Orofacial Pain: Is it in the Genes?

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage.

Experimental Pain: pain induced experimentally and assessed quantitatively by psychophysical, biomechanical, or physiological measures.

Temporomandibular Disorders (TMD): collection of medical and dental conditions affecting the temporomandibular joint (TMJ) and/or the muscles of mastication, as well as contiguous tissue components.

Burning Mouth Syndrome (BMS): a chronic pain syndrome that mainly affects middle-aged and older female patients. The term encompasses all forms of burning sensations in the oral cavity when the oral mucosa is clinically normal.

DNA Genetic Code Dictates Amino Acid Identity and Order

DNA Sequence

DNA

Is the Genetic Code.

<table>
<thead>
<tr>
<th>DNA</th>
<th>Protein Chain</th>
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<tbody>
<tr>
<td>A</td>
<td>T</td>
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<td>T</td>
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<td>C</td>
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Explore how DNA impacts HEALTH

Identify and understand the differences in DNA sequence (A, T, C, G) among human populations

http://www.ornl.gov/hgmis
Simple and Complex Genetic Diseases

Simple
- Single genes
- DNA change - often significant protein consequence
- Recognizable clinical phenotype
- Minor environmental impact
- Diagnosed by genetic testing
- Early onset

Complex
- Multiple genes + environmental factors are causal
- DNA change - slight change in function of gene product
- Clinical phenotype usually highly variable - over continuum of expression from very mild to severe
- Environmental impact - necessary for disease manifestation
- Genetic testing - Not diagnostic, may permit estimate of susceptibility or prognosis
- Adult onset, often chronic disease state

Single Nucleotide Polymorphism (SNP)
- 99.9% of human genome are the same in all people - 0.01% difference
- Approximately 1 SNP/1000 bases
- 3-6 million SNPs in the genome

 SNP & Haplotypes

Genetics and Pain
- Animal model – knockout mice
- Human clinical pain phenotype
  - Simple genetic diseases (rare)
  - Congenital insensitive to pain (CIP)
  - Congenital indifferent to pain (CIDP)
- Complex Genetic diseases
  - Gene polymorphism also affects individual response to pharmacological agents.


Animal model – knockout mice
Human clinical pain phenotype
- Simple genetic diseases (rare)
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Functional Variants Implicated in Orofacial Pain Conditions

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<td>ADRB2</td>
<td>TMD</td>
<td>5 major haplotypes</td>
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<td>5-HTR2A</td>
<td>TMD</td>
<td>T102C</td>
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- **A multi-substrate enzyme catalyzing methylation of catecholamines.**

**Soluble COMT**
- present in most tissues
- more effective in metabolizing epinephrine*

**Membrane bound COMT**
- present only in the central nervous system*
- more effective in metabolizing dopamine and norepinephrine.


**Val/Met genotype**

- Substitution of val by met reduces the thermostability of COMT enzyme resulting in reduction of enzyme activity.*

**Genomic Polymorphism of COMT**

<table>
<thead>
<tr>
<th>Haploblock label</th>
<th>COMT transcript</th>
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<tbody>
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<td>rs2097603</td>
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<tr>
<td>Membrane-bound</td>
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<td></td>
<td>rs4680</td>
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<td></td>
<td>Val46Met</td>
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<td>rs165599</td>
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- **Haploblock label %**
  - #1 Low Pain Sensitivity (LPS): G C G G 37.5%
  - #2 Average Pain Sensitivity (APS): A T C A 47.3%
  - #3 High Pain Sensitivity (HPS): A C C G 10.3%
  - Other combinations: 4.9%

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**Primary target for epinephrine.**

Plays a critical role in mediating physiological and psychological responses to environmental stressors.

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**COMT and Pain**

When transfected into human embryonic kidney cells, these genetic variants alter production of COMT.

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**Adrenergic Receptor Beta2 (ADRB2)**

**Genomic polymorphism of ADRB2**

**A**

**B**

Common haplotype

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**COMT haplotypes: In-vitro experiments**
In Sprague-Dawley rats, pharmacological inhibition of COMT alters thresholds of paw withdrawal in response to mechanical and thermal stimuli.

- 202 healthy females, followed for 3 years, to identify newly developed cases of TMD.
- Collected blood samples at baseline.
- Assessed experimental pain sensitivity and psychological traits at baseline.
**Subjective Report**

**Pain Threshold**
The least intensity of a stimulus at which the subject perceives pain.

**Pain Tolerance**
The greatest level of pain the subject can tolerate.

**Mechanical Pressure Stimulus**
Hand held algometer applied to four sites:
1. Temporalis muscles
2. Masseter muscles
3. TMJ
4. Ventral surfaces of wrists.
Recording of force (kg) at which subject reported pain threshold
Total of 4 measures

**Pressure Pain Threshold**
Measurement on Masseter Muscle
Measurement on Temporalis Muscle

**Single Heat Stimulus**
Thermode applied heat increasing at 0.5°C/sec to three sites:
right masseter muscle
right hairy forearm
the dorsal surface of the right foot
Recording of temperature at which subject reported pain threshold and pain tolerance
Total of 3 x 2 = 6 measures

**Ischemia Stimulus**
Arm rendered hypoxic with a blood pressure cuff.
Handgrip dynamometer squeezed for 20 repetitions.
Recording of elapsed time until the subject reported pain threshold and pain tolerance.
Total of 2 measures
Ischemic Pain Measurement

Dynamometer for Handgrip Examination

Repeated Thermal Stimuli (windup)
- Verbal ratings of fifteen 53 °C heat stimuli
- 1.5 second duration of each pulse
- 1 second interval between pulses
- Applied to the right hand
- Ratings on visual analog scale:
  \( D = 0 \) = No perception
  \( 100 = \text{worst imaginable pain} \)

Temporal Summation of Pain

Combined Z-Score of Different Pain Measures

Individual Z-Score Calculation
- A subject's heat pain tolerance (Arm) = 48.5 °C
- \( Z = \frac{X - \mu}{\sigma} = \frac{48.5 - 45.6}{2.57} = 0.95 \)

Combined Z-Score for a Subject

Individual Variations in Pain Perception

Number of subjects

Integral Z-score (all pain measures)
**Research Diagnosis Criteria (RDC) for TMD**

I: Myofascial pain

Self reported muscle pain + 3 or more muscle tender sites

II: Arthralgia

Self reported joint pain + TMJ tenderness

**Results**

**Each pain modality and COMT**

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**Windup and COMT/Val158Met**

Val158Met polymorphism is associated with CNS-dependent temporal integration of pain, while COMT haplotypes are not.
Clinical Implication

Individuals who produced reduced levels of COMT (HPS and APS haplotypes) may have an increased risk of developing persistent pain conditions.

COMT and the development of TMD

The presence of even a single LPS haplotype diminishes, by as much as \(2.3\) times, the risk of developing myogenous TMD.

Summary of COMT Polymorphisms and Pain

In females, APS and HPS variants of the gene encoding COMT are associated with increased responsiveness to noxious stimuli.

2.3-fold elevation in risk of TMD onset

Two major functional variants of COMT provide different profiles of association with pain perception. COMT haplotype with summed pain sensitivity Codon158 with windup

Mechanism by which diminished COMT activity influence pain perception and the development of TMD

- Reduced COMT activity results in elevated levels of catecholamines which promote the production of persistent pain states via the stimulation of beta2 adrenergic receptors in the central and peripheral nervous system.
ADRB2 and Psychological Status

ADRB2 and Somatization

- Somatization - psychological distress arising from perception of bodily dysfunction.

PILL - Pennebaker Inventory for Limbic Languidness

ADRB2 and Anxiety

- STAI - State Trait Anxiety Inventory

ADRB2 and Anxiety Mood

- POMS - Profile of Mood States

ADRB2 and Depression

- BSI - Brief Symptom Inventory

ADRB2 and Psychological Status

- Diagrams showing different psychological statuses and their relationships with ADRB2.
Individuals who carried one haplotype coding for low and one haplotype coding for high ADRB2 expression were 10 times less likely to develop TMD.

5HTTLPR and TMD

- 5HTTLPR – 5 hydroxytryptamine (serotonin) transporter gene promoter polymorphism
- The short form of this variant, designated s, is associated with low transcriptional efficiency of the 5-HTT gene promoter when compared with the longer forms, designated l and xl.

5HTR2A and TMD

- 5HTR2A : 5-hydroxytryptamine (serotonin) receptor 2A
- T102C polymorphism
- The C/C genotype was over represented in the patients whereas T/T genotype was over represented in the controls (P < 0.05).
- Suggests a possible role of the serotonergic system in this disease, particularly at the receptor level.

Cytokines

- IL1B
- BMS
- C3954T

SHTTPLR and TMD

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Until affordable sequencing methods arrive for everyday use, the identification of intermediate phenotypes (such as pain sensitivity) can serve as a good substitution.

When the time comes, we can tailor individual therapies for common orofacial pain conditions.

- Dr. William Maixner
- Dr. Luda Diatchenko
- Dr. Gary Slade
- Dr. Ray Sone Hovijitra