Defining TMD for Clinical Care - The Horizon

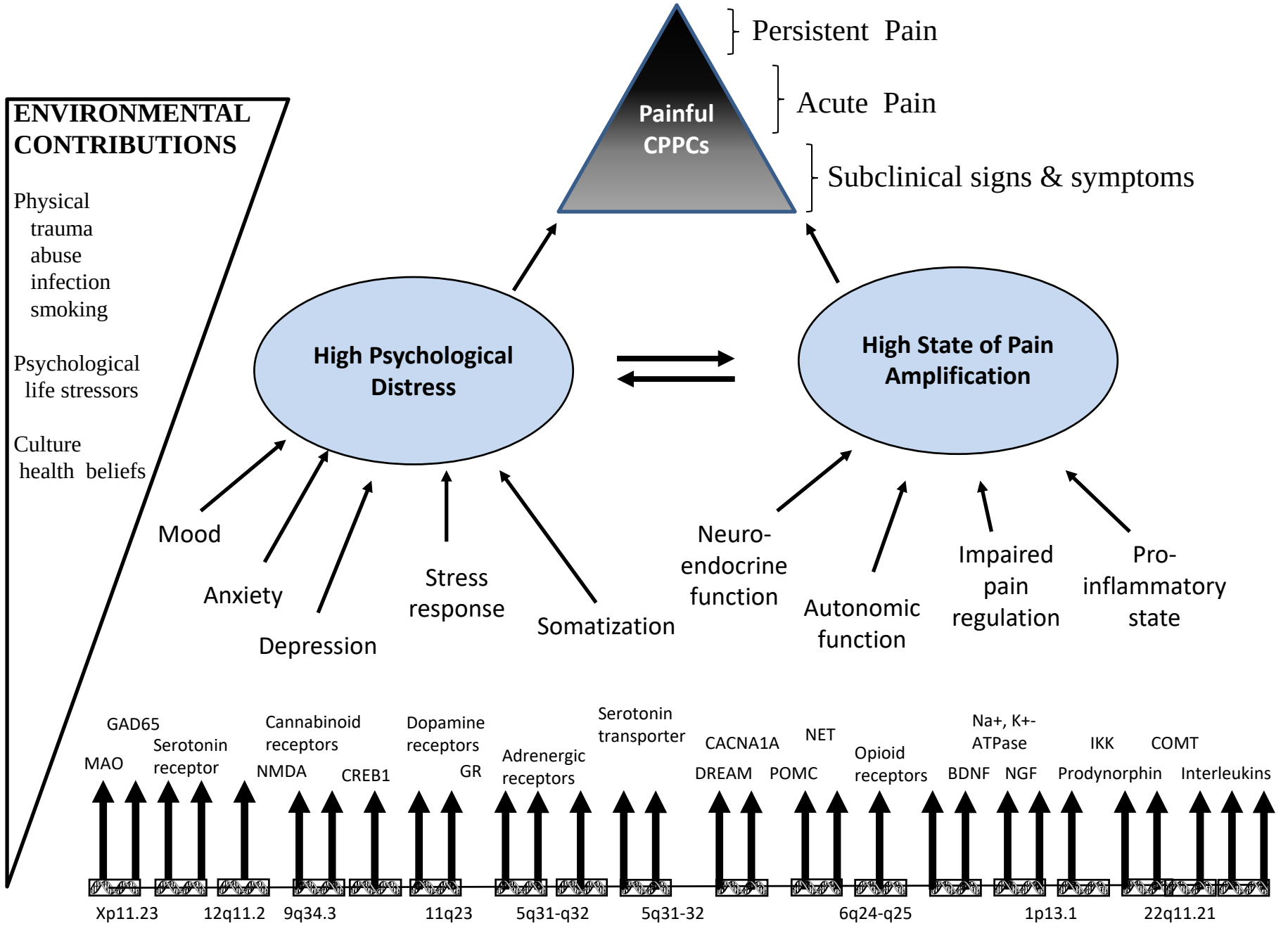
Committee on Temporomandibular Disorders (TMD):From Research Discoveries to Clinical Treatment

William Maixner DDS, PhD
Co-Director Center for Translational Pain Medicine
Vice Chair for Research
Department of Anesthesiology, Duke University

Disclosures: Algynomics Inc. cofounder and equity shareholder; ATTAGENE Inc shareholder; Orthogen Inc. equity shareholder and BoD

A Guiding Principle

Common chronic pain conditions – like TMD – present as a kaleidoscope of phenotypes that are temporally dynamic and result from GxE interactions



Diatchenko et al, Pain 123: 226-30, 2006 & Maixner et al, Journal of Pain 12, Suppl 3, 4-11, 2011

Table 5. Published Estimates of Overlap Between Index Conditions and Other COPCs

	Comorbidity (Percentage Overlap)				
Index Case Status	FM	IBS	TMD	CFS	VVD
FM		80[37]	75[82]	64[2]	NA
IBS	41[133]		16[57]	14[57]	NA
TMD	24[133]	64[2]		20[2]	NA
CFS	55[133]	58[37]	42[60]		NA
VVD	23[133]	25[75]	20[39]	8[75]	

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia; IBS, irritable bowel syndrome; TMD, temporomandibular disorders; CFS, chronic fatigue syndrome; VVD, vulvodynia; NA, not applicable.

Maixner et al. J Pain. 2016 Sep; 17(9 Suppl): T93–T107

Research Paper

PAIN

2016 Jun;157(6):1266-78.

Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study

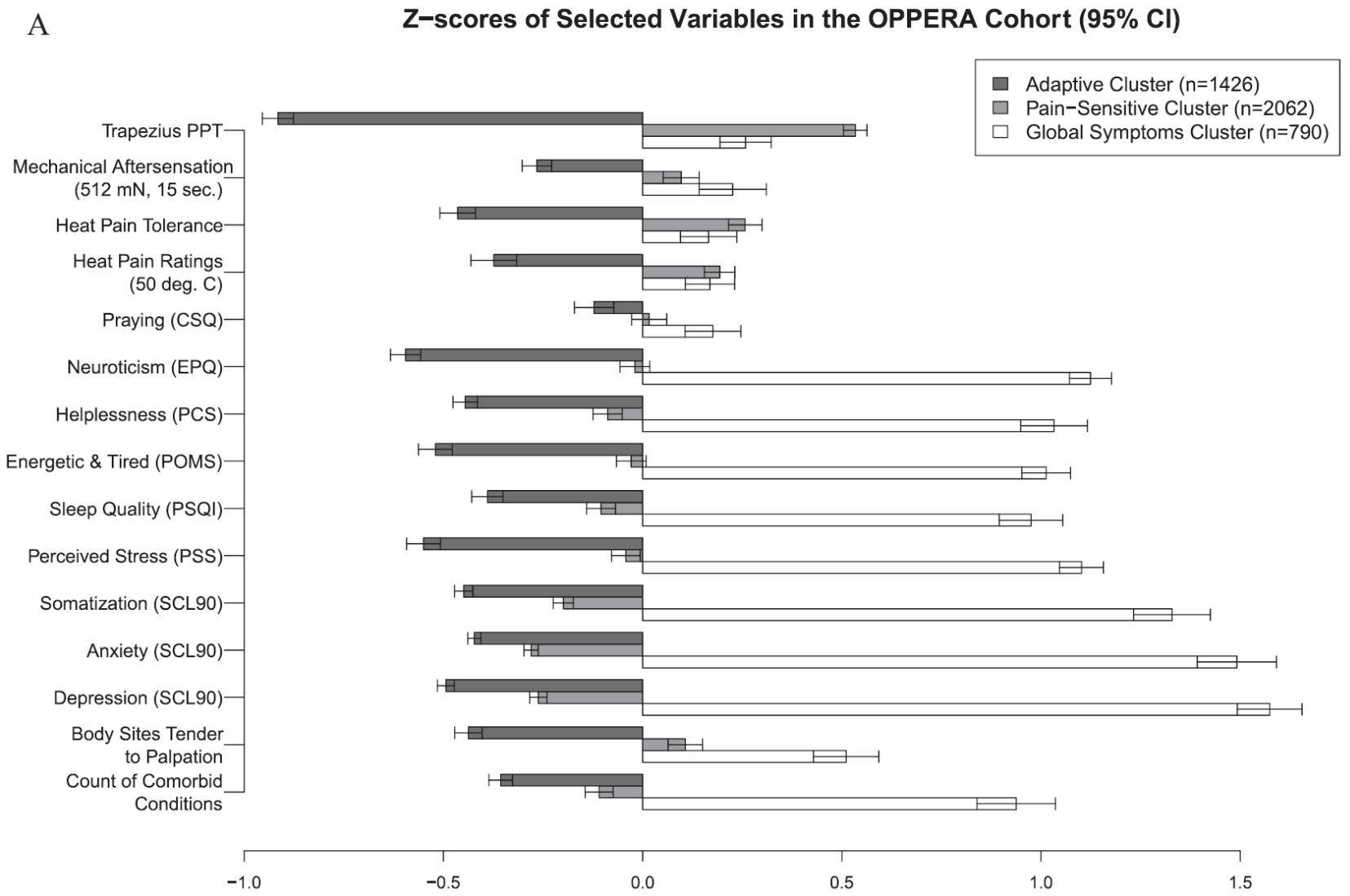
Eric Bair[a,b,c,*], Sheila Gaynor[d], Gary D. Slade[a,e,f], Richard Ohrbach[g], Roger B. Fillingim[h], Joel D. Greenspan[i], Ronald Dubner[j], Shad B. Smith[a,c], Luda Diatchenko[j], William Maixner[a,c]

Abstract

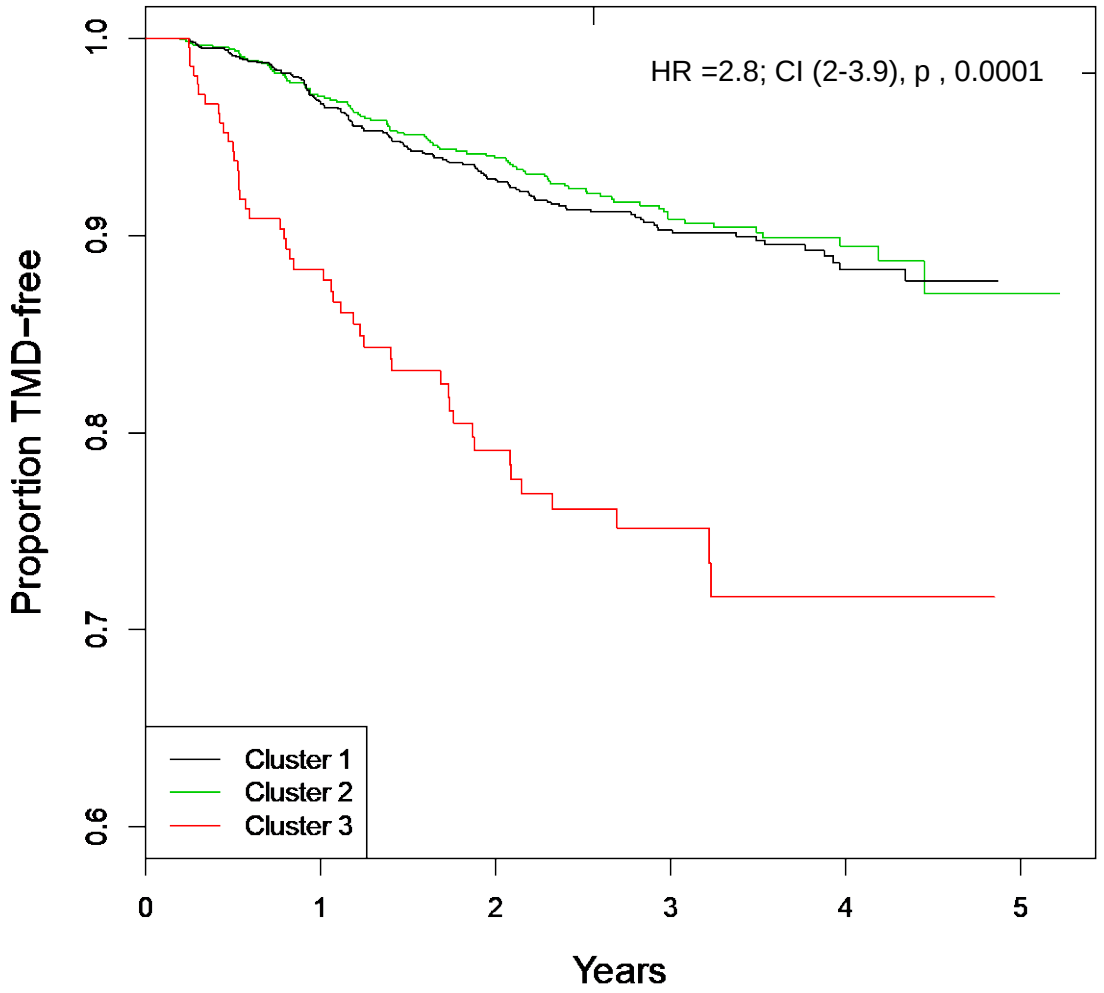
The classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish one disorder from the other (eg, back pain vs temporomandibular disorder [TMD]) or to define subtypes (eg, TMD myalgia vs arthralgia). However, anatomical criteria overlook etiology, potentially hampering treatment decisions. This study identified clusters of individuals using a comprehensive array of biopsychosocial measures. Data were collected from a case–control study of 1031 chronic TMD cases and 3247 TMD-free controls. Three subgroups were identified using supervised cluster analysis (referred to as the adaptive, pain-sensitive, and global symptoms clusters). Compared with the adaptive cluster, participants in the pain-sensitive cluster showed heightened sensitivity to experimental pain, and participants in the global symptoms cluster showed both greater pain sensitivity and greater psychological distress. Cluster membership was strongly associated with chronic TMD: 91.5% of TMD cases belonged to the pain-sensitive and global symptoms clusters, whereas 41.2% of controls belonged to the adaptive cluster. Temporomandibular disorder cases in the pain-sensitive and global symptoms clusters also showed greater pain intensity, jaw functional limitation, and more comorbid pain conditions. Similar results were obtained when the same methodology was applied to a smaller case–control study consisting of 199 chronic TMD cases and 201 TMD-free controls. During a median 3-year follow-up period of TMD-free individuals, participants in the global symptoms cluster had greater risk of developing first-onset TMD (hazard ratio = 2.8) compared with participants in the other 2 clusters. Cross-cohort predictive modeling was used to demonstrate the reliability of the clusters.

Keywords: Temporomandibular disorders, Clustering, Classification of chronic pain

A


Z−scores of Selected Variables in the OPPERA Cohort (95% CI)
Adaptive Cluster (n=1426)
Pain−Sensitive Cluster (n=2062)
Global Symptoms Cluster (n=790)
Trapezius PPT
Mechanical Aftersensation (512 mN, 15 sec.)
Heat Pain Tolerance
Heat Pain Ratings (50 deg. C)
Praying (CSQ)
Neuroticism (EPQ)
Helplessness (PCS)
Energetic & Tired (POMS)
Sleep Quality (PSQI)
Perceived Stress (PSS)
Somatization (SCL90)
Anxiety (SCL90)
Depression (SCL90)
Body Sites Tender to Palpation
Count of Comorbid Conditions
−1.0
−0.5
0.0
0.5
1.0
1.5

Hazard Ratio (C1 vs C3) for First-Onset TMD



N = 2,731 TMD-free individuals; 260 onset cases

Bair and Coworkers

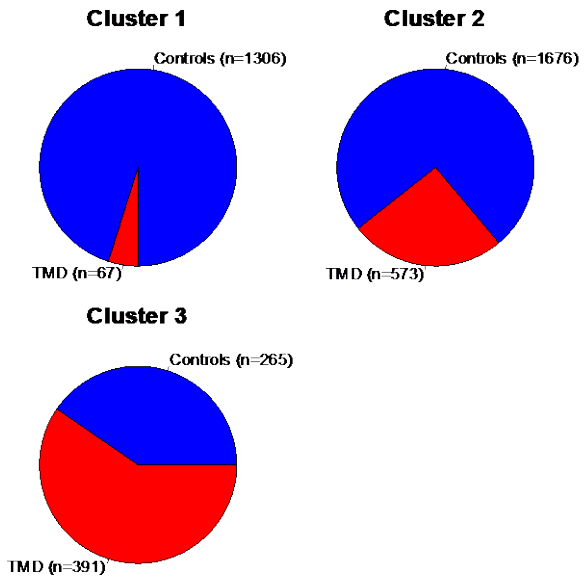
TMD Clinical Characteristics Based on Cluster Assignment

Clinical Variable	A Means (n=85)	PS Means (n=529)	GS Means (n=400)	Overall P-Value
Duration of Facial Pain (months)	6.08	7.15	6.84	0.3318
Current Facial Pain (0-100)	15.63	**18.42**	**29.46**	*<0.0001*
Facial Pain Intensity 2 wks (0-100)	45.67	**52.41**	**61.53**	*<0.0001*
% Waking Day with Pain	35.41	**32.63**	**48.31**	*<0.0001*
Pain Intensity 2 wks (0-20)	5.74	**6.12**	**8.98**	*<0.0001*
Pain Unpleasantness 2 wks (0-20)	5.14	**5.54**	**8.07**	*<0.0001*
Facial Pain Interference 2 wks (0-100)	12.50	**19.80**	**30.92**	*<0.0001*
SF12v2 Physical Functioning Scale (0-100)	91.07	**89.30**	**73.24**	*<0.0001*
No. Orofacial sites tender to palpation (0-38)	15.61	**21.61**	**25.32**	*<0.0001*
SF12v2 Mental Health Scale (0-100)	76.47	**68.31**	**43.44**	*<0.0001*
No. body sites tender to palpation (0-14)	4.16	**5.53**	**7.08**	*<0.0001*
Chronic pain in areas other than the face (%)	32.18	42.17	**64.19**	*<0.0001*
Count of 20 comorbid conditions	1.14	**1.91**	**4.25**	*<0.0001*

Bold Black = A different from PS; ***Bold Red = PS different from GS***

Bair E, et al Pain. 2016 Jun;157(6):1266-78.

Proportions of TMD Cases and Controls in Each Cluster



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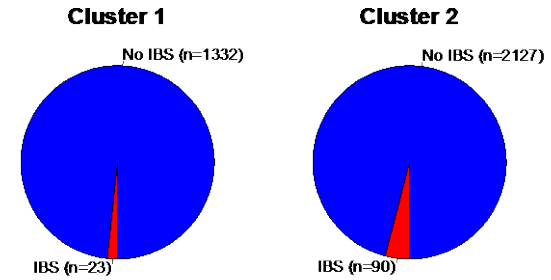
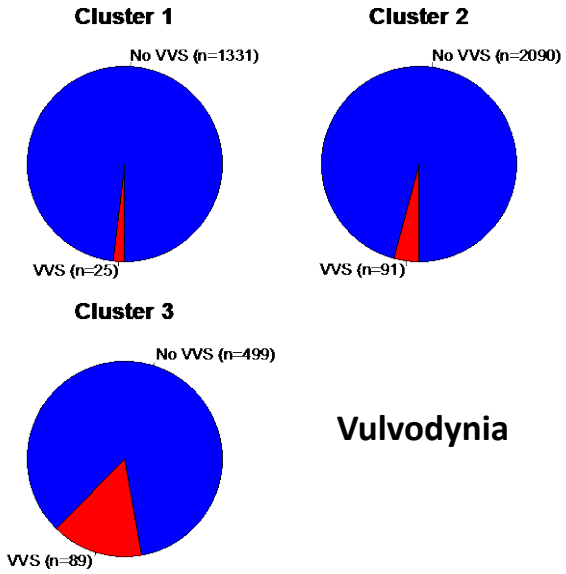
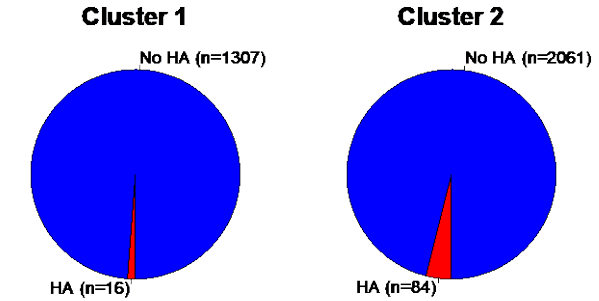
Clusters and Comorbid Pain Conditions

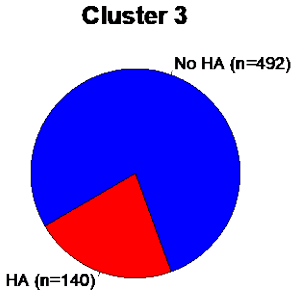


Irritable Bowl Syndrome

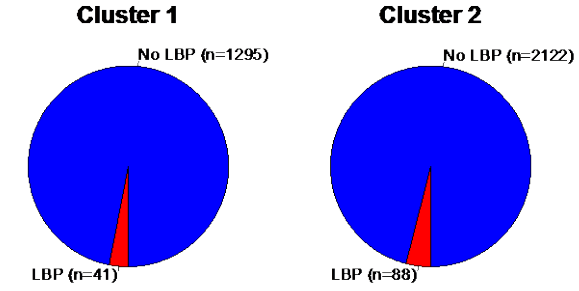


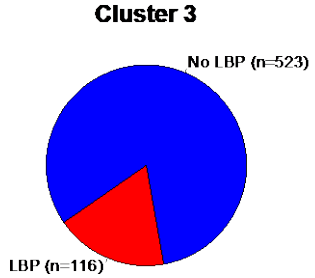
Vulvodynia





Chronic Headache





Chronic Low Back Pain

OPPERA Omic Studies

- Inflammatory cytokines (e.g., MCP1, IL1b, IL1ra, IL8) are increased and the transcriptional factor TGFβ1 is decreased TMD patients[1]

- Pathway analyses via DRG eQTL and GWAS findings reveal T&B cell signaling, Human Leukocyte Antigen (HLA) and SMAD1 alterations in TMD patients.[2-4]

[1] Slade, G. D. et al. Pain 152, 2802-2812 (2011); [2] Smith, S. B. et al. Pain 160, 579-591, (2019); [3] Parisien, M. et al.. Cell Reports 19, 1940-1952, 2017); [4] Slade, G. D. et al. Pain 154, 2335-2343, (2013)

Ongoing Immunophenotyping

- GS cluster is elevated ($p<0.05$) relative to A cluster for:
  - HLA-DR+ Helper T Lymphocytes
  - Activated Helper T Lymphocytes
  - CD25 MFI on Transitional monocytes
  - CD25+ Transitional monocytes
  - HLA-DR MFI on Nonclassical monocytes

OPPERA I – Lessons Learned

1. *It is a misnomer and no longer appropriate to regard TMD solely as a localized orofacial pain condition.*

2. *It is pointless to envisage a single cause, nor even to expect that any one cause might be necessary or sufficient to explain TMD. For the majority of people with chronic TMD, the condition is a multisystem disorder with overlapping co-morbidity.*

Summary of findings from the OPPERA prospective cohort study of incidence of first-onset temporomandibular disorder: implications and future directions
Slade et al., J Pain 2013; 14: T116-24

Target Discovery

A few putative targets identified (reverse translation) or confirmed (forward translation) by human genetic studies

- COMT/ β_2
  - Completed POC
  - NCEs under development
- Novel opioid receptor splice variants (eg. OPRM1/OPRM1-β_2)
  - NCE under development
- EGFR and associated downstream pathways
- Nicotinic receptors
- α2δ2 calcium channel subunit
- CA8
- KCNS1
- CGH1
- SCN9A/Nav1.7
- P2X7 receptor
- 5HT2a

Epiregulin and EGFR interactions are involved in pain processing

Loren J. Martin,[1,2] Shad B. Smith,[3] Arkady Khoutorsky,[4] Claire A. Magnussen,[5] Alexander Samoshkin,[6] Robert E. Sorge,[1] Chulmin Cho,[2] Noosha Yosefpour,[5] Sivaani Sivaselvachandran,[2] Sarasa Tohyama,[2] Tiffany Cole,[7] Thang M. Khuong,[7] Ellen Mir,[3] Dustin G. Gibson,[3] Jeffrey S. Wieskopf,[1] Susana G. Sotocinal,[1] Jean Sebastien Austin,[1] Carolina B. Meloto,[6] Joseph H. Gitt,[3] Christos Gkogkas,[4] Nahum Sonenberg,[4] Joel D. Greenspan,[8] Roger B. Fillingim,[9] Richard Ohrbach,[10] Gary D. Slade,[11] Charles Knott,[12] Ronald Dubner,[8] Andrea G. Nackley,[3] Alfredo Ribeiro-da-Silva,[5] G. Gregory Neely,[7] William Maixner,[3] Dmitri V. Zaykin,[13] Jeffrey S. Mogil,[1] and Luda Diatchenko[6]

[1]Department of Psychology and Alan Edwards Centre for Resear
Canada. [3]Center for Neurosensory Disorders, University of North
Montreal, Quebec, Canada. [5]Department of Pharmacology and
of Dentistry and Alan Edwards Centre for Research on Pain, Mc
Sydney, Australia. [8]Department of Neural and Pain Sciences and
Behavioral Science, University of Florida, Gainesville, Florida, US
Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [12]Battel
North Carolina, USA.

American Pain Society RESEARCH EDUCATION TREATMENT ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 12 (December), 2015: pp 1321-1333
Available online at www.jpain.org and www.sciencedirect.com

Differences in the Antinociceptive Effects and Binding Properties of Propranolol and Bupranolol Enantiomers

Loren J. Martin,[*,†,‡] Marjo H. Piltonen,[†,§] Josee Gauthier,[¶] Marino Convertino,[‖] Erinn L. Acland,[*,†,‡] Nikolay V. Dokholyan,[‖] Jeffrey S. Mogil,[*,†] Luda Diatchenko,[†,§,¶] and William Maixner[¶]

**Department of Psychology, †Alan Edwards Centre for Research on Pain, and §Department of Anesthesiology, McGill University, Montreal, Quebec, Canada.*
‡Department of Psychology, University of Toronto Mississauga, Mississauga, Ontario, Canada.
¶Center for Pain Research and Innovation and ‖Department of Biochemistry and Biophysics, University of North Carolina, Chapel Hill, North Carolina.

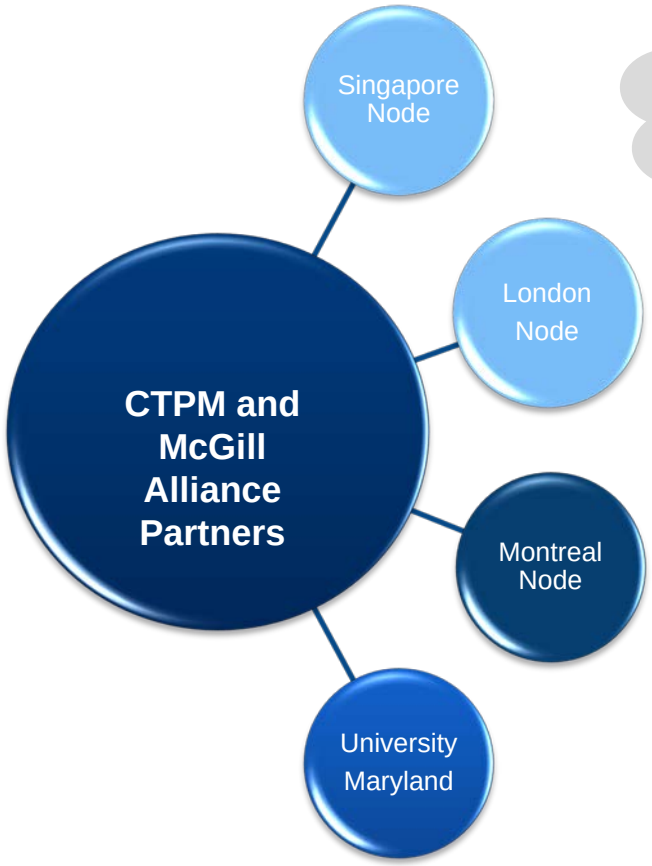
Human Molecular Genetics, 2009, Vol. 18, No. 6 **1037–1051**
doi:10.1093/hmg/ddn439
Advance Access published on December 22, 2008

Expansion of the human μ-opioid receptor gene architecture: novel functional variants

Svetlana A. Shabalina[1,*], Dmitri V. Zaykin[2], Pavel Gris[3], Aleksey Y. Ogurtsov[1], Josee Gauthier[3], Kyoko Shibata[2], Inna E. Tchivileva[3], Inna Belfer[4,5,6], Bikashkumar Mishra[4,5], Carly Kiselycznyk[4,5], Margaret R. Wallace[7], Roland Staud[8], Nikolay A. Spiridonov[9], Mitchell B. Max[4,6,†], David Goldman[5], Roger B. Fillingim[8], William Maixner[3] and Luda Diatchenko[3,*]

Future Directions

Pain Management/Pain Research Module



Center for Translational Pain Medicine

- ✓ Secure cloud system
- ✓ HIPAA compliant
- ✓ Customizable & scalable
- ✓ Core Phenotypes:
  - ❑ Medical
  - ❑ Pain
  - ❑ Symptoms
  - ❑ Coping
  - ❑ Stress
  - ❑ Sleep
  - ❑ Risk factors
  - ❑ Satisfaction
- ✓ Biologics
- ✓ LabVantage LIMS
- ✓ PEDIGENE linkage
- ✓ Reports and Analyses
- ✓ EPIC DataMart linkage

Barriers to Discovery and Development

- **Preclinical animal and human models**
  - **a need for models that capture the complexities and pathophysiology of human pain conditions**

- **Poor understanding of the human pathophysiologies that underlie persistent pain conditions**
  - **a need for conceptual models that capture the complexities and heterogeneity of human pain conditions**
  - **a need for “big data”: cellular, animal, human**
  - **a need for bioinformatics tools**
  - **mechanisms to foster collaboration**

Table 6. Number of Studies and Number of Patients Examined (Total N) Who Report an Increase in Pain Sensitivity Across Nociceptive Modalities and Across COPCs

Stimulus	*FM*	*CFS*	*IBS*	*TTH*	*Migraine*	*TMD*	*MPS/RSTPS*	*PD*
Pressure (somatic)	15 (580)			4 (178)	3 (117)	2 (42)	9 (462)	1 (20)
Pressure (rectal)			26 (822)					
Heat (somatic)	12 (480)		2 (21)	1 (50)	3 (117)	3 (76)	3 (137)	2 (42)
Heat (rectal)			1 (46)					
Cold (somatic)	8 (255)		1 (33)		1 (41)		2 (184)	
Electric (cutaneous)	4 (61)		1 (12)				2 (36)	
Electric (intramuscular)	2 (41)	1 (23)					2 (36)	1 (10)
Electric (spinal reflex)	2 (107)		1 (14)	1 (40)			1 (27)	
Electric (rectal)			2 (21)					
Ischemic	1 (60)					2 (72)		
Hypertonic saline	2 (41)					1 (22)	1 (11)	
Auditory stimulus	1 (20)		1 (15)		1 (65)			

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia syndrome; CFS, chronic fatigue syndrome; IBS, irritable bowel syndrome; TTH, tension type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft tissue pain syndrome; PD, primary dysmenorrhea.

Maixner et al. J Pain. 2016 Sep; 17(9 Suppl): T93–T107

Table 5

Potential environmental risk factors for temporomandibular disorder and cluster membership.

	A, %	SE, %	n	PS, %	SE, %	n	GS, %	SE, %	n	*P**	A vs PS†	PS vs GS†	A vs GS†
OPPERA cohort													
Lifetime history of jaw injury	8.2	0.8	1339	11.5	0.7	1824	18.9	1.6	608	<0.0001	0.0034	<0.0001	<0.0001
Lifetime history of smoking	22.0	1.1	1426	24.7	1.0	2056	41.8	1.8	789	<0.0001	0.0777	<0.0001	<0.0001
Lifetime history of hormonal contraceptive use (females)	64.9	2.0	579	70.1	1.2	1480	72.9	1.9	536	0.0121	0.0277	0.2295	0.0048
Current hormonal contraceptive use (females)	18.2	1.6	583	17.1	1.0	1494	11.7	1.4	540	0.0032	0.6166	0.0034	0.0030
Traumatic life event (LSL)	36.2	1.3	1421	40.1	1.1	2054	61.1	1.7	786	<0.0001	0.0207	<0.0001	<0.0001
UNC cohort													
Lifetime history of jaw injury	28.9	3.7	152	32.6	4.0	138	44.1	6.5	59	0.1172	0.5839	0.1699	0.0535
Lifetime history of smoking	17.1	3.1	152	26.6	3.7	139	43.1	6.1	65	0.0004	0.0679	0.0286	0.0001
Traumatic life event (LSL)	25.6	3.4	164	27.3	3.6	154	41.5	5.4	82	0.0318	0.8345	0.0380	0.0168

* *P* value for the null hypothesis that the mean value of the risk factor does not differ between the 3 clusters.

† *P* value for the null hypothesis that the mean value of the risk factor does not differ between clusters, the A and PS (or the PS/GS or A/GS, respectively).

A, adaptive cluster; GS, global symptoms cluster; LSL, Lifetime Stressor List; PS, pain-sensitive cluster.

Bair E, et al Pain. 2016 Jun;157(6):1266-78.