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ABSTRACT

Dental caries is influenced by a complex interplay of genetic and environmental factors, including dietary habits. Previous reports have characterized the influence of genetic variation on taste preferences and dietary habits. We therefore hypothesized that genetic variation in taste pathway genes (TAS2R38, TAS1R2, GNAT3) may be associated with dental caries risk and/or protection. Families were recruited by the Center for Oral Health Research in Appalachia (COHRA) for collection of biological samples, demographic data, and clinical assessment of oral health, including caries scores. Multiple single-nucleotide polymorphism (SNP) assays for each gene were performed and analyzed by transmission disequilibrium test (TDT) analysis (FBAT software) for three dentition groups: primary, mixed, and permanent. Statistically significant associations were seen in TAS2R38 and TAS1R2 for caries risk and/or protection.

KEY WORDS: dental caries, taste preference, genetic association, taste pathway genes.

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INTRODUCTION

Dental caries is the most prevalent childhood and chronic disease worldwide. Caries occurrence and progression are known to be influenced by a complex interplay of both environmental and genetic factors, with numerous contributing factors having been identified, including bacterial flora, dietary habits, fluoride exposure, oral hygiene, salivary flow, salivary composition, and tooth structure. The importance of genetic factors in caries is supported by twin studies that have estimated that 40-60% of caries susceptibility is genetically determined (Boraas *et al.*, 1988; Conry *et al.*, 1993; Bretz *et al.*, 2005, 2006; Wang *et al.*, 2010). There is also strong support, from animal model studies, for a genetic component to caries (Liu *et al.*, 1998; Shuler, 2001; Nariyama *et al.*, 2004).

To date, there have been few studies on the association of specific genes with human caries. Tuftelin was found to be associated with caries (Slayton *et al.*, 2005), as well as Ameloblastin (Deeley *et al.*, 2008). Given the strong evidence of a genetic component to dental caries, the discovery of additional genes and pathways may greatly improve the identification of individuals at risk and enhance the implementation of targeted preventive strategies at the critical stage before onset of caries.

Given the influence of dietary habits on dental caries, we hypothesized that taste pathway genes, such as genes for taste preference, might influence caries risk. Although taste preferences based on chemical tastants have been proven useful for the assessment of dietary habits, this approach has been hampered by numerous difficulties and is limited to a point in time that may not represent an individual's lifelong dietary habits. A genetics approach provides an opportunity for better discrimination between genetic and environmental components.

Therefore, in the current study, we investigated markers within the genes for "taste receptor, type-2, member 38" (TAS2R38), "taste receptor, type-1, member 2" (TAS1R2), and "guanine nucleotide binding protein, alpha transducing-3" (GNAT3) for associations with dental caries in a large cohort of families from Appalachia. Our ultimate goal is to use these results to develop

Table 1. Characteristics of Study Population

	Primary Dentition	Mixed Dentition	Permanent Dentition
Sample Size	496	562	1391
Age ($\mu \pm$ SD)	3.4 \pm 1.5	9.8 \pm 5.3	29.4 \pm 12.2
Male / Female	248 / 238	290 / 272	542 / 849
dft/DMFT			
(range: min-max)	0 – 13	0 – 16	0 – 28
(mean / median)	(1.2 / 0)	(3.0 / 2)	(7.6 / 7)
dfs/DMFS			
(range: min-max)	0 – 40	0 – 50	0 – 122
(mean / median)	(2.2 / 0)	(6.2 / 3)	(16.9 / 11)

targeted intervention strategies for dental caries based on specific environmental modifications, in the context of specific genetic backgrounds such as taste preferences.

MATERIALS & METHODS

Study participants were drawn from the ongoing oral health etiology studies of the Center for Oral Health Research in Appalachia (COHRA), a partnership between the University of Pittsburgh and West Virginia University. As previously described (Polk *et al.*, 2008), a family recruitment approach identified eligible resident households with at least one biological parent-child pair including a child between ages 1 and 18 living in the same household, regardless of caries status. Exclusion criteria included individuals with neurological impairment, a severe physical handicap, psychosis, and families with either of the parent-child pair having a reduced ability to form blood clots or resist infection. The COHRA study population includes a range of socio-economic status (median annual household income less than \$25,000), and is fairly representative of the general Appalachian population, which ranks very low compared with the rest of the nation in terms of many oral health measures and access to oral health care (Grembowski *et al.*, 1987; Janes *et al.*, 1999; Purnell, 1999). Statistical analysis was limited to Caucasian families due to the small non-Caucasian sample size and potential complications of genetic heterogeneity. After receiving informed consent approved by the institutional review boards of both universities, COHRA ascertains representative families from West Virginia and Pennsylvania, and applies a full range of oro-dental, behavioral, and microbiological assessments (Polk *et al.*, 2008). Each participant also provided a sample for DNA extraction (blood, buccal tissue, mouthwash, or saliva). See Table 1 for the characteristics of the study participants, all of whom were members of COHRA families.

The caries assessments were performed by trained dental professionals (dentists and dental hygienists) who were calibrated periodically across all sites. Intraclass correlation coefficient (ICC) analysis was applied to quantify the consistency of caries assessments among and within the examiners. Note that very high concordance rates were observed for both inter-examiner reliability (ICC between 0.86 and 0.99) and intra-examiner reliability (ICC > 0.99).

Each tooth was identified as either permanent or primary, and each surface on each tooth was scored as decayed, missing due to caries, or filled. We calculated the standard decayed, filled,

teeth/surface scores dfs/dft (Drury *et al.*, 1999) for primary teeth to avoid misidentification of unerupted teeth in children, and DMFT/DMFS for permanent teeth using the cavitated enamel and dentin lesion definition. Three groupings of individuals were used for analysis: “primary” = individuals with only primary teeth (caries score dft/dfs); “mixed” = individuals with at least one primary tooth and at least one permanent tooth (caries scores dft+DMFT and dfs+DMFS); and “permanent” = individuals with only permanent teeth (caries scores DMFT/DMFS). For analysis, we dichotomized the original dft/DMFT caries scores by caries status [assigning 0 values for individuals with no caries (dft/DMFT = 0) and 1 for individuals with any caries (dft/DMFT > 0)].

DNA Sample Preparation

Subject genomic DNA was extracted from either blood, buccal tissue, or mouthwash with the Genra Puregene kit (Qiagen, Valencia, CA, USA) or from saliva by means of the Oragene DNA Self Collection kit (DNA genotek, Ottawa, ON, Canada). A participant’s DNA was extracted according to standard manufacturer protocols and quantified with the Taqman RNaseP Detection Reagent (Applied Biosystems, Carlsbad, CA, USA) for standardization to 2 ng/ μ L.

Genotyping Methods

Genotyping for TAS2R38-SNP(1-3) (rs713598, rs1726866, rs10246939), TAS1R2-SNP(1-2) (rs4920566, rs9701796), and GNAT3-SNP(1-2) (rs2074674, rs6962693) with Taqman SNP Genotyping Assays (Applied Biosystems) in 5- μ L reactions with 4.5 ng DNA was amplified on a Tetrad PTC 225 thermocycler (MJ Research, Waltham, MA, USA). Genotype amplification detection and analysis were performed on the ABI 7900HT with ABI SDS software (Applied Biosystems). See Table 2 for SNP details. The error rate of additional SNP assays, genotyped in triplicate under identical conditions and confirmed with a separate method utilizing restriction site alterations, revealed a 0.4% genotyping discrepancy rate (data not shown).

Statistical Analysis

We used the transmission disequilibrium test (TDT) to assess association in the presence of linkage disequilibrium between the SNPs and the dental caries phenotypes. The Family Based

Table 2. Candidate Gene Markers Studied

Gene	Marker	Public ID	Base Change
Taste Receptor, Type-2, Member 38	TAS2R38-SNP1	rs713598	C/G
Taste Receptor, Type-2, Member 38	TAS2R38-SNP2	rs1726866	G/A
Taste Receptor, Type-2, Member 38	TAS2R38-SNP3	rs10246939	C/T
Taste Receptor, Type-1, Member 2	TAS1R2-SNP1	rs4920566	G/A
Taste Receptor, Type-1, Member 2	TAS1R2-SNP2	rs9701796	G/C
Guanine Nucleotide Binding Protein, alpha transducing-3	GNAT3-SNP1	rs2074674	G/A
Guanine Nucleotide Binding Protein, alpha transducing-3	GNAT3-SNP2	rs6962693	T/G

Association Test (FBAT), an extension of the TDT (Laird *et al.*, 2000; Rabinowitz and Laird, 2000; Horvath *et al.*, 2001) was used for both SNP and haplotype analyses (haplotypes are patterns of alleles within multiple SNPs that are together on the same chromosome strand in an individual). To detect allelic associations with both caries risk and caries protection, we evaluated each caries score twice, first assessing transmission patterns to the individuals affected with caries (to detect risk alleles), and second assessing transmission to individuals with no caries (for protection). The default threshold for statistical significance was applied (*i.e.*, p -values ≤ 0.05). All reported SNP genotypes were in Hardy-Weinberg Equilibrium.

RESULTS

We analyzed dental records for 496 people in primary, 562 in mixed, and 1391 in permanent dentition (Table 1). The average ages for these 3 dentition groups were 3.4, 9.8, and 29.4 yrs, respectively. The male-to-female ratios were comparable for both primary and mixed dentition, while there were substantially more females in the permanent dentition group. The summary statistics of the dft/DMFT and dfs/DMFS scores are also listed, showing the median dft/DMFT and dfs/DMFS increasing with the average age of the 3 study group categories (Table 1).

Analysis of our data revealed a significant association of the G, G, and C individual alleles representing the P, A, and V amino acid substitutions in the TAS2R38 gene with protection from caries in the “primary” group ($p = 0.007, 0.03, 0.01$, respectively) (Table 3). Haplotype analysis supported these findings, with significant association of GGC, GGX, and XGC (X representing any nucleotide) haplotypes in the “primary” group with caries protection ($p = 0.005, 0.004, 0.02$) (Table 4). The corresponding opposing haplotypes CAT and CAX were significantly associated in the “primary” group with caries risk (0.02, 0.03, respectively), which verified the validity of our findings (Table 4). Analysis of 2 SNPs in the TAS1R2 gene revealed significant association of the C allele of the TAS1R2-SNP2 in the “mixed” group for both caries protection ($p = 0.03$) and caries risk ($p = 0.02$) (Table 3). No statistically significant results were found in the permanent group (results not shown in detail).

DISCUSSION

In spite of the many methodological challenges, studies have demonstrated the importance of dietary habits, nutritional status,

Table 3. FBAT Single SNP Association Analyses on 2 Taste Preference Genes

SNP Name	Primary Dentition	Mixed Dentition
<i>Gene: TAS2R38</i>		
TAS2R38-SNP1	Protective / G / ($p = 0.007$)	
TAS2R38-SNP2	Protective / G / ($p = 0.03$)	
TAS2R38-SNP3	Protective / C / ($p = 0.01$)	
<i>Gene: TAS1R2</i>		
TAS1R2-SNP1		
TAS1R2-SNP2		Protective / C / ($p = 0.03$) Risk / C / ($p = 0.02$)

Note: Reporting format: Effect (Risk or Protective) / Allele Name (A,C,G,T) / FBAT P-value. No statistically significant results in permanent dentition.

and chemically determined taste sensitivity with respect to caries risk (Bretz *et al.*, 2006). We have taken advantage of the growing knowledge of the genetic components of taste preference and dietary habits to investigate the association of taste receptors and pathways with caries, resulting in evidence for association of TAS2R38 and TAS1R2 genotypes and/or haplotypes with caries.

The haplotypes of 3 SNPs representing the corresponding amino acid substitutions (A49P, A262V, V296I) in TAS2R38 have been well-characterized for their influence on the bitter taste sensitivity to specific classes of chemicals, including PROP (propylthiouracil) and PTC (phenylthiocarbamide). The proline, alanine, and valine combination (PAV) represented by the nucleotides (GGC) is associated with bitter sensitivity or “supertasters”, while the alanine, valine, and isoleucine combination (AVI) represented by the nucleotides (CAT) is associated with bitter insensitivity or “non-tasters”. Additional intermediate taster haplotypes, including AAV (CGC) and AAI (CGT), are more rare (Drayna, 2005). Supertasters have been associated with an increased density of anterior fungiform taste papillae and increased sensitivity to a wide variety of taste and oral sensations, including sweetness, mouth-feel, fats, and oral irritation (reviewed in Tepper, 2008). Analysis of our data revealed a significant association of the G, G, and C individual alleles representing the P, A, and V substitutions of supertasters with caries protection in the “primary” group. This is further supported by the similar association of the GGC, GGX, and XGC haplotypes. In addition, the CAT haplotype representing the AVI non-taster and CAX haplotype were associated with caries risk. This suggests a role for this gene in

Table 4. Haplotype Association Analyses for TAS2R38 in Primary Dentition

Risk -3 SNPs	Protective -3 SNPs	Risk -2 SNPs	Protective -2 SNPs
CAT (p = 0.02)	GGC (p = 0.005)	Taste1-2 CA (p = 0.03)	Taste1-2 GG (p = 0.004) Taste2-3 GC (p = 0.02)

Note: No statistically significant results in mixed or permanent dentition.

carries that may act through influences on dietary habits that then result in differing cariogenic and/or nutritional status.

These results are particularly interesting, considering that phenotypic inversions and other age-related biological responses have been characterized for TAS2R38 haplotypes or chemically determined bitter sensitivity, including correlations to food preferences, liking, and use, including sweet preferences. It has been shown that bitter sensitivity of the TAS2R38 supertaster haplotype declines with age, including a substantial transition during puberty (Bell and Tepper, 2006). While studies in adults have been inconsistent in correlating bitter sensitivity to sweet sensitivity, a study in preschool children (3.5-4.5 yrs) demonstrated that correlation of PROP determined supertaster children with increased sweet sensitivity, but, strikingly, these supertasters were sweet “likers” and consumed more sweet foods and beverages (Keller and Tepper, 2004). In another study, the supertaster haplotype of children (5-10 yrs) was similarly correlated to increased sweet sensitivity, liking, and consumption, while the mothers had no correlation to sweet preference (Mennella *et al.*, 2005). However, the counterintuitive association of the supertaster genotype/haplotype as protective in presumably sweet-liking children suggests that the mechanism is more complex than sugar consumption.

Consumption of fruits and vegetables, especially cruciferous vegetables, has been associated with reduced risk of cancer, with bitterness indicated as the primary reason for avoidance (Drewnowski and Gomez-Carneros, 2000; Murillo and Mehta, 2001). In adults, studies investigating the relationship of bitter sensitivity to cruciferous vegetable preferences have been varied (reviewed in Tepper, 2008). The most consistent relationship appears in studies with preschool children, including two studies showing that preschool non-tasters gave broccoli higher ‘liking’ ratings and consumed more bitter vegetables than preschool supertasters (Keller *et al.*, 2002; Bell and Tepper, 2006).

Other taste and dietary preferences also correlate with bitter sensitivity, including bitter citrus, cheese, and carbonated beverages (reviewed in Tepper, 2008). Interestingly, comparison of two independent studies of preschool female non-tasters and female college students, respectively, suggested an inversion with age in dietary fat consumption (Yackinous and Guinard, 2002; Keller and Tepper, 2004). It is possible that the association of TAS2R38 with caries in the primary dentition may reflect biological processes that change with age, a greater influence of social and cultural influences on adult habits, or a combination of both. While this association is supported by the consistency in the genotype and haplotype associations and could be explained by age-related processes, the potential for undetected association in the mixed and permanent dentitions exists. A larger study group and additional statistical models

may be needed to identify associations in these groups, especially if the phenotypic effect is smaller. Additionally, the focus of this analysis on genetic factors does not account for the potential of environmental confounders.

In addition to the influences of the TAS2R38 receptor on taste preferences and dietary habits, a specific sweet receptor has been identified as a heterodimer of the TAS1R2 and TAS1R3 gene products. Analysis of our data revealed a significant association of the C allele of TAS1R2-SNP2 with both caries risk and protection in the “mixed” group. The absence of additional supporting genotype or haplotype association suggests caution in excluding these associations as potential type I errors. However, it is possible that the C allele is interacting with additional SNPs that were not genotyped in our study and are associated separately with caries risk or protection.

In summary, our results have identified two genes important in taste-sensing that are associated with dental caries risk and/or protection. These results highlight the importance of understanding the role of taste preferences in caries and the utility of a genetics approach that overcomes the methodological challenges of laboratory taste preference assessment and reported dietary habits. Ultimately, the characterization of genes involved in taste preference and their genetic association with caries will contribute to greater screening of susceptible individuals and inform intervention strategies. Studies have shown that dietary intervention strategies in infants can have some level of influence on food acceptance (Mennella *et al.*, 2008). It is possible that different intervention strategies may prove more productive for individual subgroups of taste receptor genotypes and thereby contribute to early and targeted dental caries prevention.

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