



Published in final edited form as:

J Am Dent Assoc. 2009 July ; 140(7): 896–905.

Genetic variations associated with red hair color and fear of dental pain, anxiety regarding dental care and avoidance of dental care

Catherine J. Binkley, DDS, MSPH, PhD [associate professor],

Department of Surgical and Hospital Dentistry, Room 337, School of Dentistry, University of Louisville, Louisville, Ky. 40292.

Abbie Beacham, PhD [assistant professor],

Department of Psychology, College of Liberal Arts and Sciences, University of Colorado Denver.

William Neace, PhD [assistant professor],

Department of Psychology, College of Arts and Sciences, University of Hartford, West Hartford, Conn.

Ronald G. Gregg, PhD [professor],

Department of Biochemistry and Molecular Biology, School of Medicine, University of Louisville, Ky.

Edwin B. Liem, MD [adjunct clinical assistant professor], and

Department of Anesthesiology, School of Medicine, University of Louisville, Ky, and an attending physician, Norton Suburban Hospital, Louisville.

Daniel I. Sessler, MD [professor and the chair]

Department of Outcomes Research, The Cleveland Clinic, Cleveland.

Abstract

Background—Red hair color is caused by variants of the melanocortin-1 receptor (*MC1R*) gene. People with naturally red hair are resistant to subcutaneous local anesthetics and, therefore, may experience increased anxiety regarding dental care. The authors tested the hypothesis that having natural red hair color, a *MC1R* gene variant or both could predict a patient's experiencing dental care–related anxiety and dental care avoidance.

Methods—The authors enrolled 144 participants (67 natural red-haired and 77 dark-haired) aged 18 to 41 years in a cross-sectional observational study. Participants completed validated survey instruments designed to measure general and dental care–specific anxiety, fear of dental pain and previous dental care avoidance. The authors genotyped participants' blood samples to detect variants associated with natural red hair color.

Results—Eighty-five participants had *MC1R* gene variants (65 of the 67 red-haired participants and 20 of the 77 dark-haired participants) ($P < .001$). Participants with *MC1R* gene variants reported significantly more dental care–related anxiety and fear of dental pain than did participants with no *MC1R* gene variants. They were more than twice as likely to avoid dental care as were the participants with no *MC1R* gene variants, even after the authors controlled for general trait anxiety and sex.

Conclusion—Dental care–related anxiety, fear of dental pain and avoidance of dental care may be influenced by genetic variations.

Clinical Implications—Dentists should evaluate all patients, but especially those with naturally red hair, for dental care–related anxiety and use appropriate modalities to manage the patients' anxiety.

Keywords

Dental care–related anxiety; access to care; dental anesthesia; anxiety disorders; dental care utilization; genetics; behavioral sciences; melanocortin-1 receptor gene

The relationship among pain during dental procedures, dental care–related anxiety and avoidance of dental care is complex.¹ Although some patients find dental treatment merely troublesome, others find it intolerable to the extent of developing specific dental phobias. An estimated 11 to 20 percent of the population experiences extreme dental care–related anxiety,² with an additional 45 percent reporting moderate degrees of dental care–related fear.³ Despite considerable advances in technology and treatment modalities to minimize discomfort, the prevalence of dental care–related fear has remained essentially unchanged for the past 56 years.² Dental care–related fear is relevant because it may be a barrier to accessing care.⁴ People with heightened dental care–related fear fail to obtain routine preventive care and have more cavities and more teeth extracted than do people with no fear of dental care.^{5,6}

Anxious patients may not advise dental professionals about previous painful and traumatic dental experiences and may not report their associated anxiety, owing to their discomfort.⁷ Conversely, dental professionals may not make substantive efforts to identify patients with high levels of anxiety-related symptoms or take special measures to address patients' distress.⁸ Specific phobias regarding dental treatment typically are consequent to painful dental procedures and discomfort that exacerbate anxiety and potentiate avoidance of dental procedures.^{4,9-11}

Recently, the American Dental Association held its first Access to Care Summit,¹² which included discussions about the fact that access-to-care issues also include pain, fear and anxiety. Thus, there is a need to understand phenomena such as the enhanced sensitivity seen in red-haired people along with similar issues throughout the general population.

Factors associated with increased dental care–related anxiety and fear include the person's sex, trait anxiety and anxiety sensitivity. Sex is a commonly reported factor in differences in dental care–related fear, with female patients being more likely to have significantly greater fear than male patients.¹³ Trait anxiety—a general predisposition to feelings of being anxious—has been associated with dental care–related anxiety and fear.¹⁴ Anxiety sensitivity, commonly known as the “fear of fear,” is sensitivity to internal anxiety sensations and a fear that pain sensations signal harm.^{10,15} Anxiety sensitivity plays a large role in the perception of pain, anticipatory anxiety and avoidance of anxiety-provoking stimuli such as dental treatment. In more recent models of anxiety disorders, anxiety sensitivity has been identified as an independent risk factor for the development of panic and anxiety disorders and has been associated with painful dental procedures, pain anticipation and avoidance of dental care.^{9,16}

The influence of genetics on anxiety has been studied,¹⁷ including the role of the proopiomelanocortin gene, hormones derived from the proopiomelanocortin gene called melanocortins and the five receptors that are activated by melanocortin genes.¹⁸ The results of basic research with rats indicates that the melanocortinergeric pathway is involved in anxiety-like behavior¹⁹ and that the melanocortin-4 receptor (*MC4R*) gene has been implicated in anxiety.¹⁸ The melanocortin-1 receptor (*MC1R*) gene, initially believed to be found only in the tissues that cause fair skin and red hair in about 5 percent of whites,²⁰ also has been found in the brain,²¹ in which it is part of the pathway that processes pain, anxiety and fear.

We demonstrated previously that sensitivity to general²² and cutaneous local²³ anesthesia is reduced in humans with *MC1R* gene variants. After reports of our studies^{22,23} were published in the lay press, we received more than 100 personal communications from redheads who reported that dental anesthesia often failed or that unusually large doses of local anesthetics were required to achieve adequate analgesia. A blogger²⁴ also reported ineffective dental local anesthesia in redheads.^{22,25} Patients with a history of ineffective local anesthesia may develop increased anxiety regarding dental treatment and avoid dental care. Therefore, we tested the hypothesis that having natural red hair color, a *MC1R* gene variant or both; sex; trait anxiety; and anxiety sensitivity could predict a patient's experiencing dental care-specific anxiety, fear of dental pain and avoidance of dental care.

METHODS

Participants

After we received approval from the University of Louisville's Human Subjects Protection Program Office and written informed consent from the participants, we studied healthy (classified as P1 or P2 according to the American Society of Anesthesiologists Physical Status Classification System) white volunteers aged 18 to 41 years with natural red or dark (black or dark brown) hair. (We did not include light-haired people in our study because we wanted to compare the people most likely to have genetic variants [red-haired people] with people who we thought would not have genetic variants [dark-haired people], based on the methodology used in two previous studies.^{21,22}) We regarded the study participants as white if they were mainly of northern European descent as indicated by self-report. The participants were drawn from the greater Louisville, Ky., area, which is a metropolitan area with a population exceeding 1 million. We used G*Power (a share-ware program based on Cohen, 1988²⁶) with an α of .05 and two-tailed tests of significance to make an a priori estimate that 74 participants in each hair color group would provide 80 percent power for detecting a small-to-medium effect size ($r = 0.25$) in the relationship between dental care-related anxiety and hair color.

On the basis of research results suggesting that serious mental disorders may affect subjective ratings and interpretation of pain,²⁴ we screened participants for psychiatric symptoms. Screening interviews were conducted by four doctoral psychology students who were trained and monitored by a licensed psychologist who used videotapes produced by the developers of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (SCID), Research Version,²⁷ and role-play to ensure the interviewers' understanding and their ability to resolve discrepancies. Before data collection, each interviewer conducted approximately 10 practice interviews. Criterion raters rated the practice interviews to achieve acceptable agreement ($\kappa = 0.80$). The interviewers conducted interviews using the SCID, Research Version, to assess potential participants' current and lifetime prevalence of Axis-I psychiatric disorders. The SCID modules they administered to participants were mood episodes, psychotic symptoms, mood disorders, substance use disorders, anxiety disorders, somatoform disorders and acute stress disorder.

During the study, we audiotaped a random sample of 20 percent of the interviews and rated them to monitor drift in adherence to interviewing guidelines.²⁸ If participants reported high levels of psychological distress, we referred them to the University of Louisville Psychological Services Center for follow-up and excluded them from the study. Among the 151 participants enrolled, we excluded seven from the study owing to psychological symptoms (for example, severe mental illness, psychotic symptoms, suicidal ideation) identified during the baseline interview. Most of the excluded participants were red-haired men, which resulted in an unbalanced group; however, the regression analyses we used in this study accounted for this discrepancy.

Participants' survey instruments

Participants provided their demographic data including sex, age, education and income. They also completed Liddell and Locker's questionnaire,^{1,11} which collects information about dental care utilization during the previous five years and includes an avoidance-of-dental-care question ("Have you ever avoided seeking dental treatment for as long as possible?"). We coded participants who answered "yes" to the question 1 and those who answered "no" 0. Participants completed Corah's dental anxiety scale,²⁹ the most widely used screening instrument for dental care-related anxiety, which has good internal consistency and test-retest reliability ($r = 0.86$). The survey consists of four questions concerning participants' feelings about going to the dentist, waiting in the dental office, waiting in the dental chair and waiting for deep cleaning. Scores range from 1 (most relaxed) to 5 (most anxious); total scores range from 4 to 20.

Participants also completed the Fear of Dental Pain,³⁰ an 18-item self-report questionnaire measuring pain-related fear of a variety of painful dental stimuli. The results of two studies involving college and dental students, patients and the general population ($n = 485$) provided high internal consistency ($\alpha = .93$) with satisfactory test-retest reliability ($r > 0.75$).³⁰ Scoring of the Fear of Dental Pain questionnaire can be accomplished by adding the responses (1 to 5) for a score ranging from 18 to 90. The mean scores for male and female participants were 50.73, with a standard deviation (SD) of ± 13.82 . Factor analysis indicated a strong one-dimensional factor, accounting for about 50 percent of the variance.

Participants also completed the State-Trait Anxiety Inventory (STAI)³¹ and the Anxiety Sensitivity Index (ASI).¹⁶ The STAI is a 40-item generic measure of state and trait anxiety. State anxiety refers to situational feelings such as worry, tension and nervousness. Trait anxiety refers to a general proneness to feelings of anxiety. On a four-point scale (1 = not at all, 4 = very much so), respondents rate 20 state (how you feel right now) and 20 trait (how you generally feel) anxiety feelings. STAI has strong internal consistency for both state and trait items (state $\alpha = .93$ and trait $\alpha = .90$). It has been used widely in a variety of patient and clinical populations and in dental settings.³² ASI is used to assess anxiety sensitivity or the belief that anxiety experiences are aversive and, therefore, often result in avoidance of experiences with which anxiety symptoms are associated (for example, dental procedures or pain). On a five-point scale (0 = very little, 4 = very much), respondents indicate the degree to which each item represents their "usual way of thinking." ASI includes items that assess sensations commonly associated with heightened cardiovascular reactivity.¹⁶ It effectively discriminates between trait anxiety and fear of bodily sensations commonly experienced with elevated anxiety,³³ and it is used to assess dental treatment-related phobia and avoidance.⁹

Genotyping

We genotyped participants' blood samples to detect variants associated with natural red hair color. The *MC1R* gene is highly polymorphic, and we determined the genotype of each participant for 12 variants (R151C, R142H, R160W, D294H, D84E, S83P, 29insA, N279S, V60L, V92M, R163Q, I155T). We also sequenced the entire coding region of the *MC1R* gene for 52 participants. In concordance with the results of a study of variants that most likely decrease the function of the *MC1R* gene most dramatically,³⁴ we labeled the following single-nucleotide polymorphisms as variant: 29insA, S83P, D84E, R142H, R151C, I155T, R160W and D294H. We classified participants as having *MC1R* gene variants for purposes of analyses if they had one or two of these variant alleles. The remaining alleles—V60L, V92M, R163Q and N279S—are likely least variant or neutral. (A complete description of the methods we used for genotyping in our study is available as supplemental data to the online version of this article [found at "<http://jada.ada.org>"].)

Statistical analysis

Initially, we used bivariate analyses to examine hair color, variant status and sex differences in dental care–related anxiety, fear of dental pain, state and trait anxiety, anxiety sensitivity measures and avoidance of dental care. We used analysis of variance to examine differences among participants who had no variants, one variant or two variants. In the main analysis, we used a forced-entry regression approach to examine the relationship among hair color, variant status or both; sex; state and trait anxiety; and anxiety sensitivity that we used as predictor (that is, independent) variables for dental care–related anxiety, fear of dental pain and avoidance of dental care, which served as the criterion (that is, dependent) variables. We used linear regression analyses for the continuous criterion variables (dental care–related anxiety and fear of dental pain) and logistic regression analyses for the dichotomous criterion variable (avoidance of dental treatment).

We conducted a series of linear regression analyses to assess the relative contribution of both hair color and *MC1R* gene variant status in connection with the other predictor variables (sex, trait anxiety and anxiety sensitivity) for predicting dental care–related anxiety and fear of dental pain. We first examined the correlation matrix to assess the degree to which predictor variables were correlated with the criterion variables (dental care–related anxiety and fear of dental pain) and to examine the intercorrelations among the predictor variables. We then conducted a regression analysis with all predictors in the model, including hair color and *MC1R* gene variant status. We assessed those models for multicollinearity and examined the relative importance of using hair color versus *MC1R* gene variant status. Finally, we conducted separate regression analyses that included either hair color or *MC1R* gene variant status.

To determine potential interactions in the regression models, we investigated the effect of sex as a moderator (pre-existing factor) because female patients have reported higher levels of dental care–related anxiety and fear of dental pain than have male patients.¹³ We created variables for the interaction of sex and hair color or variant status (sex × hair color and sex × *MC1R* gene variants).

We conducted linear regression analyses (one for dental care–related anxiety and one for fear of dental pain) by using all of the predictor variables that we theorized were important. We conducted a second set of regression analyses to remove multicollinearity that was evident in the full models. We conducted logistic regression analysis for avoidance of dental care. We used a probability of 5 percent or more as the criterion of significance. We conducted data analyses by means of commercially available software. We used a probability of 5 percent or more as the criterion of significance.

RESULTS

There were 85 participants with *MC1R* gene variants; 65 of 67 red-haired participants and 20 of 77 dark-haired participants ($\chi^2_1 = 74.7, P < .001$). Demographic characteristics of the red-haired and dark-haired participants and those with and without *MC1R* gene variants were similar (Table 1). In contrast, dental care–related anxiety and fear of dental pain was significantly greater among red-haired participants of both sexes than among dark-haired participants of both sexes. Among all participants, having one or two variants resulted in even more significant differences in dental care–related anxiety and fear of dental pain than having no variants (Table 2).

Avoidance of dental care among all study participants was 36 percent (52 of 144), with red-haired participants being twice as likely to report avoiding going to the dentist (31 of 67 [46 percent]) as were those with dark hair (21 of 77 [27 percent]) ($\chi^2_1 = 6.64, P = .02$). Participants with *MC1R* gene variants also were more likely to report avoiding dental care (38

of 85 [45 percent]) than were those without variants (14 of 59 [24 percent], $\chi^2_1 = 6.64$, $P = .01$).

To determine which variables should be included in regression analyses, we conducted a series of independent-group t tests to examine whether there were hair color or sex differences in state and trait anxiety or in anxiety sensitivity scores. We found no significant differences between groups for state or trait anxiety or for anxiety sensitivity. The only sex difference we found was with men (mean $38.41 \pm SD 11.3$) having significantly higher levels of trait anxiety than did women (mean $34.71 \pm SD 11.4$; $t_{141} = -2.07$, $P = .04$).

We found no significant differences among the three groups (no variants, one variant and two variants) in state or trait anxiety or in anxiety sensitivity. Using a dichotomous variable of 0 equals no variants and 1 equals one or two variants, we then conducted a series of independent-group t tests. The only difference in variant status (none or one or two variants) we found was that participants with *MC1R* gene variants had significantly higher levels of anxiety sensitivity (mean $16.51 \pm SD 8.5$) than did participants with no variants (mean $13.49 \pm SD 8.4$; $t_{142} = -2.10$, $P = .04$).

The results of regression analyses indicated that neither the interaction of sex and hair color ($P = .96$) nor sex and *MC1R* gene variants ($P = .81$) was significant in predicting dental care-related anxiety. The results of the same analyses for fear of dental pain with the interaction of sex and hair color ($P = .41$) and sex and variants ($P = .43$) also were not significant. Thus, we concluded that sex was not a potential moderating variable and did not include it in further analyses.

All predictor variables but sex significantly correlated with the two criterion variables (dental care-related anxiety and fear of dental pain) (Table 3). Moreover, *MC1R* gene variants status consistently correlated more strongly with each of the criterion variables than did self-reported hair color. Intercorrelations among predictor variables generally were low, with the exception of the correlation between hair color and *MC1R* gene variant status ($r = .72$).

Regression analyses

We report the full series of analyses for dental care-related anxiety as outlined in the Methods section and, given space considerations, the final analysis for fear of dental pain.

Dental care-related anxiety: full model

The results of the analysis for predicting dental care-related anxiety by hair color, *MC1R* gene variant status, sex, trait anxiety and anxiety sensitivity are reported in Table 4. Only trait anxiety was a significant predictor of dental care-related anxiety ($P = .006$), with *MC1R* gene variant status being marginally significant ($P = .076$). We found that hair color was not significant in predicting dental care-related anxiety when we included the *MC1R* gene in the model and that the relative importance of the *MC1R* gene ($\beta = .202$) was much higher than that of hair color ($\beta = .016$). Tolerance, a standardized unit of measure ranging from 0 (high multicollinearity) to 1 (no high multicollinearity), for both hair color (.48) and *MC1R* gene variant status (.47) was low (tolerances of 1.0 indicate orthogonality among predictor variables; those lower than .50 generally indicate poor tolerance owing to substantial redundancy), indicating that the model estimates are not stable because of multicollinearity created by including both of those predictor variables. Therefore, we conducted separate regression analyses that included only hair color or *MC1R* gene variant status.

Dental care-related anxiety: hair color only

The regression analysis results with *MC1R* gene variant status removed from the model are reported in Table 5. Two items from Table 5 are noteworthy. One is that the tolerance for hair color was much improved when we removed the redundancy created by including *MC1R* gene variant status. The other is that the standard error (SE) of the regression coefficient associated with hair color also was much reduced when we compared it with that in the full model reported in Table 4. This shows that the full model is biased by multicollinearity when both hair color and *MC1R* gene variant status are included in the regression equation. More importantly, however, is that hair color, although significant in the reduced model (Table 5), is not significant when *MC1R* gene variant status is included in the model (Table 4).

Dental care-related anxiety: *MC1R* gene-only variant status

One reason that *MC1R* gene variant status was only marginally significant in the full model is that its SE was inflated because of the multicollinearity caused by the redundancy between it and hair color. To examine this possibility, we conducted another regression model that included only *MC1R* gene variant status. These results are in Table 6. Overall, the regression model was significant ($F_{4,138} = 6.69, P < .001$).

We found that the *MC1R* gene variant status was a highly significant predictor of dental care-related anxiety ($\beta = .213, P = .008$). Moreover, its tolerance was acceptable (.95), and its SE (.585) was reduced in comparison with its SE (.838) in the full model (Table 4). That is, after we removed the multicollinearity created by including both hair color and *MC1R* gene variant status, we found that the *MC1R* gene was a highly significant predictor of dental care-related anxiety.

Of the predictor variables in the model presented in Table 6, only *MC1R* gene variants and trait anxiety were significant predictors of dental care-related anxiety. Participants with higher trait anxiety scores tended to exhibit more dental care-related anxiety than did participants with lower trait anxiety scores. Nevertheless, participants with *MC1R* gene variants exhibited greater dental care-related anxiety than did participants with no variants even after we accounted for differences in trait anxiety, sex and anxiety sensitivity.

Our overall conclusions from this series of analyses are that hair color and *MC1R* gene variant status are redundant predictors of dental care-related anxiety and that *MC1R* gene variant status was the more important predictor variable.

Fear of dental pain: *MC1R* gene variant status only

Similar to what we did for dental care-related anxiety analyses, we conducted a series of linear regression analyses to examine predictors of fear of dental pain. The results yielded the same conclusions as those for dental care-related anxiety: hair color was redundant with *MC1R* gene variant status, and *MC1R* gene variant status was more important in predicting fear of dental pain than was hair color. The results of the final regression model with only *MC1R* gene variant status are shown in Table 6. Overall, the regression model was significant ($F_{4,138} = 7.45, P < .001$). Together, all predictor variables accounted for 17.8 percent of the variability in fear of dental pain, and *MC1R* gene variant status was a significant predictor of fear of dental pain. Participants with higher anxiety sensitivity scores tended to exhibit more fear of dental pain than did participants with lower anxiety sensitivity scores, even after we accounted for differences in variants, sex and trait anxiety.

Avoidance of dental care: *MC1R* gene variant status only

We used logistic regression analysis to examine the relative contributions of the predictor variables to categorizing participants as “avoidant = 1” or “nonavoidant = 0” of dental

treatment. The overall logistic regression model was significant ($\chi^2_4 = 17.54, P = .002$) and accounted for 15.8 percent of the variability in categorizing participants. We found that variant status was a significant predictor in the model (odds ratio [OR] = 2.46; $P = .023$; 95 percent confidence interval [CI] 1.13-5.36), indicating that participants with *MC1R* gene variants were more than twice as likely to avoid routine dental treatment as were those without *MC1R* gene variants, after we accounted for sex, anxiety sensitivity and trait anxiety.

DISCUSSION

The results of our study support our hypothesis that natural red hair color, *MC1R* gene variants or both are associated with increased dental care–related anxiety, fear of dental pain and, ultimately, avoidance of dental care. As we expected, most red-haired participants had *MC1R* gene variants, but one-quarter (20 of 77) of dark-haired participants also had genetic variants. The presence of one or two variants was more strongly predictive of dental care–related anxiety and fear of dental pain than was hair color only, even after we accounted for variance induced by sex, trait anxiety and anxiety sensitivity. These results suggest that the *MC1R* gene may play a role in anxiety.

The *MC1R* gene is part of a family of five melanocortin receptors, and although the melanocortin-3 receptor and *MC4R* genes are more abundant in the central nervous system than is the *MC1R* gene, the receptors have similar affinities for α -melanocyte-stimulating hormone³⁵ and crosstalk between ligands seems likely. It also is possible that a person with *MC1R* gene variants could have simultaneous variants of the other melanocortin receptors. The melanocortin system has been associated with anxietylike behavior¹⁸ and contributes to anxietylike behavior in rats.¹⁹

Mogil and colleagues³⁶ investigated the role of *MC1R* genes in pain perception and opioid analgesic effectiveness. They reported reduced sensitivity to electrical pain stimulation and increased response to a morphine metabolite among participants with two *MC1R* gene variants compared with results in those with one or no *MC1R* gene variants. The authors suggested that involvement of *MC1R* genes in analgesia could be mediated through *MC1R* genes expressed in the brain. Another possibility is that dysfunctional peripheral *MC1R* gene variants produce compensatory up-regulation of central melanocortins that, in turn, increase baseline pain sensitivity via stimulation of *MC4R* genes. Other explanations might be postulated, and currently available information does not provide the basis for identifying a specific mechanism by which *MC1R* gene variants might influence anxiety, pain sensitivity or anesthetic requirement. Whether resistance to local anesthesia is due to central up-regulation of melanocortin receptor ligands or some other mechanism remains unknown.²² The results of our study suggest that additional research on the role of the melanocortin pathway in anxiety, pain perception and effectiveness of local anesthetics may be indicated.

We found that anxiety sensitivity was particularly salient in predicting fear of dental pain and avoidance of dental care. In a recent study, the role of anxiety sensitivity in perceptions of pain across noxious stimuli was well-established.³⁷ In our study, the variance accounted for by anxiety sensitivity was consistent with the finding of a previous study that people with elevated anxiety sensitivity tend to avoid situations in which they may experience autonomic arousal.³⁸ From a clinical perspective, it may be important to identify patients who may have elevated levels of dental care–related anxiety and anxiety sensitivity. These patients, owing to their attention to internal pain and anxiety-related somatic cues, may be at risk of avoiding dental care.

An unexpected finding was that all participants who were divorced, separated or widowed had *MC1R* gene variants. These participants, however, were older (32 ± 6 years) than were those

who were either currently married or never married (27 ± 5 years). Given the relatively small sample size of our study, the generalizability of this finding may be limited. Nonetheless, the results of our study suggest that further examination of potential relationships between variant status, marital status, other demographic factors and psychological and behavioral factors would be worthwhile.

The participants in our study did not have diagnosable psychological disorders or high levels of psychological symptoms. A limitation of our approach, however, was that we depended on the participants to provide retrospective recall, so we were unable to measure pain ratings in experimental or real-time clinical conditions.

CONCLUSIONS

Our results suggest that *MC1R* gene variants and their phenotype red hair color are associated with increased dental care–related anxiety, fear of dental pain and avoidance of dental care. Anxiety sensitivity, which was not assessed when measuring dental care–related anxiety or generalized state and trait anxiety, also is a salient predictor of fear of dental pain and dental care avoidance. Dentists should evaluate all patients, but especially those with natural red hair, for dental care–related anxiety and anxiety sensitivity and use appropriate modalities to manage the patient's anxiety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by National Institutes of Health grant 1 R21 DE 016064-01 (Bethesda, Md.).

ABBREVIATION KEY

ASI, Anxiety Sensitivity Index.; MC1R, Melancortin-1 receptor.; MC4R, Melancortin-4 receptor.; SCID, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-4th Edition.; STAI, State-Trait Anxiety Inventory..

References

1. Liddell A, Locker D. Gender and age differences in attitudes to dental pain and dental control. *Community Dent Oral Epidemiol* 1997;25(4):314–318. [PubMed: 9332809]
2. Smith TA, Heaton LJ. Fear of dental care: are we making any progress? *JADA* 2003;134(8):1101–1108. [PubMed: 12956352]
3. Dionne RA, Gordon SM, McCullagh LM, Phero JC. Assessing the need for anesthesia and sedation in the general population. *JADA* 1998;129(2):167–173. [PubMed: 9495047]
4. Berggren U, Meynert G. Dental fear and avoidance: causes, symptoms, and consequences. *JADA* 1984;109(2):247–251. [PubMed: 6590605]
5. Vassend O. Anxiety, pain and discomfort associated with dental treatment. *Behav Res Ther* 1993;31(7):659–666. [PubMed: 8216168]
6. Willumsen T, Vassend O, Hoffart A. A comparison of cognitive therapy, applied relaxation, and nitrous oxide sedation in the treatment of dental fear. *Acta Odontol Scand* 2001;59(5):290–296. [PubMed: 11680648]
7. Heaton LJ, Carlson CR, Smith TA, Baer RA, de Leeuw R. Predicting anxiety during dental treatment using patients' self-reports: less is more. *JADA* 2007;138(2):188–195. [PubMed: 17272373]
8. Freeman R. Assessing and managing dental phobia in general practice: some practical suggestions. *Br Dent J* 1998;184(5):214–216. [PubMed: 9581035]

9. Gross PR. Is pain sensitivity associated with dental avoidance? *Behav Res Ther* 1992;30(1):7–13. [PubMed: 1540116]
10. Klages U, Kianifard S, Ulusoy O, Wehrbein H. Anxiety sensitivity as predictor of pain in patients undergoing restorative dental procedures. *Community Dent Oral Epidemiol* 2006;34(2):139–145. [PubMed: 16515678]
11. Locker D, Shapiro D, Liddell A. Negative dental experiences and their relationship to dental anxiety. *Community Dent Health* 1996;13(2):86–92. [PubMed: 8763138]
12. Crozier, S. ADA convenes major summit on finding dental care access solutions; *ADA News*. Apr 6. 2009 p. 16-17. “www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=3526”. Accessed May 19, 2009
13. Heft MW, Meng X, Bradley MM, Lang PJ. Gender differences in reported dental fear and fear of dental pain. *Community Dent Oral Epidemiol* 2007;35(6):421–428. [PubMed: 18039283]
14. Lago-Mendez L, Diniz-Freitas M, Senra-Rivera C, Seoane-Pesqueira G, Gandara-Rey JM, Garcia-Garcia A. Dental anxiety before removal of a third molar and association with general trait anxiety. *J Oral Maxillofac Surg* 2006;64(9):1404–1408. [PubMed: 16916676]
15. Haukebo K, Skaret E, Ost LG, et al. One- vs. five-session treatment of dental phobia: a randomized controlled study. *J Behav Ther Exp Psychiatry* 2008;39(3):381–390. [PubMed: 18005932]
16. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther* 1986;24(1):1–8. [PubMed: 3947307]
17. Smoller JW, Gardner-Schuster E, Misiaszek M. Genetics of anxiety: would the genome recognize the DSM? *Depress Anxiety* 2008;25(4):368–377. [PubMed: 18412063]
18. Chaki S, Okuyama S. Involvement of melanocortin-4 receptor in anxiety and depression. *Peptides* 2005;26(10):1952–1964. [PubMed: 15979204]
19. Liu J, Garza JC, Truong HV, Henschel J, Zhang W, Lu XY. The melanocortinergic pathway is rapidly recruited by emotional stress and contributes to stress-induced anorexia and anxiety-like behavior. *Endocrinology* 2007;148(11):5531–5540. [PubMed: 17673512]
20. Raimondi S, Sera F, Gandini S, et al. MC1R variants, melanoma and red hair color phenotype: a meta-analysis. *Int J Cancer* 2008;122(12):2753–2760. [PubMed: 18366057]
21. Xia Y, Wikberg J, Chhajlani V. Expression of melanocortin 1 receptor in periaqueductal gray matter. *Neuroreport* 1995;6(16):2193–2196. [PubMed: 8595200]1995
22. Liem EB, Lin CM, Suleman MI, et al. Anesthetic requirement is increased in redheads. *Anesthesiology* 2004;101(2):279–283. [PubMed: 15277908]
23. Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology* 2005;102(3):509–514. [PubMed: 15731586]
24. Lei, HH. Melanocortin-1 Gene for Red Hair & Pain Tolerance. 2005. “www.blisstree.com/geneticsandhealth/melanocortin-1-gene-for-red-hair-and-pain-tolerance/”. Accessed May 19, 2009
25. Harrell, E. Redheaded women can stand higher pain levels claims study. *News.Scotsman.com*. Aug. 10. 2005 “<http://news.scotsman.com/weirdoddandquirkystories/Redheaded-women-can-stand-higher.2650605.jp>”. Accessed May 19, 2009
26. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Vol. 2nd ed.. Lawrence Earlbaum Associates; Hillsdale, NJ: 1988.
27. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN)*. Biometrics Research, New York State Psychiatric Institute; New York City: 2002.
28. First, M.; Gibbon, M. *Users Guide for the Structured Clinical Interview for DSM-IV Axis-1 Disorders: Research Version*. Biometrics Research; New York City: 1996.
29. Corah NL. Development of a dental anxiety scale. *J Dent Res* 1969;48(4):596. [PubMed: 5256508]
30. van Wijk AJ, Hoogstraten J. The Fear of Dental Pain questionnaire: construction and validity. *Eur J Oral Sci* 2003;111(1):12–18. [PubMed: 12558803]

31. Spielberger, C. STAI Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press; Palo Alto, Calif.: 1983.
32. Newton JT, Buck DJ. Anxiety and pain measures in dentistry: a guide to their quality and application. *JADA* 2000;131(10):1449–1457. [PubMed: 11042984]
33. Taylor S. Anxiety sensitivity: theoretical perspectives and recent findings. *Behav Res Ther* 1995;33(3):243–258. [PubMed: 7726801]
34. García-Borrón JC, Sánchez-Laorden BL, Jiménez-Cervantes C. Melanocortin-1 receptor structure and functional regulation. *Pigment Cell Res* 2005;18(6):393–410. [PubMed: 16280005]
35. Abdel-Malek Z. Melanocortin receptors: their functions and regulation by physiological agonists and antagonists. *Cell Mol Life Sci* 2001;58(3):434–441. [PubMed: 11315190]
36. Mogil JS, Ritchie J, Smith SB, et al. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet* 2005;42(7):583–587. [PubMed: 15994880]
37. Thompson T, Keogh E, French CC, Davis R. Anxiety sensitivity and pain: generalisability across noxious stimuli. *Pain* 2008;134(12):187–196. [PubMed: 17532572]
38. Wilson KA, Hayward C. Unique contributions of anxiety sensitivity to avoidance: a prospective study in adolescents. *Behav Res Ther* 2006;44(4):601–609. [PubMed: 16023074]

TABLE 1
 Participants' characteristics by hair color and *MC1R** gene variant status (N = 144).

CHARACTERISTIC	DARK HAIR (n = 77)	RED HAIR (n = 67)	P VALUE	NO VARIANTS (n = 59)	<i>MC1R</i> GENE VARIANTS (n = 85)	P VALUE
<i>MC1R</i> Gene Variant Status			< .001			†
None	57	2		—	—	
1 or 2	20	65		—	—	
Sex (No. [%])			.29			.23
Male	39 (51)	28 (42)		31 (52)	36 (42)	
Female	38 (49)	39 (51)		28 (47)	49 (58)	
Mean Age (Year [Range])	26.6 (18-41)	28.3 (19-40)	.06	26.8 (18-40)	27.8 (19-40)	.28
Education (No. [%])			.15			.27
High school or less	9 (12)	7 (10)		6 (10)	10 (12)	
Vocational/Associate	6 (8)	4 (6)		4 (7)	6 (7)	
Some university	36 (47)	23 (34)		26 (45)	33 (39)	
Completed university	10 (13)	21 (31)		8 (14)	23 (27)	
Postgraduate	15 (19)	12 (18)		14 (24)	13 (15)	
Unknown	1 (1)	0 (0)		1 (2)	0 (0)	
Marital Status (No. [%])			.03			.01
Currently married	14 (18)	15 (22)		12 (20)	17 (20)	
Previously married	3 (4)	13 (19)		0 (0)	16 (19)	
Never married	60 (78)	39 (58)		47 (80)	52 (61)	
Last Dental Visit (No. [%])			.39			.37
Within past year	36 (47)	28 (42)		31 (53)	33 (39)	
1-2 years ago	30 (39)	22 (33)		20 (34)	32 (38)	
3 or more years ago	11 (14)	17 (25)		8 (14)	20 (24)	

* *MC1R*: Melanocortin-1 receptor.

† —: Not applicable, variant by variant.

TABLE 2
Differences in dental and psychological factors by hair color and *MC1R** gene variants (N = 144).

FACTOR	DARK HAIR (n = 77)	RED HAIR (n = 67)	P VALUE	NO <i>MC1R</i> GENE VARIANTS (n = 59)	ONE <i>MC1R</i> GENE VARIANT (n = 28)	TWO <i>MC1R</i> GENE VARIANTS (n = 57)	P VALUE
Dental Anxiety Scale Score (Mean [± SD] [†])	8.27 (3.3)	9.63 (3.9)	.03	7.73 (3.0)	9.79 (3.6)	9.68 (3.9)	<.01 [‡]
Fear of Dental Pain (Mean [± SD])	50.56 (16.6)	55.40 (18.3)	.09	47.90 (16.8)	55.93 (17.1)	56.37 (17.5)	.02 [‡]
Avoidance of Dental Care (No. [%])							
Yes	21 (27)	31 (46)	.02	14 (24)	9 (32)	29 (51)	<.01 [§]
No	56 (73)	36 (54)		45 (76)	19 (68)	28 (49)	
Anxiety Sensitivity (Mean [± SD])	14.22 (8.6)	16.48 (8.4)	.12	13.49 (8.4)	17.36 (8.5)	16.09 (8.5)	.09 [‡]
State Anxiety (Mean [± SD])	31.87 (10.1)	32.64 (10.5)	.65	31.27 (9.9)	34.37 (10.8)	32.21 (10.3)	.43 [‡]
Trait Anxiety (Mean [± SD])	36.39 (10.0)	36.45 (11.7)	.97	35.14 (9.8)	38.93 (11.1)	36.52 (11.6)	.31 [‡]

* *MC1R*: Melanocortin-1 receptor.

[†] SD: Standard deviation.

[‡] Analysis of variance.

[§] χ^2 test.

TABLE 3

Correlations between predictor variables and criterion variables.

PREDICTOR VARIABLE	DENTAL ANXIETY (PEARSON CORRELATION COEFFICIENT)	FEAR OF DENTAL PAIN (PEARSON CORRELATION COEFFICIENT)
Trait Anxiety	.32*	.23*
Anxiety Sensitivity	.29*	.36*
Melanocortin-1 Receptor Gene Variant Status	.27*	.23*
Red Hair Color	.18 [†]	0.14
Sex (Male = 1)	-0.05	-0.11

* $P < .01$.[†] $P < .05$.

TABLE 4
Dental care–related anxiety: full regression model with hair color and *MC1R** gene variant status.

PREDICTOR VARIABLE	B [†]	STANDARD ERROR	β [‡]	P VALUE	TOLERANCE [§]
Sex	−0.542	0.582	−0.074	.353	.95
Trait Anxiety	0.085	0.031	0.251	.006	.73
Anxiety Sensitivity	0.057	0.038	0.134	.137	.75
<i>MC1R</i> Gene Variant Status	1.497	0.838	0.202	.076	.47
Red Hair Color	0.12	0.822	0.016	.884	.48

* *MC1R*: Melanocortin-1 receptor.

[†] B: Unstandardized regression coefficient.

[‡] β: Standardized regression coefficient.

[§] Tolerance is a standardized unit of measure ranging from 0 (high multicollinearity) to 1 (no high multicollinearity); tolerances of 1.0 indicate orthogonality among predictor variables; those lower than .50 generally indicate poor tolerance owing to substantial redundancy.

TABLE 5

Dental care–related anxiety: hair color only.

PREDICTOR VARIABLE	B*	STANDARD ERROR	β^{\dagger}	P VALUE	TOLERANCE ‡
Sex	-.622	.585	-.085	.289	.96
Trait Anxiety	.091	.031	.268	.004	.74
Anxiety Sensitivity	.061	.039	.142	.118	.75
Red Hair Color	1.166	.581	.159	.047	.97

* B: Unstandardized regression coefficient.

 † β : Standardized regression coefficient. ‡ Tolerance is a standardized unit of measure ranging from 0 (high multicollinearity) to 1.0 (no high multicollinearity); tolerances of 1.0 indicate orthogonality among predictor variables; those lower than .50 generally indicate poor tolerance owing to substantial redundancy.

TABLE 6
Final regression models for dental care–related anxiety and fear of dental pain.

PREDICTOR VARIABLE	DENTAL CARE-RELATED ANXIETY-MCIR*		FEAR OF DENTAL PAIN-MCIR		
	B [†]	Standard Error	β^{\ddagger}	B	P Value
Sex	-.543	.580	-.074	-4.029	.150
Trait Anxiety	.085	.030	.249	.165	.261
Anxiety Sensitivity	.058	.038	.135	.583	.002
MCIR Gene Variant Status	1.584	.585	.213	5.777	.042

* MCIR: Melanocortin-1 receptor.

[†]B: Unstandardized regression coefficient.

[‡] β : Standardized regression coefficient.