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HUMAN TASTE GENETICS*

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■ **Abstract** Humans show substantial differences in taste sensitivity to many different substances. Some of this variation is known to be genetic in origin, and many other inter-individual differences are likely to be partially or wholly determined by genetic mechanisms. Recent advances in the understanding of taste at the molecular level have provided candidate genes that can be evaluated for contributions to phenotypic differences in taste abilities. This approach has provided an understanding of variation in the ability to taste phenylthiocarbamide (PTC), and has resolved long-standing controversies about the genetics of this classic human genetic trait. Significant coding sequence variation exists in taste receptor genes, which suggests that PTC tasting may indicate more general taste sensory variation. However, many aspects of taste perception remain poorly characterized. Better understanding of the molecular components of salty and sour tastes is still needed, as is a more complete picture of second messenger and downstream signaling mechanisms for all taste modalities. More general studies of linkage and association between genetic markers and taste phenotypes may reveal genes encoding proteins that were previously unsuspected to be involved in this sensory process.

INTRODUCTION

Taste perception serves as a primary gatekeeper controlling voluntary ingestion of substances by humans. As the role of diet has gained importance in human health, it has become increasingly important to understand dietary choices made by individuals. Differences in taste perception appear to play an important role in these choices, and recent advances in our understanding of human taste perception provide an opportunity to examine genetic differences in these sensory perceptions.

Molecular Mechanisms of Taste

Humans can distinguish five major taste classes: sweet, sour, bitter, salty, and umami, a savory flavor exemplified by the amino acid glutamate (45, 50, 52).

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Decades of careful work by sensory physiologists have shown that salty and sour perception are mediated by ion channels, whereas sweet, bitter, and umami tastes are mediated by G-protein coupled receptors (GPCRs), all of which are expressed in taste cells within taste buds on the tongue (32, 72). Initial work in rodents demonstrated the existence of a group of genes that encode two main classes of taste GPCRs, the Tas1r family and the Tas2r family (1, 38, 54). Subsequent work extended these findings, with several important differences, to humans where these genes are designated *TAS1R* (or *T1R*) and *TAS2R* (or *T2R*), respectively (48, 55). There are 25 apparently functional *TAS2R* genes in humans, whose products are responsible for bitter perception (17, 19, 43). The human TAS1R family contains just 3 genes, *TAS1R1*, *TAS1R2*, and *TAS1R3*, whose products form heterodimers that serve as either sweet receptors (TAS1R 2 + 3) or umami (TAS1R 1 + 3) receptors (48, 58, 85). These GPCRs couple to specific intracellular G proteins. G α-gustducin participates in bitter and sweet taste transduction (56, 81), and $G\gamma_{13}$ is involved in bitter perception (39). Additional G proteins are also involved in these processes, but many specifics of this are currently unclear, such as what other G proteins are involved or whether different receptors couple to different G proteins.

The receptors for salty and sour tastes are less well understood. Salt perception may be mediated by one of several ion channels. Evidence originally supported an amiloride-sensitive sodium channel as the mediator of salty taste (36, 70), although evidence for the involvement of another as yet undetermined channel in this process has emerged (62). Sour taste is mediated by an acid sensor that, despite numerous proposed cellular mechanisms, is still of uncertain molecular composition (44).

The molecular sensors for all five taste classes act through second messenger systems to initiate neural signaling. These second messenger systems include phospholipase C–, cyclic AMP–, and IP_3–responsive mechanisms, although the precise second messenger mechanisms employed in many instances are not fully understood (51). In many cases the second messenger systems cause release of calcium from intracellular stores (3, 10, 18), leading to initiation of cell depolarization and transmission of neural impulses to the brain via the chroda tympani and glossopharyngeal nerves (37).

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Variation in Taste Ability

Measurement of taste sensitivity is a large and active area of research known as taste psychophysics. Psychophysics has addressed many problems inherent in taste measurements in humans, including subjective aspects of perception, sensitization and desensitization to tastants, and multiple taste modalities presented by some tastants. Psychophysical studies show variation in human sensitivity to many specific tastants. However, many of these reports focused on a single tastant, and comprehensive systematic surveys are still needed to document the breadth and

magnitude of taste variation for all taste classes. The simplest and best understood taste variation in humans is the ability to taste phenylthiocarbamide (PTC). A chance discovery made by Fox in 1931 (4) revealed that although many individuals perceive PTC as intensely bitter, this substance is relatively tasteless to a large fraction of the population. Recent progress understanding the molecular basis of this trait illustrates how advances of the human genome project, newly developed methods in gene association studies, and molecular understanding of taste mechanisms can be used to resolve long-standing controversies in taste biology and point the way to broader applications of human genetic methods in chemosensory science.

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PTC Genetics—A Long-Standing Puzzle

Within two years of its discovery, a number of investigators demonstrated that variation in PTC taste ability was genetically determined (11, 73). Nontaster status was transmitted in a simple autosomal recessive fashion (46, 47), and this view received additional support from many independent studies, including some very large ones, over the course of the next 50 years (34, 57, 64, 66). Gradually, however, results began to accumulate that suggested this view was either incomplete or inaccurate. There were a number of reports of two nontaster parents giving rise to taster children, at odds with a single recessive Mendelian locus (25, 57). In addition, genetic epidemiological studies suggested that although a single major gene could account for much of this trait, other genetic and possibly nongenetic factors also contributed to it (61, 67). The situation was complicated further by conflicting results of linkage studies. These studies first showed linkage to the KEL blood group antigen (later determined to reside on chromosome 7q) (22, 23), but these results proved difficult to replicate (74), and a comprehensive genome-wide linkage study of the closely related tastant propylthiouracil (PROP) produced primary evidence for linkage on chromosome 5q (68).

There was a large-scale effort to resolve the formal genetics of this trait using the Utah C.E.P.H. families, a group of 45 families exceptionally well characterized in previous genetic studies (26). The Utah family study produced overwhelming evidence that a single major locus on chromosome 7 was responsible for most of the phenotypic variance that exists in the population (27). Other genetic variation also influenced this trait. About half of the Utah C.E.P.H. families demonstrated linkage to chromosome 7q and nowhere else in the genome, and in these families PTC taste ability segregated as a simple Mendelian trait. Haplotype analysis demonstrated a 4-Mb region at 7q35–36 that segregated with the trait in these families. This interval contained some 150 known and predicted genes, including the KEL blood group antigen gene, a number of *TAS2R* genes, and a related group of *GPCR* genes annotated as potential odorant receptor genes. Sequencing these genes in tasters and nontasters revealed a number of differences, including one that correlated very highly with nontaster status. This variant specified either a proline or an alanine

within the coding sequence of a newly identified taste receptor, later designated TAS2R38.

An important breakthrough was made when this variant was observed to also correlate in a group of apparently unrelated nontasters drawn from outside the Utah population (43). An exhaustive survey of this genomic region showed identity by descent (IBD) spanning a minimal region of approximately 30 kb in these nontasters. Within this region was a single gene containing the coding variant originally observed to correlate with taster status. This gene, now designated *TAS2R38* (also called *PTC*), proved to be the PTC/PROP taste receptor. Variation in this gene accounts for all of the bimodality in PTC taste perception in the population and approximately 75% of the total phenotypic variance (43, 65). Although at least some of the remaining variance appears to be genetic in nature, the DNA variation responsible for this has not yet been identified.

One suggestive piece of evidence regarding the source of the additional variance is the finding of a modest linkage score between PTC taste ability and markers on chromosome 16p (27). The peak score is near the p terminus of the chromosome, indistinguishable from the location of the gene encoding $G\gamma_{13}$, which is involved in bitter taste transduction (39). Follow-up studies of this finding have not been reported and appear to be warranted.

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Variation in the *PTC* Gene

The *PTC* gene consists of a single coding exon 1002 bp in length that encodes a 7-transmembrane domain GPCR 333 amino acids long. The nontaster allele of the *PTC* gene differs from the taster allele at three locations, encoding amino acid differences at position 49 within the first intracellular domain, position 262 within the sixth transmembrane domain, and position 296 within the seventh transmembrane domain of this protein, respectively (Table 1). These differences occur on two predominant haplotypes. One contains a proline, an alanine, and a valine at the three variant sites, respectively, encoding the major taster or PAV form, whereas the other haplotype encodes an alanine, a valine, and an isoleucine, respectively, at these three positions, producing the major nontaster or AVI form of the receptor (43). These haplotypes together constitute the majority of haplotypes of this gene observed worldwide. However, a number of minor haplotypes have been observed, most of which occur only in sub-Saharan African populations (82) and are detailed in Table 2.

Although the 5 SNPs in the *PTC* gene are theoretically capable of combining to produce 32 different haplotypes, only 7 haplotypes have been observed to date despite extensive searches. Beyond the major taster and major nontaster haplotypes, five additional haplotypes of the *PTC* gene have been identified, as shown in Figure 1. These include presumptive recombinants between the two major haplotypes that are designated AAV, PVI, and AAI, plus two additional rare haplotypes containing variants at amino acid positions 80 and 274, giving rise to haplotypes related to the uncommon AAI haplotype, designated ARARI and AHACI. So far, one of

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TABLE 1 SNP variation in the *TAS2R38* (*PTC*) gene. Position of the variant nucleotide, the alternative base pairs at each variant position, position of the encoded variant amino acid, the alternative amino acids at each variant position, the frequency of each allele in a sample of 200 chromosomes from populations worldwide, and the location of the variant amino acid positions in relation to the predicted secondary structure of the protein are indicated

Variant nucleotide position	Alleles	Variant amino acid position	Alleles	Frequency	Predicted location
145	C	49	Proline	0.36	First intracellular loop
	G		Alanine	0.64	
239	A	80	Histidine	0.995	Second extracellular loop
	G		Arginine	0.005	
785	C	262	Alanine	0.38	Sixth transmembrane domain
	T		Valine	0.62	
820	C	274	Arginine	0.99	Fourth extracellular loop
	T		Cysteine	0.01	
886	G	296	Valine	0.38	Seventh transmembrane domain
	A		Isoleucine	0.62	

these haplotypes, AAV, has been shown to confer intermediate PTC sensitivity in vivo, and another haplotype, AAI, generates intermediate responses to PTC in ex vivo assays of receptor activity (18). Thus, the TAS2R38 PTC system presents opportunities for detailed structure-function analysis of bitter taste perception that can combine both in vivo and ex vivo approaches.

Lessons for the Genetics of Complex Traits

The genetics of PTC occupy a position intermediate between that of a Mendelian trait and a complex trait. PTC tasting displays many features of complex traits, including a continuously distributed quantitative phenotype, with deficits common in the population, plus frequent non-Mendelian inheritance and inconsistent linkage results. However, with the identification of the underlying gene, it is clear that most of the phenotypic variance is due to a single gene of large effect. Taking PTC tasting as a model of common disease, variation in this trait supports the "common disease-common variant" hypothesis. Relatively ancient variation, now common in the population, underlies this trait.

TAS2R38 Gene Evolution

The *TAS2R* genes show remarkable variation across species. For example, the human *TAS2R38* gene shows only 65% amino acid identity to the most closely related gene in the mouse (24). Given that the human taster and nontaster alleles of this gene are 99% identical at the amino acid level, it is possible that the most

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TABLE 2 SNP and haplotype variation in *TAS2R* genes. For each *TAS2R* gene, the number of polymorphic nucleotides in the coding region, the number of polymorphic amino acid positions, and the number of different protein coding haplotypes of each gene known to date are listed. The number of different protein coding haplotypes of *TAS2R 43*, *45*, and *55* is not yet known

TAS2R gene	# of polymorphic nucleotide positions	# of polymorphic amino acid positions	# of different protein coding haplotypes
1	3	2	3
3	3	1	2
4	8	7	8
5	7	6	7
7	6	5 + 1 stop	5
8	6	5	6
9	7	7	8
10	6	3	4
13	1	1	2
14	4	2	3
16	8	4	5
38	5	7	7
39	2	2	2
41	4	2	3
43	7	5	
44	17	11 + 2 stop	7
45	6	6	
46	6	3 + 2 stop	6
47	5	3	4
48	12	9	9
49	11	9	7
50	7	3	4
55	5	4	
60	2	1	2

closely related murine gene does not serve as a PTC receptor at all, but instead is a receptor for some other bitter substance. Given the natural differences in the diet of these two species, it is possible that mice have no receptor highly specific for PTC (34).

The great apes have a clearly identifiable TAS2R38 orthologue, although it contains several differences from the human gene. The few individual animals

sequenced to date are homozygous for an allele containing a proline at position 49, an alanine at position 262, and a valine at position 296, analogous to the major taster (PAV) allele in humans (43). This is somewhat surprising in light of reports that chimpanzees demonstrate apparent taster and nontaster individuals, at frequencies similar to those in humans (30). Greater understanding of *TAS2R* gene sequences and PTC tasting phenotypes in chimpanzees may shed important new information on recent human and chimp ecological and dietary histories.

PTC, PROP, and Supertasting

Early studies showed that a variety of compounds, all containing the N−C=S (thiocyanate) moiety, displayed the same bimodal taste response in human subject populations, and that taster status for PTC correlated strongly with taster status for all of these compounds (5, 35). For various reasons, later studies began to employ PROP in place of PTC (76), with the view that it was psychophysically equivalent, and indeed in vivo and in vitro studies of TAS2R38 receptor function confirmed that this receptor mediates responses to both PTC and PROP. However, many observations now indicate that PTC and PROP, despite their similarities, display many important differences as tastants. In human taster subjects, PTC is detectable at two- to threefold lower concentrations than PROP, and in ex vivo functional assays of the PAV taster receptor PTC produces a response at similar two- to threefold lower concentration than PROP (18). In addition, concentration response curves in biochemical assays of the taster form of the receptor show steeper sigmoidal response to PTC than to PROP (18). These observations suggest that the authentic function of the TAS2R38 receptor is to detect PTC or some other compound of closely related structure, and that PROP represents a suboptimal and perhaps somewhat artificial ligand for this receptor.

Psychophysical studies of PROP identified an additional class of individuals who report a very intense subjective perception of this substance, referred to as supertasters (7). However, this group of individuals is not observed in blind sorting tests that determine taste thresholds (27, 40). Instead, such tests show that all subjects reside in one of only two groups, nontasters and tasters. Recent reports suggest that the subjective rating of PROP taste intensity is not correlated with variation in the TAS2R38 gene (6), but instead appears to be correlated with the number of taste buds (7) and also aspects of personality (80). Thus, it appears that when measured by perceived taste intensity alone, the PROP supertaster phenotype exists and it may be under genetic control, but the phenomenon of supertasting may be influenced by factors other than chemoreception.

Population Genetics of the *PTC* Gene

The sense of bitter taste functions to prevent ingestion of toxic substances in plants, most of which taste bitter. If this is true, then the high frequency of the nontaster AVI haplotype, approximately 45% worldwide (34), presents a paradox. This allele could have come to high frequency in the population by three mechanisms: genetic

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drift, population subdivision, or natural selection. Genetic drift, in which variation in gene frequencies arise due to random fluctuations, initially appeared to be a likely explanation for two reasons. First, the length of the conserved haplotypes extending beyond this gene was very short [∼30 kb (43)], suggesting these variants are ancient in origin. Second, measuring the worldwide distribution of haplotype frequencies supports the view that a small subgroup of sub-Saharan Africans, carrying only two of the seven alleles present there, emerged from Africa and rapidly expanded to occupy the remainder of the world, consistent with the "Out of Africa" hypothesis of modern human origins (2). Such genetic bottlenecks, a common event in human history, tend to increase the effects of genetic drift.

A second possibility was population subdivision, which holds that the high frequency of the nontaster allele is a phenomenon confined to one group (for example, Caucasians). This possibility was quickly eliminated when it was found that both the PAV and AVI haplotypes are common in all populations (43, 82).

The third possibility was that these two major forms were maintained by balancing natural selection, a hypothesis first put forward by Fisher (30). In balancing natural selection, Darwinian forces act to simultaneously maintain two or more forms of a gene in the population. Often, the forces acting to eliminate a mutation that is deleterious in the homozygous state are balanced by forces that maintain the mutation in the heterozygous state, which is beneficial to the organism. To test this possibility and differentiate it from genetic drift, we analyzed the frequency of PTC haplotypes in populations worldwide and tested for effects of selection using the F_{st} and Tajima's D stastistics. A haplotype relatedness tree for the PTC gene is shown in Figure 2. This data gave rise to a Tajima's D value of $+1.59$, which under realistic assumptions about population growth provides significant support for balancing natural selection (82). In essence, the two major PTC haplotypes are too divergent and too common to be due to genetic drift, which typically produces negative Tajima's D values. Instead, selective forces appear to have maintained both taster and nontaster alleles in populations worldwide.

This result raises another paradox. If bitter taste receptors protect us from ingesting toxic substances, what selective force maintains the nontaster allele? Our hypothesis to explain this is based on the observation that the nontaster allele does not contain gene-inactivating alterations, such as a stop codon or a deletion, and the nontaster allele is not generated by a collection of different small genetic changes, as might be expected if its existence were due to mutation of the normal taster allele. Therefore, we hypothesize that the AVI allele encodes a functional receptor for some other toxic bitter substance not yet identified. This hypothesis is supported by our finding that the AVI allele appears to be as fully expressed at the RNA level as at the PAV allele (18).

This hypothesis addresses an important issue in chemosensory biology. At the moment, the ligand(s) recognized by most of the bitter receptors are unknown. A number of functional assay systems have been developed in attempt to "deorphanize" these receptors. If the situation in T2R38 extends to other bitter receptor genes, this task may need to consider all the alleles of each receptor. To gain a

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TABLE 3 SNP variation in TAS1R genes. Number of variants currently known in nucleic acid and protein sequence, determined in a sample of 100 individuals worldwide

Gene	Size, bp	# of SNPs in coding sequence	# of variant amino acid sites
TAS1R1	2526	17	13 + 1 stop
TAS1R2	2520	18	10
TAS1R3	2559	12	6

SNPs, single nucleotide polymorphisms; stop, variant site that alternatively encodes an amino acid or a stop codon.

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better view of the global variation in the T2R gene repertoire, we and others (77, 79) performed exhaustive DNA sequencing and haplotype analysis of these genes in a series of populations worldwide.

Bitter Taste Receptor Gene Variation

Surveys of *TAS2R* genes worldwide revealed that a high degree of coding sequence polymorphism is common in these genes (Table 3). On average they contain 4.2 coding single nucleotide polymorphisms (SNPs) per gene. Like T2R38, only a fraction of all the possible haplotypes for each of these genes occur in the population. In total, the 25 human *TAS2R* genes specify 151 different haplotypes distinguishable by DNA sequence that exist at a frequency of >10% in at least one population studied. These 151 haplotypes are made up of both synonymous and nonsynonymous cSNPs. Seventy-two percent of the cSNPs in the human *T2R* genes are nonsynonymous and encode amino acid substitutions. Of these, 59% are nonconservative and substitute significantly different amino acids. When only nonsynonymous cSNPs are considered, the *TAS2R* gene repertoire contains 110 different protein coding haplotypes.

Note that of the three amino acid substitutions that make up the difference between the taster and nontaster alleles for PTC, two of them (ala262val and val 296 ile) are relatively conservative (33), and yet they have a significant effect on taste sensitivity both in vivo and in vitro. This is known from the phenotype specified by the uncommon AAV haplotype, which presumably arose by an ancient recombination event between the taster PAV and nontaster AVI alleles. Careful phenotype measurements in AAV individuals show that they have an intermediate sensitivity to PTC, and cell-based biochemical functional assays reveal a two- to threefold-lower sensitivity to PTC in vitro. This suggests that although 41% of TAS2R cSNPs specify a conservative amino acid change, they may physiologically affect receptor function.

Population genetic analyses of the variation present across the entire *TAS2R* gene family presents a diverse picture. No other *T2R* genes show a pattern of worldwide variation similar to that of TAS2R38, the PTC receptor, where widely divergent alleles are maintained at high frequencies in many different populations worldwide. This has led to the speculation that whatever the ligands are for

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the receptors encoded by these genes, a prominent bimodal distribution of taste sensitivity to them will exist, as for the PTC tasters and nontasters specified by TAS2R38. For other *TAS2R* genes, widely divergent alleles exist, but the different alleles frequently exist at high frequency in only one region or continent, such as in TAS2R49. The variant alleles of these genes appear to have arisen under the effects of natural selection, but because they are not worldwide in distribution, it appears they came to locally high frequency because of local selection. Under this scenario individuals who carry such alleles can avoid consumption of toxic substances occurring in plants that are typically not distributed worldwide. Importantly, both types of variation appear to be the result of natural selection. This is evidence that the *TAS2R* gene sequence variants are functionally significant and not simply functionally neutral polymorphisms within the encoded receptors.

Finding a broad array of functionally different alleles for each *TAS2R* gene would explain another puzzling aspect of human bitter taste perception. The range of molecular sizes, shapes, and chemical functionalities of bitter substances is extremely broad, similar to the structural diversity present in different odorants. Humans, however, carry several hundred different odorant receptor genes, in contrast to only 25 bitter taste receptor genes. Some of the apparent deficit of bitter receptor genes may be accounted for by the large number of different alleles present for *TAS2R* genes, if, as we hypothesized for TAS2R38, different alleles serve as receptors for different bitter tastants.

A small number of reports show phenotypic variation in sensitivity to diverse bitter tastants (12), including quinine (71), sucrose octaacetate, denatonium benzoate, tetracycline (83), and chloramphenicol (75). Other than chloramphenicol, there has been little study of the possible genetic influences on this variation. None of these compounds share similar chemical structures. Also, in contrast to PTC, most of the variation in taste sensitivity to these compounds appears to be unimodally distributed in the population. This could mean that unlike PTC there is no single major allele underlying the variation in taste sensitivity to these substances. However, many human *TAS2R* genes display very high allelic diversity, and the unimodal distributions could represent the additive effects of multiple alleles, which cannot be resolved using the relatively small subject populations tested to date. There has also been one report of a large kindred that displays a more general insensitivity to a variety of bitter substances (P. Breslin, C. Tharp, D. Reed, T. Huque, J. Brand, unpublished observations). Although a detailed segregation analysis of the trait in this family has not been reported, the occurrence of the trait in this family is consistent with a genetic factor.

TAS2R gene coding sequence variants are being studied in genetic association studies and ex vivo assays of receptor function. For the moment these approaches appear complementary. Ex vivo assays are typically performed using artificial components. Such components include mammalian cell lines expressing artificially constructed chimeric G alpha proteins, and taste receptor proteins containing amino-terminal additions from the first extracellular domain of the visual pigment rhodopsin, which has so far been necessary to promote efficient expression and translocation of these receptors to the cell surface. Although such

ex vivo systems provide substantial benefits for high-throughput studies that may quickly identify presumptive ligands, confirmatory in vivo studies will be an important requirement.

Sweet and Umami Receptor Genes

Like bitter perception, taste sensitivity to two other classes of tastants, sweet and umami, are mediated by seven transmembrane domain GPCRs. Initial evidence accumulated in rodent systems indicated a truncated form of the metabotropic glutamate receptor (taste mGluR4), similar to the glutamate receptor involved in glutaminergic neurotransmission in the central nervous system, was responsible for umami perception (21). However, this receptor contained neither a clear signal sequence nor the prototypical glutamate binding domains typically present in such receptors. In addition, knockout mice lacking this gene still readily perceived the taste of glutamate (20). These observations motivated additional studies that ultimately elucidated the role of *TAS1R* gene products, acting as heterodimers, in both umami and sweet taste perception (85).

In contrast to the extensive *TAS2R* gene family, there are only three *TAS1R* genes, designated *TAS1R1*, *TAS1R2*, and *TAS1R3*. These genes reside in a cluster on chromosome 1p36, and they encode similar proteins of 841, 839, and 852 amino acids, respectively (49). In contrast to the short first extracellular domain of the TAS2R bitter receptors, the TAS1R receptors are predicted to contain a large first extracellular domain, which is likely involved in ligand recognition and binding. Unlike the single coding exon of the *TAS2R* genes, the *TAS1R* genes all contain six known exons, distributed over approximately 25 kb, 20 kb, and 3.2 kb of genomic sequence, respectively. TAS2R1 is alternatively spliced, with at least four different isoforms identified so far. These three receptors act as heterodimers in combinatorial fashion, with TAS1R1 + TAS1R3 acting as amino acid receptors, and TAS1R2 + TAS1R3 acting as sweet receptors.

Variation in Umami and Sweet Tastes

Quantitative measure of sensitivity to L-glutamate has been complicated by the fact that monosodium glutamate (MSG), which is widely employed as a flavor enhancer in foods and often used for psychophysical taste measurements, presents subjects with an additional salty taste from the constituent sodium. Simple MSG taste thresholds show a bimodal distribution in the population (P. Breslin, D. Reed, R. Keast, C. Tharp, S. Lui, O. Ohmed, unpublished observations; 53). Additional psychophysical measurements were developed to carefully differentiate the effects of sodium versus glutamate, which showed that an estimated 10% of a group of European subjects were glutamate hypotasters, and 3.5% could be considered unable to taste glutamate at all. This trait has not been subject to genetic characterization, such as segregation analysis in families or twin studies, so it is not yet known how much of the variance, if any, is genetic in nature. Correlation of this phenotypic variation with specific genetic variation has not been reported.

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Broad population surveys of sensitivity to sweet substances have not been reported. The limited studies that have been reported typically show a relatively narrow, unimodal distribution of taste thresholds (12). Precise measurements of sweet taste abilities across broad populations using modern psychophysical measurement methods are warranted.

We recently completed an extensive survey of worldwide variation in the *TAS1R* genes. In the coding regions of these three genes, we identified a total of 47 SNPs, 29 of which cause amino acid substitutions (Table 3). The *TAS1R* genes encode proteins roughly twice as large as the TAS2R proteins, and thus the sweet and umami receptors contain proportionally much less amino acid sequence diversity than bitter receptors. The more limited diversity in TAS1R2 and TAS1R3 may account for the lesser degree of variation in sweet taste ability in the population. However, the lack of large-scale and precise cataloging of phenotypes for human sweet taste perception probably makes this conclusion premature.

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Salty Taste

Much effort has been made to understand the molecular mechanisms that underlie salty taste, and a number of different proteins have been put forward as mammalian salt taste receptors. Most prominent among these is the amiloride-sensitive sodium channel (36, 70). Although this protein clearly serves an important role in salt perception in rodents, two observations suggest that human salt perception is mechanistically different. First, studies show that the amiloride sensitivity of human NaCl perception appears to be more specific to a minor sour component of this taste, and not primarily saltiness (62). Second, studies show that human salt perception can be inhibited by chlorhexidrine, suggesting another sodium ion channel is the primary mediator of this taste (14).

One small study of a European population demonstrated that sensitivity to both sodium and potassium chloride displays a relatively narrow unimodal distribution (12), and a single twin study of NaCl preferences showed no evidence for genetic influences on this trait (8). However, in African populations a bimodal distribution of taste sensitivity to NaCl has been observed (59), and an inquiry into possible genetic origins of this variation could be of great interest.

Sour Taste

Sensory physiologists suggest that sour taste is mediated by a detector of H^+ ions. However, numerous observations show that this simple model is probably inadequate. For example, although there is a correlation between the pH of strong inorganic acid tastants and signaling from gustatory afferent nerves in rats (9, 60), there is only a low correlation between sour taste perception and the pH of organic acid stimuli tastant substances (31). In addition, a remarkably broad range of mechanisms have been put forward as the molecular basis for sour sensation, including blockage of K^+ channels by protons, H^+-gated calcium channels, proton conduction via Na+ channels, activation of the proton-gated channel BNC-1, and,

most recently, proton passage through acid-sensing ion channels (ASICs) (78). However, all of these proposed mechanisms have been identified in nonhuman systems, and it remains possible that only one or even none of these mechanisms may account for the primary human sour-sensing apparatus.

Human variation in sour taste is not well characterized. Data so far suggest relatively narrow unimodal distribution of sensitivities to hydrochloric, citric, acetic, and picric acids in European populations (12, 13), and a twin study of hydrochloric acid taste thresholds suggests this variation is not primarily genetic in origin (41). Given that organic acids are more likely encountered as tastants by humans, HCl may well be a nonoptimal tastant for measuring sourness. At this point, the heritability of variation in sour taste sensitivity might be better revisited using population surveys, twin studies, and other methodologies using a variety of common organic acids.

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Additional Tastes

The substantial majority of taste sensation in humans seems to be accounted for by the five main taste modalities described above. However, other taste modalities have been suggested. One of these is the taste of fats, which are an important source of calories in modern and premodern human diets. A specific taste of fat has not been demonstrated, although fats clearly impart a sensation ("mouth feel") that is desirable to humans. It may be significant that cells of the tongue produce a unique lipase, called lingual lipase. The protein encoded by this highly expressed gene may produce one or more lipid breakdown products that are recognized by a specialized chemosensory mechanism of unknown composition.

Another possible taste is that of water (50). Although water may have an effect on the taste sensory apparatus in other organisms, human subjects typically describe pure water as tasteless, and no strong psychophysical evidence exists that would assign a separate taste modality to water.

Taste Second Messenger Signaling

Bitter, sweet, and umami tastes are mediated by GPCRs. Mammalian G proteins are comprised of three different classes, designated α, β, and γ, which act in a heterotrimeric structure on the inside of the plasma membrane that couples to the transmembrane GPCR and transmits ligand binding signals to intracellular second messenger systems. Humans have 15 different Gα genes, 5 Gβ genes, and 11 Gγ genes. Some of these genes appear to be specifically involved in taste signaling, such as Gα gustducin and Gγ_{13}. Although Gβ_3 shows localization to taste cells in rodents and can function in vitro to generate bitter signaling (39), a Gβ protein highly specific to taste transduction in humans has not yet been identified. Gα gustducin knockout mice show greatly reduced sensitivity to both bitter and sweet substances, indicating the functional convergence of bitter and sweet signaling pathways and possible ancient evolutionary relatedness of these two taste modalities (69).

Beyond G protein activation, subsequent steps in taste signaling are mediated by phospholipase C and the TRPM5 ion channel (63) and possibly by other systems in rodents. Knockout mice lacking the phospholipase Cβ2 gene fail to detect both bitter and sweet substances (84), and given the similarity between human and rodent sensory mechanisms for these two tastes, naturally occurring human variation in PLCβ2 and TRMP5 may have an effect on individual perception. Second messenger and downstream signaling for salty and sour tastes is currently less well understood.

Overall, it appears that variation in the tastant binding receptors confers an evolutionary advantage, but second messenger and downstream signaling may be under selection away from diversity, as it may be beneficial for organisms to maintain a single most efficient transmission system for each taste modality. Thus, it is currently unclear whether the genotypic and phenotypic variation ascribable to receptors will be repeated in the second messenger and downstream signaling components in humans.

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Unanswered Questions

The field of human taste genetics is at an exciting juncture. Several recent discoveries demonstrate the power of human genetic approaches, but many interesting and important questions have yet to be answered. First, keep in mind that we do not yet know how much of the variation in human taste abilities is genetic in origin. Age, sex, and exposure to different diets and foods are known to affect some taste abilities (7, 40). Disentangling genetic from nongenetic factors will require twin studies, segregation analysis, and other methods. If, unlike PTC taste ability, sensitivity to other tastants is specified by a number of different genes, or by many allelic variants of one gene, each with small effects, this task will not be simple and may require large subject populations to produce clear conclusions.

An important area of bitter taste research currently addresses the coding problem, that is, what ligands are recognized by each of the bitter taste receptors? As we suggest above, this problem may be better rephrased as: What is the bitter tastant ligand for each of the $>$110 different bitter receptor proteins encoded by human populations worldwide? This question needs to be answered by a combination of in vivo studies using psychophysical measurements of taste abilities and their association with *TAS2R* gene variants plus in vitro biochemical studies of receptor ligand interactions.

Another largely unexamined area is variation in genes encoding taste-specific second messenger systems and downstream signaling components. Although SNPs associated with a number of these genes have been reported (http://www.ncbi.nlm.nih.gov/projects/SNP/), it is not clear how much variation remains to be discovered, nor do we know what effects such variants might have on taste perception.

Recent human genetic studies of taste perception were strongly driven by the identification of genes encoding receptors and second messenger components of taste transduction. However, many gaps still exist in our knowledge of cellular

and molecular aspects of taste perception. This suggests that a more traditional approach, involving linkage and whole-genome association studies, might identify genes that are currently not known or suspected to be involved in our sense of taste.

Taste perception appears to play a large role in a number of different behaviors with important effects on human health, including alcohol consumption, nicotine usage, and food choices (29, 76). Many of these behaviors, such as alcohol consumption, have a substantial genetic contribution (42). It is possible that some of this genetic contribution is mediated at the level of inherited variation in taste preferences. Supporting this view is a recent finding that variation in *TAS2R38* (*PTC*) gene is strongly correlated with the perceived taste of alcohol, and, remarkably, with alcohol consumption (28). As efforts to better understand and modulate potentially harmful dietary choices gain importance, so will our need to understand the genetic underpinnings of individual differences in taste perception.

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LITERATURE CITED

1. Adler E, Hoon M, Mueller K, Chandrashekar J, Ryba N, Zuker C. 2000. A novel family of mammalian taste receptors. *Cell* 100:693–702
2. Akey J, Eberle M, Rieder M, Carlson C, Shriver M, et al. 2004. Population history and natural selection shape patterns of genetic variation in 132 genes. *PLoS Biol.* 2(10):e 286
3. Alkabas M, Dodd J, Al-awqati Q. 1988. A bitter substance induces a rise in intracellular calcium in a subpopulation of rat taste cells. *Science* 1047–50
4. Anonymous. 1931. Tasteblindness. *Science* 73(Suppl.):14
5. Barnicot N, Harris H, Kalmus H. 1951. Taste thresholds of further eighteen compounds and their correlation with P.T.C. thresholds. *Ann. Eugenics* 16:119–28
6. Bartoshuk L, Davidson A, Kidd J, Kidd K, Speed W, et al. 2004. *Supertasting is not explained by the PTC/PROP gene*. Presented at 26th Annu. Meet. Assoc. Chemrecept. Sci., April 24–28
7. Bartoshuk L, Duffy V, Miller I. 1994. PTC/PROP tasting: anatomy, psychophysics and sex effects. *Physiol. Behav*. 56:1165–71
8. Beauchamp G, Bertino M, Engelman K. 1985. Sensory basis of human salt consumption. In *NIH Workshop on Nutrition and Hypertension*, ed. M Horan, M Blaustein, J Dunbar, W Kachadorian, N Kaplan, A Simopoulos. pp. 113–24. New York: Biomed. Info. Corp.

Annu. Rev. Genom. Hum. Genet. 2005.6:217-235. Downloaded from www.annualreviews.org
Access provided by East Carolina University on 11/02/16. For personal use only.

9. Beidler L, Gross G. 1971. The nature of taste receptor sites. In *Contributions to Sensory Physiology*, ed. W Neff. pp. 97–127. New York: Academic
10. Bernhardt S, Naim M, Zehavi U, Lindemann B. 1996. Changes in IP_3 and cytosolic Ca^{2+} in response to sugars and non-sugar sweeteners in transduction of sweet taste in the rat. *J. Physiol*. 490:325–36
11. Blakeslee A. 1931. Genetics of sensory thresholds: taste for phenyl thio carbamide. *Science* 74:607
12. Blakeslee A, Salmon T. 1935. Genetics of sensory thresholds: individual taste reactions for different substances. *Proc. Natl. Acad. Sci. USA* 21:84–90
13. Breslin P. 2000. Human gustation. In *The Neurobiology of Taste and Smell*, ed. T Finder, W Silver, D Restrepo. pp. 423–61. New York: Wiley-Liss
14. Breslin P, Tharp C. 2001. Reduction of saltiness and bitterness after a chlorhexidrine rinse. *Chem. Senses* 26:105–16
15. Deleted in proof
16. Deleted in proof
17. Bufe B, Hofmann T, Krautwurst D, Raguse J, Meyerhof W. 2002. The human TAS2R16 receptor mediates bitter taste in response to beta-glucopyranosides. *Nat. Genet*. 32:397–401
18. Bufe B, Breslin P, Kuhn C, Reed D, Tharp C, et al. 2005. The molecular bases of individual differences in phyenythiocarbamide and propylthiouracil bitterness perception. *Curr. Biol*. 15:1–20
19. Chandrashekar J, Mueller K, Hoon M, Adler E, Feng L, et al. 2000. T2Rs function as bitter taste receptors. *Cell* 100:703–11
20. Chaudari N, Roper S. 1998. Molecular and physiological evidence for glutamate (umami) taste transduction via a G protein-coupled receptor. *Ann. N. Y. Acad. Sci*. 855: 398–406
21. Chaudhari N, Landin A, Roper S. 2000. A metabotropic glutamate receptor variant functions as a taste receptor. *Nat. Neurosci*. 3:113–19
22. Chautard-Freire-Maia E. 1974. Linkage relationships between 22 autosomal markers. *Ann. Hum. Genet*. 38:191–98
23. Conneally PM, Dumont-Driscoll M, Huntzinger RS, Nance WE, Jackson CE. 1976. Linkage relations of the loci for Kell and phenylthiocarbamide taste sensitivity. *Hum. Hered*. 26:267–71
24. Conte C, Ebeling M, Marcuz A, Nef P, Andres-Barquin P. 2003. Evolutionary relationships of the *Tas2r* receptor gene families in mouse and human. *Physiol. Genomics* 14:73–82
25. Das S. 1958. Inheritance of the PTC taste character in man: an analysis of 126 Rarhi Brahmin families of West Bengal. *Ann. Hum. Genet*. 22:200–12
26. Dausset J, Cann H, Cohen D, Lathrop M, Lalouel J-M, White R. 1990. Program description—Centre d'Etude du Polymorphisme Humain (CEPH)—collaborative mapping of the human genome. *Genomics* 6:575–77
27. Drayna D, Coon H, Kim U-K, Elsner T, Cromer K, et al. 2003. 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*. 112:567–72
28. Duffy V, Davidson A, Kidd J, Kidd K, Speed W, et al. 2004. Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. *Alcohol. Clin. Exp. Res*. 28(11):1629–37
29. Enoch M, Harris C, Goldman D. 2001. Does a reduced sensitivity to bitter taste increase the risk of becoming nicotine addicted? *Addict. Behav*. 26:399–404
30. Fisher R, Ford E, Huxley J. 1939. Taste-testing in Anthropoid apes. *Nature* 144:750
31. Ganzevles P, Kroeze J. 1987. Effects of adaptation and cross-adaptation to common ions on sourness intensity. *Physiol. Behav*. 40:641–46
32. Gilbertson T, Damak S, Margolskee R. 2000. The molecular physiology of taste transduction. *Curr. Opin. Neurobiol*. 10: 519–27

Annu. Rev. Genom. Hum. Genet. 2005.6:217-235. Downloaded from www.annualreviews.org
Access provided by East Carolina University on 11/02/16. For personal use only.

33. Grantham R. 1974. Amino acid difference formula to help explain protein evolution. *Science* 185(4154):862–64
34. Guo S-W, Reed D. 2001. The genetics of phenylthiocarbamide perception. *Ann. Hum. Biol*. 28:111–42
35. Harris H, Kalmus H. 1949. Chemical specificity in genetical differences of taste sensitivity. *Ann. Eugenics* 15:32–45
36. Heck G, Mierson S, DeSimone J. 1984. Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway. *Science* 223:403–5
37. Hellekant G, Danilova B, Ninomiya Y. 1997. Primate sense of taste: behavioral and single chroda tympani and glossopharyngeal nerve fiber recordings in the rhesus monkey, Macca mulatta. *J. Neurophysiol*. 77:978–93
38. Hoon M, Adler E, Lindemeier J, Battey J, Ryba N, Zuker C. 1999. Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity. *Cell* 96(4):541–51
39. Huang L, Shanker Y, Dbuauskaite J, Zheng J, Yan W, et al. 1999. Gg13 colocalizes with gustducin in taste receptor cells and mediates IP_3 responses to bitter denatonium. *Nat. Neurosci*. 2:1055–62
40. Kalmus H. 1958. Improvement in the classification of the taster genotypes. *Ann. Hum. Genet*. 22:222–30
41. Kaplan A, Fischer R, Karras A, Griffin F, Powell W, et al. 1967. Taste thresholds in twins and siblings. *Acta Genet. Med. Gemellol*. 16:229–43
42. Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose R. 1987. Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. *Alcohol. Clin. Exp. Res*. 11:349–56
43. Kim U-K, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. 2003. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 299:1221–25
44. Kim U-K, Breslin P, Reed D, Drayna D. 2004. Genetics of human taste perception. *J. Dental Res*. 83:448–53
45. Kinnamon S, Margolskee R. 1996. Mechanisms of taste transduction. *Curr. Opin. Neurobiol*. 6:506–13
46. Lee BF. 1937. A genetic analysis of taste deficiency in the American Negro. *Ohio J. Sci*. 34:337–42
47. Levit S, Soboleva G. 1935. Comparative intrapair correlations of fraternal twins and siblings. *J. Genet*. 30:389–96
48. Li X, Staszewski L, Xu H, Durick K, Zoller M, Adler E. 2002. Human receptors for sweet and umami taste. *Proc. Natl. Acad. Sci. USA* 99:4692–96
49. Liao J, Schultz P. 2003. Three sweet receptor genes are clustered in human chromosome 1. *Mamm. Genome* 14:291–301
50. Lindemann B. 1996. Taste perception. *Physiol. Rev*. 76:719–66
51. Lindemann B. 2001. Receptors and transduction in taste. *Nature* 413:219–25
52. Lindemann B, Ogiwara Y, Ninomiya Y. 2002. The discovery of umami. *Chem. Senses* 27:843–44
53. Lugaz O, Pillias A, Faurion A. 2002. A new specific aguesia: Some humans cannot taste L-glutamate. *Chem. Senses* 27:105–15
54. Margolskee R. 2002. Molecular mechanisms of bitter and sweet taste transduction. *J. Biol Chem*. 277:1–4
55. Matsunami H, Montmayeur J, Buck L. 2000. A family of candidate taste receptors in human and mouse. *Nature* 404:601–4
56. McLaughlin S, McKinnon P, Margolskee R. 1992. Gustducin is a taste-cell-specific G protein closely related to the transducins. *Nature* 357:563–69
57. Merton B. 1958. Taste sensitivity to PTC in 60 Norwegian families with 176 children. Confirmation of the hypothesis of single gene inheritance. *Acta Genet. Stat. Med*. 8: 114–28
58. Nelson G, Chandrashekar J, Hoon M, Feng L, Zhao G, et al. 2002. An amino acid taste receptor. *Nature* 416:199–202
59. Odeigah P. 1994. Smell acuity of acetone and its relationship to taste ability to

phenylthiocarbamide in a Nigerian population. *East Afr. Med. J.* 71:462–66
60. Ogiso K, Shimizu Y, Watanabe K, Tonosaki K. 2000. Possible involvement of undissociated acid molecules in the acid response of the chorda tympani nerve of the rat. *J. Neurophysiol.* 83(5):2776–79
61. Olsen JM, Boehnke M, Neiswanger K, Roche AF, Sierbogel RM. 1989. Alternative genetic models for the inheritance of the phenylthiocarbamide taste deficiency. *Genet. Epidemiol.* 6:423–34
62. Ossebaard C, Smith D. 1995. Effect of amiloride on the taste of NaCl, Na-gluconate and KCl in humans: implications for Na+ receptor mechanisms. *Chem. Senses* 20:37–46
63. Perez C, Huang L, Rong M, Kozak J, Preuss A, et al. 2002. A transient receptor potential expressed in taste receptor cells. *Nat. Neurosci.* 5:1169–76
64. Pons J. 1960. A contribution to the heredity of the P.T.C. taste character. *Ann. Hum. Genet.* 24:71–76
65. Prodi D, Drayna D, Forabosco P, Palmas M, Maestrale G, et al. 2004. Bittter taste study in a Sardinian genetic isolate supports the association of phenylthiocarbamide sensitivity to the *TAS2R38* bitter receptor gene. *Chem. Senses* 29:697–702
66. Rao D, Morton N. 1977. Residual family resemblance for PTC taste sensitivity. *Hum. Genet.* 36:317–20
67. Reddy BM, Rao DC. 1989. Phenylthiocarbamide taste sensitivity revisited; complete sorting test supports residual family resemblance. *Genet. Epidemiol.* 6:413–21
68. Reed D, Nanthakumar E, North M, Bell C, Bartoshuk L, Price RA. 1999. Localization of a gene for bitter taster perception to human chromosome 5p15. *Am. J. Hum. Genet.* 64:1478–80
69. Ruiz-Avila L, Wong G, Damak S, Margolskee R. 2001. *Proc. Natl. Acad. Sci. USA* 98:8868–73
70. Schiffman S, Lockhead E, Maes F. 1983. Amiloride reduces the taste intensity of Na+ and Li+ salts and sweeteners. *Proc. Natl. Acad. Sci. USA* 80:6136–40
71. Smith S, Davies P. 1973. Quinine taste thresholds: a family study and a twin study. *Ann. Hum. Genet.* 37:227–32
72. Smith D, Margolskee R. 2001. Making sense of taste. *Sci. Am.* 284:32–39
73. Snyder LH. 1931. Inherited taste deficiency. *Science* 74:151–52
74. Spence MA, Falk CT, Neiswanger K, Field LL, Marazita ML, et al. 1984. Estimating the recombination frequency for the PTC-Kell linkage. *Hum. Genet.* 67:183–86
75. Sugino Y, Umemoto A, Mizatani S. 2002. Insensitivity to bitter taste of chloramphenical: an autosomal recessive trait. *Genes Genet. Syst.* 77:59–62
76. Tepper B. 1998. Genetics of perception ’98, 6-n-propylthiouracyl: a genetic marker for taste, with implications for food preference and dietary habits. *Am. J. Hum. Genet.* 63: 1271–76
77. Ueda T, Ugawa S, Ishida Y, Shibata Y, Murakami S, Shimada S. 2001. Identification of coding single nucleotide polymorphisms in human taste receptor genes involving bitter tasting. *Biochem. Biophys. Res. Commun.* 285:147–51
78. Ugawa S. 2003. Identification of sour taste receptor genes. *Anat. Sci. Int.* 78:205–10
79. Wang X, Thomas SD, Zhang J. 2004. Relaxation of selective constraint and loss of function in the evolution of human bitter taste receptor genes. *Hum. Mol. Genet.* 13(21):2671–78
80. White T, Longo M. 2004. *Personality traits and PROP sensitivity*. Presented at Annu. Meet. Assoc. Chemorecept. Sci., April 24–28
81. Wong G, Gannon K, Margolskee R. 1996. Transduction of bitter and sweet taste by gustducin. *Nature* 381:796–800
82. Wooding S, Kim U-K, Bamshad M, Jorde L, Drayna D. 2004. Natural selection and molecular evolution in PTC, a bitter taste receptor gene. *Am. J. Hum. Genet.* 74:637–46
83. Yokimukai Y, Coawrt B, Beauchamp G.

Annu. Rev. Genom. Hum. Genet. 2005.6:217-235. Downloaded from www.annualreviews.org
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1993. Individual differences in sensitivity to bitter-tasting substances. *Chem. Senses* 18:669–81

84. Zhang Y, Hoon M, Chandrashekar J, Mueller K, Cook B, et al. 2003. Coding of sweet, bitter, and umami tastes: different receptor cells sharing similar signalling pathways. *Cell* 112:293–301
85. Zhao GQ, Zhang Y, Hoon M, Chandrashekar J, Erlenback I, et al. 2003. The receptors for mammalian sweet and umami taste. *Cell* 115:255–66

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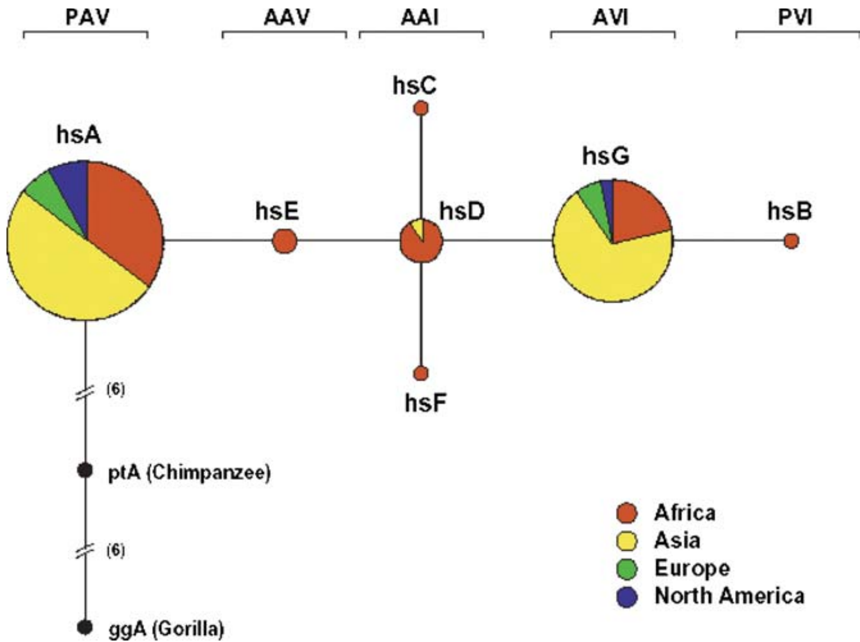

Figure 1 Haplotypes in the *TAS2R38* (*PTC*) gene. The haplotype frequencies were determined in a sample of 100 chromosomes from populations worldwide. Each *TAS2R38* gene haplotype is represented by a circle, with the size of each circle proportional to the worldwide frequency of that haplotype. The frequency of the haplotype in different populations is indicated by the fraction of the circle represented by each color. Lines connecting the circles each represent one amino acid difference between the two haplotypes connected (82).

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TAS2R38 gene haplotypes

- 5 SNPs
  - 3 common SNPs
    - Pro ⇨ Ala at 49
    - Ala ⇨ Val at 262
    - Val ⇨ Ile at 296
  - 2 rare SNPs
    - His ⇨ Arg at 80
    - Arg⇨ Cys at 274
- 7 haplotypes
  - Two main haplotypes
    - PHARV taster
    - AHVRI non-taster
  - 3 rare haplotypes - exclusively African
- Chimpanzee & gorilla
  - PHARV haplotype

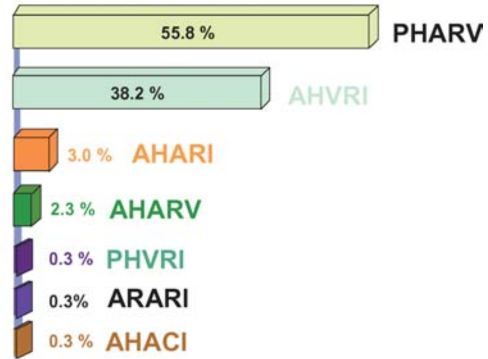

Figure 2 Haplotype relatedness for *TAS2R38* gene. The haplotypes are identified across the top line, designated by the amino acids present at the variant positions at 49, 262, and 296.

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