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Genetic Analysis of Chemosensory Traits in Human Twins

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Abstract

We explored genetic influences on the perception of taste and smell stimuli. Adult twins rated the chemosensory aspects of water, sucrose, sodium chloride, citric acid, ethanol, quinine hydrochloride, phenylthiocarbamide (PTC), potassium chloride, calcium chloride, cinnamon, androstenone, Galaxolide™, cilantro, and basil. For most traits, individual differences were stable over time and some traits were heritable (h^2 from 0.41 to 0.71). Subjects were genotyped for 44 single nucleotide polymorphisms within and near genes related to taste and smell. The results of these association analyses confirmed previous genotype–phenotype results for PTC, quinine, and androstenone. New associations were detected for ratings of basil and a bitter taste receptor gene, *TAS2R60,* and between cilantro and variants in three genes (*TRPA1*, *GNAT3,* and *TAS2R50*). The flavor of ethanol was related to variation within an olfactory receptor gene (*OR7D4*) and a gene encoding a subunit of the epithelial sodium channel (*SCNN1D*). Our study demonstrates that person-to-person differences in the taste and smell perception of simple foods and drinks are partially accounted for by genetic variation within chemosensory pathways.

Key words: taste, smell, olfaction, genotype, odorant

Introduction

Humans from similar environments with similar exposure to foods and beverages often differ dramatically in preferences. One explanation for these individual differences is that people vary in their perception of the components of food, for example, flavor molecules such as sugars and salts, and volatiles found in meats and vegetables (Reed et al. 2006; Reed and Knaapila 2010). This hypothesis has received support from the discovery that alleles of some peripheral taste and smell receptors affect sensory perception. For instance, the extreme differences among individuals in the perception of the bitter compound phenylthiocarbamide (PTC) and structurally related compounds are due almost entirely to an allele of the bitter receptor *TAS2R38* (Kim et al. 2003; Bufe et al. 2005); goitrin is structurally similar to PTC and found in many vegetables, for example, brussels sprouts (Fenwick and Griffiths 1981), and its perception is influenced by the same receptor allele (Wooding et al. 2010). Likewise, other bitter compounds such as quinine are perceived differently by people with particular genetic variants near the *TAS2R19* receptor (Reed et al. 2010), and people differ in their ability to perceive distinctions among concentrations of sucrose depending on alleles of the sweet receptor *TAS1R3* (Fushan et al. 2009; Mennella et al. in press). Genetic differences are not limited to taste—odor perception is also influenced by genotypes of olfactory receptors (Menashe et al. 2007; Eriksson et al. 2010; Pelchat et al. 2010)—with the best known example being the relationship between alleles of the olfactory receptor *OR7D4* and the perception of androstenone (Keller et al. 2007; Knaapila et al. 2012).

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Much less is known about individual differences in the perception of the common chemicals we ingest that have a complex flavor. One such example is ethanol (alcohol), which is an amalgamation of taste, irritation, and smell (Bachmanov et al. 2003). There are large individual differences in each of these realms, and so, we wondered if the perception of ethanol might also be heritable and affected by genetic differences among people. Foods like herbs might also be perceived differently by people because of genetic differences, and in this study, we tested the taste and smell responses of human subjects to two, cilantro and basil. We chose cilantro because people express a diversity of liking for the herb (Tullo 2010), and we chose basil for comparison because we assumed it was more universally liked.

The aim of this study was to determine the heritability of the perceptual responses to commonly used flavor stimuli. The broader intent of this work is to bridge the gap between the biology of sensory differences and how they affect food liking and intake. To this end, monozygotic (MZ) and dizygotic (DZ) twins provided written consent, donated DNA, were photographed, and rated the intensity of taste and smell stimuli, including ethanol and herbs. The heritability of selected phenotype measures, that is, the degree to which genetic variation influenced a particular trait, was determined by structural equation modeling. For traits that showed significant heritability or family aggregation, genetic associations were evaluated for variant sites chosen to be within or near taste and smell genes.

Materials and methods

Subjects

The sample included MZ and DZ pairs of twins. Experimenters recruited and tested participants at an annual gathering of twins, Twins Days Festival, in Twinsburg, OH over several years. Subjects were required to be at least 21 years of age to participate; there was no upper age limit. Subjects of all races and both sexes participated (Table 1). Zygosity was assessed with three methods: self-reported identity, experimenter ratings of photographs for physical similarity, and the congruence of genotypes for all single nucleotide polymorphisms that were genotyped (described below; see DNA collection and genotyping). The procedures were approved by the Institutional Review Board (#4) of the University of Pennsylvania.

Table 1 Subject characteristics

Characteristic	MZ	DZ
N of individuals (*N* of twin pairs)	502 (251)	70 (35)[a]
Age, years: mean ± SD (range)	40 ± 15 (21–77)	39 ± 16 (21–82)
Caucasian/otherwise	426/76	58/12
Female/male	406/96	53/17

MZ, monozygotic (genetically identical) twins; DZ, dizygotic (not genetically identical) twins; otherwise, not Caucasian, most of whom were African–American (MZ = 33; DZ = 8).
[a]Thirty-one DZ pairs were same sex, and four were of the opposite sex.

Taste and smell tests

Subjects rated the following compounds for their taste: water, sucrose, sodium chloride, citric acid, ethanol, quinine hydrochloride, potassium chloride, calcium chloride, and PTC. For smell, subjects rated cinnamon, ethanol, androstenone, Galaxolide™, the flavor of ethanol, and the herbs cilantro and basil. Details concerning concentrations, order of presentation, the preparation of the materials, and pilot testing are provided in the Supplemental Methods.

The taste solutions were rated for seven quantitative variables: sweetness, saltiness, sourness, bitterness, burn, liking, and intensity. The four odorants were rated for one qualitative trait (detection) and two quantitative traits (liking and intensity). The two herbs were each rated for one quantitative trait (pleasantness) and one qualitative trait (quality) in each of the two tests (odor and flavor). In total, there were 96 quantitative and 8 qualitative traits.

DNA collection and genotyping

DNA was purified, quantified, and used for genotyping of the variant sites within taste and smell genes, for example, bitter and odorant receptors. Markers are listed in Supplemental Table 1, and the procedure for genotyping and details of the statistical analysis are given in the Supplemental Methods.

Data analysis

The data were subject characteristics (age, sex, and race), ratings of the sensory stimuli (taste solutions, odorants, and herbs), and genotype. We focused on traits that were most reliable over days or years, that is, test–retest correlation coefficient of $r > 0.40$. For the reliable quantitative traits, means and standard deviations (SD) were computed as were the effects of potential covariates (e.g., age). Race was not considered as a potential covariate because most subjects were Caucasian (see Results), and there was insufficient statistical power to compare racial groups directly. Thus, individuals of all races were used in all analyses except those involving genetic association (see Genetic modeling). Correlation coefficients were computed for all paired comparisons between reliable traits and presented as a heatmap (King et al. 2005).

Genetic modeling

The difference in genetic relatedness between MZ twins (which share all the variation in their genes) and DZ twins (which share on average half of their genes) was used to partition total variation in ratings into their subcomponents, additive genetic (A), shared environmental (C), and nonshared

environment (E). A full description of the models and tests of significance are provided in the Supplemental Methods, and follow procedures previously used to assess chemosensory traits were presented in the study by Knaapila et al. 2012.

Genetic association

For traits with a heritable or familial contribution, genotype–phenotype associations were tested using algorithms implemented in the population-based linkage analysis package named PLINK (Purcell et al. 2007). Missing genotype data were imputed by comparison with data from the identical co-twin where possible and cleaned by removing subjects with more than 20% missing genotypes, and removing genetic variants with a minor allele frequency <5% (Supplemental Table 1). Analyses were conducted with one twin drawn randomly from each pair and then re-conducted using the other twin and the pattern of results was compared. The assumption is that true associations will follow a similar pattern in both populations. Variants that met nominal thresholds for statistical significance for both analyses were considered potentially reliable ($P < 0.05$), but all results are presented as Supplemental Data.

Results

Subjects

A total of 600 subjects were enrolled in this study, but 28 were eliminated from the analysis because they (or their co-twin) failed to follow instructions or had a history of alcohol dependence. The remaining 572 subjects were, on average, middle age (range 21–82 years), and most were Caucasian and female (Table 1). All twins participated with their co-twins, and therefore, the final data set included 286 twin pairs. The outcome of pilot testing is summarized separately in the Supplemental Results section.

Refinement of phenotypes

Most subjects were tested only once, but a few were tested twice or more, on consecutive days or consecutive years. For quantitative data, correlation coefficients were thus computed for subjects who were tested on consecutive days (Supplemental Tables 2 and 3) or in consecutive years (Supplemental Table 4). For the categorical data, the concordance rates on consecutive days were 100% for detection of cinnamon, 76% for detection of ethanol, 53% for detection of androstenone, and 76% for detection of Galaxolide. We selected the reliable phenotypes for the next stage in the analysis. These traits are listed together with their test–retest correlation coefficients in Table 2.

Descriptive statistics and covariates

The mean and SD for each of the 58 reliable quantitative traits are reported in Table 2. For the taste solutions,

Table 2 Test–retest correlation coefficients (Pearson *r*) for the traits considered reliable, their average ratings, and correlation (*r*) between the ratings and age

Item	Measure	Test–retest correlation	*N*	Mean	SD	Correlation with age
Sucrose	Sweetness	0.54*	570	4.68	2.00	–0.06
	Liking	0.52*	569	4.51	1.71	–0.20*
	Intensity	0.41*	570	3.14	1.56	0.07
NaCl	Sweetness	0.52*	569	0.31	0.83	0.13*
	Bitterness	0.45*	570	1.25	1.95	–0.14*
	Liking	0.59*	569	1.67	1.64	0.08*
Citric acid	Sweetness	0.57*	386	0.70	1.28	–0.10*
	Saltiness	0.54*	385	1.15	1.68	–0.02
	Sourness	0.42*	385	3.67	2.39	0.05
	Bitterness	0.70*	388	2.91	2.49	–0.01
	Burn	0.50*	385	3.67	2.39	0.00
	Liking	0.47*	386	1.45	1.48	0.01
10% ethanol	Saltiness	0.42*	386	0.89	1.41	0.01
	Sourness	0.46*	387	1.70	2.19	0.07
20% ethanol (taste)	Sweetness	0.43*	571	0.83	1.49	0.09*
	Saltiness	0.62*	567	0.95	1.59	0.03
	Sourness	0.43*	570	2.01	2.43	0.08
	Bitterness	0.57*	570	4.13	2.67	0.05
	Liking	0.52*	567	1.14	1.61	0.08
	Intensity	0.49*	566	5.78	1.47	–0.04
20% ethanol (flavor)	Sweetness	0.52*	386	1.25	1.76	–0.03
	Saltiness	0.44*	386	1.02	1.55	0.09
	Sourness	0.49*	382	2.06	2.34	0.13*
	Bitterness	0.56*	383	4.23	2.54	0.12*
	Burn	0.49*	388	4.59	2.24	–0.08
	Liking	0.61*	388	1.78	1.94	–0.07
	Intensity	0.41*	388	5.81	1.33	0.04
Quinine	Sweetness	0.69*	388	0.43	0.82	0.11*
	Saltiness	0.53*	387	0.77	1.28	–0.01
	Bitterness	0.51*	388	3.95	2.49	0.03
	Burn	0.63*	387	1.44	1.92	–0.11*
	Intensity	0.40*	386	3.88	2.08	0.08
PTC	Sourness	0.41*	571	1.69	2.44	0.08*
	Bitterness	0.6*	571	4.33	2.87	0.02
	Burn	0.67*	571	1.70	2.29	–0.11*
	Liking	0.5*	569	1.40	1.76	0.08
	Intensity	0.73*	570	4.39	2.61	–0.01

Table 2 Continued

Item	Measure	Test–retest correlation	*N*	Mean	SD	Correlation with age
KCl	Sweetness	0.57*	368	0.36	0.81	0.01
	Sourness	0.42*	366	1.41	2.14	0.10
	Burn	0.40*	369	0.90	1.47	–0.02
$CaCl_2$	Sweetness	0.94*	302	0.30	0.74	–0.07
	Saltiness	0.83*	301	2.71	2.59	–0.06
	Sourness	0.82*	300	2.24	2.53	–0.02
	Bitterness	0.56*	303	5.06	2.44	0.04
	Burn	0.51*	302	2.01	2.23	–0.06
Cinnamon	Detection	NA	258	1.00	NA	NA
	Liking	0.73*	257	6.43	1.28	–0.20*
	Intensity	0.43*	257	5.23	1.27	0.01
20% ethanol (odor)	Detection	NA	258	0.76	NA	NA
Androstenone	Detection	NA	258	0.53	NA	NA
	Liking	0.62*	136	1.94	1.68	0.07
	Intensity	0.50	136	3.66	2.40	0.09
Galaxolide	Detection	NA	258	0.76	NA	NA
	Liking	0.71*	195	4.69	2.02	–0.06
Cilantro (odor)	Pleasantness	0.56*	256	–3.15	4.69	0.13*
Basil (odor)	Pleasantness	0.43*	255	1.28	5.23	–0.04
Cilantro (flavor)	Pleasantness	0.88*	257	–1.90	5.98	–0.10
Basil (flavor)	Pleasantness	0.78*	255	–2.19	6.14	–0.02

Results are shown for the traits that met reliability criterion (test–retest correlation, $r > 0.40$). Test–retest correlations are from ratings in consecutive years for all traits except for $CaCl_2$, odorants, and herbs (cilantro and basil), for which the test–retest correlations are from ratings in consecutive days because they were tested only in 2010 or 2011. For test–retest correlations, $N = 139$ for all taste stimuli except $N = 88$ for KCl, $N = 47$ for $CaCl_2$, and $N = 17$–34 for odorants and herbs. Potential range for ratings of herbs was 0.0–13.7; for all other stimuli, 0.0–7.7. For the trait "Detection," the mean fraction of all subjects who could smell the odorant is provided.
NA, not applicable.
*$P < 0.05$.

in general, subjects responded as predicted; for instance, sucrose was rated as very sweet and was also very much liked. However, many subjects reported that high concentrations of ethanol were salty, an unexpected observation. We also noted that there was more variability among individuals in ratings of bitter than of other taste stimuli. For the odorants, we found no unanticipated patterns: all subjects could detect cinnamon and a few subjects were anosmic to androstenone and Galaxolide. When subjects could smell androstenone, it was disliked, whereas cinnamon and Galaxolide were liked. For the herbs, the average flavor ratings of pleasantness were similar. As expected, some

Table 3 Average rating of taste and smell stimuli by women and men

Item	Measure	Women		Men		*P* value
		Mean	SD	Mean	SD	
Sucrose	Sweetness	4.68	2.03	4.66	1.84	0.90
	Liking	4.55	1.74	4.33	1.61	0.23
	Intensity	3.11	1.60	3.25	1.39	0.39
NaCl	Sweetness	0.30	0.82	0.35	0.84	0.57
	Bitterness	1.10	1.81	1.86	2.34	0.00*
	Liking	1.69	1.67	1.62	1.53	0.68
Citric acid	Sweetness	0.65	1.23	0.91	1.44	0.10
	Saltiness	1.06	1.57	1.48	2.04	0.05*
	Sourness	3.62	2.42	3.84	2.29	0.48
	Bitterness	3.00	2.49	2.58	2.48	0.19
	Burn	0.54	0.97	0.58	0.99	0.74
	Liking	1.37	1.46	1.78	1.54	0.03*
10% ethanol	Saltiness	0.87	1.42	0.95	1.38	0.67
	Sourness	1.57	2.13	2.19	2.36	0.03*
20% ethanol (taste)	Sweetness	0.79	1.46	0.98	1.57	0.23
	Saltiness	0.89	1.55	1.19	1.74	0.08
	Sourness	1.98	2.45	2.15	2.39	0.53
	Bitterness	4.11	2.71	4.21	2.51	0.73
	Liking	0.99	1.47	1.77	1.97	0.00*
	Intensity	5.87	1.48	5.42	1.36	0.00*
20% ethanol (flavor)	Sweetness	1.17	1.72	1.58	1.91	0.07
	Saltiness	1.04	1.60	0.92	1.36	0.53
	Sourness	1.94	2.30	2.54	2.44	0.04
	Bitterness	4.25	2.59	4.12	2.35	0.68
	Burn	4.61	2.25	4.49	2.21	0.66
	Liking	1.61	1.86	2.45	2.11	0.00*
	Intensity	5.85	1.30	5.65	1.43	0.23
Quinine	Sweetness	0.37	0.72	0.65	1.11	0.01*
	Saltiness	0.77	1.31	0.79	1.18	0.88
	Bitterness	3.99	2.50	3.78	2.49	0.51
	Burn	1.53	2.00	1.11	1.53	0.08
	Intensity	3.90	2.06	3.80	2.16	0.70
PTC	Sourness	1.64	2.43	1.91	2.46	0.30
	Bitterness	4.40	2.89	4.06	2.77	0.26
	Burn	1.70	2.29	1.70	2.27	0.99
	Liking	1.32	1.75	1.75	1.79	0.02
	Intensity	4.43	2.62	4.19	2.54	0.37
KCl	Sweetness	0.37	0.87	0.60	1.16	0.04*
	Sourness	1.52	2.22	1.74	2.17	0.40
	Burn	0.96	1.59	1.25	1.63	0.13

Table 3 Continued

Item	Measure	Women		Men		*P* value
		Mean	SD	Mean	SD	
$CaCl_2$	Sweetness	0.26	0.66	0.49	1.10	0.06
	Saltiness	2.65	2.63	3.04	2.38	0.34
	Sourness	2.23	2.55	2.36	2.42	0.75
	Bitterness	5.06	2.51	4.98	2.15	0.83
	Burn	1.98	2.24	2.13	2.16	0.66
Cinnamon	Detection	1.00	NA	1.00	NA	0.61
	Liking	6.65	1.12	5.58	1.53	0.00*
	Intensity	5.31	1.25	4.91	1.31	0.04*
20% ethanol (odor)	Detection	0.78	NA	0.66	NA	0.07
Androstenone	Detection	0.55	NA	0.43	NA	0.13
	Liking	1.88	1.68	2.28	1.69	0.30
	Intensity	3.68	2.34	3.59	2.74	0.87
Galaxolide	Detection	0.77	NA	0.74	NA	0.65
	Liking	4.84	1.97	4.12	2.14	0.05*
Cilantro (odor)	Pleasantness	–3.28	4.63	–2.64	4.93	0.53
Basil (odor)	Pleasantness	1.20	5.34	1.57	4.81	0.37
Cilantro (flavor)	Pleasantness	–1.98	5.96	–1.60	6.11	0.79
Basil (flavor)	Pleasantness	–2.22	6.17	–2.09	6.08	0.92

For the trait "Detection," the mean fraction of subjects who could smell the odorant is provided. Sex-difference was tested by two–sided *t*-test for all other traits except detection of the odorants, for which chi-square test was used. NA, not applicable.

Table 4 MZ and DZ twin correlations

Item	Measure	*N* (pair)	*r* (MZ)	*N* (pair)	*r* (DZ)
Sucrose	Sweetness	251	0.16	35	0.43
	Liking	250	0.32	35	0.06
	Intensity	251	0.17	35	0.08
NaCl	Sweetness	250	0.09	35	0.04
	Bitterness	251	0.25	35	0.17
	Liking	251	0.31	35	0.35
Citric acid	Sweetness	172	0.10	22	–0.24
	Saltiness	171	0.20	22	–0.12
	Sourness	172	0.16	22	0.14
	Bitterness	172	0.18	22	0.23
	Burn	172	0.27	22	–0.14
	Liking	172	0.21	22	–0.02
10% ethanol	Saltiness	170	0.15	22	–0.14
	Sourness	172	0.19	22	0.04

Table 4 Continued

Item	Measure	*N* (pair)	*r* (MZ)	*N* (pair)	*r* (DZ)
20% ethanol (taste)	Sweetness	251	0.25	35	0.09
	Saltiness	250	0.21	34	–0.07
	Sourness	250	0.12	35	0.26
	Bitterness	251	0.09	35	0.28
	Liking	250	0.24	35	0.28
	Intensity	250	0.27	35	–0.04
20% ethanol (flavor)	Sweetness	171	0.19	21	–0.30
	Saltiness	171	0.11	21	–0.19
	Sourness	170	0.24	21	–0.26
	Bitterness	170	0.29	20	0.33
	Burn	172	0.22	22	0.08
	Liking	172	0.27	22	0.25
	Intensity	172	0.24	22	–0.24
Quinine	Sweetness	172	0.14	22	–0.07
	Saltiness	171	0.16	22	–0.09
	Bitterness	172	0.37	22	0.38
	Burn	172	0.42	22	0.06
	Intensity	172	0.35	22	–0.09
PTC	Sourness	251	0.40	35	0.42
	Bitterness	250	0.63	35	0.53
	Burn	250	0.45	35	0.16
	Liking	251	0.42	34	0.23
	Intensity	251	0.71	35	0.45
KCl	Sweetness	200	0.19	30	0.07
	Sourness	200	0.25	30	–0.04
	Burn	202	0.38	30	0.31
$CaCl_2$	Sweetness	128	0.18	21	0.04
	Saltiness	127	0.25	21	0.33
	Sourness	128	0.42	21	0.29
	Bitterness	128	0.16	22	–0.23
	Burn	126	0.26	21	–0.16
Cinnamon	Liking	114	0.44	15	–0.01
	Intensity	114	0.39	15	0.60
Androstenone	Liking	56	0.51	9	0.38
	Intensity	56	0.48	9	0.28
Galaxolide	Liking	82	0.25	10	–0.22
Cilantro (odor)	Pleasantness	113	0.41	15	0.08
Basil (odor)	Pleasantness	113	0.38	15	0.25
Cilantro (flavor)	Pleasantness	114	0.52	15	0.39
Basil (flavor)	Pleasantness	114	0.42	15	0.43

(Number of pair is shown in the table). Traits were chosen for modeling if $r[MZ] > r[DZ]$, and $r[MZ] > 0.20$.

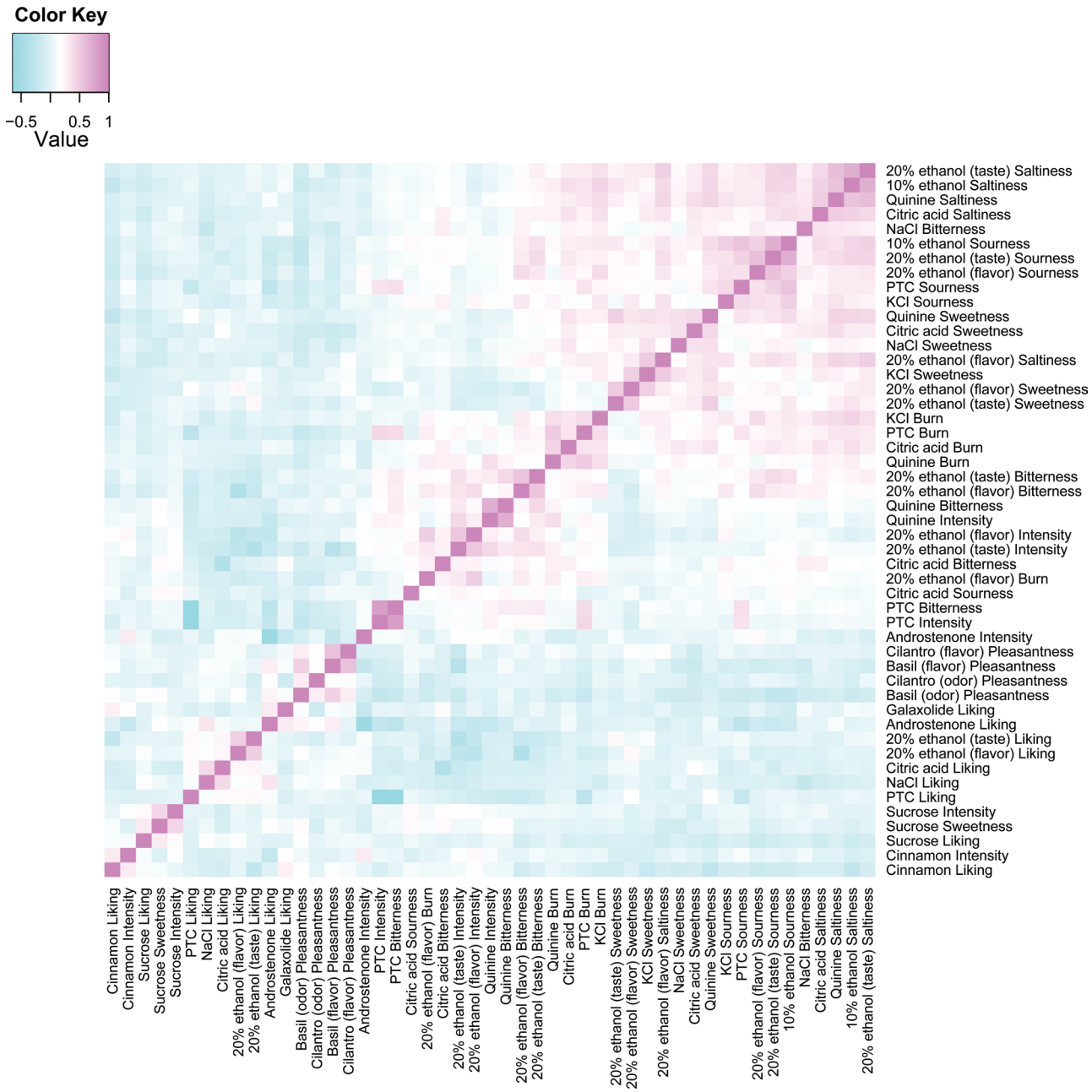

Figure 1 Heatmap of reliable quantitative traits. Traits that are most highly positively correlated are shown in pink–red; negatively correlated traits, in blue–green. Specific *r* values are presented in Supplemental Table 5.

subjects disliked cilantro, whereas others liked it, but subjects were just as diverse in their liking for basil.

The correlations of the reliable quantitative traits with age are also reported in Table 2. Of these 58 traits, 14 traits (24%) were significantly correlated with age ($P < 0.05$). The largest effects were for liking: Younger subjects liked the taste of sucrose and the smell of cinnamon more than did older subjects ($r = -0.20$, $P < 0.05$). Overall, although significant in many instances, the contribution of age was generally small.

Women and men differed most in ratings of liking (rather than intensity or taste quality), and this was true for a range of stimuli: Men liked citric acid, ethanol, and PTC more and cinnamon and Galaxolide less than did women (Table 3). Overall, subjects of different ages and sexes differed in some aspects of taste and smell traits, so age and sex were used as covariates for genetic modeling.

The reliable quantitative traits were related and the overall trends captured in a heatmap (Figure 1), and specific correlation coefficients are given in Supplemental Table 5. There were 1286 pairings of variables, of which 591 were correlated (46%), i.e., the *P* value indicated they were significantly different from 0. Subjects who rated one item as very bitter were

Table 5 Results from genetic modeling using the AE model

Item	Quality	Addictive genetic effects	Nonshared environmental effects
		a^2 (95% CI)	e^2 (95% CI)
Sucrose	Liking	0.27 (0.15–0.38)#	0.73 (0.62–0.85)
NaCl	Bitterness	0.22 (0.11–0.34)#	0.78 (0.66–0.89)
Citric acid	Saltiness	0.18 (0.03–0.32)	0.82 (0.68–0.97)
	Burn	0.27 (0.10–0.41)#	0.73 (0.59–0.90)
	Liking	0.19 (0.05–0.33)#	0.81 (0.67–0.95)
20% ethanol (taste)	Sweetness	0.23 (0.11–0.34)#	0.77 (0.66–0.89)
	Saltiness	0.20 (0.08–0.32)#	0.80 (0.68–0.92)
	Intensity	0.25 (0.13–0.36)#	0.75 (0.64–0.87)
20% ethanol (flavor)	Sourness	0.20 (0.06–0.34)#	0.80 (0.66–0.94)
	Burn	0.21 (0.07–0.34)#	0.79 (0.66–0.93)
	Liking	0.25 (0.11–0.39)#	0.75 (0.61–0.89)
	Intensity	0.21 (0.05–0.35)#	0.79 (0.65–0.95)
Quinine	Burn	0.41 (0.27–0.53)*	0.59 (0.47–0.73)
	Intensity	0.34 (0.20–0.46)#	0.66 (0.54–0.80)
PTC	Bitterness	0.64 (0.56–0.71)#	0.36 (0.29–0.44)
	Burn	0.44 (0.34–0.53)#	0.56 (0.47–0.66)
	Liking	0.42 (0.31–0.51)#	0.58 (0.49–0.69)
	Intensity	0.71 (0.65–0.77)*	0.29 (0.23–0.35)
KCl	Sourness	0.19 (0.06–0.32)#	0.81 (0.68–0.94)
	Burn	0.36 (0.24–0.47)#	0.64 (0.53–0.76)
$CaCl_2$	Sourness	0.36 (0.21–0.50)#	0.64 (0.50–0.79)
	Burn	0.28 (0.11–0.43)#	0.72 (0.57–0.89)
Cinnamon	Liking	0.32 (0.14–0.48)#	0.68 (0.52–0.86)
Androstenone	Liking	0.53 (0.28–0.70)#	0.47 (0.30–0.72)
	Intensity	0.52 (0.26–0.69)#	0.48 (0.31–0.74)
Galaxolide	Liking	0.19 (0.00–0.39)	0.81 (0.61–1.00)
Cilantro (odor)	Pleasantness	0.38 (0.22–0.52)#	0.62 (0.48–0.78)
Basil (odor)	Pleasantness	0.39 (0.22–0.54)#	0.61 (0.47–0.78)
Cilantro (flavor)	Pleasantness	0.52 (0.38–0.63)#	0.48 (0.37–0.62)

See Supplemental Table 6 for the other models and fit statistics.
95% CI, 95% confidence interval.
*$P < 0.05$ for heritability.
#$P < 0.05$ for familiality; heritability is significant if shared environmental effects are assumed to be 0.

likely to rate other items as very bitter; in fact, all the items reliably rated for bitterness were positively correlated (from $r = 0.09$ to $r = 0.54$, $P < 0.05$). This was less true for overall intensity, for which 62% of the ratings were significantly and positively correlated, and this was even less true for liking/pleasantness, for which only 38% of the ratings were significantly and positively correlated. Subjects liked some items better than others, but there was little tendency to like or dislike every item. For instance, subjects who gave high liking ratings to sucrose did not necessarily do so for Galaxolide ($r = -0.01$, not significant). This was also true for intensity; taste and odor intensity ratings were unrelated.

Genetic modeling

We examined the traits for within-pair correlations between MZ and DZ twins before genetic modeling to screen for preliminary evidence of genetic influences. Only traits that met the following criteria were modeled: 1) there were reliable individual differences, 2) MZ correlations exceeded a threshold, (r [MZ] > 0.20), and 3) the MZ correlation also exceeded the DZ correlation (r [MZ] > r [DZ]). The MZ and DZ correlations for the reliable quantitative traits are listed in Table 4; correlations for the traits selected for modeling are underlined. Results of the modeling, estimates of the contribution of additive genetic effects (A) (heritability estimates), and nonshared environmental (E) effects are listed in Table 5. Details regarding the modeling, including results from fitting all submodels and fit statistics, are given in Supplemental Table 6.

The contribution of additive genetic effects (heritability) to trait variability was highest for the intensity of PTC (0.71). Heritability was significant also for the burn of quinine (0.41) (Table 5). For these traits, the omission of the additive genetic component (A) from the full genetic model (ACE) resulted in a significant decrease ($P < 0.05$) in goodness of fit of the model, indicating the significance of the A component.

Most other traits selected for genetic modeling showed significant familiality (the sum of additive genetic and shared environmental effects), but it was not possible to unequivocally separate the contributions of the additive genetic (A) and shared environmental (C) components. For most traits, we were able to leave out either the A or the C component, but not both, from the full ACE model without a significant decrease in model fit, indicating the significance of the combination of A and C components (familiality). If we assume that the shared environmental effects are not important (MZ > DZ correlation) and thus omit the C component, comparing the AE (additive and environment) model against the E model shows that leaving out the A component caused a significant decrease in model fit, indicating the significance of the A component. Results from the AE genetic model based on the assumption that C is less important showed moderate familiality for several ratings of taste and smell stimuli (Table 5).

Association

We tested associations of allelic variants of 44 markers (Supplemental Table 1) with 27 traits for a total of 1188

Table 6 Summary of genotype–phenotype associations

Stimuli	Rating	Chr	Marker	Gene	Sample	Minor	Het	Major	*P* value
Quinine	Intensity	12	*rs1548803*	*TAS2R8†*	1	4.3	4.0	3.4	0.02546
					2	4.5	3.7	3.5	0.01674
		12	*rs10772420*	*TAS2R19*	1	4.8	3.9	3.0	1.26E-05
					2	4.6	4.2	2.7	4.36E-06
		12	*rs12226920*	*TAS2R20*	1	2.5	3.7	4.3	0.000209
					2	2.3	3.7	4.3	3.99E-05
		12	*rs10845279*	*TAS2R49*	1	2.5	3.7	4.4	7.44E-05
					2	2.4	3.7	4.4	1.68E-05
	Burn	12	*rs1548803*	*TAS2R8†*	1	2.1	1.4	1.1	0.007904
					2	2.1	1.4	1.2	0.03632
		12	*rs10772420*	*TAS2R19*	1	2.0	1.4	1.0	0.00659
					2	2.3	1.4	1.0	0.001058
		12	*rs12226920*	*TAS2R20*	1	0.4	1.6	1.6	0.03603
					2	0.6	1.4	1.8	0.009322
		12	*rs10845279*	*TAS2R49*	1	0.4	1.6	1.6	0.03444
					2	0.5	1.4	1.8	0.004999
Cilantro	Pleasantness	8	*rs11988795*	*TRPA1*	1	3.8	6.3	6.4	0.02439
					2	3.9	6.1	6.4	0.02348
		7	*rs1524600*	*GNAT3*	1	2.7	4.3	6.2	0.02602
					2	1.3	4.4	6.1	0.01975
		12	*rs10772397*	*TAS2R50*	1	5.0	5.2	6.9	0.03452
					2	3.9	5.5	6.8	0.005465
Basil	Pleasantness	7	*rs4595035*	*TAS2R60*	1	8.2	8.2	6.8	0.03965
					2	10.2	8.0	7.6	0.01987
Ethanol	Burn	19	*rs61729907*	*OR7D4*	1	4.1	4.0	4.9	0.02011
					2	3.0	4.0	4.8	0.01005
		19	*rs5020278*	*OR7D4*	1	4.7	3.9	4.9	0.04362
					2	3.5	4.2	4.8	0.04724
		1	*rs586965*	*SCNN1D*	1	2.8	4.7	4.9	0.002655
					2	3.8	4.0	4.8	0.01942

Chr, chromosome. Samples are described in the text; Gene, gene nearest the marker. Receptors are in clusters†; Minor, mean rating of subjects homozygous for the minor allele; Het, mean rating of heterozygous subjects; Major, mean ratings of individuals homozygous for the major allele.
Only markers that demonstrated the same pattern of allelic effects with an associated *P* value < 0.05 in both samples are included. Associations between the PTC perception and the bitter receptor *TAS2R38* are shown in Supplemental Table 7.

possible associations. The results that met nominal thresholds for significance in both samples (Twin 1 and Twin 2) are listed in Table 6 except for ratings of PTC, which are well known to be related to *TAS2R38* genotype and are reported in detail as supplemental data ($P < 9.558\text{E-}40$; Supplemental Table 7). Previously described associations between the cluster of bitter receptor genes on chromosome 12 and quinine were detected, as well as associations between variants in bitter receptors and herbs (cilantro and basil) and between gustducin (*GNAT3*) and *TRPA1* variants for cilantro. The distribution of cilantro ratings stratified by the three variants is shown in Supplemental Figure 1. There was an unexpected association between *OR7D4* (the olfactory receptor previously linked to androstenone perception) and ethanol

Table 7 Trait reliability, heritability, and association outcomes

Stimuli	Measured	Reliable	Her or Fam	Associated
Water	SW, SA, SO, BI, BU, L, IN			
Sucrose	SW, SA, SO, BI, BU, L, IN	SW, L, IN	L	
NaCl	SW, SA, SO, BI, BU, L, IN	SW, BI, L	BI	
Citric acid	SW, SA, SO, BI, BU, L, IN	SW, SA, SO, BI, BU, L	BU, L	
3% ethanol	SW, SA, SO, BI, BU, L, IN			
10% ethanol	SW, SA, SO, BI, BU, L, IN	SA, SO		
20% ethanol (taste)	SW, SA, SO, BI, BU, L, IN	SW, SA, SO, BI, L, IN	SW, SA, IN	
20% ethanol (odor)	DET, L, IN	DET		
20% ethanol (flavor)	SW, SA, SO, BI, BU, L, IN	SW, SA, SO, BI, BU, L, IN	SO, BU, L, IN	BU
Quinine	SW, SA, SO, BI, BU, L, IN	SW, SA, BI, BU, IN	BU, IN	IN, BU
PTC	SW, SA, SO, BI, BU, L, IN	SO, BI, BU, L, IN	BI, BU, L, IN	BI, BU, L, IN
KCl	SW, SA, SO, BI, BU, L, IN	SW, SO, BU	SO, BU	
$CaCl_2$	SW, SA, SO, BI, BU, L, IN	SW, SA, SO, BI, BU	SO, BU	
Cinnamon	DET, L, IN	DET, L, IN	L	
Androstenone	DET, L, IN	DET, L, IN	L, IN	
Galaxolide	DET, L, IN	DET, L		
Cilantro (odor)	P	P	P	
Cilantro (flavor)	P	P	P	P
Basil (odor)	P	P	P	P
Basil (flavor)	P	P		
Total number of traits	104 (96 quantitative)	58	27	9

SW, sweetness; SA, saltiness; SO, sourness; BI, bitterness; BU, burn; IN, intensity; L, liking; DET, detection; P, pleasantness; Her or Fam, heritable or familial as determined by the genetic modeling.

flavor (but not taste) perception. Finally, there was also an unexpected association between the sensory qualities of ethanol and the putative salt receptor gene *SCNN1D*.

In addition to the association analysis on the quantitative traits, we examined the genotype–phenotype relationship between odor detection (yes/no) and genotype. Specifically, we tested the hypothesis that *OR7D4* R88W is associated with the perception of androstenone (Keller et al. 2007). We found that a lower percentage of individuals with the RR genotype reported they did not smell the androstenone stimulus compared with individuals with RW or WW genotype (Pearson $\chi_{(1)}^2 = 17.38$, $P < 0.001$; Figure 2). There was no association apparent between *OR7D4* genotype and the detection of another musky odorant, Galaxolide (Pearson $\chi_{(1)}^2 = 0.84$, $P = 0.36$; Figure 2).

Table 7 provides a summary of all traits measured and the ones that were most reliable, heritable or familial, and associated with genotypes. A total of 104 traits were measured, and 58 were reliable; of these reliable traits, 27 were heritable or aggregated in families (in this case, twin pairs); of these traits, nine were associated with genetic variants within or near candidate genes.

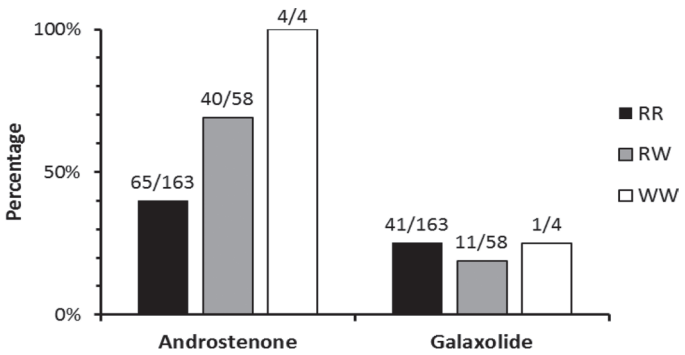

Figure 2 Detection of the odor of androstenone and Galaxolide by *OR7D4* R88W (*rs61729907*) genotype: fraction of individuals who answered "No" to the question "Did you smell something?"

Discussion

The aim of this study was to understand how and why people differ in their perception of some simple stimuli related to common food and drinks. The genetics of flavor perception in humans has been dominated by two

examples: individual differences in the bitterness of PTC and in the smell of androstenone. There have been few attempts to measure taste and smell traits in genetically informative human populations (Reed et al. 1997; Reed and Knaapila 2010), but individual differences arising from genetic variation extend beyond these two examples. We, therefore, asked twins to rate flavor stimuli, including traditional taste solutions used in psychophysical tests, as well as odorants, ethanol, and herbs. We employed stimuli that ranged from the most studied (PTC and androstenone) to the less studied (e.g., potassium chloride and basil), and so we were able to evaluate the importance of genetic influences on less-studied measures in relation to known heritable traits. We found that many of the measures were stable over time and showed significant heritability or family aggregation. Using these data, we also confirmed previously known genotype–phenotype relationships and found several new associations.

Individual differences

The taste and smell stimuli were chosen with several goals in mind. We chose simple taste solutions that were exemplars of specific taste qualities (e.g., sodium chloride for saltiness). We chose ethanol because it is widely consumed, but it has a complex flavor, and we chose odorants, some because they were well liked and easily detected (e.g., cinnamon) and others because their genetics were already characterized (i.e., androstenone). We also chose two herbs, cilantro and basil, to expand our study from simple to complex chemosensory stimuli. The ratings followed the pattern we expected: Subjects could easily recognize as sweet and liked sucrose; they recognized and disliked the bitter, salty, and sour solutions. The greatest variation among subjects was for bitterness—the standard deviation for ratings of bitterness was double those of other quality ratings such as saltiness. Subjects also differed greatly in how bitter they perceived ethanol and potassium chloride to be, on par with individual differences for PTC. Subjects rated citric acid as both bitter and sour, but their ratings of citric acid as bitter were more reliable. Thus, although bitter–sour confusion is apparent, subjects were consistent in their misidentification of the sour quality as bitter. All considered together, people differ more in the perception of bitterness than other taste qualities.

Implications for genetic association

One of the important steps in genetic association studies is to establish that traits are reliable. This step is especially critical for flavor traits because heritability of perception depends on the particular odorant and tastant used as well as the method of testing. The ability to perceive androstenone is a heritable trait (Wysocki and Beauchamp 1984; Knaapila et al. 2008a), but the perception of other odorants is often not (Knaapila et al. 2008b). The same is true for taste stimuli, some are heritable but many are not. Why some taste and smell traits are more stable and heritable than others is not known, but it may be that some fluctuate in response to physiological state more than do others (Elson et al. 2010; Yoshida et al. 2010). In general, we obtained the most reliable phenotypes when subjects rated the specific quality for the appropriate chemical (e.g., the sweetness of sucrose) and the intensity and the liking or pleasantness of these chemicals. The exception is salty for sodium chloride—for the concentration used herein, ratings of bitterness were much more reliable than ratings of saltiness. Hedonic evaluations were the most reliable of all. As one of many examples, subjects gave nearly identical ratings for the pleasantness of the flavor of cilantro from day to day. The only exception to this general observation was for liking of bitter stimuli. Most subjects disliked bitter (even if they could perceive it only weakly), and because of this "floor" effect, there was less person-to-person variation in ratings. For bitter, intensity measures were more reliable, more heritable, and more associated with genotype than were measures of liking.

Age and sex effects

Age effects were small. One surprise was the marked reduction of liking for sucrose in older subjects. It may be that the environment has changed and young people have experienced sweeter foods than have old people, many of whom were born before the widespread addition of refined sugar to convenience foods and drinks. But it may be due to developmental changes too. A longitudinal study found that liking for sweetness is stronger when the subjects were children than when they were young adults (Desor and Beauchamp 1987). In the current cross-sectional study, younger adults preferred sweet more than did older adults, so liking for sweetness may continue to wane over the lifespan, beyond childhood. The similar reduction in reported liking for cinnamon with age hints at the possibility that liking for sweet and flavors paired with sweet may go together. Sex differences were also small, except for liking for ethanol. Men liked the taste and the flavor of ethanol more than did women. In general, men drink ethanol more than do women (Wilsnack et al. 2009), but it is not clear if they like it more because they are more familiar with the flavor or vice versa.

Effect of concentration and delivery method

To examine how differences in stimulus concentration might affect genetic analyses and how the way we delivered the stimuli might affect the ratings, we compared three concentrations of ethanol (3%, 10%, and 20%) and found that the reliability of ratings and their heritability increased at higher concentrations. If this observation applies to other stimuli, it would suggest that the concentration of a stimulus needs to be high enough to elicit a distinct perception that is easy to rate, so it may be more effective to use strong concentrations of solutions

for large-scale genetic testing. We also had subjects experience ethanol in three ways: smell only, taste only, and smell and taste combined (flavor). Ratings of ethanol flavor were more reliable and more related to genotype than were ratings of either taste or smell alone. These results suggest that more intense stimuli, which people can both smell and taste, provide the most profitable avenue for analyzing genetic differences.

Aggregation in families and heritability

This study was the largest of which we are aware to estimate the heritability of flavor-related traits. The heritability for the best-known stimuli, PTC, was similar to values obtained in other studies, for example, (Kim et al. 2003). We also replicated our earlier observation that quinine perception is heritable (Hansen et al. 2006). What was surprising was the number of traits that aggregated in families and were potentially due to additive genetic factors (depending on assumptions of the modeling). In general, many traits can aggregate in families but are not heritable (for example, the language spoken in the home) and thus these genotype–phenotype associations should be interpreted with additional caution. We mentioned above that the most reliable traits were for liking and this was also true for the aggregation of the traits in families. We originally thought that liking might be more idiosyncratic because it is presumably more affected by individual experience and learning, but this was not the case.

Genotype–phenotype associations

We conducted genotype–phenotype analyses with candidate genes for the chemical senses. We replicated associations previously identified for the perception of stimuli included in our set—between *TAS2R38* and PTC perception (Bufe et al. 2005), between *OR7D4* and androstenone perception (Keller et al. 2007), and between bitter receptors on chromosome 12 and quinine perception (Reed et al. 2010). In addition, we detected several new associations. One was between the liking of the flavor of 20% ethanol and a salt receptor gene (Chandrashekar et al. 2010)—this finding was unexpected but supported by the perceptual ratings of ethanol as salty. This rating of ethanol as salty was a surprise but has been reported by other investigators (Mattes and DiMeglio 2001; Scinska et al. 2000). Ethanol perception was also related to alleles of the *OR7D4* receptor. This finding was puzzling; ethanol is probably not a ligand for this receptor (Joel Mainland, personal communication). It may be that the results are spurious, or it may be that *OR7D4* is in linkage disequilibrium with a nearby olfactory receptor that responds to ethanol. In addition to this new association, we also found an association between the odor of basil and a bitter receptor gene, *TAS2R60*. Bitter receptors are found in the human nose (Mack and Kramer 2011), so there is potential for them to be important in food flavor perception but initiate a sensation unrelated to taste, for example, a tingle. This genetic variant has been associated with food perception before (Hayes et al. 2010). Finally, we found three gene variants linked to the liking of the flavor of cilantro—a bitter receptor (*TAS2R50*), a signaling component for taste, common to both bitter and sweet perception (*GNAT3*, gustducin) and a receptor for pungent chemicals found in foods, *TRPA1* (Xu et al. 2006). These findings may partially explain the large individual differences among people in their opinion of cilantro.

Several associations have been reported between sensory phenotype and genotype that we did not replicate here. This may be due in part to the criteria we used when deciding which phenotypes to include. Specifically, we found no associations between *TAS1R3* and the ratings of sucrose (Fushan et al. 2009), but the genetic variant associated with high sugar sensitivity is more common in people of African descent, who were excluded from our genotype–phenotype association analysis. In addition, the phenotyping method used by Fushan et al. also differed from our study. We also failed to replicate associations between *TAS1R2* and sweet liking (Eny et al. 2010) and between PTC and the gustin gene (Padiglia et al. 2010). A next step would be to conduct chemosensory genome-wide association studies—there have been at least four such studies thus far (Eriksson et al. 2010; Jaeger et al. 2010; Knaapila et al. 2012; Reed et al. 2010), and further research would likely yield additional replicable genetic associations.

Conclusion

Many aspects of human perception of taste and smell stimuli are at least partially determined by genotype. The choice of food and drink is central to human health, so understanding why some foods are preferred while others are not has practical significance. The overall aim of this study was to determine the heritability of perceptual responses to commonly used taste and smell stimuli, to ethanol, and to two herbs. We found novel associations and confirmed those previously reported. We have laid a foundation for studying how taste and smell genotypes might affect daily food consumption by determining how genotype affects chemosensory responses to food, to bridge the gap between the biology of sensory differences, and how they influence liking and food intake.

Supplementary material

Supplementary material can be found at http://www.chemse.oxfordjournals.org/

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