The OPPERA Case-Control Study: Putative Risk Factors and Mechanisms for Persistent TMD Pain

Chairpersons
Ambra Michelotti and Richard Ohrbach

OPPERA: Orofacial Pain Prospective Evaluation and Risk Assessment
# The OPPERA Case-Control Study: Putative Risk Factors and Mechanisms for Persistent TMD Pain

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
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<tr>
<td>8:00</td>
<td>John Kusiak</td>
<td>Introductory Remarks Regarding the OPPERA Program</td>
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<tr>
<td>8:05</td>
<td>Gary Slade</td>
<td>OPPERA Study Overview and Quantitative Sensory Testing</td>
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<td>8:25</td>
<td>Richard Ohrbach</td>
<td>OPPERA Psychosocial and Clinical Profiles</td>
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<td>8:45</td>
<td>William Maixner</td>
<td>OPPERA Study – Emerging Genetic Findings and Discoveries</td>
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<td>9:05</td>
<td>Peter Svensson</td>
<td>Commentary</td>
</tr>
<tr>
<td>9:10</td>
<td>Ambra Michelotti</td>
<td>Discussion</td>
</tr>
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</table>
OPPERA Study Overview and Quantitative Sensory Testing

Gary Slade
University of North Carolina – Chapel Hill

Supported by NIH/NIDCR Grant U01DE17018
Disclosure

Gary Slade is a consultant and equity stock holder in Algynomics Inc., a company providing research services in personalized pain medication and diagnostics.
Scope of presentation

Part 1
• Aims of the OPPERA project
• Heuristic model
• Study design
• Overview of methods
• Sociodemographic factors associated with TMD

Part 2
• Quantitative sensory testing (QST)
  – Univariate associations with TMD
  – Principal component analysis of 33 QST measures
  – Multivariable modeling of five QST measures
Part 1. Aims of OPPERA

To determine if

- sociodemographic characteristics,
- responses to noxious stimuli,
- psychosocial profiles, and
- genetic variants in 300 candidate genes

are associated with elevated risk of first-onset TMD and increased odds of chronic TMD.
Four study designs

1. Prospective cohort study of first-onset TMD.
   - 3-monthly screening questionnaires of all people. Clinical assessment of each person who screens positively and one matched control who screens negatively.

2. Baseline case-control study of chronic TMD

3. Matched case-control study of incident TMD
   - ~300 incident cases of 1st onset TMD
   - ~300 controls without TMD

4. Prospective case-cohort study of symptom persistence
   - ~300 incident cases of 1st onset TMD
   - ~300 controls without TMD

185 people with chronic TMD

3,263 people without TMD
Baseline case-control study

• Volunteers were recruited by community-wide advertisements, emails, flyers and word-of-mouth
  – Baltimore MD, Buffalo NY, Chapel Hill NC, and Gainesville FL
  – 185 cases with examiner-classified TMD
  – 1,633 controls who did not have TMD when examined
• Data collection took place from May 2006 – November 2008
  – Telephone interview
  – Self-completed questionnaires
  – Clinical examination of head, neck and body¹
  – Quantitative sensory testing
  – Autonomic function
  – Blood sample for genotyping

Inclusion and exclusion criteria

OPPERA-wide inclusion criteria
• Aged 18-44 yrs
• Written consent to undertaken study procedures

OPPERA-wide exclusion criteria
• Nine health-related conditions (eg. kidney disease, heart disease, uncontrolled diabetes, psychiatric illness requiring hospitalization)
• Pregnant or nursing
• Traumatic facial injury or surgery during the preceding six months. [Does not include surgery only to remove teeth]
• Currently receiving orthodontic treatment
## Classification of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Telephone interview</th>
<th>Clinical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TMD cases</strong></td>
<td>• Orofacial pain ≥ 15 days in 30 days prior to interview</td>
<td>• ≥ 5 days of regional pain in past 30 days in the examiner-defined orofacial region</td>
</tr>
<tr>
<td></td>
<td>• Orofacial pain ≥5 days/month in the five months before that</td>
<td>• either ≥3 TM muscle groups or ≥1 TM joint painful to palpation or jaw movement</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>No orofacial pain in the month before interview and &lt;5 days/month in the five months before that</td>
<td>• &lt; 5 days of pain in past 30 days in the examiner-defined orofacial region</td>
</tr>
<tr>
<td></td>
<td>&lt;5 headaches/month in past 3 months</td>
<td>• <em>Findings from muscle/joint palpation and jaw movement were not used as eligibility criteria for controls</em></td>
</tr>
<tr>
<td></td>
<td>Do not wear night guard or occlusal splint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never diagnosed with TMD</td>
<td></td>
</tr>
</tbody>
</table>

*Kappa values for inter-examiner reliability ranged from 0.77 to 1.0*
Analysis of associations with TMD

• Psychological scales/subscales and measures of pain sensitivity were computed using published algorithms
  – When up to 50% of constituent items were missing, data were imputed using expectation-maximization method

• Continuous measures were transformed to z-scores, and used as explanatory variables in binary logistic regression models to estimate standardized odds ratios for TMD

• Multivariable logistic regression models evaluated multiple explanatory variables
  – Area under ROC curve was used as an indicator of the model’s capacity to discriminate cases from controls
**Principal component analysis**

Aims were to reduce dimensionality of the data and to identify latent variables.

Four steps:

1. Variable selection from within major domains of the heuristic model (pain sensitivity, psychological distress, autonomic function)
2. Evaluation of the correlation matrix
3. Extraction of principal components and parallel analysis to select number of components
4. Varimax rotation with generation of factor loadings and bootstrap estimation of 95% confidence intervals for loadings
Sample size calculations

• Primary endpoints were for the prospective cohort study
  – required sample size of 3,200 people with no TMD at baseline
  – minimum-detectable risk ratios of 2.0 for up to 10 genetic markers
  – allowing for SNPs with rare allele prevalence as low as 15%
  – specifying 99.5% confidence intervals and type II error of 0.2
  – assuming annual incidence of first onset TMD of 1.8%

• For the baseline case-control study of 185 cases and 50% sample of controls from baseline of the prospective cohort study
  – minimum detectable odds ratios of 1.7 for binary predictor variables with exposure prevalence as low as 15%
  – minimum-detectable standardized odds ratio of 1.25 for continuous predictor variables
  – thresholds of P=0.05 for type I error and 0.2 for type II error
## Demographic associations with TMD

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Controls</th>
<th>TMD cases</th>
<th>Adjusted* odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of people</td>
<td>column %</td>
<td>No. of people</td>
</tr>
<tr>
<td>35-44</td>
<td>344</td>
<td>21.1</td>
<td>53</td>
</tr>
<tr>
<td>25-34</td>
<td>451</td>
<td>27.6</td>
<td>60</td>
</tr>
<tr>
<td>18-24</td>
<td>838</td>
<td>51.3</td>
<td>72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Controls</th>
<th>TMD cases</th>
<th>Adjusted* odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of people</td>
<td>column %</td>
<td>No. of people</td>
</tr>
<tr>
<td>Female</td>
<td>925</td>
<td>56.6</td>
<td>155</td>
</tr>
<tr>
<td>Male</td>
<td>708</td>
<td>43.4</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Controls</th>
<th>TMD cases</th>
<th>Adjusted* odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of people</td>
<td>column %</td>
<td>No. of people</td>
</tr>
<tr>
<td>non-White</td>
<td>794</td>
<td>48.6</td>
<td>40</td>
</tr>
<tr>
<td>White</td>
<td>839</td>
<td>51.4</td>
<td>145</td>
</tr>
</tbody>
</table>

* Adjusted for study site and other demographic characteristics
Age- and gender-associations with TMD: US population and OPPERA

A

US population (NHIS 2007-09)

B

OPPERA

Age group (years)

Prevalence in US population ± 95% CI

Proportion of cases ± 95% CI

0.00

0.02

0.04

0.06

0.08

0.10

18-24

25-34

35-44

45-54

55-64

65-74

>=75

Female

Male

18-24

25-34

35-44

45-54

55-64

65-74

>=75

Female

Male
Part 2. Quantitative sensory testing

- 9 measures of sensitivity to mechanical cutaneous stimuli
  - threshold, tolerance
  - temporal summation
  - aftersensations

- Pressure pain threshold measured at 5 locations
  - masseter, temporalis, TM joint
  - trapezius, lateral epidondyle

- 19 measures of sensitivity to thermal stimuli
  - threshold, tolerance
  - temporal summation
  - aftersensations
Univariate associations with TMD* – mechanical and pressure pain –

* Association between single pain measures and TMD, adjusted for study site, age, gender and race
Univariate associations with TMD* – thermal pain –

* Association between single pain measures and TMD, adjusted for study site, age, gender and race
Summary of principal component analysis

Five components accounted for 72% of variance:
1. thresholds and tolerance from multiple modalities
2. mechanical cutaneous pain ratings, aftersensations, and temporal summation
3. heat pain temporal summation ("windup")
4. overall heat pain ratings
5. heat pain aftersensations

For all components, $\alpha \geq 0.87$
Variables selected from each component

Five components accounted for 72% of variance:

1. thresholds and tolerance from multiple modalities
2. mechanical cutaneous pain ratings, aftersensations, and temporal summation
3. heat pain temporal summation (“windup”)
4. overall heat pain ratings
5. heat pain aftersensations

For all components, $\alpha \geq 0.87$

Variables selected for this analysis:

1. Pressure pain threshold at lateral epicondyle (reverse coded)
2. 0-100 rating of single cutaneous stimulus at 256 mN
3. Change from 1st rating (0-100) to greatest subsequent rating (0-100) during 48°C temporal summation
4. Area Under Curve (AUC) of 0-100 ratings during 48°C temporal summation
5. 0-100 rating 30 sec after 10th thermal stimulus at 48°C
## Correlations among 5 QST measures

<table>
<thead>
<tr>
<th></th>
<th>Pressure pain threshold</th>
<th>Thermal windup</th>
<th>Thermal area under curve</th>
<th>Thermal aftersensations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical cutaneous</td>
<td>0.18</td>
<td>0.37</td>
<td>-0.09</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(0.13, 0.22)</td>
<td>(0.33, 0.41)</td>
<td>(-0.13, -0.04)</td>
<td>(0.27, 0.35)</td>
</tr>
<tr>
<td>Pressure pain</td>
<td>0.33</td>
<td>0.02</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.29, 0.37)</td>
<td>(-0.02, 0.07)</td>
<td>(0.11, 0.20)</td>
<td></td>
</tr>
<tr>
<td>Thermal windup</td>
<td></td>
<td>0.13</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.09, 0.18)</td>
<td>(0.32, 0.40)</td>
<td></td>
</tr>
<tr>
<td>Thermal AUC</td>
<td></td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.04, 0.06)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stratified associations: pressure pain

Odds ratios for lateral epicondyle pressure pain threshold (reversed)

* Odds ratios for TMD, adjusted for study site, age, gender and race
Stratified associations: pressure pain

Odds ratios for lateral epicondyle pressure pain threshold (reversed)

* Odds ratios for TMD, adjusted for study site, age, gender and race
Summary of stratified associations

- In general, standardized odds ratios for one QST measure did not vary across strata of low, mid and high tertiles of the other QST measures.
- This suggests independence of effects, that is:
  - no confounding
  - no interaction
Multivariable models for odds of TMD - stepwise selection of five variables -

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Odds ratios from multivariable logistic regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure pain threshold</td>
<td>2.0</td>
</tr>
<tr>
<td>Mechanical cutaneous</td>
<td>1.4</td>
</tr>
<tr>
<td>Thermal windup</td>
<td>1.2</td>
</tr>
<tr>
<td>Thermal area under curve</td>
<td>ns</td>
</tr>
<tr>
<td>Thermal aftersensation</td>
<td>ns</td>
</tr>
</tbody>
</table>

Model discrimination (AUC) 0.81

* Models additional adjust for study site, age, gender and race
Multivariable models for odds of TMD - stepwise selection of five variables -

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Explanatory variables coded as z-scores</th>
<th>Explanatory variables dichotomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure pain threshold</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Mechanical cutaneous</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Thermal windup</td>
<td>1.2</td>
<td>ns</td>
</tr>
<tr>
<td>Thermal area under curve</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Thermal aftersensation</td>
<td>ns</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Model discrimination (AUC) 0.81 0.80

* Models additional adjust for study site, age, gender and race
Multivariable models for odds of TMD
- count of QST values in upper tertile -

* Odds ratios for TMD, adjusted for study site, age, gender and race
Multivariable models for odds of TMD - count of QST values in upper tertile -

Odds ratios for TMD

Odds Ratio (95% CI)

Number of QST variables in upper tertile

ROC Curves for Comparisons

Study site, AUC=0.57

* Odds ratios for TMD, adjusted for study site, age, gender and race
Multivariable models for odds of TMD - count of QST values in upper tertile -

* Odds ratios for TMD, adjusted for study site, age, gender and race
Multivariable models for odds of TMD
- count of QST values in upper tertile -

* Odds ratios for TMD, adjusted for study site, age, gender and race
Conclusions

In the baseline OPPERA case-control study:

• Greater age, female gender and white race were associated with increased odds of TMD

• Moderately strong univariate associations with TMD were found for pressure pain thresholds at multiple body sites and rating of mechanical cutaneous pain at the finger
  – Weaker associations with TMD were found for other mechanical cutaneous measures and for thermal measures at the arm

• Exploratory factor analysis of 33 QST measures identified five principal components
  – thresholds to various stimuli
  – mechanical cutaneous pain
  – thermal ratings, windup, and after sensations

continued
Conclusions

• Stratified analysis of five QST variables, one from each component, suggested they were independently associated with TMD

• Conventional, stepwise multivariable logistic regression modeling identified three variables that contributed to odds of TMD
  – they added only modestly to sociodemographic characteristics in discriminating cases from controls

• A person-level summary variable, created by counting the number of variables with values in the upper tertile of the distribution, provided similar ability to discriminate cases from controls
  – it showed increasing odds of TMD associated with each additional high score, up to four high scores
## Acknowledgments

- This study is sponsored by National Institute of Dental and Craniofacial Research, National Institutes of Health (U01DE17018).
- Battelle Memorial Institute serves as the OPPERA Data Coordination Center.

<table>
<thead>
<tr>
<th>OPPERA Epidemiology Core</th>
<th>OPPERA QST Working Group</th>
</tr>
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<tbody>
<tr>
<td>Eric Bair</td>
<td>Joel Greenspan</td>
</tr>
<tr>
<td>Cristina Baraian</td>
<td>Bill Maixner</td>
</tr>
<tr>
<td>Flora Mulkey</td>
<td>Ron Dubner</td>
</tr>
</tbody>
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The OPPERA Case-Control Study:
Putative Risk Factors and Mechanisms for Persistent TMD Pain

Psychosocial and Clinical Profiles

Richard Ohrbach
School of Dental Medicine
University at Buffalo

Supported by NIH/NIDCR Grant U01DE17018
Aims of OPPERA

To determine if:
- sociodemographic characteristics,
- responses to noxious stimuli,
- psychosocial profiles, and
- genetic variants in 300 candidate genes

are associated with elevated risk of first-onset TMD and increased odds of chronic TMD.
Scope of presentation

With a cohort of non-TMD controls and chronic TMD cases, assess associations using the following variables:

Part 1
• Psychological constructs and measures
  – Univariate associations with TMD
  – Principal component analysis of 21 psychological measures
  – Multivariable modeling of 4 psychological measures

Part 2
• Clinical constructs and measures
  – Univariate associations with TMD
  – Multivariable modeling of six clinical measures
High Psychological Distress

Mood
Anxiety
Depression
Stress response
Somatization

High State of Pain Amplification

Persistent TMD
Transient TMD
Subclinical signs & symptoms

ENVIRONMENTAL CONTRIBUTIONS

Physical environment
- eg. trauma, infection
Social environment
- eg. life stressors
Culture
- eg. health beliefs
Demographics

GAD65
MAO
Serotonin transporter
Cannabinoid receptors
Dopamine receptors
Adrenergic receptors
Serotonin transporter
CACNA1A
DREAM
POMC
NET
Opioid receptors
Na+, K+-ATPase
IKK
COMT
NGF
Prodynorphin
Interleukins

ENVIRONMENTAL
CONTRIBUTIONS

Physical environment
- eg. trauma, infection
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Demographics

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ENVIRONMENTAL
CONTRIBUTIONS

Physical environment
- eg. trauma, infection
Social environment
- eg. life stressors
Culture
- eg. health beliefs
Demographics
Psychological Questionnaires

- **Pre-Clinic**
  - Coping Strategies Questionnaire-Revised (CSQ-R)
  - Eysenck Personality Questionnaire-Revised (EPQ)
  - Kohn Reactivity Scale (KOHN)
  - Life Experiences Survey (LES)
  - Lifetime Stressor List & PSTD Checklist for Civilians (LSL/PCL-C)
  - Perceived Stress Scale (PSS)
  - Trait Anxiety Inventory
  - Pennebaker Inventory for Limbic Languidness (PILL)
  - Pain Catastrophizing Scale (PCS)
  - Symptom Checklist 90-Revised (SCL-90R)

- **In-Clinic**
  - Profile of Mood States-Bipolar (POMS-Bi)
  - State Anxiety Inventory
  - In-Vivo Coping
SCL-90R

* p < .0001
Standardized Odds Ratios – Psychosocial Measures

SOR adjusted for study site, age, gender, and race. 
Effect estimates use imputation for missing data, total n=1808.
# Component Loadings for PCA Model in Controls (n=1633)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Component 1</th>
<th>Component 2</th>
<th>Component 3</th>
<th>Component 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI Y1 State-Trait Anxiety Inventory</td>
<td>0.78</td>
<td>0.13</td>
<td>-0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>STAI Y2 State-Trait Anxiety Inventory</td>
<td>0.79</td>
<td>0.14</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall Positive Affect Score</td>
<td>-0.85</td>
<td>0.17</td>
<td>0.11</td>
<td>0.06</td>
</tr>
<tr>
<td>Overall Negative Affect Score</td>
<td>0.49</td>
<td>0.39</td>
<td>-0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>PSS Perceived Stress Scale</td>
<td>0.69</td>
<td>0.16</td>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>EPQ-R Extraversion Scale</td>
<td>-0.61</td>
<td>0.21</td>
<td>0.13</td>
<td>-0.05</td>
</tr>
<tr>
<td>EPQ-R Neuroticism Scale</td>
<td>0.55</td>
<td>0.18</td>
<td>0.17</td>
<td>-0.01</td>
</tr>
<tr>
<td>SCL 90R Depression Scale</td>
<td>0.29</td>
<td>0.69</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>SCL 90R Somatization Full Scale</td>
<td>-0.13</td>
<td>0.84</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>SCL 90R Anxiety Scale</td>
<td>0.10</td>
<td>0.81</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>SCL 90R Hostility Scale</td>
<td>0.09</td>
<td>0.74</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>PILL Global Score</td>
<td>-0.12</td>
<td>0.67</td>
<td>0.13</td>
<td>0.03</td>
</tr>
<tr>
<td>CSQ_Praying Scale</td>
<td>0.02</td>
<td>-0.20</td>
<td>0.55</td>
<td>0.31</td>
</tr>
<tr>
<td>Global Kohn Scale</td>
<td>0.26</td>
<td>-0.17</td>
<td>0.46</td>
<td>-0.25</td>
</tr>
<tr>
<td>PCS Rumination</td>
<td>-0.10</td>
<td>0.08</td>
<td>0.88</td>
<td>-0.07</td>
</tr>
<tr>
<td>PCS Magnification</td>
<td>-0.05</td>
<td>0.15</td>
<td>0.79</td>
<td>0.01</td>
</tr>
<tr>
<td>PCS Helplessness</td>
<td>-0.01</td>
<td>0.12</td>
<td>0.83</td>
<td>-0.05</td>
</tr>
<tr>
<td>CSQ_Distraction Scale</td>
<td>0.05</td>
<td>-0.19</td>
<td>0.32</td>
<td>0.67</td>
</tr>
<tr>
<td>CSQ_Ignoring Pain Scale</td>
<td>-0.04</td>
<td>0.13</td>
<td>-0.33</td>
<td>0.79</td>
</tr>
<tr>
<td>CSQ_Distancing Scale</td>
<td>0.13</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.72</td>
</tr>
<tr>
<td>CSQ_Coping Scale</td>
<td>-0.12</td>
<td>0.07</td>
<td>-0.01</td>
<td>0.79</td>
</tr>
<tr>
<td>Cumulative Variance</td>
<td>0.18</td>
<td>0.35</td>
<td>0.49</td>
<td>0.60</td>
</tr>
<tr>
<td>Cronbach's Alpha</td>
<td>0.87</td>
<td>0.85</td>
<td>0.54</td>
<td>0.74</td>
</tr>
</tbody>
</table>
## Component Loadings for PCA Model in Controls (n=1633)

<table>
<thead>
<tr>
<th>Scale/Inventory</th>
<th>Component 1</th>
<th>Component 2</th>
<th>Component 3</th>
<th>Component 4</th>
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<tbody>
<tr>
<td>STAI Y1 State-Trait Anxiety Inventory</td>
<td>0.78</td>
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<td>STAI Y2 State-Trait Anxiety Inventory</td>
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<tr>
<td>Overall Positive Affect Score</td>
<td>-0.85</td>
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<td>Overall Negative Affect Score</td>
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<td><strong>PSS Perceived Stress Scale</strong></td>
<td>0.69</td>
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<td>EPQ-R Extraversion Scale</td>
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<tr>
<td>EPQ-R Neuroticism Scale</td>
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<td>SCL 90R Depression Scale</td>
<td>0.29</td>
<td>0.69</td>
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<tr>
<td><strong>SCL 90R Somatization Full Scale</strong></td>
<td>-0.13</td>
<td>0.84</td>
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<tr>
<td>SCL 90R Anxiety Scale</td>
<td>0.10</td>
<td>0.81</td>
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<td>SCL 90R Hostility Scale</td>
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<td>PILL Global Score</td>
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<td>CSQ Praying Scale</td>
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<td>-0.20</td>
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<td>PCS Rumination</td>
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<td>0.08</td>
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<td>CSQ Distancing Scale</td>
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<td><strong>CSQ Coping Scale</strong></td>
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<td>Cumulative Variance</td>
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<tr>
<td>Cronbach's Alpha</td>
<td>0.87</td>
<td>0.85</td>
<td>0.54</td>
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**Component 1**

<table>
<thead>
<tr>
<th>Component 1</th>
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<th>Component 3</th>
<th>Component 4</th>
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<tbody>
<tr>
<td>PSS</td>
<td>Somat</td>
<td>Helplessness</td>
<td></td>
</tr>
<tr>
<td>Somat</td>
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<td>Helplessness</td>
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<tr>
<td>Coping</td>
<td>-0.1</td>
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<td>0.04</td>
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**Component 4**

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<th>Component 4</th>
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<td>Somat</td>
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<tr>
<td>Somat</td>
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<tr>
<td>Helplessness</td>
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</tr>
<tr>
<td>Coping</td>
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</table>

Cronbach's Alpha: 0.87, 0.85, 0.54, 0.74
Stratified associations: four psychology measures
Predicted proportion of TMD cases

![Graph showing predicted proportion of TMD cases with somatization and perceived stress z-scores.](image-url)
# Multivariable models for odds of TMD - stepwise selection of four variables -

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Odds ratios from multivariable logistic regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Explanatory variables coded as z-scores</td>
</tr>
<tr>
<td>Stress (PSS)</td>
<td>1.1</td>
</tr>
<tr>
<td>Somatization (SCL90)</td>
<td>2.0</td>
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<tr>
<td>Helplessness (PCS)</td>
<td>1.1</td>
</tr>
<tr>
<td>Coping (CSQ)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Model discrimination (AUC)*

---

* Models additional adjust for study site, age, gender and race
1. **Selected variables:**
   - Somatization (SCL90R)
   - Perceived Stress (PSS-10)
   - Coping (CSQ)
   - Helplessness (PCS)

2. Create count variable: increment if value is in upper tertile for each scale.

3. Odds ratios for TMD

4. 
   - Study site, AUC=0.57
   - + demographics, AUC=0.76
   - + psychological count, AUC=0.80

5. Clinically sensible index of only 4 psychological variables achieved 0.68 Sensitivity and 0.75 Specificity in predicting cases and controls.
Conclusions

In the baseline OPPERA case-control study:

• Multiple psychosocial variables were associated with increased odds of chronic TMD (but most are modest in magnitude)

• Exploratory factor analysis of 21 measures suggests 4 major psychosocial factors:
  - Overall psychological function
  - Affective Distress/Stress
  - Passive Coping
  - Active Coping

• Stratified analysis of four psychological variables, one from each factor, suggested they were independently associated with TMD

continued
Conclusions

• Conventional, stepwise multivariable logistic regression modeling
  - identified three variables that contributed to the odds of chronic TMD, but
  - they added only modestly to sociodemographic characteristics in discriminating cases from controls

• A person-level summary variable, created by counting the number of variables with values in the upper tertile of the distribution,
  - provided similar ability to discriminate chronic cases from controls
  - showed increasing odds of TMD associated with each additional high score, up to four high scores
High Psychological Distress

Mood
  - Mood
  - Anxiety
  - Depression

Stress response
  - Adrenergic receptors
  - Serotonin transporter

Somatization
  - Neuro-endocrine function

High State of Pain Amplification

Neuro-inflammatory state
  - Pro-inflamatory state

Impaired pain regulation
  - Autonomic function

Persistent TMD

Transient TMD

Subclinical signs & symptoms

ENVIRONMENTAL CONTRIBUTIONS

Physical environment
  - eg. trauma, infection

Social environment
  - eg. life stressors

Culture
  - eg. health beliefs

Demographics

GAD65
MAO
Serotonin receptor
Cannabinoid receptors
Dopamine receptors
GR
Adrenergic receptors
Serotonin transporter

CACNA1A
DREAM
POMC
NET
Opioid receptors
BDNF
NGF
Prodynorphin
Interleukins

Xp11.23
12q11.2
9q34.3
11q23
5q31-q32
5q31-32
6q24-q25
1p13.1
22q11.21
Overview of Clinical Data

- **Condition-specific physical variables**
  - Jaw trauma
  - Sleep bruxism
  - Overuse behaviors
  - Orthodontic treatment
  - Limitation in jaw function
  - Associated musculoskeletal dysfun
  - Interference in TMJ function
  - Non-pain symptoms

- **Clinical examination variables**
  - Mobility
  - Movement pain
  - TMJ noise
  - Masticatory palpation pain
  - Non-masticatory palpation pain

- **Health-related variables**
  - Headache
  - Low back pain
  - Irritable bowel syndrome and abdominal problems
  - Gynecologic
  - Functional symptoms and body pain
  - Anthropometric
  - Medical history

610 clinical items distributed across 65 content areas.
71 variables were selected or constructed. 59 are associated with case status.

Standardized Odds Ratios - Clinical Measures

SOR adjusted for study site, age, gender, and race.
Body Palpation Score

Odds ratios for body palpation pain (≥3 sites) and TMD

- Headaches
- Traumatic yawning
- Neural/sensory conditions
- Para-functional score
- Comorbid conditions

Odds Ratios Table:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unadjusted</th>
<th>0-1</th>
<th>≥2</th>
<th>No</th>
<th>Yes</th>
<th>0</th>
<th>1</th>
<th>≥1</th>
<th>0-24</th>
<th>≥25</th>
<th>0-1</th>
<th>≥2</th>
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<tbody>
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</table>

[-standardized odds ratio graph with 95% CI for each condition]
Odds ratios for body palpation pain (≥3 sites) and TMD

Odds ratios for headache (≥2 types) and TMD

Odds ratios for traumatic yawning and TMD

Odds ratios for neural/sensory conditions and TMD

Odds ratios for parafunction score (≥25) and TMD

Odds ratios for comorbid conditions (≥2) and TMD
### Multivariable models for odds of TMD - stepwise selection of four variables -

<table>
<thead>
<tr>
<th>Explanatory variable (categorical)</th>
<th>Odds ratios from multivariable logistic regression model</th>
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</thead>
<tbody>
<tr>
<td>Body palpation (3 or more, vs 0-2)</td>
<td>11.8</td>
</tr>
<tr>
<td>Yawn as trauma (yes, vs no)</td>
<td>5.7</td>
</tr>
<tr>
<td>Number headache types (2 or more, vs 0-1)</td>
<td>2.0</td>
</tr>
<tr>
<td>Hx neural sensory conditions (yes, vs no)</td>
<td>1.6</td>
</tr>
<tr>
<td>Comorbid disorders (2 or more, vs 0-1)</td>
<td>1.7</td>
</tr>
<tr>
<td>Parafunction (25-62, vs 0-24)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Model discrimination (AUC)*: ###

* * Models additional adjust for study site, age, gender and race*
1. **Selected variables:**
   - # headache types (CPSQ)
   - Jaw injury, yawning (CPSQ)
   - Comorbid disorder count (CPSQ)
   - Parafuction score (OBC)
   - # body sites positive to palpation
   - Hx neural/sensory conditions

2. Create count variable: increment if value is in upper tertile for each scale.

3. **Odds ratios for TMD**

4. **ROC Curves for Comparisons**

5. Clinically sensible index of 6 diverse clinical variables achieved 0.76 Sensitivity and 0.85 Specificity in predicting cases and controls.
Conclusions

1. TMD cases are sicker.
2. History of injury is more common among cases.
3. History of orthodontic treatment is more common among cases.
4. History of headache, and more types of headache, are more common among cases.
5. History of back pain, and more episodes of back pain, are more common among cases.
6. History of IBS is more common among cases.
7. Comorbid conditions are more common among cases.
8. Cases report more TMJ noises.
9. Examiners detect more sounds in cases than controls.
10. Closed lock and open lock history are common among cases.
11. Pain from palpation is symmetrical.
12. Distribution of palpation findings among muscles sites are as expected.
13. Cases report more oral behaviors.

continued
Conclusions

In the baseline OPPERA case-control study:

• Multiple clinical variables were associated with increased odds of chronic TMD -- and most have meaningful magnitude

• Stratified analysis of six clinical variables, selected from diverse domains, suggested they were independently associated with chronic TMD

• Conventional, stepwise multivariable logistic regression modeling identified six variables that contributed to the odds of chronic TMD

• A person-level summary variable, created by counting the number of variables with values in the upper tertile of the distribution, provided similar ability to discriminate chronic cases from controls & showed increasing odds of TMD associated with each additional high score, up to six high scores
Acknowledgments

• This study is sponsored by NIDCR, National Institutes of Health (U01DE17018).

• Battelle Memorial Institute serves as the OPPERA Data Coordination Center.

• Personnel involved in this part of the project:

  Roger Fillingim (OPPERA PI)           Sharon Gordon (UMB)
  Gary Slade (Stats/EpiCore)            Pei Feng Lim (UNC)
  Flora Mulkey (Stats/EpiCore)          Margaret Ribeiro-Dasilva (UF)
  Yoly Gonzalez (UB)                    Chuck Greene (EAP member)
                                          Karon Cook (EAP member)
The OPPERA Case-Control Study:
Putative Risk Factors and Mechanisms for Persistent TMD Pain
IADR San Diego, March 19, 2011

OPPERA Study – Emerging Genetic Findings and Discoveries

William Maixner
University of North Carolina – Chapel Hill

Supported by NIH/NIDCR Grant U01DE17018
Disclosure

William Maixner is a founder, officer and equity stock holder in Algynomics Inc., a company providing research services in personalized pain medication and diagnostics.
Operational Aims from OPPERA’s Baseline Case-Control Study

• To identify a set of SNPs, genes and cellular pathways that distinguish cases from controls

• To create a set of SNPs, genes and cellular pathways that capture the main etiologic constructs for TMD
High Psychological Distress

High State of Pain Amplification

Persistent TMD

Transient TMD

Subclinical signs & symptoms

ENVIRONMENTAL CONTRIBUTIONS

- Physical environment: eg. trauma, infection
- Social environment: eg. life stressors
- Culture: eg. health beliefs
- Demographics

High State of Pain Amplification

Impaired pain regulation

Pro-inflammatory state

Mood

Anxiety

Depression

Stress response

Somatization

Neuro-endocrine function

Autonomic function

Endocrine function

Mood

GAD65

Serotonin receptor

Cannabinoid receptors

Dopamine receptors

Adrenergic receptors

Serotonin transporter

CACNA1A

DREAM

POMC

Opioid receptors

BDNF

NGF

Prodynorphin

Interleukins

NA+, K+-ATPase

IKK

COMT

Xp11.23

12q11.2

9q34.3

11q23

5q31-q32

5q31-32

6q24-q25

1p13.1

22q11.21

PAINFUL TMD

Persistent TMD

Transient TMD

Subclinical signs & symptoms
## Association Methods

<table>
<thead>
<tr>
<th>Candidate Gene</th>
<th>Genome-Wide Association</th>
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<tbody>
<tr>
<td>Hypothesis driven (&quot;confirmatory&quot;)</td>
<td>Hypothesis neutral (&quot;exploratory&quot;)</td>
</tr>
<tr>
<td>Relatively inexpensive per sample</td>
<td>Expensive per sample (but price decreasing)</td>
</tr>
<tr>
<td>Relatively expensive per SNP</td>
<td>Very inexpensive per SNP</td>
</tr>
<tr>
<td>Good power in moderately sized studies</td>
<td>Requires very large sample sizes</td>
</tr>
<tr>
<td>Results are easily interpreted</td>
<td>Results may require much work to interpret</td>
</tr>
<tr>
<td>Limited to few genes at a time</td>
<td>“Genome-wide” coverage</td>
</tr>
</tbody>
</table>
Pain Research Panel

Assessment of 3295 SNPs from 350 genes implicated in key pathways that regulate the perception of pain

- Affymetrix ParAllele microarray platform using Molecular Inversion Probe (MIP) technology
- 3 domains relevant to hypothesized risk pathways
- Genes coding for proteins that mediate or modify the therapeutic effects of pharmacological agents used to treat pain
- SNP choice selective for putatively functional loci
- LD coverage of entire gene at $r^2 > 0.8$
- 160 ancestry-informative markers
Association Tests

348 combined TMD cases vs 1612 controls

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>GENE</th>
<th>Call Rate</th>
<th>MAF (W)</th>
<th>MAF (B)</th>
<th>OR</th>
<th>P</th>
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<tr>
<td>5</td>
<td>rs2963155</td>
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<td>NR3C1</td>
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<td>0.133</td>
<td>0.18</td>
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<td>8.41E-05</td>
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<tr>
<td>5</td>
<td>rs33389</td>
<td>NR3C1</td>
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<td>13</td>
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<td>HTR2A</td>
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<td>0.64</td>
<td>0.00034</td>
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<td>7</td>
<td>rs7800170</td>
<td>CHRM2</td>
<td>99.95</td>
<td>0.531</td>
<td>0.66</td>
<td>0.72</td>
<td>0.00062</td>
</tr>
</tbody>
</table>

Logistic Regression model:

\[ y = \beta \varnothing + \beta_1(\text{allele dosage}) + \beta_2(\text{sex}) + \beta_3-6(5 \text{ sites}) + \beta_7-8(2 \text{ race eigenvectors}) + e \]
Association Tests

348 combined TMD cases vs 1612 controls: Tier 1

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>GENE</th>
<th>Call Rate</th>
<th>MAF (W)</th>
<th>MAF (B)</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs3024496</td>
<td>IL10</td>
<td>100.0%</td>
<td>0.52</td>
<td>0.36</td>
<td>0.76</td>
<td>0.0059</td>
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<tr>
<td>4</td>
<td>rs7696139</td>
<td>ADRA2C</td>
<td>99.64%</td>
<td>0.22</td>
<td>0.60</td>
<td>0.74</td>
<td>0.0072</td>
</tr>
<tr>
<td>20</td>
<td>rs1556832</td>
<td>ADRA1D</td>
<td>100.0%</td>
<td>0.53</td>
<td>0.23</td>
<td>1.29</td>
<td>0.0082</td>
</tr>
<tr>
<td>1</td>
<td>rs1800896</td>
<td>IL10</td>
<td>99.95%</td>
<td>0.53</td>
<td>0.27</td>
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<td>1</td>
<td>rs2236857</td>
<td>OPRD1</td>
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<td>0.33</td>
<td>1.32</td>
<td>0.0087</td>
</tr>
</tbody>
</table>

Logistic Regression model:

\[ y = \beta_0 + \beta_1(\text{allele dosage}) + \beta_2(\text{sex}) + \beta_3-6(\text{5 sites}) + \beta_7-8(\text{2 race eigenvectors}) + e \]
**Association Tests**

1434 controls with PILL (somatization) score

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>GENE</th>
<th>Call Rate</th>
<th>MAF (W)</th>
<th>MAF (B)</th>
<th>BETA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>rs3765550</td>
<td>MPDZ</td>
<td>100.0%</td>
<td>0.44</td>
<td>0.18</td>
<td>3.47</td>
<td>3.94E-05</td>
</tr>
<tr>
<td>1</td>
<td>rs2498982</td>
<td>INADL</td>
<td>100.0%</td>
<td>0.44</td>
<td>0.28</td>
<td>3.19</td>
<td>7.00E-05</td>
</tr>
<tr>
<td>12</td>
<td>rs9658478</td>
<td>NOS1</td>
<td>99.88%</td>
<td>0.00</td>
<td>0.07</td>
<td>10.64</td>
<td>8.33E-05</td>
</tr>
<tr>
<td>12</td>
<td>rs208288</td>
<td>P2RX7</td>
<td>100.0%</td>
<td>0.08</td>
<td>0.25</td>
<td>4.57</td>
<td>0.00015</td>
</tr>
<tr>
<td>8</td>
<td>rs1563945</td>
<td>PNOC</td>
<td>100.0%</td>
<td>0.15</td>
<td>0.32</td>
<td>-3.44</td>
<td>0.00063</td>
</tr>
</tbody>
</table>

Linear Regression model:

\[ y = \beta_0 + \beta_1(\text{allele dosage}) + \beta_{2-4}(4 \text{ sites}) + \beta_{5-6}(2 \text{ race eigenvectors}) + e \]
# Putative Genetic Polymorphisms Associated with TMD Case Status

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR3C1</td>
<td>Glucocorticoid receptor gene</td>
<td>HPA Axis Function and inflammation</td>
</tr>
<tr>
<td>HTR2A</td>
<td>Serotonin 2A receptor</td>
<td>Pain transmission , TMD, CWP</td>
</tr>
<tr>
<td>CAMK4</td>
<td>Calcium/calmodulin-dependent protein kinase 4 gene</td>
<td>Pain transmission and opioid analgesia</td>
</tr>
<tr>
<td>CHRM2</td>
<td>Muscarinic cholinergic receptor 2</td>
<td>Mood and inflammation</td>
</tr>
<tr>
<td>IFRD1</td>
<td>Interferon-related developmental regulator 1</td>
<td>Induced by NFG, neutrophil function</td>
</tr>
<tr>
<td>GRK5</td>
<td>G protein-coupled receptor kinase 5</td>
<td>Regulation of G protein-coupled receptors including ADRB2</td>
</tr>
<tr>
<td>COMT</td>
<td>Catecholamine-O-transferase</td>
<td>Pain transmission, TMD and opioid function</td>
</tr>
<tr>
<td>ADRA2C</td>
<td>Alpha-2C</td>
<td>Pain transmission</td>
</tr>
<tr>
<td>OPRD</td>
<td>Delta opioid receptor</td>
<td>Pain transmission</td>
</tr>
<tr>
<td>IL10</td>
<td>Interleukin 10</td>
<td>Inflammation and Pain</td>
</tr>
<tr>
<td>GRIN2A</td>
<td>Ionotropic N-methyl-D-aspartate (NMDA) receptor 2A</td>
<td>LTP, Pain transmission</td>
</tr>
</tbody>
</table>
Association Tests

127 TMD cases and 231 “supercontrols”

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>GENE</th>
<th>Call Rate</th>
<th>MAF (W)</th>
<th>MAF (B)</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>rs1563826</td>
<td>EREG</td>
<td>100.0%</td>
<td>0.21</td>
<td>0.51</td>
<td>0.41</td>
<td>3.66E-05</td>
</tr>
<tr>
<td>14</td>
<td>rs10498313</td>
<td>PRKD1</td>
<td>97.48%</td>
<td>0.21</td>
<td>0.15</td>
<td>1.89</td>
<td>0.00011</td>
</tr>
<tr>
<td>1</td>
<td>rs2236857</td>
<td>OPRD1</td>
<td>99.93%</td>
<td>0.27</td>
<td>0.32</td>
<td>1.83</td>
<td>0.0019</td>
</tr>
<tr>
<td>5</td>
<td>rs2963155</td>
<td>NR3C1</td>
<td>99.98%</td>
<td>0.22</td>
<td>0.24</td>
<td>0.52</td>
<td>0.0021</td>
</tr>
<tr>
<td>7</td>
<td>rs1140475</td>
<td>EGFR</td>
<td>100.0%</td>
<td>0.12</td>
<td>0.08</td>
<td>2.08</td>
<td>0.0023</td>
</tr>
</tbody>
</table>

Logistic Regression model:

\[ y = \beta_0 + \beta_1(\text{allele dosage}) + \beta_2-4(4 \text{ sites}) + \beta_5-6(2 \text{ race eigenvectors}) + e \]
EREG/EGFR Pathways and Pain

- **EREG**
  - Epiregulin is a mitogenic peptide that binds to EGFR
  - Active in multiple cell types, including fibroblasts, macrophages, keratinocytes

- **EGFR**
  - Anti-ErbB antibody treatment has been shown to be analgesic in cancer treatment
  - EGFR regulates DOR and MOR via tyrosyl phosphorylation and activation of GRK2
Future Directions
Deconstructing Heterogeneous TMD Cases into Homogenous Subgroups

• Not all pain patients are created equal – several pathways to pain and suffering

• Need to assess intermediate phenotypes associated with causal pathways

• Statistical approaches that identify relatively homogenous patient subgroups or clusters based on intermediate phenotypes and clinical signs and symptoms.
  – Principal Component Analysis to determine latent constructs
  – Clustering of latent constructs
  – Machine Learning

• Integrate the information associated with many polymorphisms - each expressing a relatively small effect on the phenotype or cluster of interest.
Analysis of Signaling Pathways
Creating Biological Pathways Using SNP Data from the Pain Research Panel

ResNet Database

Compounds, protein targets, and molecular, cellular and physiological effects

Pain Panel SNP Data

Mechanistic Model

New biomarkers and drug targets
OPPERA TMD Pathways Data (Extreme Phenotypes)

<table>
<thead>
<tr>
<th>Pathway</th>
<th># related pathways</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR -&gt; signaling pathways</td>
<td>7</td>
<td>0.00129</td>
</tr>
<tr>
<td>GFR -&gt; signaling pathways</td>
<td>3</td>
<td>0.00516</td>
</tr>
<tr>
<td>TGFBR -&gt; signaling pathways</td>
<td>3</td>
<td>0.01026</td>
</tr>
<tr>
<td>AdenosineR -&gt; AP-1 signaling</td>
<td></td>
<td>0.01361</td>
</tr>
<tr>
<td>FibronectinR -&gt; AP-1/ELK-SRF/SREBF signaling</td>
<td></td>
<td>0.01423</td>
</tr>
<tr>
<td>DopamineR2 -&gt; AP-1/CREB/ELK-SRF signaling</td>
<td></td>
<td>0.01727</td>
</tr>
<tr>
<td>NeurotensinR -&gt; ELK-SRF/AP-1/EGR signaling</td>
<td></td>
<td>0.01904</td>
</tr>
<tr>
<td>VasopressinR2 -&gt; CREB/ELK-SRF/AP-1/EGR signaling</td>
<td></td>
<td>0.02339</td>
</tr>
<tr>
<td>EndothelinRa -&gt; AP-1/CREB signaling</td>
<td></td>
<td>0.03353</td>
</tr>
<tr>
<td>ICAM1 -&gt; AP-1/CREB/ELK-SRF signaling</td>
<td></td>
<td>0.03353</td>
</tr>
<tr>
<td>TLR -&gt; AP-1 signaling</td>
<td></td>
<td>0.04296</td>
</tr>
<tr>
<td>NGFR -&gt; AP-1/CEBPB/CREB/ELK-SRF/TP53 signaling</td>
<td></td>
<td>0.04310</td>
</tr>
<tr>
<td>T-cell receptor -&gt; AP-1 signaling</td>
<td></td>
<td>0.04467</td>
</tr>
<tr>
<td>EctodysplasinR -&gt; AP-1 signaling</td>
<td></td>
<td>0.04467</td>
</tr>
<tr>
<td>VEGFR -&gt; ATF/CREB/ELK-SRF signaling</td>
<td></td>
<td>0.04533</td>
</tr>
<tr>
<td>CCR5 -&gt; TP53 signaling</td>
<td></td>
<td>0.04889</td>
</tr>
</tbody>
</table>
Pathway Analysis – Human Pain Sensitivity
EGFR Receptor Antagonist Produces Analgesia in Multiple Pain Assays Assessed in Mice

Data provided by Jeff Mogil – McGill University
Clustering and Pathway Analysis – Mechanism Based Diagnostic Classification and Therapeutic Target Identification Based on Pain Signatures
• Overlap of factors, with single factor predominating in each cluster
• Multiple factors represent challenge for therapy selection
Clusters Contrasted Against Healthy Controls to Detect SNPs Associate with Subtypes of FM

<table>
<thead>
<tr>
<th>Cluster 1 (n=67) High Pain</th>
<th>Cluster 2 (n=76) Dysfunctional</th>
<th>Cluster 3 (n=66) Adaptive Copers</th>
<th>Cluster 4 (n=49) Non-Fatigued</th>
<th>Cluster 5 (n=24) Effective Sleepers</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABRB3</td>
<td>3.8E-05</td>
<td>0.20</td>
<td>ATP6V1B2</td>
<td>0.0014</td>
</tr>
<tr>
<td>IL 8</td>
<td>0.0011</td>
<td>1.9</td>
<td>APP</td>
<td>0.0010</td>
</tr>
<tr>
<td>GRIN2A</td>
<td>0.0014</td>
<td>1.9</td>
<td>JHBDJ</td>
<td>0.0014</td>
</tr>
<tr>
<td>VIL2</td>
<td>0.0018</td>
<td>2.0</td>
<td>ACCN2</td>
<td>0.0016</td>
</tr>
<tr>
<td>PRKCF</td>
<td>0.0023</td>
<td>0.53</td>
<td>CPX4</td>
<td>0.0022</td>
</tr>
<tr>
<td>IAAR1</td>
<td>0.0029</td>
<td>3.6</td>
<td>GAL</td>
<td>0.0024</td>
</tr>
<tr>
<td>NALP12</td>
<td>0.0033</td>
<td>0.39</td>
<td>GRIA4</td>
<td>0.0028</td>
</tr>
<tr>
<td>N1RK2</td>
<td>0.0035</td>
<td>2.0</td>
<td>GBP2</td>
<td>0.0030</td>
</tr>
<tr>
<td>EPHB2</td>
<td>0.0036</td>
<td>0.51</td>
<td>GBP1</td>
<td>0.0030</td>
</tr>
<tr>
<td>IRPM8</td>
<td>0.0038</td>
<td>0.50</td>
<td>DRD3</td>
<td>0.0036</td>
</tr>
</tbody>
</table>
NTRK -> AP-1 pathways –
gene SNPs contributions

dark blue – SNPs contributing to pathway P<0.05
light blue – SNPs contributing to pathways 0.05<P<0.1

Diatchenko
Different Genes – Common Cluster

Patient 1

Patient 2

Diatchenko
Conclusions

1. A set of SNPs, genes and cellular pathways that distinguish cases from controls have been identified.

2. Methods that integrate SNPs, genes and cellular pathways that capture the main etiologic constructs for TMD are feasible and are in the process of being developed.

3. Future initiatives that will further the diagnosis and treatment of TMD and related conditions require:
   a) Novel informatic tools
   b) Large scale phenotyping and genomic studies (GWAS, sequencing)
   c) Access to large, well characterized TMD populations
Acknowledgments

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