# VARIATION IN *MC1R* GENE PREDICTS DENTAL PAIN SENSITIVITY

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## BACKGROUND

- Both acute and chronic orofacial pain, including dental pain, can result in generalized distress, disability, lost productivity, and/or poorer quality of life (McNeil et al., 2014a)
- The experience of orofacial pain also can detrimentally impact essential oral health behavior and dental treatment-seeking behavior, with fear of pain and dental care-related fear suggested as mechanistically important (Armfield, 2007; McNeil et al., 2014b)
- Recently, attention has been paid to genetic correlates of the orofacial pain experience in an effort to more comprehensively understand the phenomenon and to inform intervention research and practice (e.g., Maixner et al., 2011; Randall et al., 2017; Smith et al., 2011)
- In addition to others, the melanocortin-1 receptor gene (*MC1R*) has been implicated as potentially important in the experience of orofacial pain because variation is associated with increased fear of pain and dental care-related fear (e.g., Binkley et al., 2009; Randall et al., 2017)
  - *MC1R*, on chromosome 16, codes for a protein involved in normal pigmentation, and is present in tissue of brain pathways that process pain and fear (Xia et al., 1995)
  - Nearly all people with red hair, and approximately 30% of dark-haired Caucasian people, have at least one of several common *MC1R* variants (e.g., Binkley et al., 2009)
- The study of orofacial pain, and especially acute dental pain experience, would be benefitted by use of experimental, objective approaches to the assessment of pain perception

**To further the understanding of genetic contributions to orofacial pain perception, the aim of this study was to determine whether *MC1R* variation predicts dental pain sensitivity**

## METHOD

- **Participants:** Adults were recruited from the community using ads that targeted individuals across the entire range of level of dental care-related fear
- **Psychological Assessment:** As part of a larger battery, participants completed the Fear of Pain Questionnaire-III, a 30-item self-report measure of pain-related fear (Severe, Minor, and Medical/Dental Pain subscales) with established norms for clinical and non-clinical samples and strong reliability and validity (McNeil & Berryman, 1989)
- **Genotyping:** Saliva samples were collected with Oragene•DISCOVER tubes (DNA Genotek), using standard protocol; DNA was extracted from samples and genotyped for the most common single nucleotide polymorphism (SNP; rs1805007; minor allele: T), which has been shown to drive the associations between *MC1R* variation and fear of pain and dental care-related fear (Randall et al., 2017)
- **Assessment of Dental Pain Sensitivity:** An electric pulp tester (EPT; Kerr Vitality Scanner 2006; SybronEndo; See Figure 1) was applied in random order to each of the Ramford teeth (numbers 3, 9, 12, 19, 25, and 28) with voltage increasing as a function of time probe contacted tooth
  - Pain tolerance was recorded as voltage at which participants indicated intensity of electrical stimulation was too painful to continue (see Figure 2), averaged across teeth tested; Participants provided subjective rating of pain intensity at its greatest for each tooth (Visual Analog Scale, 0-100), averaged across teeth for analyses
- **Procedure:** Participants met with dental hygienist and research assistant in dental operatory, where they provided saliva sample and completed pain sensitivity assessment before completing psychological assessment

## RESULTS

**Sample Characteristics**

- 96 Caucasian participants completed study protocol (consistent with previous work [Binkley et al., 2009] for comparability)
  - *M* age = 34.8 years, *SD* = 11.6, range = 20-66
  - 55 (57%) female
  - *M* education = 16.4 years, *SD* = 2.8, range = 9-25
- Distribution of Fear of Pain Questionnaire-III scores was normal (*M* = 84.2, *SD* = 18.0, range 34-133)
- 18 participants (19%) had the minor allele at rs1805007, consistent with proportion observed in larger, demographically similar sample (Randall et al., 2017)

**Dental Pain Sensitivity**

- The entire possible range of pain tolerance was represented (1-80)
  - Across Ramford teeth, *M* pain tolerance = 46.0, *SD* = 15.6, range = 19.2-80
- The entire possible range of subjective rating of pain intensity was represented (0-100)
  - Across Ramford teeth, *M* pain rating = 50.1, *SD* = 21.1, range = 7.2-100
- Pain tolerance was associated with subjective rating of pain intensity, $r = -.32$, $p = .002$
- Fear of pain was associated with subjective rating of pain intensity, $r = .20$, $p = .04$
- Objective, systematic measurement of pain tolerance was possible with the EPT (Figure 1) for all participants (see Figure 2 for example), with reliable responding observed (Cronbach's alpha = .77) and tolerance of electrical pain stimulation associated with tolerance of intraoral pressure pain stimulation ($r = .29$, $p = .005$)

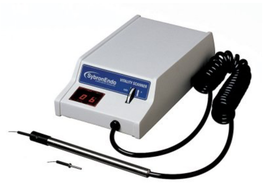

*Figure 1*. Electric Pulp Tester (EPT; Kerr Vitality Scanner 2006)

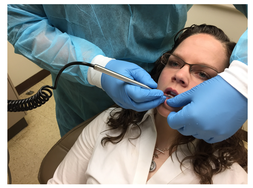

*Figure 2*. Testing dental pain sensitivity using EPT in mock participant

***MC1R* Variation and Dental Pain Sensitivity**

- Neither sex nor age were associated with pain tolerance ($p > .05$)
- Controlling for fear of pain, presence of minor allele at rs1805007 was predictive of lower pain tolerance, $R^2 = .11$, $F(2,93) = 5.62$, $p = .005$ (see Table 1)

Table 1. *Dental Pain Tolerance Measured using Electric Pulp Tester Predicted by Presence of Minor Allele at rs1805007*

| Predictor Variable | Unstandardized regression coefficient (B) | Standard Error | Standardized Regression Coefficient (β) | Significance Value (*p*) |
|---|---|---|---|---|
| Fear of Pain Questionnaire-III Score | -.20 | .09 | -.23 | .02 |
| **Minor Allele (T) at rs1805007** | **-8.73** | **3.91** | **-.22** | **.03** |

## CONCLUSIONS & DISCUSSION

- Variation in *MC1R* – specifically, presence of the minor allele at rs1805007 – predicts increased sensitivity to dental pain (i.e., lower pain tolerance)
- Results suggest that dental pain perception may be a critical intermediary in the previously observed associations between *MC1R* variation and fear of pain and dental care-related fear (Randall et al., 2017)
- Risk alleles at certain *MC1R* SNPs may predispose individuals to be more sensitive to orofacial pain, including dental pain, which may result in greater likelihood of distressing and more negative experiences with dental treatment
- Of note, this study provides evidence that the use of an EPT for objective assessment of orofacial pain sensitivity is reliable and valid, further establishing the paradigm as likely to have good utility in future studies where a straightforward and transportable technology is desired for systematic measurement of dental pain sensitivity
- Limitations include attention being paid to only one gene, a relatively small sample size, and heterogeneity of the sample
- Future work should: (1) identify mechanisms underpinning associations between *MC1R* and dental pain sensitivity, and implications for both acute and chronic manifestations of orofacial pain, and (2) aim to clarify the role of orofacial pain perception in the association between *MC1R* variation and dental care-related fear, which is an important barrier to oral healthcare

## SIGNIFICANCE & INNOVATION

- This study advances the literature on genetic influences on orofacial pain perception, which is important for comprehensive conceptualization of the phenomenon and also because of potential implications for the management of orofacial/dental pain
- This is the first known study to link *MC1R* variation to increased dental pain sensitivity
- The study is further innovative because of its use of an experimental pain induction paradigm (which appears inconsistently in the dental pain/fear literature), with results demonstrating reliability and validity of an easy-to-use device that allows for systematic and objective quantification of dental pain sensitivity

## CONTACT INFORMATION

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