Original investigation

Genetic Vulnerability to Menthol Cigarette Preference in Women

Cheryl Oncken MD, MPH¹, Richard Feinn PhD², Jonathan Covault MD, PhD³, Valerie Duffy PhD⁴, Ellen Dornelas PhD^{5,6}, Henry R. Kranzler MD⁷, Heather Z. Sankey MD⁸

¹Department of Medicine and Obstetrics and Gynecology, University of Connecticut School of Medicine, Farmington, CT; ²Department of Medical Sciences, Frank H. Netter MD School of Medicine, Quinnipiac University, Hamden, CT; ³Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT; ⁴Department of Allied Health Sciences, Allied Health Sciences, College of Agriculture and Natural Resources, University of Connecticut, Storrs, CT; ⁵Division of Oncology, Department of Medicine, Hartford Hospital, Hartford, CT; ⁶Department of Medicine, University of Connecticut School of Medicine, Farmington, CT; ⁷Department of Psychiatry, University of Pennsylvania Perelman School of Medicine and Philadelphia VAMC, Philadelphia, PA; ⁸Department of Obstetrics and Gynecology, Baystate Medical Center, Springfield, MA

Corresponding Author: Cheryl Oncken, MD, MPH, Department of Medicine and Obstetrics and Gynecology, University of Connecticut Health Center, 263 Farmington Ave, MC 3805, Farmington, CT 06030, USA. Telephone: 860-679-3425; Fax: 860-679-1454; E-mail: oncken@nso2.uchc.edu

Abstract

Background: Smokers may prefer menthol cigarettes to mask the bitter taste of nicotine. Variation in the taste receptor gene, *TAS2R38*, may contribute to preference for menthol cigarettes.

Aims: To determine whether two common haplotypes of *TAS2R38* (proline-alanine-valine [PAV] and alanine-valine-isoleucine [AVI]), which have been associated, respectively, with bitter taste or a lack of bitter taste produced by propylthiouracil, are associated with preference for menthol cigarettes.

Methods: Data on smoking and blood for DNA extraction and genotyping were obtained from 323 pregnant non-Hispanic or Hispanic Caucasian smokers. We genotyped three *TAS2R38* single nucleotide polymorphisms (rs713598, rs1726866, and rs10246939) and constructed haplotypes. We examined associations between menthol preference and the frequency and distribution of the AVI and PAV haplotypes among study participants.

Results: Participants smoked an average of 16 cigarettes per day before pregnancy. The PAV and AVI haplotype frequencies were 48% and 45%, respectively. Non-Hispanic women were less likely than Hispanic women to smoke menthol cigarettes. As hypothesized, the frequency of the PAV haplotype was greater in menthol than non-menthol smokers in both non-Hispanics (54% vs. 30%; $\chi^2 = 13.04$, $P < .001$) and Hispanics (53% vs. 25%; $\chi^2 = 5.77$, $P = .016$). This effect persisted after controlling for potential confounders in multivariate logistic regression. Menthol smokers had a greater number of PAV haplotypes/individual than non-menthol smokers [non-Hispanics odds ratio (OR) = 3.02 (1.56–5.85); $P = .001$; Hispanics OR = 3.60 (1.23–10.56); $P = .020$].

Conclusions: These preliminary data support the hypothesis that a genetic propensity to experience heightened bitter taste perception increases the preference for menthol cigarettes.

Introduction

Nicotine use evokes unpleasant bitter and irritant sensations.^{1,2} The addition of menthol to cigarettes can mask this bitterness or irritant effect. Menthol has a minty odor³ and elicits perceptions of oral and nasal cooling-irritation⁴ with activation of TRP-channels involved in oral thermoreception and nociception.⁵ Consequently, menthol may increase tolerance of the unpleasant sensations of smoking, thereby facilitating tobacco smoking and increasing the risk of addiction. Menthol cigarettes are commonly used by women (who have a biological predisposition to experience heightened bitter taste),⁶ younger smokers, and racial and ethnic minorities.⁷

Of interest is the extent to which a genetic propensity to taste heightened bitterness contributes to the likelihood of smoking menthol cigarette.² One of the most polymorphic and researched taste receptor genes for bitter taste is *TAS2R38*, which accounts for 50%–85% of the variability in an individual's response to the bitter taste of thiourea compounds such as phenylthiocarbamide and propylthiouracil.^{8,9} This and other genes in the *TAS2R* family encode small proteins (of about 400 amino acids), which act as receptors for ligands that stimulate bitter taste perception.¹⁰ The *TAS2R* genes explain variability in bitterness perception and the likelihood of consuming vegetables^{11–13} and alcoholic beverages.^{14,15}

TAS2R38 has two common haplotypes (proline-alanine-valine [PAV] and alanine-valine-isoleucine [AVI]) defined by three single nucleotide polymorphisms (SNPs) that encode amino acid changes: Pro49Ala, Ala262Val, and Val296Ile. The *TAS2R38* haplotypes comprised of these SNPs (PAV and AVI) differentiate tasters of propylthiouracil bitterness (PAV/PAV and PAV/AVI genotypes) from non-tasters (AVI/AVI homozygotes).^{16–18} One study showed an association between *TAS2R38* diplotype and propylthiouracil taste threshold: PAV/PAV individuals tasted propylthiouracil at a very low threshold, PAV/AVI individuals at an intermediate threshold, and AVI/AVI individuals were non-tasters.¹⁷

Because an individual's response to nicotine *per se* could impact smoking behavior, previous studies have examined associations between the *TAS2R38* PAV and AVI haplotypes and smoking quantity and measures of nicotine dependence. Collectively, these studies suggest that the PAV haplotype may be associated with decreased smoking initiation,¹⁹ a lower smoking quantity^{20,21} and dependence,²⁰ although the results may be influenced by race/ethnicity and gender. In the present study, we examined whether the two common haplotypes of *TAS2R38* were associated with a preference for menthol cigarettes among pregnant smokers. We hypothesized that women who are more susceptible to heightened bitter taste perception, as shown by a higher prevalence of the PAV haplotype, are more likely to smoke menthol cigarettes. We also examined the impact of these *TAS2R38* haplotypes on other smoking variables (ie, measures of nicotine dependence and cigarettes smoked per day).

Methods

The study was conducted at the University of Connecticut Health Center (Farmington, CT), Hartford Hospital (Hartford, CT), the Hospital of Central Connecticut (New Britain, CT), and Baystate Medical Center (Springfield, MA). Institutional review boards at all participating institutions approved the study. Baseline demographics, self-reported race and ethnicity (ie, non-Hispanic or Hispanic), smoking variables, menthol cigarette use, and a blood sample for genotyping were obtained from pregnant smokers participating in a clinical trial for smoking cessation²² or a study of the relations among maternal genetics, cigarette smoking, and birth weight. We

conducted a secondary data analysis of women who self-identified as Caucasian to examine associations between menthol use and *TAS2R38* haplotypic variation.

DNA was extracted from whole blood at the Core Laboratory at the University of Connecticut Health Center. Haplotypes were determined from SNPs rs713598, rs1726866, and rs10246939 at positions 145, 785, and 886 of the *TAS2R38* gene mRNA. DNA was amplified using the Taqman assay (Life technologies, Foster City, CA) and the 7900HT Real-Time PCR System. Genotypes were determined using vendor-supplied SNP assays. Genotype frequencies were in Hardy-Weinberg equilibrium for all three SNPs ($P_s > .5$). rs713598, rs1726866, and rs10246939 each give rise to three non-synonymous substitutions—proline to alanine at residue 49, alanine to valine at residue 262, and valine to isoleucine at residue 296, respectively. The SNPs result in two common *TAS2R38* haplotypes (AVI and PAV) and three uncommon haplotypes (alanine-alanine-valine, alanine-alanine-isoleucine, proline-valine-valine). We assumed that heterozygotes at all three SNPs (eg, genotypes CG TC CT) were common haplotype heterozygotes (eg, PAV/AVI rather than alanine-alanine-valine/proline-valine-isoleucine), as the probability of having two rare haplotypes is extremely low.²³

We compared the baseline characteristics of menthol users and nonusers in self-identified Caucasians (non-Hispanic or Hispanic) with *t* tests for continuous variables and chi-square analyses for categorical variables. We used chi-square analyses to examine associations of ethnicity with cigarette type (menthol or non-menthol) and genotype. The Cochran–Mantel–Haenszel test was used to examine the association between cigarette type and PAV haplotype stratifying by ethnicity. We used multivariate logistic regression to control for subject characteristics in predicting menthol or non-menthol preference. We used the Akaike information criterion, the Bayesian information criterion, pseudo- R^2 , and odds ratios to determine which genetic model (additive, dominant, or recessive) best fit the data. Analyses were conducted using SPSS v22 and the alpha level for statistical significance was set at 0.05.

Results

Three hundred twenty-three women identified themselves as Caucasian non-Hispanic or Hispanic (Table 1) and the majority (81%) were menthol smokers. Non-Hispanics were significantly less likely to use menthol cigarettes than Hispanics (56% vs. 95%, $\chi^2 = 75.7$, 1 *df*, $P < .001$). Non-Hispanics also trended towards a lower PAV haplotype frequency (43% vs. 51%; $\chi^2 = 3.60$, 1 *df*, $P = .06$) compared with Hispanics. Consequently, we report the results separately by ethnicity.

Baseline characteristics of the study population are outlined in Table 1. Menthol smokers were younger and more likely to be single than non-menthol smokers. However, smoking variables such as cigarettes smoked per day, age of smoking initiation, living with another smoker in the household, and nicotine dependence scores as measured by the Fagerstrom Test for Nicotine Dependence²⁴ were similar between menthol versus non-menthol smokers.

The PAV and AVI haplotype frequencies were 48% and 45%, respectively. Other minor haplotypes (alanine-alanine-isoleucine 18/646 haplotypes; alanine-alanine-valine 23/646 haplotypes; proline-valine-valine 1/646 haplotypes) constituted approximately 7% of the sample. The number of AVI and PAV haplotypes were strongly inversely related ($r = -.87$). In 88% of the subjects there was a direct correspondence between the number of PAV and AVI haplotypes (2 PAV with 0 AVI, 1 PAV with 1 AVI, 0 PAV with 2 AVI) suggesting that these haplotypes can be considered complementary. Consequently, the following analysis focuses on the PAV haplotype (associated with bitter taster status).

Table 1. Baseline Characteristics by Ethnicity and Menthol Use

Characteristic	Menthol smokers (non-Hispanics, <i>n</i> = 63; Hispanics <i>n</i> = 200)	Non-menthol smokers (non- Hispanics, <i>n</i> = 50; Hispanics <i>n</i> = 10)	Total (non-Hispanics, <i>n</i> = 113; Hispanics <i>n</i> = 210)
Age (mean ± <i>SD</i>)			
Non-Hispanic	24.1 ± 5.0	26.6 ± 5.8 [^]	25.2 ± 5.5 [*]
Hispanic	23.6 ± 4.4	26.6 ± 7.1	23.7 ± 4.5
BMI (mean ± <i>SD</i>)			
Non-Hispanic	26.6 ± 6.7	25.5 ± 6.2	26.1 ± 6.5
Hispanic	26.9 ± 6.7	27.0 ± 5.9	26.9 ± 6.6
Marital status (% single)			
Non-Hispanic	45 (71%)	21 (42%) ^{^^}	66 (58%) [*]
Hispanic	158 (79%)	4 (40%) ^{^^}	162 (77%)
Education (% ≥ high school)			
Non-Hispanic	43 (68%)	36 (74%)	79 (71%) [*]
Hispanic	70 (35%)	5 (50%)	75 (36%)
Cigarettes/day (mean ± <i>SD</i>)			
Non-Hispanic	18.3 ± 11.0	18.1 ± 5.8	18.2 ± 9.1 [*]
Hispanic	14.3 ± 10.0	13.9 ± 8.8	14.3 ± 9.9
Age first cigarette (mean ± <i>SD</i>)			
Non-Hispanic	15.0 ± 3.6	15.6 ± 2.9	15.3 ± 3.3
Hispanic	15.8 ± 3.2	17.7 ± 3.6	15.9 ± 3.2
FTND score ^a (mean ± <i>SD</i>)			
Non-Hispanic	3.4 ± 2.0	3.9 ± 1.8	3.7 ± 1.9
Hispanic	3.6 ± 2.0	3.3 ± 2.2	3.6 ± 2.0

BMI = body mass index.

^aFagerstrom Test for Nicotine Dependence (24).

^{*}*P* < .01 (for the comparison between non-Hispanic and Hispanic groups).

[^]*P* < .05, ^{^^}*P* < .01 (for the comparison of menthol vs. non-menthol within ethnic groups).

Analyzed separately by ethnicity, the frequency of the PAV haplotype was greater among the menthol smokers than non-menthol smokers for non-Hispanics (54% vs. 30%, respectively; $\chi^2 = 13.04$, 1 *df*, *P* < .001) and Hispanics (53% vs. 25%, respectively; $\chi^2 = 5.77$, 1 *df*, *P* = .016). A Cochran–Mantel–Haenszel test of the association between menthol smoking and presence of the PAV haplotype stratified by ethnicity resulted in a common odds ratio (OR) of 3.52 (95% CI = 1.74% to 7.10%), with similar estimates within ethnic groups (non-Hispanic OR = 3.62 or Hispanic OR = 3.26) and homogeneity of the odds ratio (nonsignificant homogeneity Breslow–Day test, *P* = .89).

Consistent with the primary study objective, multivariate logistic models were run to test whether the PAV-menthol smoking association remained significant after controlling for demographic differences between groups of smokers. Women with minor haplotypes paired with the PAV haplotype were included in the analyses. Controlling for age and marital status, the number of PAV haplotypes was associated with menthol smoking within both non-Hispanic and Hispanic women (Table 2). Because the overall prevalence of menthol use was much lower in non-Hispanic participants, the PAV effects associated with larger differences in the frequency of menthol use (34%, 58%, 85% for 0, 1, and 2 PAVs, respectively) than for the Hispanic participants (90%, 95%, 100% for 0, 1, and 2 PAVs, respectively).

We also compared three genetic models (additive, dominant, and recessive) to determine which best fit the data (Table 3), as evidenced by lower valued of Akaike information criterion and Bayesian information criterion, a higher *R*², and a higher odds ratio. A difference in Bayesian information criterion between 2 and 6 is considered positive evidence against the model with the higher Bayesian information criterion and a difference between 6 and 10 is considered strong evidence against the model.²⁵ In non-Hispanics, the additive model demonstrated the best fit, while in Hispanics the dominant model showed the poorest fit.

Table 2. Associations Between Number of Proline-Alanine-Valine (PAV) Haplotypes and Menthol Smoking^a

	% Menthol smokers	OR ^b (95% CI)
Non-Hispanic (<i>n</i> = 113)		
0 PAV (<i>n</i> = 35)	34%	3.02 (1.56% to 5.85%)
1 PAV (<i>n</i> = 58)	59%	<i>P</i> = .001
2 PAV (<i>n</i> = 20)	85%	
Hispanic (<i>n</i> = 210)		
0 PAV (<i>n</i> = 52)	90%	3.60 (1.23% to 10.56%)
1 PAV (<i>n</i> = 101)	95%	<i>P</i> = .020
2 PAV (<i>n</i> = 57)	100%	

CI = confidence interval; OR = odds ratio.

^aResults adjusted for age and marital status.

^bOR determined by the number of PAV's as a predictor of menthol smoking.

We examined associations between number of PAV haplotypes and number of cigarettes smoked per day and found a nonsignificant linear trend. In non-Hispanics, participants with 0 PAV's smoked a mean (*SD*) of 19.5 (6.1) cigarettes/day; participants with 1 PAV haplotype smoked 18.3 (11.0) cigarettes per day, and those with 2 PAV haplotypes smoked 15.5 (6.3) cigarettes per day (*P* = .11). In Hispanics, participants with 0 PAV's smoked on average 15.5 (12.2) cigarettes/day, those with 1 PAV haplotype smoked 14.4 (9.7) cigarettes per day, and those with 2 PAV haplotypes smoked 13.1 (7.8) cigarettes per day (*P* = .22).

Discussion

This study provides support, in a Caucasian sample of pregnant smokers, that a woman's likelihood of smoking menthol cigarettes is influenced by her genetic tendency to experience heightened bitter

Table 3. Comparison of Genetic Models

Model	AIC	BIC	R ² *	OR
Non-Hispanic				
Additive	144.8	150.2	.160	9.64
Dominant	149.6	155.1	.108	3.62
Recessive	149.8	155.2	.106	5.79
Hispanic				
Additive	78.6	85.3	.086	10.43
Dominant	81.3	88.0	.046	3.26
Recessive	77.9	84.6	.096	Undefined**

AIC = Akaike information criterion; BIC = Bayesian information criterion. The odds ratio (OR) is an association between PAV and preference for menthol cigarettes. Additive model, the OR is for 0 haplotype copies to 2 copies; Dominant model, the OR is for haplotype carrier (1 or 2 copies) vs. no haplotypes; Recessive model, the OR is for the homozygous diplotype (2 copies of haplotype) versus 0 or 1 copy.

*Pseudo-R² is Nagelkerke.

**There were 0 non-menthol smokers with 2 proline-alanine-valine haplotypes so OR could not be estimated.

taste. Specifically, we found that the number of TAS2R38 PAV haplotypes predicted a preference for menthol cigarettes, particularly among non-Hispanic women. Menthol preference was associated with younger age and a greater likelihood of being single; however, after controlling for these potential confounders the association between haplotype and menthol preference remained significant in both non-Hispanic and Hispanic female smokers. There was some support for an additive model for PAV effects on menthol cigarette smoking, but only seen among the non-Hispanics. As the Hispanic women were most likely to smoke menthol cigarettes, we were unable to determine the best fit model.

To the best of our knowledge, this is the first report of an association between variation in TAS2R38 and preference for menthol cigarettes. The Food and Drug Administration's Tobacco Specific Advisory Committee recommended an examination of the role that menthol plays in masking bitterness and allowing smokers who are "genetically more sensitive to bitterness to better tolerate tobacco smoke and therefore become a smoker."² Other investigators have examined associations between other smoking variables and both bitter taste phenotype and genotype.^{19,26,27} Collectively, these studies suggest that individuals who are more susceptible to bitter taste may be less likely to become smokers or have lower smoking rates. A genetic study of 2037 black and European American individuals found that the PAV haplotype was inversely and the AVI haplotype positively associated with smoking quantity in blacks (but not European Americans). In black women, AVI haplotype was associated with multiple measures of greater nicotine dependence.²⁰ In a German study, individuals with at least one PAV haplotype smoked fewer cigarettes per day than individuals without this haplotype.²¹ Consistent with the results from the German study, we found that women with more PAV haplotypes smoked fewer cigarettes, although this finding was not statistically significant likely due to a small sample size.

In this study, menthol smokers were younger than non-menthol smokers, consistent with epidemiological data.⁷ Further, Hispanic women were more likely to be menthol smokers than non-Hispanic women. Indeed, less than 5% of women who self-identified as Hispanic in our study smoked non-menthol cigarettes. Although the magnitude of the association between the number of PAV haplotypes/individual and menthol cigarette use was similar in non-Hispanics

and Hispanics, we observed a larger effect of the PAV haplotype on the rate of menthol use in non-Hispanics because most Hispanic women in our sample smoked menthol cigarettes. The very high prevalence of menthol use in Hispanic women of reproductive age (>90%) may be due to a myriad of factors in the environment such as targeted marketing and social influence, or other genetic factors not measured in this study.²⁸ It is also noteworthy that the majority of Hispanic Women in our study were Puerto Rican²²; in national samples Puerto Ricans have higher rates of menthol smoking (62%) than Hispanic individuals of Mexican origin (25%).²⁸

Nonetheless, our analyses showed a significant association between genotype and menthol preference in both non-Hispanic and Hispanic women, suggesting that the bitter taste genotype contributes to the variability in menthol taste preference in both ethnic groups. The importance of understanding the role that taste receptor genetics plays in menthol preference is underscored by a recent decision by the European Union, which proposed regulations to ban menthol from cigarettes.²⁹

The majority of our sample had either taster (ie, PAV) or non-taster (ie, AVI) haplotypes; however, we also found that 7% of the haplotypes in our study were uncommon ones. This haplotype distribution is consistent with another report in Caucasians^{16,17} and with the frequency of PAV and AVI haplotypes in African, Asian, European, and North American populations, suggesting that natural selection has acted to maintain taster and non-taster alleles of TAS2R38.²³ A study of rarer TAS2R38 haplotypes showed that they likely produce an intermediate response between those associated with the PAV and AVI haplotypes and phenylthiocarbamide or propylthiouracil ligands, although more studies are needed to confirm this finding.¹⁷

It is noteworthy that bitter taste receptors have been identified in bronchial airway smooth muscles.^{30,31} Indeed a number of agonist treatments are currently being developed to target these taste receptor cells and improve bronchial airflow. Consequently, the possibility exists that the association between smoking and bitter taste receptor haplotypes may be due to mechanisms other than oral taste sensations and may include respiratory responses as well.

A major strength of this study is the focus on a well-characterized gene that has been hypothesized to be related to menthol cigarette preference, including a biological hypothesis.² One limitation is that we used self-reported race and ethnicity rather than ancestry informative markers.³² The study also was limited by the relatively small sample size and the inclusion of only pregnant Caucasian women, so the results may not generalize to men, women of other races or older women. However, it seems likely that our results would apply to other Caucasian women of reproductive age. In our experience, pregnant women do not typically change cigarette brands or menthol preference after learning that they are pregnant; however, the possibility does exist that some women would switch to menthol cigarettes to block the heightened bitterness perception experienced during the first trimester of pregnancy.³³

In summary, we found a genetic association between variation in the bitter taste receptor gene and menthol cigarette preference in a sample of pregnant Caucasian women. Further studies are needed to confirm these findings in samples that include men, non-pregnant women and other racial groups.

Funding

This study was funded in part by the Patrick and Catherine Weldon Donaghue Medical Research Foundation, DA15167, academic enhancement funds to CO, and the General Clinical Research Center at the University of Connecticut Health Center. Oral Presentation: Preliminary results from this study were presented at the SRNT-Europe Annual Meeting September 19, 2014.

Declaration of Interests

CO is currently conducting an NIH-funded clinical trial for smoking cessation in pregnancy and receives free nicotine and placebo inhalers from Pfizer. She has received research support from Pfizer and Nabi Biopharmaceuticals and has served on an advisory board for Pfizer. HRK has been a consultant or advisory board member for Alkermes, Lilly, Lundbeck, Otsuka, Pfizer, and Roche and is a member of the American Society of Clinical Psychopharmacology's ACTIVE Group, which is supported by AbbVie, Alkermes, Ethypharm, Lilly, Lundbeck, and Pfizer. The other authors have no conflicts of interest to report.

References

- Oliveira-Maia AJ, Stapleton-Kotloski JR, Lyall V, et al. Nicotine activates TRPM5-dependent and independent taste pathways. *Proc Natl Acad Sci U S A*. 2009;106(5):1596–1601. doi:10.1073/pnas.0810184106.
- Committee TPSA. *Menthol Cigarettes and Public Health: Review of Scientific Evidence and Recommendations*. Rockville, MD: Food and Drug administration; 2011. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/tobacco/products/scientificadvisorycommittee/ucm269697.pdf. Accessed September 30, 2014.
- Goyert HF, Frank ME, Gent JF, Hettinger TP. Characteristic component odors emerge from mixtures after selective adaptation. *Brain Res Bull*. 2007;72(1):1–9. doi:10.1016/j.brainresbull.2006.12.010.
- Cliff MA, Green BG. Sensory irritation and coolness produced by menthol: evidence for selective desensitization of irritation. *Physiol Behav*. 1994;56(5):1021–1029. doi:10.1016/0031-9384(94)90338-7.
- Willis DN, Liu B, Ha MA, Jordt SE, Morris JB. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. *FASEB J*. 2011;25(12):4434–4444. doi:10.1096/fj.11-188383.
- Bartoshuk LM, Duffy VB, Miller IJ. Ptc/Prop Tasting—Anatomy, Psychophysics, and Sex Effects (Vol 56, Pg 1165–1171, 1994). *Physiol Behav*. 1995;58(1):203.
- Caraballo RS, Asman K. Epidemiology of menthol cigarette use in the United States. *Tob Induc Dis*. 2011;9(suppl 1):S1. doi:10.1186/1617-9625-9-S1-S1.
- Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science*. 2003;299(5610):1221–1225. doi:10.1126/science.1080190.
- Drayna D, Coon H, Kim UK, et al. Genetic analysis of a complex trait in the Utah Genetic Reference Project: a major locus for PTC taste ability on chromosome 7q and a secondary locus on chromosome 16p. *Hum Genet*. 2003;112(5–6):567–572. doi:10.1007/s00439-003-0911-y.
- Wooding S. Phenylthiocarbamide: a 75-year adventure in genetics and natural selection. *Genetics*. 2006;172(4):2015–2023.
- Sandell MA, Breslin PA. Variability in a taste-receptor gene determines whether we taste toxins in food. *Curr Biol*. 2006;16(18):R792–794. doi:10.1016/j.cub.2006.08.049.
- Duffy VB, Hayes JE, Davidson AC, Kidd JR, Kidd KK, Bartoshuk LM. Vegetable intake in college-aged adults is explained by oral sensory phenotypes and TAS2R38 genotype. *Chem Senses*. 2010;35(3–4):137–148. doi:10.1007/s12078-010-9079-8.
- Wooding S, Gunn H, Ramos P, Thalmann S, Xing C, Meyerhof W. Genetics and bitter taste responses to goitrin, a plant toxin found in vegetables. *Chem Senses*. 2010;35(8):685–692. doi:10.1093/chemse/bjq061.
- Allen AL, McGeary JE, Hayes JE. Polymorphisms in TRPV1 and TAS2Rs Associate with Sensations from Sampled Ethanol. *Alcohol Clin Exp Res*. 2014;38(10):2550–2560. doi:10.1111/acer.12527.
- Duffy VB, Peterson JM, Bartoshuk LM. Associations between taste genetics, oral sensation and alcohol intake. *Physiol Behav*. 2004;82(2–3):435–445. doi:10.1016/j.physbeh.2004.04.060S0031938404002112.
- Hayes JE, Bartoshuk LM, Kidd JR, Duffy VB. Supertasting and PROP bitterness depends on more than the TAS2R38 gene. *Chem Senses*. 2008;33(3):255–265. doi:10.1093/chemse/bjm084.
- Behrens M, Gunn HC, Ramos PC, Meyerhof W, Wooding SP. Genetic, functional, and phenotypic diversity in TAS2R38-mediated bitter taste perception. *Chem Senses*. 2013;38(6):475–484. doi:10.1093/chemse/bjt016.
- Bufe B, Breslin PA, Kuhn C, et al. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. *Curr Biol*. 2005;15(4):322–327. doi:10.1016/j.cub.2005.01.047.
- Cannon DS, Baker TB, Piper ME, et al. Associations between phenylthiocarbamide gene polymorphisms and cigarette smoking. *Nicotine Tob Res*. 2005;7(6):853–858. doi:10.1080/14622200500330209.
- Mangold JE, Payne TJ, Ma JZ, Chen G, Li MD. Bitter taste receptor gene polymorphisms are an important factor in the development of nicotine dependence in African Americans. *J Med Genet*. 2008;45(9):578–582. doi:10.1136/jmg.2008.057844.
- Keller M, Liu X, Wohland T, et al. TAS2R38 and its influence on smoking behavior and glucose homeostasis in the German Sorbs. *PLoS One*. 2013;8(12):e80512. doi:10.1371/journal.pone.0080512.
- Oncken C, Dornelas E, Greene J, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. *Obstet Gynecol*. 2008;112(4):859–867. doi:10.1097/AOG.0b013e318187e1ec.
- Wooding S, Kim UK, Bamshad MJ, Larsen J, Jorde LB, Drayna D. Natural selection and molecular evolution in PTC, a bitter-taste receptor gene. *Am J Hum Genet*. 2004;74(4):637–646. doi:10.1086/383092.
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*. 1991;86(9):1119–1127.
- Raftery AE. Bayesian model selection in social research. *Sociol Methodol*. 1995;25:111–163. doi:10.2307/271063.
- Snedecor SM, Pomerleau CS, Mehlinger AM, Ninowski R, Pomerleau OF. Differences in smoking-related variables based on phenylthiocarbamide “taster” status. *Addict Behav*. 2006;31(12):2309–2312. doi:10.1016/j.addbeh.2006.02.016.
- Enoch MA, Harris CR, Goldman D. Does a reduced sensitivity to bitter taste increase the risk of becoming nicotine addicted? *Addict Behav*. 2001;26(3):399–404.
- Delnevo CD, Gundersen DA, Hrywna M, Echeverria SE, Steinberg MB. Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes. *Am J Prev Med*. 2011;41(4):357–365. doi:10.1016/j.amepre.2011.06.039.
- Agaku IT, Omaduvie UT, Filippidis FT, Vardavas CI. Cigarette design and marketing features are associated with increased smoking susceptibility and perception of reduced harm among smokers in 27 EU countries. *Tob Control*. 2014;1–8. doi:10.1136/tobaccocontrol-2014-051922.
- Deshpande DA, Wang WC, McIlmoyle EL, et al. Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. *Nat Med*. 2010;16(11):1299–1304. doi:10.1038/nm.2237.
- Kinnamon SC. Taste receptor signalling—from tongues to lungs. *Acta Physiol (Oxf)*. 2012;204(2):158–168. doi:10.1111/j.1748-1716.2011.02308.x.
- Halder I, Shriver M, Thomas M, Fernandez JR, Frudakis T. A panel of ancestry informative markers for estimating individual biogeographical ancestry and admixture from four continents: utility and applications. *Hum Mutat*. 2008;29(5):648–658. doi:10.1002/humu.20695.
- Duffy VB, Bartoshuk LM, Striegel-Moore R, Rodin J. Taste changes across pregnancy. *Ann N. Y. Acad. Sci*. 1998;855:805–809.