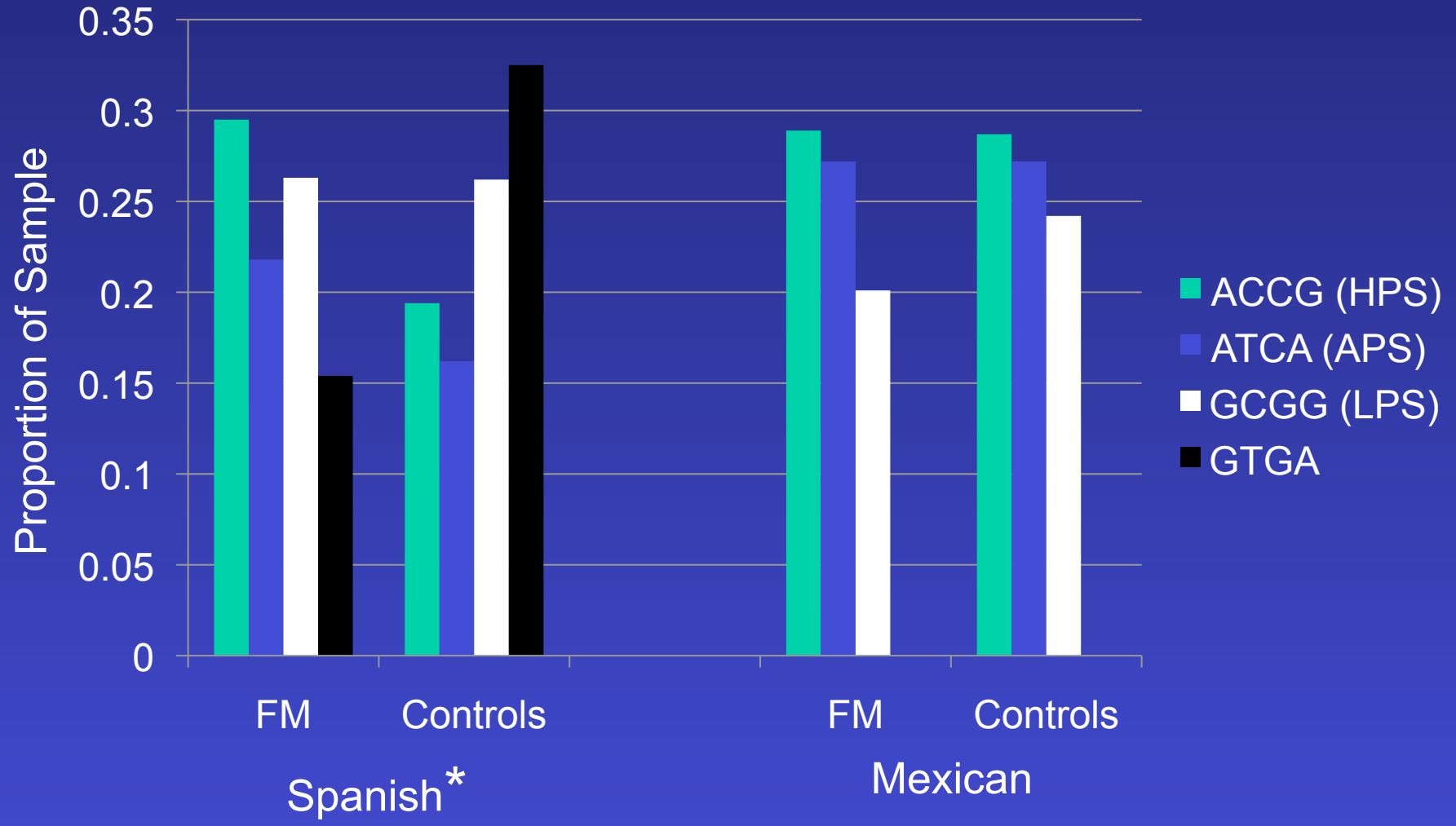


COMT Haplotype and TMD Incidence
(Diatchenko, et al, 2005)

Individuals with at least one low pain sensitive (LPS) haplotype were at lower risk for development of TMD compared to those with no LPS haplotypes.

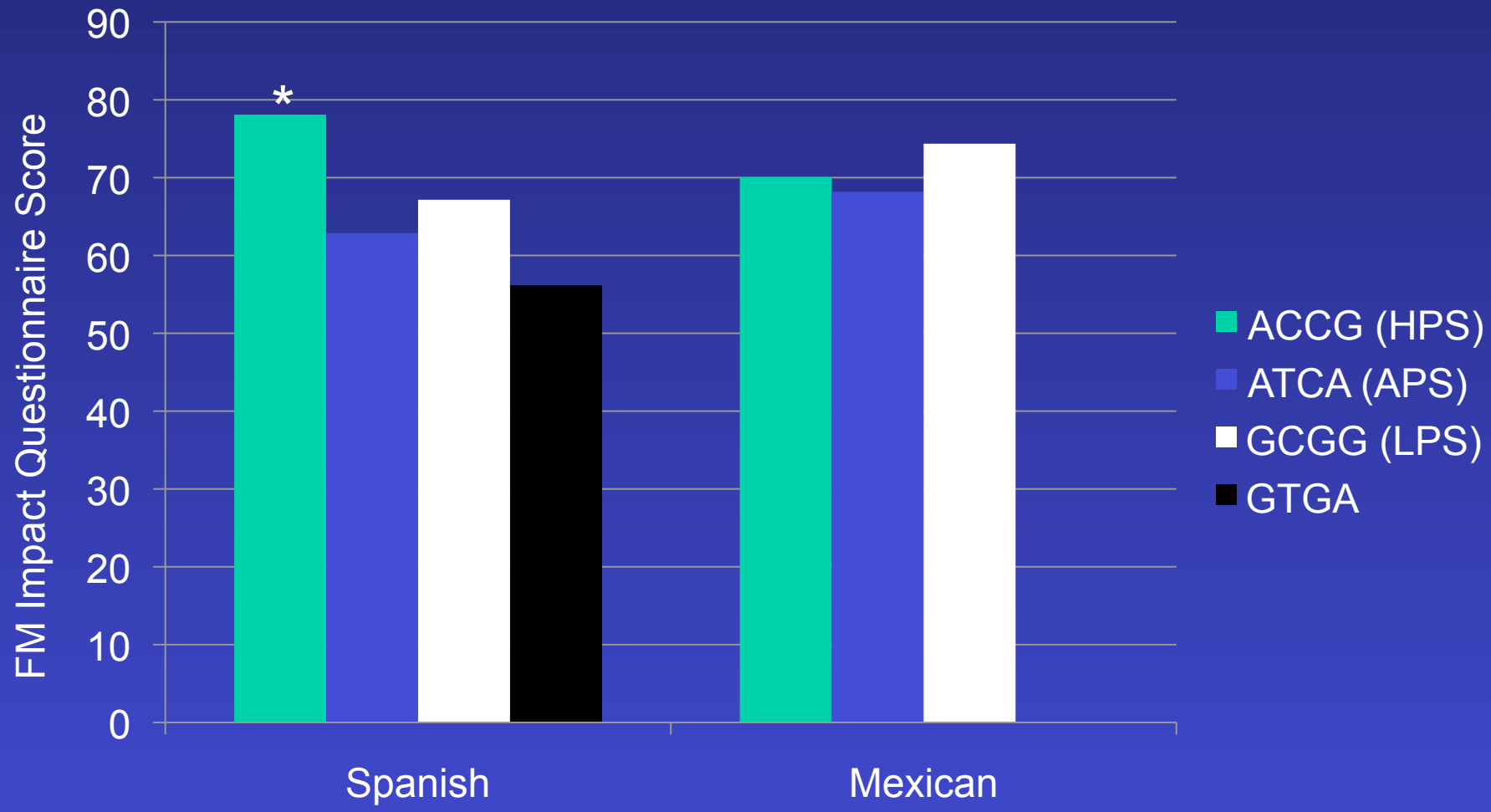


COMT Haplotypes among Mexican and Spanish FM Patients and Controls (Vargas-Alarcon, et al, 2007)



Haplotypes constructed from 4 *COMT* SNPs: rs6269, rs4633, rs4818, rs4680

COMT Haplotypes and FIQ Scores Mexican and Spanish FM Patients (Vargas-Alarcon, et al, 2007)

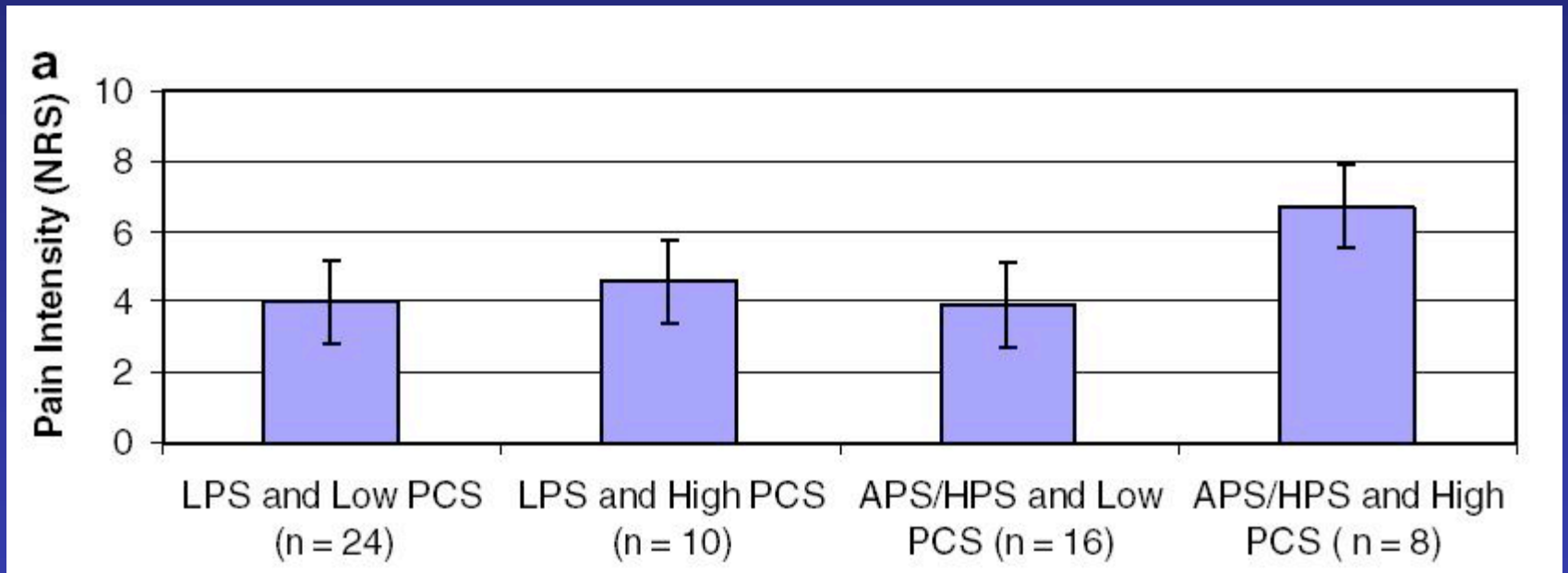


Combined Influences of *COMT* and Catastrophizing on Shoulder Pain (George, et al, 2008)

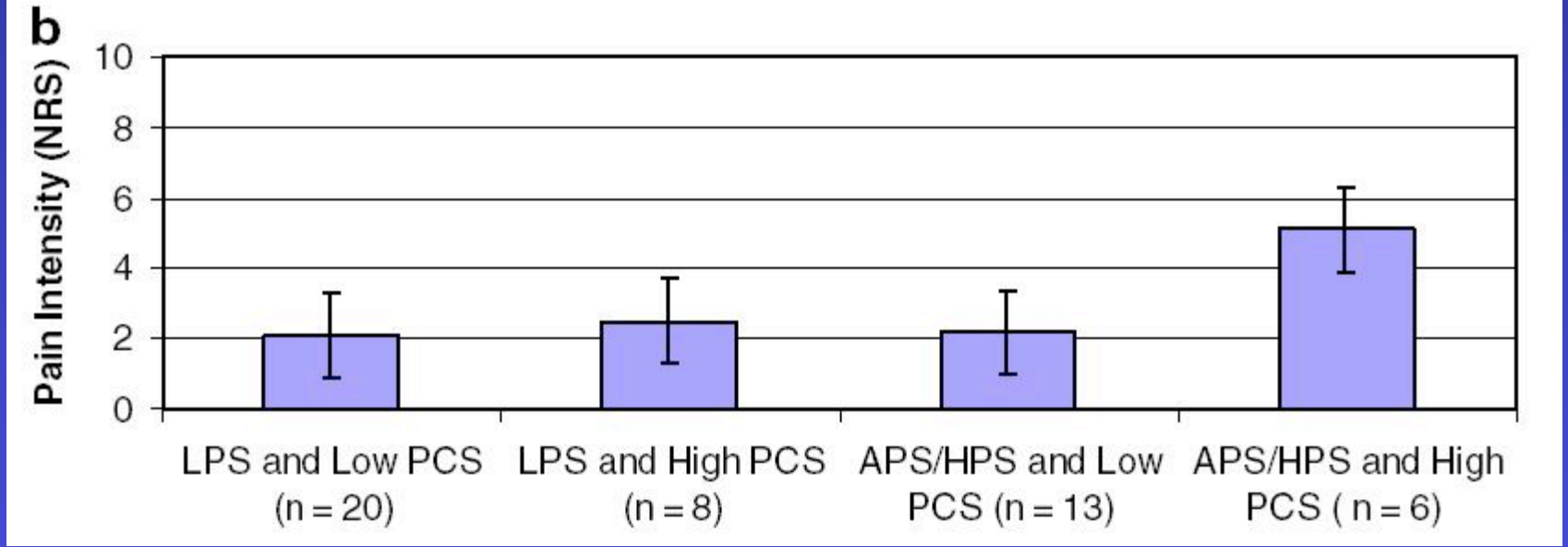
- 58 (24 F, 34 M) patients with chronic shoulder pain, undergoing arthroscopic surgery
- Pre-operative testing
  - Psychological questionnaires (catastrophizing)
  - Psychophysical testing
  - Buccal swab for DNA (COMT diplotypes from Diatchenko, et al, 2005)
- Arthroscopic surgery
- Post-operative testing (3-5 months later)

Combined Influences of Pain Catastrophizing and COMT Haplotype

Pre-Operative Pain



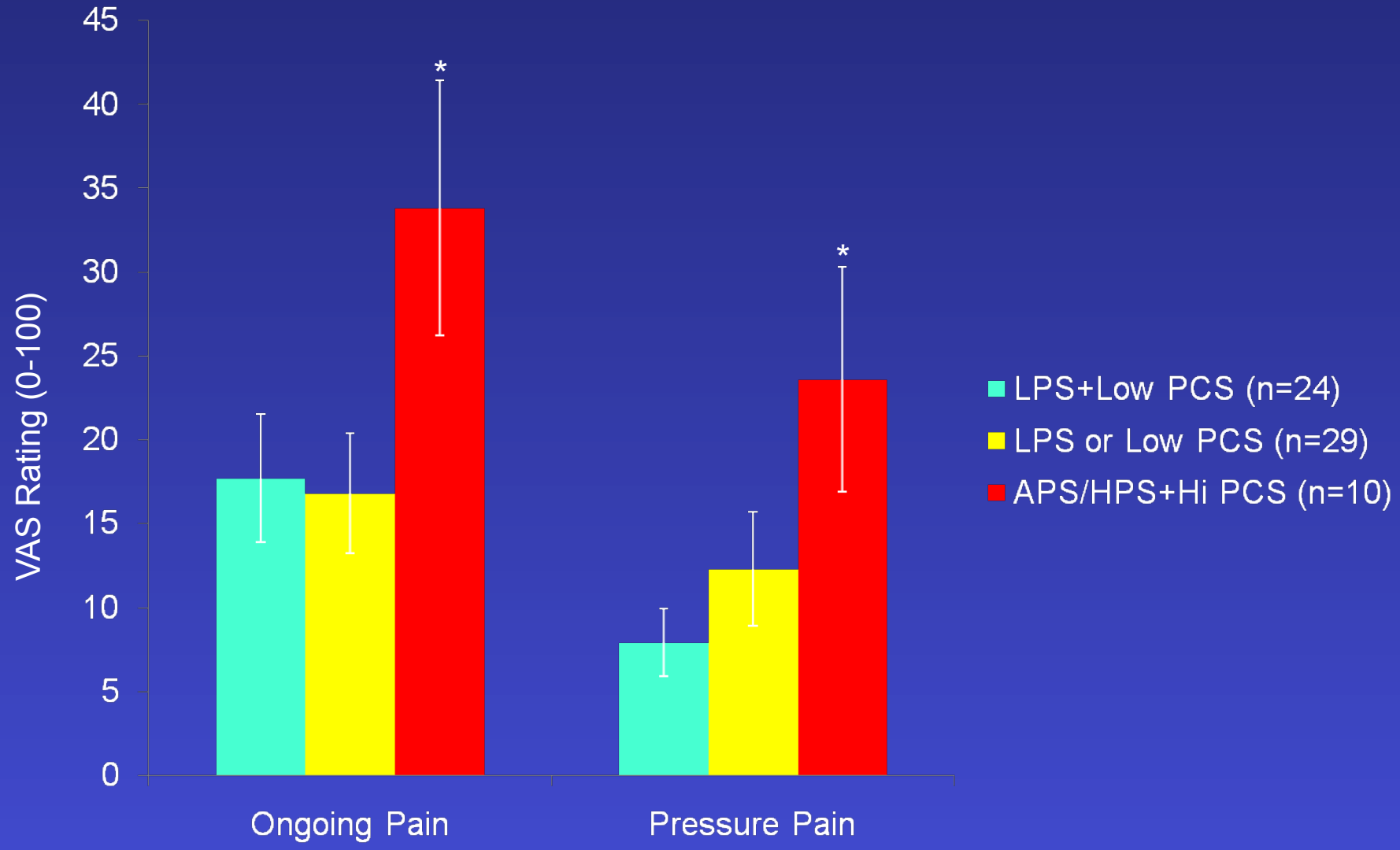
Post-Operative Pain



Replication in DOMS Model of Shoulder Pain
(George, et al, 2008)

- 63 (35 F, 28 M) healthy young (age=20.9) participants
- Delayed Onset Muscle Soreness Protocol with Kin-Com isokinetic dynamometer
  - Assessed VAS ongoing pain 24, 48, **72** hours later
  - Assessed VAS pain in response to 4 kg/cm^2 pressure to rotator cuff tendon insertion
- Psychological questionnaires (catastrophizing)
- Buccal swab for DNA (COMT diplotypes from Diatchenko, et al, 2005)

Catastrophizing and *COMT* in Experimental Shoulder Pain

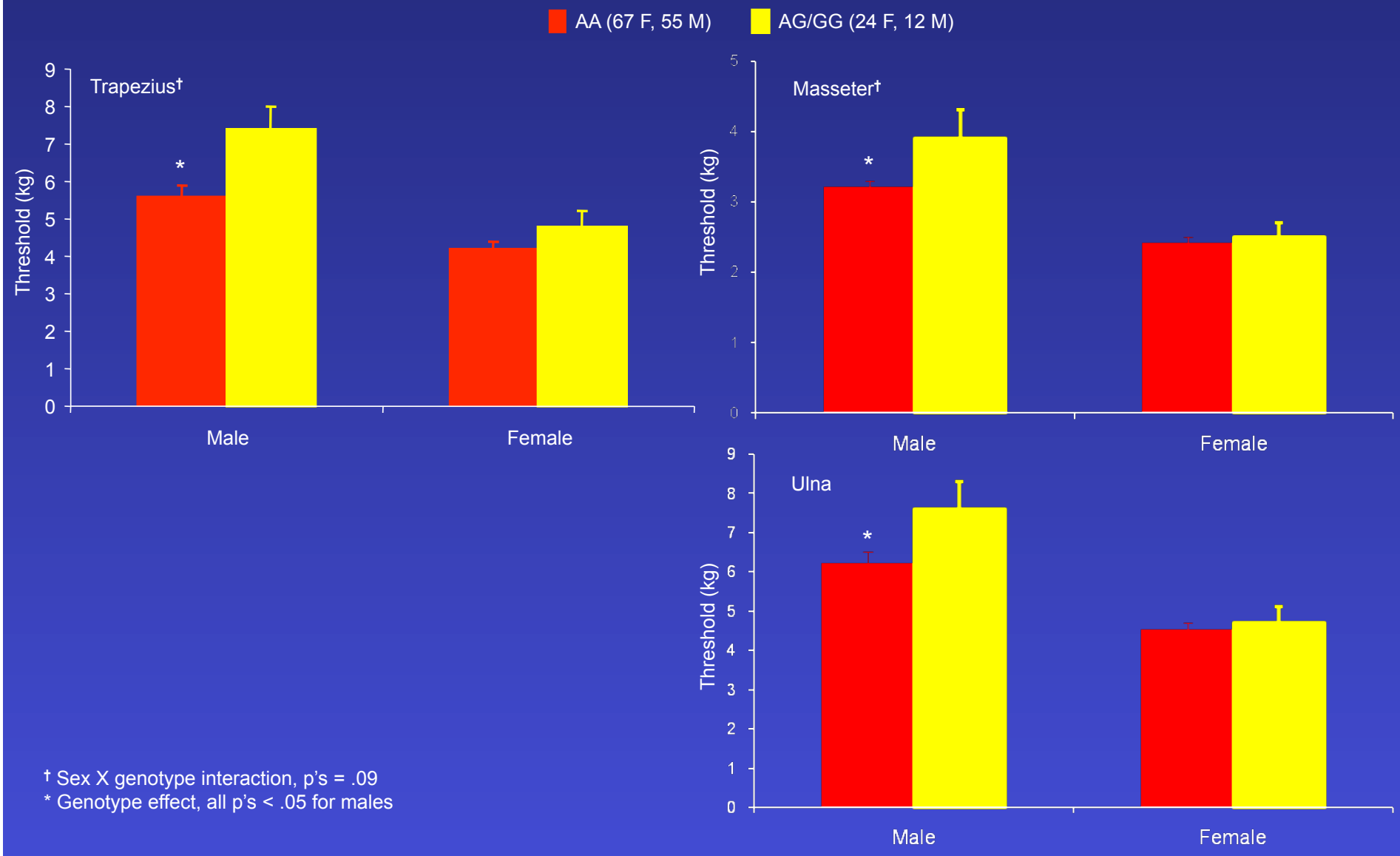


* APS/HPS+Hi PCS group > other groups, $p < .05$

Is the mu-Opioid Receptor Gene (*OPRM1*) Associated with Baseline Pain Sensitivity?

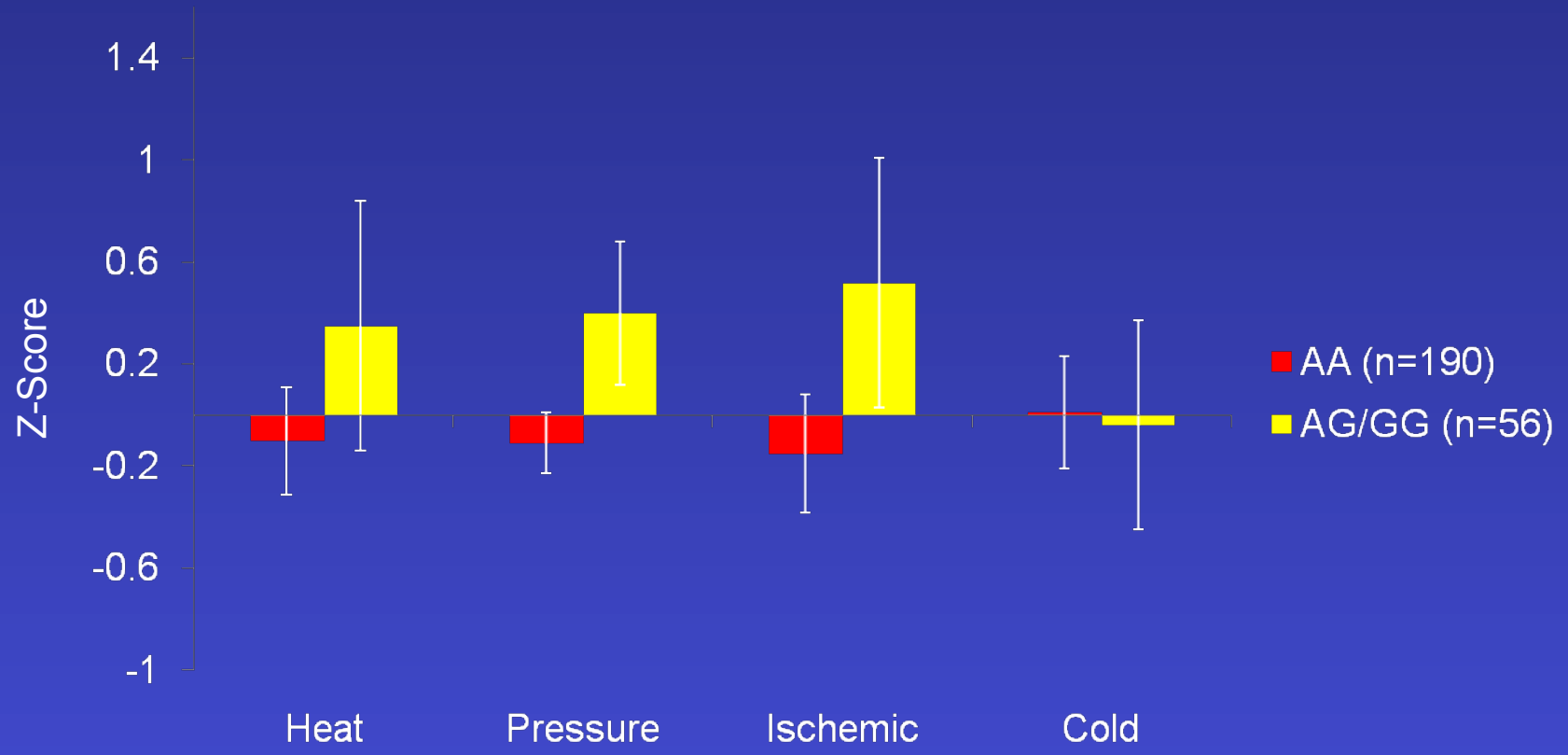
- Uhl (1999) suggested *OPRM1* was a strong candidate for a "pain gene"
- The A118G variant mu receptor shows greater binding affinity for beta-endorphin (Bond, et al, 1998)
- We studied baseline pain sensitivity in 167 (96 F, 71 M) individuals and determined A118G genotype using PCR

OPRM1 A118G Genotype and Pressure Pain Thresholds among Females and Males



† Sex X genotype interaction, p's = .09
* Genotype effect, all p's < .05 for males

OPRM1 A118G Genotype and Pain Responses in a Second Cohort



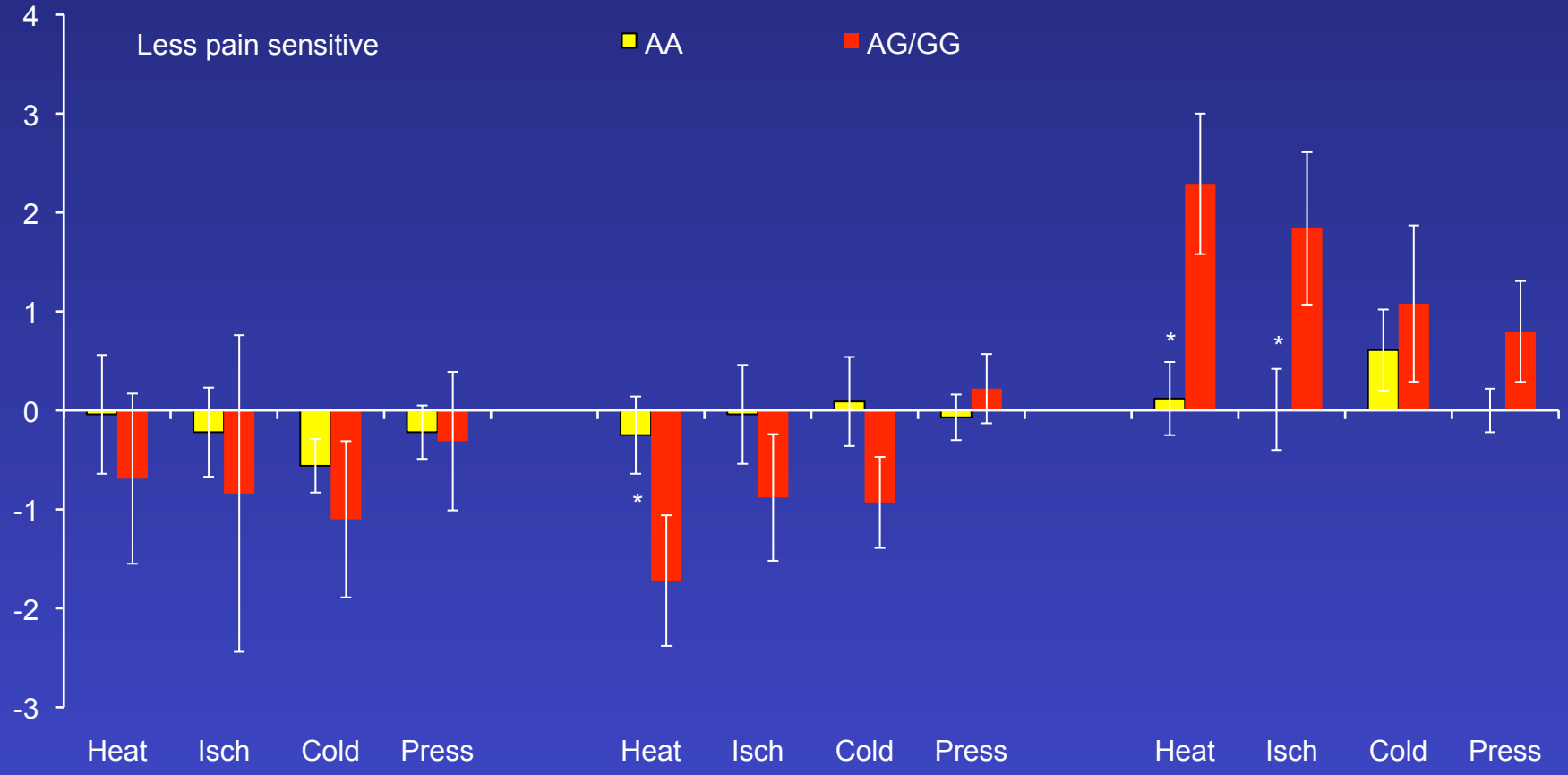
all p's > .05

But, this was a multi-ethnic cohort…

	AA	AG	GG
African American	75 (92.6%)	6 (7.4%)	0 (0%)
Hispanic-Whites	57 (72.2%)	21(26.6%)	1 (0.4%)
Non-Hispanic Whites	63 (71.6%)	24 (27.3%)	1 (0.4%)

$p < .05$

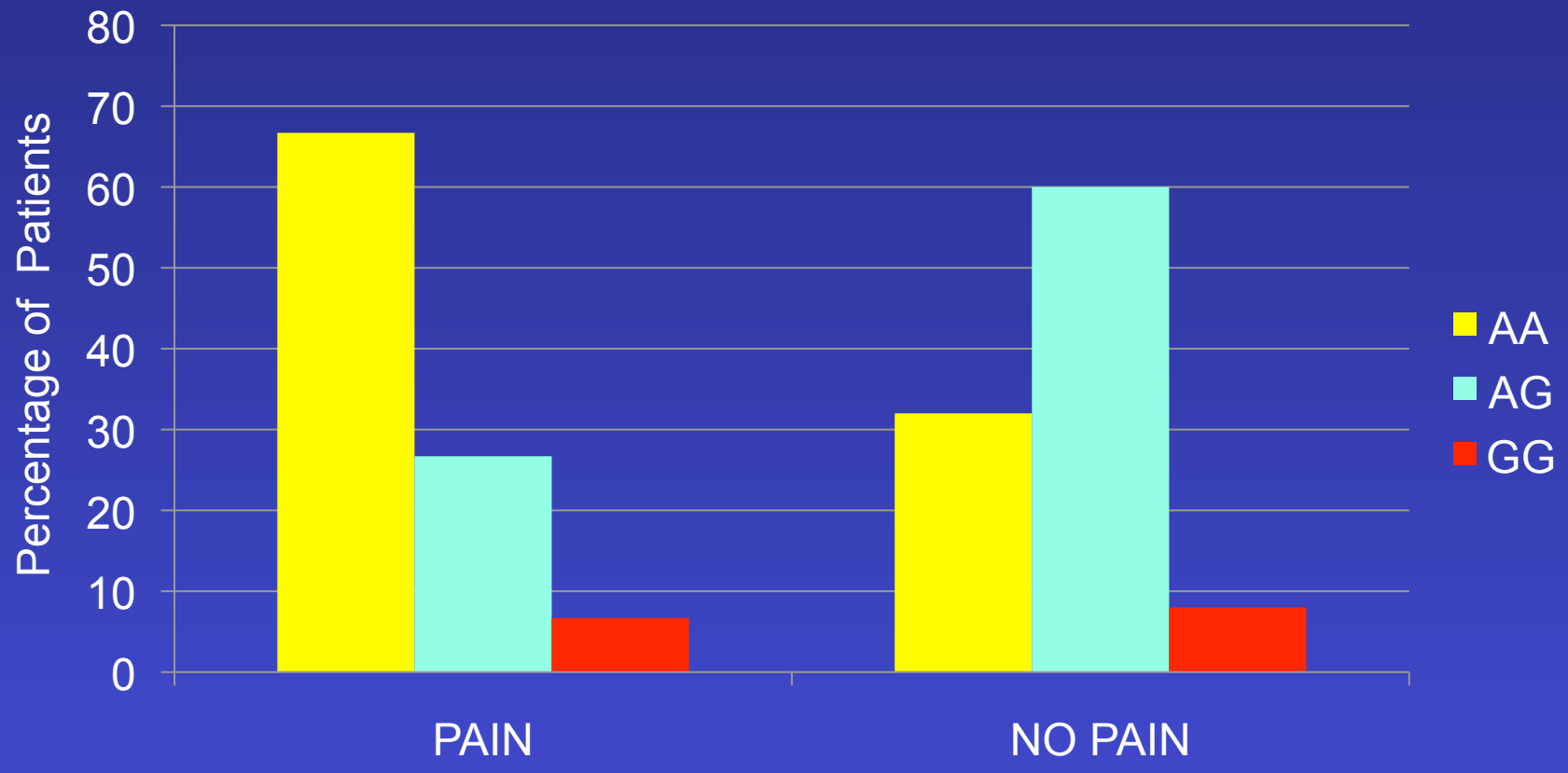
OPRM1 A118G Genotype and Pain Responses Across Ethnic Groups



* Significant genotype effect

OPRM1 and Foot Ulcer Pain in Diabetics

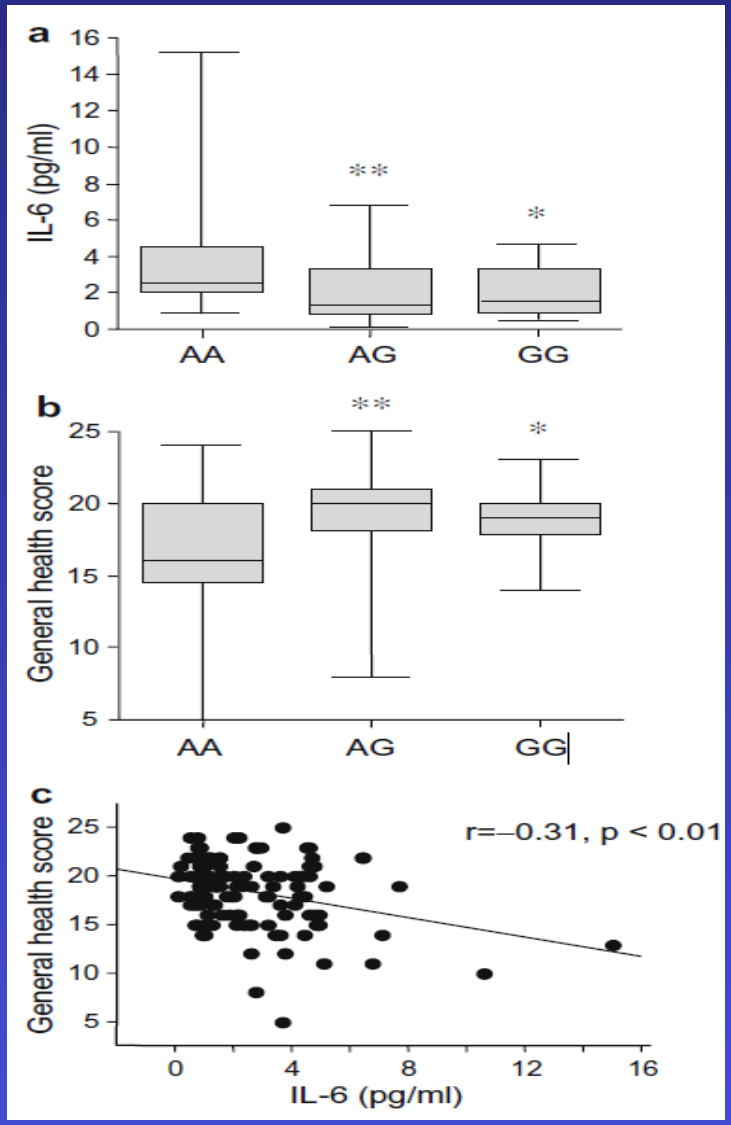
(Cheng, et al, 2009)



OPRM1, Cytokines and General Health

(Matsunaga, et al, 2009)

Carriers of the 118G allele had lower serum levels of IL-6 and higher self-reported general health compared to AA carriers.



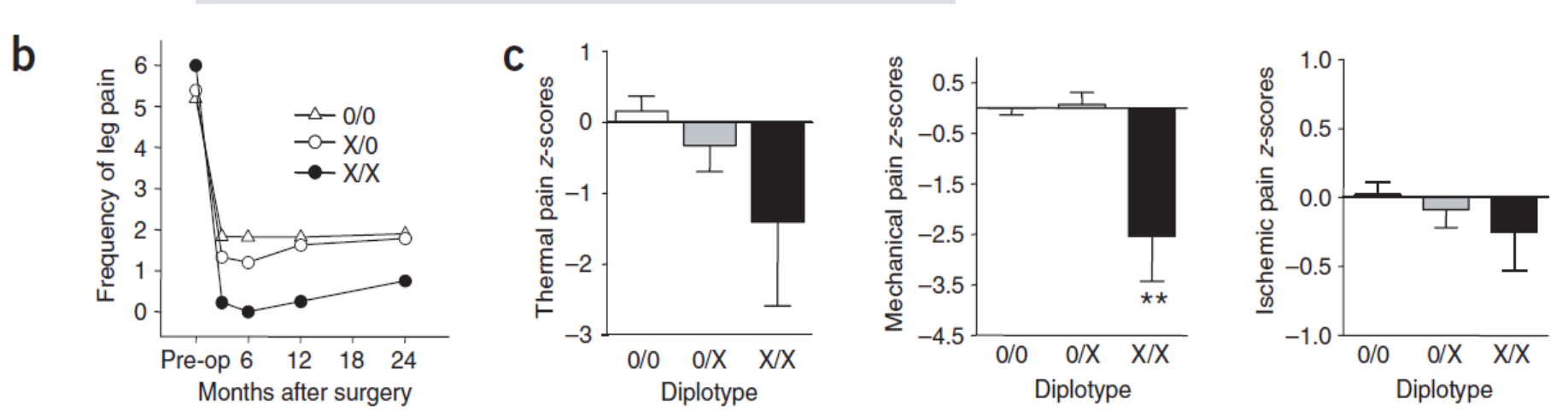
GTP Cyclohydrolase Gene (*GCH1*)
(Tegeder, et al, 2006)

- Enzyme involved in production of 6(R)-L-*erythro*-5,6,7,8-tetrahydrobiopterin (BH4).
- BH4 is a key cofactor in the synthesis of several pain neuromodulators including catecholamines, serotonin and nitric oxide, and BH4 induces pain hypersensitivity.
- GTP cyclohydrolase and BH4 were increased after nerve injury and inhibition of GTP cyclohydrolase reduced neuropathic & inflammatory pain in rats

GTP Cyclohydrolase Gene (*GCH1*)

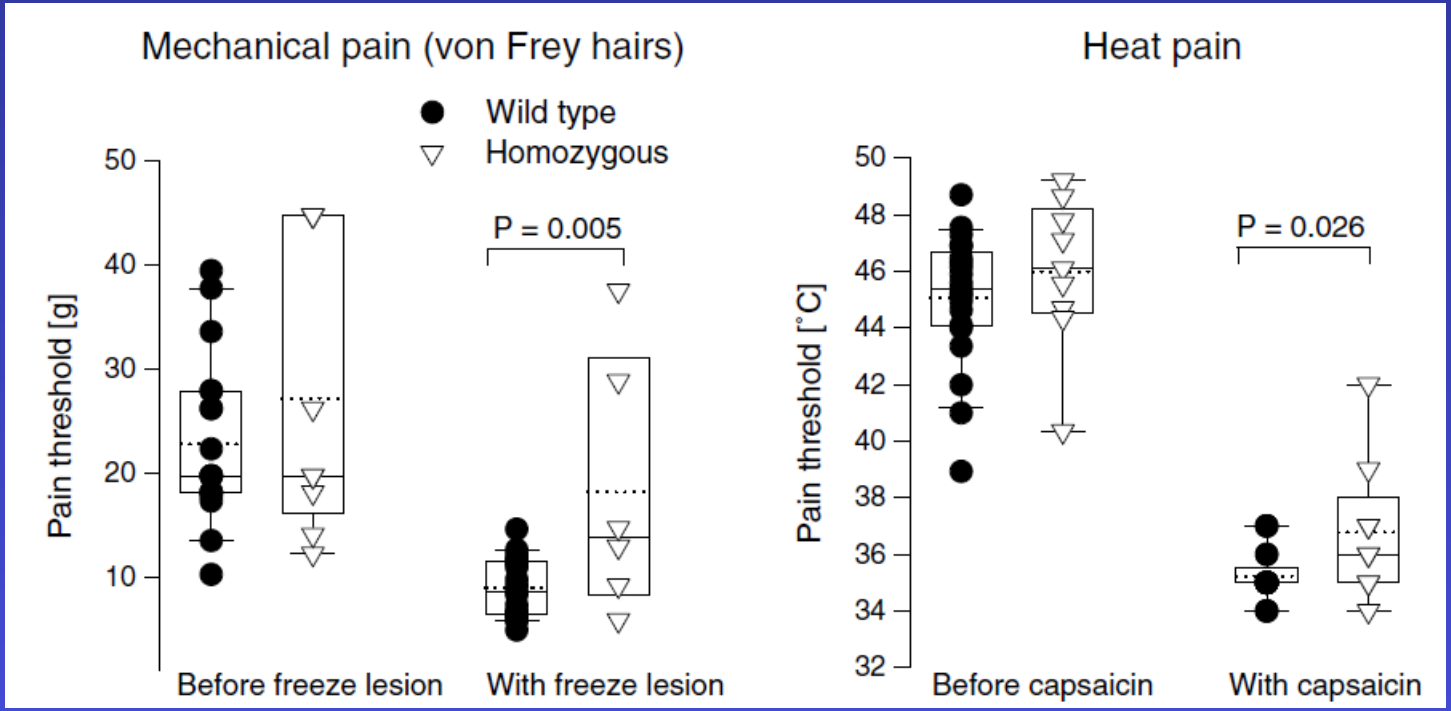
(Tegeder, et al, 2006)

A pain protective haplotype of *GCH1* was associated with reduced frequency of leg pain after discectomy (B) and with lower sensitivity to experimental pain in 2 cohorts (C)



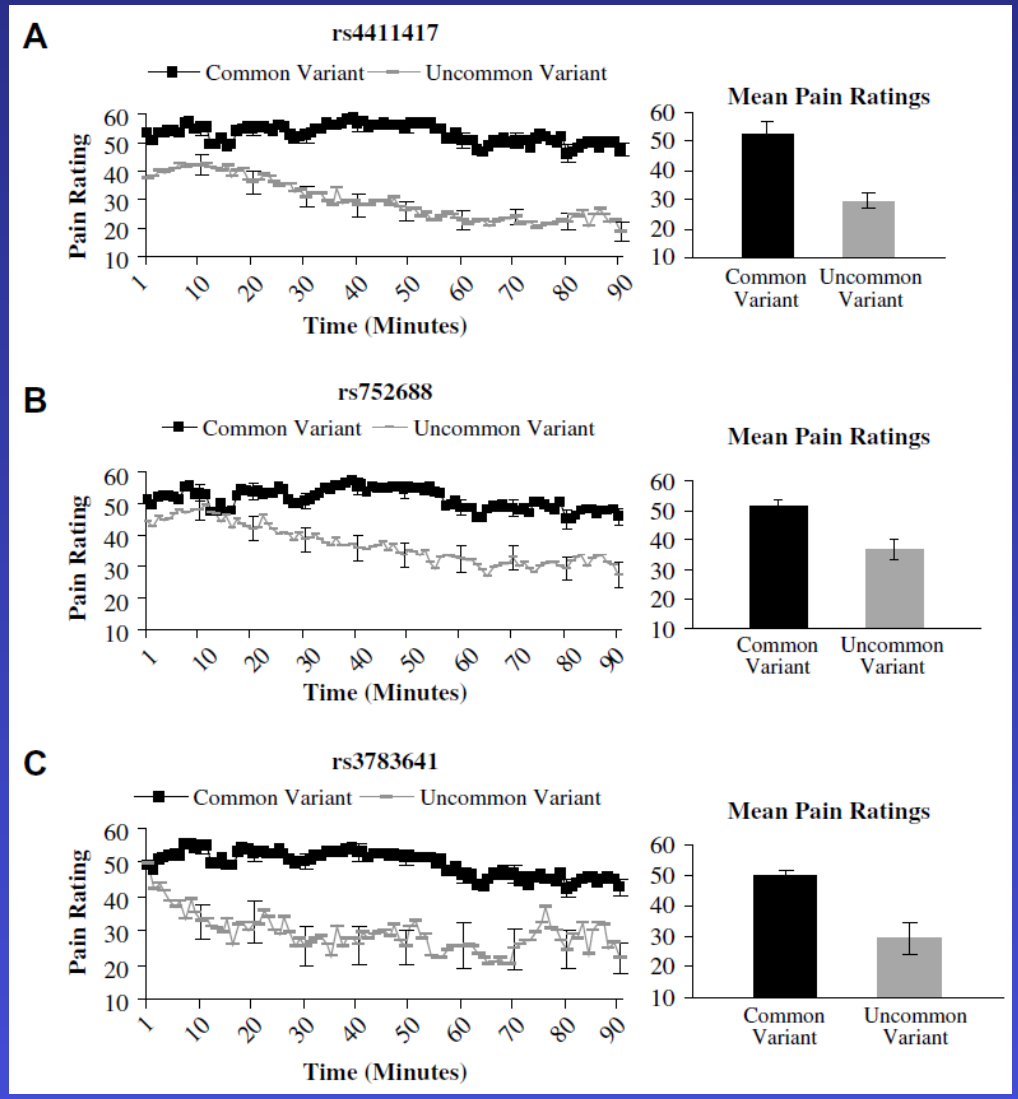
GTP Cyclohydrolase Gene (*GCH1*)
(Tegeder, et al, 2008)

The pain protective haplotype of *GCH1* was associated with reduced hyperalgesia following a freeze lesion and following capsaicin application.



GTP Cyclohydrolase Gene (*GCH1*)
(Campbell, et al, 2009)

Three of the SNPs identified by Tegeder, et al were significantly associated with pain ratings following application of topical capsaicin. The linear combination of SNPs accounted for 35% of the variance in pain ratings.

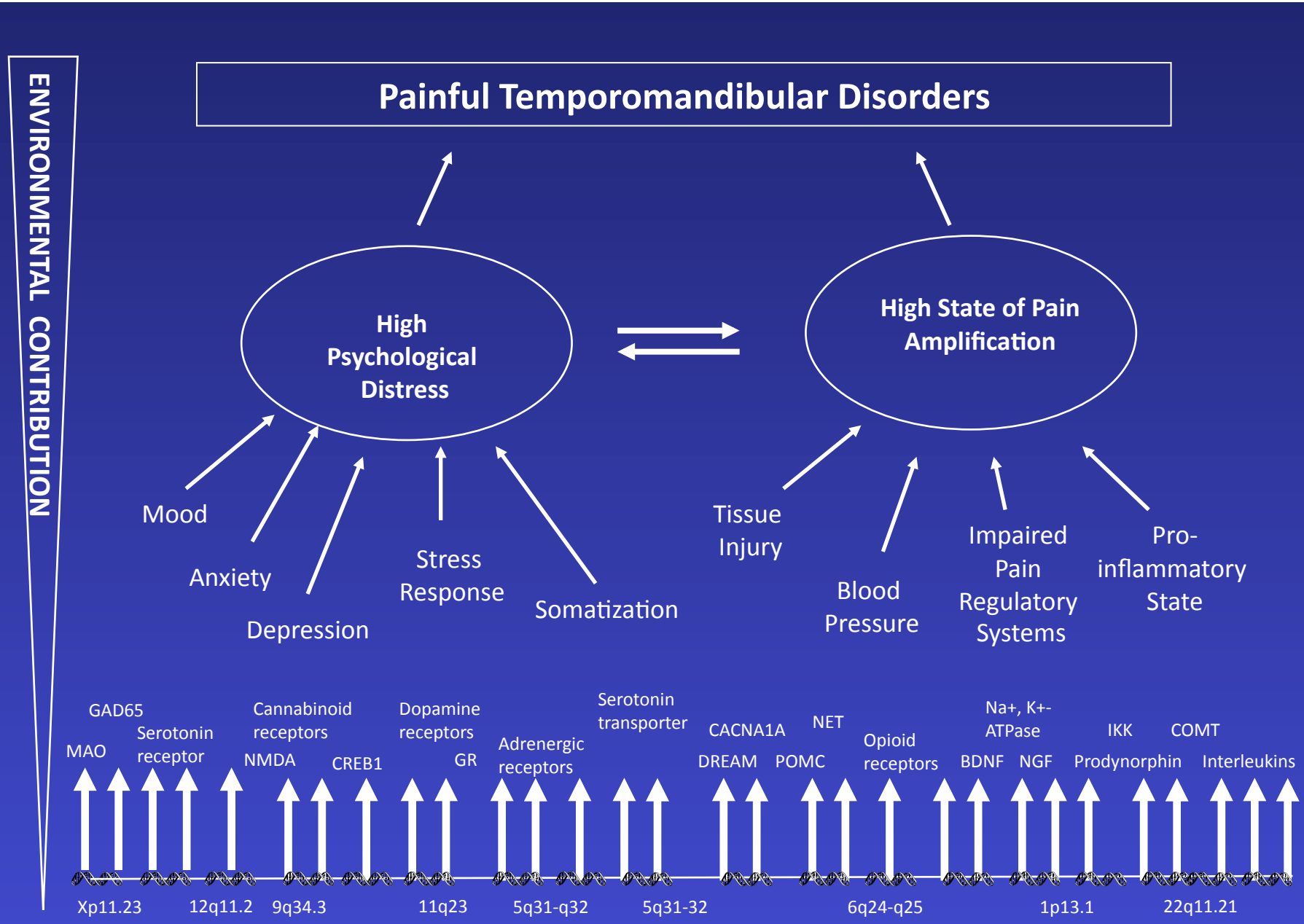


Association of *IL6* With Low Back Pain

- A haplotype (GGGA) constructed from 4 SNPs was more frequent in patients with discogenic sciatica compared to controls (Noponen-Hietala, et al, 2005)
- Patients with GGGA haplotype reported more days with back/leg pain and more sick days over a three-year follow-up (Karppinen, et al, 2008)

Overview

- Conceptual & methodological considerations
- Non-genetic risk factors for chronic pain
- Genetic risk factors for chronic pain
- **Conceptual model and future directions**

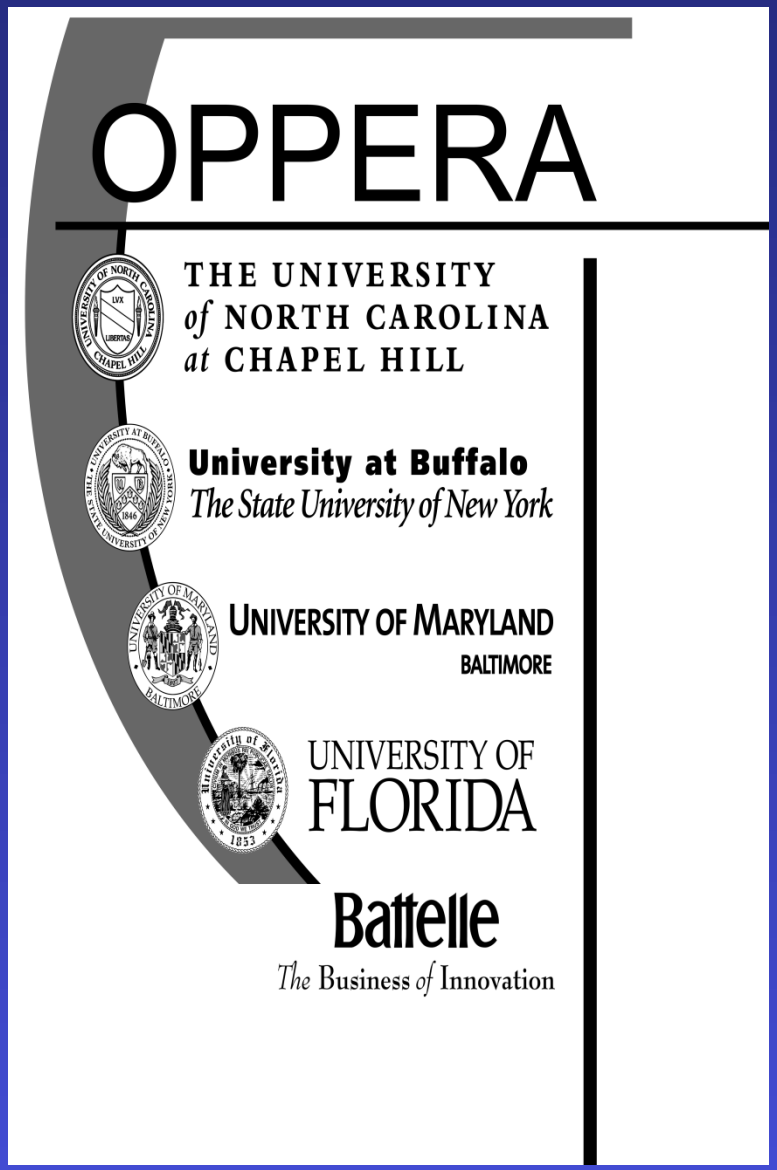


Diatchenko, et al, 2005

OPPERA Study (PI, Dr. William Maixner)

Orofacial **P**ain: **P**rospective **E**valuation and **R**isk **A**ssessment

Central Hypothesis: Pain amplification and psychological factors, both of which are influenced by genetic variants and environmental events, represent causal influences for TMD onset and persistence.



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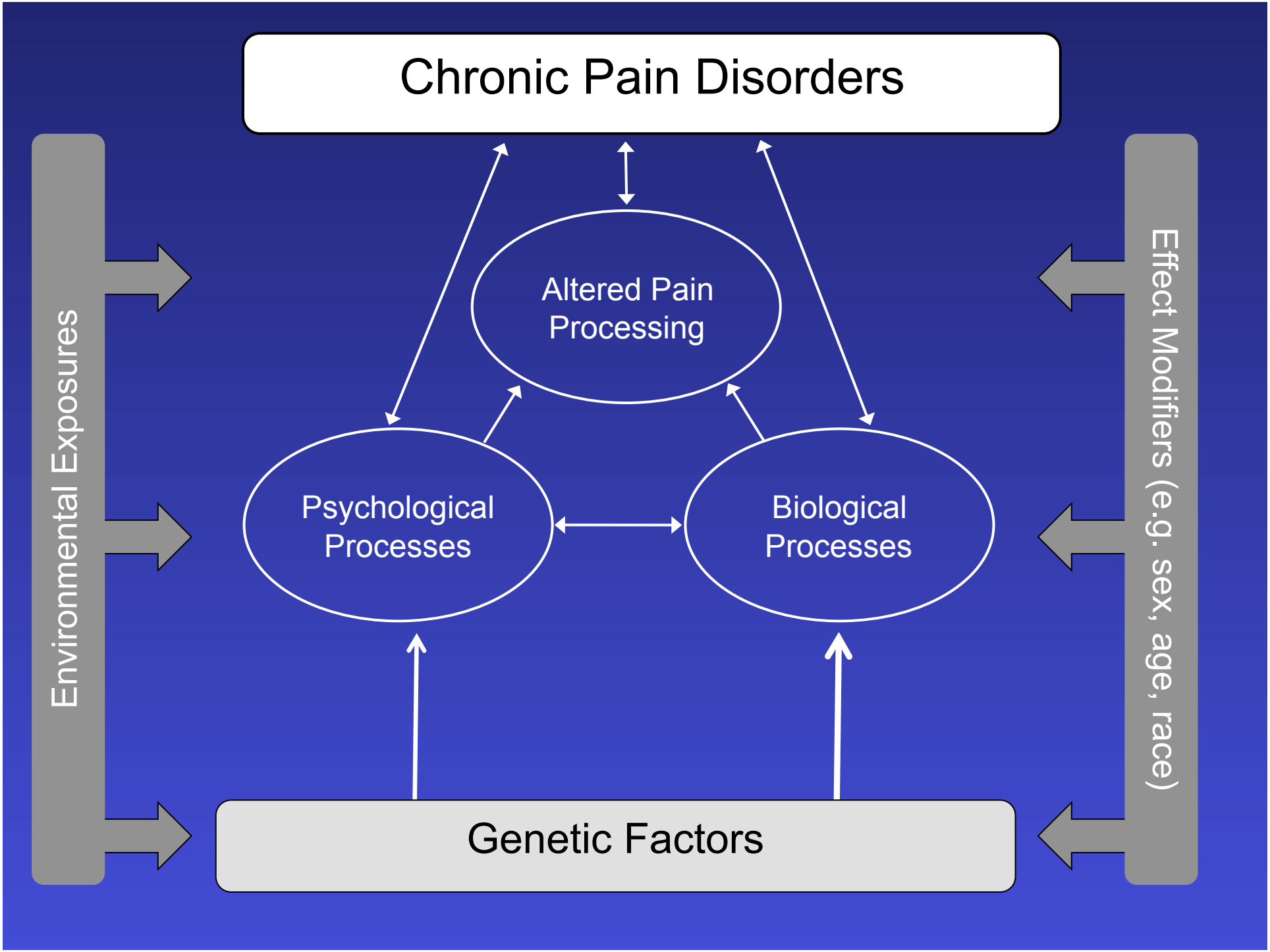
Chronic Pain Disorders
Environmental Exposures
Effect Modifiers (e.g. sex, age, race)
Altered Pain Processing
Psychological Processes
Biological Processes
Genetic Factors

Summary

- Multiple non-genetic factors predict future onset of chronic pain (demographics, psychosocial)
- Likely genetic risk factors include genes encoding proteins involved in response to injury (e.g. *IL6, GCH1*) and central pain modulation (e.g. *COMT, OPRM1*)
- Genetic and non-genetic risk factors interact
- Implications for trial design include:
  - sample size considerations (allele frequency)
  - choice of patient population
  - phenotypic measures (QST, psychosocial factors)

Thank You