Do polymorphisms in chemosensory genes matter for human ingestive behavior?

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Abstract

In the last decade, basic research in chemoreceptor genetics and neurobiology have revolutionized our understanding of individual differences in chemosensation. From an evolutionary perspective, chemosensory variations appear to have arisen in response to different living environments, generally in the avoidance of toxins and to better detect vital food sources. Today, it is often assumed that these differences may drive variable food preferences and choices, with downstream effects on health and wellness. A growing body of evidence indicates chemosensory variation is far more complex than previously believed. However, just because a genetic polymorphism results in altered receptor function in cultured cells or even behavioral phenotypes in the laboratory, this variation may not be sufficient to influence food choice in free living humans. Still, there is ample evidence to indicate allelic variation in *TAS2R38* predicts variation in bitterness of synthetic pharmaceuticals (e.g., propylthiouracil) and natural plant compounds (e.g., goitrin), and this variation associates with differential intake of alcohol and vegetables. Further, this is only one of 25 unique bitter taste genes (*TAS2Rs*) in humans, and emerging evidence suggests other TAS2Rs may also contain polymorphisms that a functional with respect to ingestive behavior. For example, *TAS2R16* polymorphisms are linked to the bitterness of naturally occurring plant compounds and alcoholic beverage intake, a *TAS2R19* polymorphism predicts differences in quinine bitterness and grapefruit bitterness and liking, and *TAS2R31* polymorphisms associate with differential bitterness of plant compounds like aristolochic acid and the sulfonyl amide sweeteners saccharin and acesulfame-K. More critically with respect to food choices, these polymorphisms may vary independently from each other within and across individuals, meaning a monolithic one-size-fits-all approach to bitterness needs to be abandoned. Nor are genetic differences restricted to bitterness. Perceptual variation has also been associated with polymorphisms in genes involved in odors associated with meat defects (boar taint), green/grassy notes, and cilantro, as well as umami and sweet tastes (*TAS1R1/2/3*). Here, a short primer on receptor genetics is provided, followed by a summary of current knowledge, and implications for human ingestive behavior are discussed.

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1. Introduction

The term `taste' is often used by the public to describe flavor, the integrated sensation arising from the combination of input from the taste, olfactory and somatosensory systems (Delwiche, 2004; Mattes, 2009). `Taste' in this colloquial sense is reported by consumers as the greatest factor in food purchase decisions (IFIC, 2012). While `price' and `healthfulness' have grown in their influence in recent year, as of 2012, `taste' remains the top consideration in purchase decisions (IFIC, 2012). A substantial body of evidence indicates individuals differ greatly in flavor perception, due in part to genetic variations in chemoreceptor genes. These differences in biology have been implicated as drivers of food choice, highlighting the need for behavioral scientists, sensory practitioners and product developers to be aware of these differences. Collectively, these data also suggest variability across individuals is not a source of noise to be minimized in sensory testing; rather, this variation is what is interesting, both in its own right from a basic science standpoint, and in translation as a potential driver of differential food choices (i.e. market segmentation).

Recently it has become clear that variation in chemosensation is far more complex than previously believed. Of the 25 unique bitter taste genes in humans (*TAS2Rs*), the most studied is *TAS2R38*, which explains differential bitterness of synthetic thiourea compounds (e.g. propylthiouracil) and natural plant toxins (e.g. goitrin). Notably, *TAS2R38* variation also associates with differential intake of both alcohol and vegetables. However, this is just one of many examples to emerge within the last few years. Nor are such differences limited to bitterness, as differences in chemosensory perception have also been documented for odor (*OR7D4*), as well as umami and sweet tastes (*TAS1R1/TAS1R3* and *TAS1R2/TAS1R3* respectively). Other evidence suggests variation in the gustin (*CA6*) and gustducin (*GNAT3*) genes may also associate with variation in the intensity of bitter and sweet sensations, respectively.

Functional variation in taste, smell and oral somatosensory systems may affect myriad sensory attributes elicited by food. Much of this variation has a genetic basis, and as personalized genomics becomes more feasible, it is likely that food manufacturers will target products to particular groups based on preferences predicted by genetics. The largest challenge will be to assemble a broad range of genetic variability into a small number of groups (segments) that manufacturers can target on the basis of differential preferences.

Additionally, growing evidence suggests `taste' receptors are expressed in many other tissues in the body (we place taste in quotes to emphasize activation of these receptors may not elicit a conscious perception). The degree to which extra-oral chemoreceptors influence metabolic processes or ingestive behavior via postprandial learning are just beginning to be explored; nor do we have a good understanding how polymorphisms in the genes encoding these receptors may influence learning or metabolism. This is an extremely active area of research (e.g. (Behrens & Meyerhof, 2010; Breer, Eberle, Frick, Haid, & Widmayer, 2012; Clark, Liggett, & Munger, 2012; Dotson, Vigues, Steinle, & Munger, 2010; Dotson, et al., 2008; Sclafani, Glass, Margolskee, & Glendinning, 2010)), so it is likely our understanding will increase greatly over the coming decade.

In this review, a brief overview on receptor genetics is provided, followed by a summary of current knowledge on functional variation to date with examples for taste, smell and oral somatosensation. Throughout, we highlight the implications for human ingestive behavior outside of the laboratory, as well as gaps in our current knowledge. The next two sections provide an overview of some foundational biological concepts relevant to chemoreceptor genetics; readers who are comfortable with these concepts may want to skip ahead to section 4.

2. Approaches from Quantitative and Molecular Genetics

Although learning and prior exposure may play a role, a substantial proportion of the observed variation in chemosensory perception may be attributed to genetic variation. Researchers have attempted to elucidate these mechanisms by using several distinct but complementary methods from quantitative and molecular genetics. These are detailed below in sections 2.2 and 2.3 after a brief discussion of nomenclature.

2.1 Imperfect relationships between phenotypes and genotypes

Understandably, many studies in the chemical senses confuse phenotypes and genotypes, so it is worth explicitly defining these terms here. According to the National Human Genome Research Institute, a phenotype is an observable trait within an individual. Typical examples would include height or blood type; the classic chemosensory example is the ability to taste (or not taste) phenylthiocarbamide (PTC) at low concentrations. From a behavioral perspective, anything that can be measured reliably and stably may be considered a potential phenotype (e.g. salt detection thresholds, suprathreshold bitterness intensity, sweet liking, food intake patterns, blood pressure, etc). In contrast, genotype refers to the collection of genes an individual carries, and in the case of a single nucleotide, it can refer to the two alleles an individual inherits from their mother and father at that specific position. Critically, the phenotype is the product of both genetics and the environment, and some observable traits are primarily genetic, while others are mostly due to environment. Also, an observable phenotype may arise from multiple diverse genotypes. Thus, phenotype–genotype associations may be imperfect, and underlying genotypes cannot always be inferred from the observed phenotype (e.g see Table 3 in (Hayes, Bartoshuk, Kidd, & Duffy, 2008)).

2.2 Quantitative Genetics – Twin Designs

Traditionally, twin studies were used to determine the genetic component of a trait (e.g., (Wysocki & Beauchamp, 1984)). While there are now many different twin study designs (see (van Dongen, Slagboom, Draisma, Martin, & Boomsma, 2012) for a review), in the classical twin study design, resemblance in monozygotic twins (`identical' twins who share all their segregating genetic material) is compared to that of dizygotic twins (`fraternal' twins who share half their genetic material on average). These types of designs allow heritability estimates to be calculated, and have been extremely important in determining the amount of variation of a trait that is attributable to genetic influences; in these models, the remaining variance is assumed to arise from environmental factors. For example, twin studies in the UK suggest that in females, the heritability is high (over 40%) for intake of certain foods such as garlic, coffee, and fruit and vegetables (Teucher, et al., 2007). Other groups have found a genetic influence on bread choice and frequency of consumption (Hasselbalch, et al., 2010) and even liking and consumption of chocolate and other sweet foods (Keskitalo, 2007 #461}. Food neophobia (a fear of new foods) also appears to have a strong heritable component (Cooke, Haworth, & Wardle, 2007; Knaapila, et al., 2011). However, while extremely useful, these designs do not provide information about the specific gene or genes responsible; rather, they provide a quantitative estimate of the overall heritability of a trait without identifying the molecular basis of the trait.

2.3 Molecular Genetics – Candidate Gene, Candidate SNP, and Genome Wide Association Studies

With the advent of PCR[1] and subsequent advances in molecular biology, new genetic techniques became possible which allow identification of the individual genetic components that underlie these heritability estimates from quantitative genetics. These molecular approaches attempt to pinpoint the causal variation to a particular location within the genome. Candidate gene approaches require background knowledge of the mechanism of the trait of interest, and attempt to examine variation in a particular gene in relation to the trait or function of interest. In the case of chemosensory receptors, an example of this approach would be the examination of variations in putative odorant receptors in relation to olfactory ability (e.g. (Keller, Zhuang, Chi, Vosshall, & Matsunami, 2007)). Genome-wide association studies (GWAS) are slightly different from the candidate gene approach in that they do not require *a priori* knowledge. Rather, the phenotype or clinical outcome (for example, detection threshold) is examined in relation to thousands of variants on a microarray. Variants that associate with the measure of interest are identified, independent of theory or biological mechanism. Not all variants are examined, as some polymorphisms are in linkage disequilibrium (LD) with others. LD refers to the phenomena where loci that are in close proximity on the same chromosome are often inherited together. This means that one individual polymorphism may be highly predictive of others (i.e. the polymorphisms not statistically independent). These patterns can be exploited to make the process more efficient, as it means a smaller number of variants can be tested, if they are known to predict other unmeasured variants (Wilkening, Chen, Bermejo, & Canzian, 2009). However, due to the large number of individual mutations being tested, the chance of false-positives remains quite high. Accordingly, the correction of multiple comparisons means that an extremely small p-value is required to declare a relationship exists. However, this adjustment also means that a true association can sometimes be missed, which is where a candidate gene or candidate polymorphism approach has an advantage, as they are biologically informed rather than atheoretical like GWAS. Each approach has advantages and disadvantages, and both contribute to our understanding how genetic variation contributes to a specific trait of interest.

3. Brief Refresher on Receptor Biology

The lock-and-key model was proposed in 1894 by Emile Fisher to describe enzyme specificity, and it is still a useful way to conceptualize how molecules (ligands) bind to and activate chemoreceptors. Chemoreceptors are found in the mouth, nose and throat, serving as binding sites for myriad volatile and non-volatile chemicals in our environment. Transduction events mediated by these receptors cause signaling cascades that culminate in sensations of taste, smell and irritation. These receptors are made of proteins encoded by genes scattered across multiple chromosomes. Inherited variations in these genes may lead to differences in the translated protein, altering the functionality of the receptor, which may lead to either impaired or enhanced perception of individual chemicals across different people.

3.1 DNA to proteins

The sequence of nucleotides (A,G,C and T) in DNA (Deoxyribonucleic acid) is extremely similar across all humans (i.e., generally conserved), and any two unrelated individuals share about 99.9% of their respective genomes (Feuk, Carson, & Scherer, 2006). The `central dogma of molecular biology' originally advanced by Francis Crick is

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[1]PCR is the Polymerase Chain Reaction, which makes it possible to amplify DNA. Kary Mullis and Michael Smith shared the 1993 Nobel Prize in Chemistry for their work on PCR.

straightforward: DNA is read in groups of three nucleotides called codons, and these codons are transcribed to an intermediary molecule, Ribonucleic Acid (RNA). RNA is then translated to one amino acid, and the amino acids are joined together to form proteins.

Transcription of DNA into RNA is catalyzed by the enzyme RNA polymerase, which binds to the gene promoter. The promoter is a regulatory region of the gene that binds molecules that activate or repress transcription downstream of the promoter. Genes typically contain regions of introns and exons, and only the exons are expressed as proteins. The DNA double helix is opened into two strands: the sense strand and the antisense strand, and it is the antisense strand that is used as the template from which the complementary messenger RNA (mRNA) molecule is copied, resulting in an RNA molecule (strand) which contains the same information as the other `sense' strand of DNA. This RNA strand is then modified to remove the non-protein-coding introns, and join the exons together, in a post-transcriptional process known as splicing. It is possible to splice different areas of exons together, giving different `splice variants' which generate different forms of a protein (known as isoforms). This allows a single gene to encode more than one protein.

After splicing, mRNA forms a complex with tRNA (transfer RNA) and a ribosome. tRNA molecules recognize specific codons on the mRNA and bind specific amino acids. A peptide bond to the next amino acid is formed and the tRNA molecule moves on to the next codon to join another amino acid. Thus, a chain is formed, ending when a stop codon is reached.

3.2. Genetic differences across individuals: SNPs, Alleles, Haplotypes and CNVs

Spontaneous mutations may arise anywhere in the DNA, causing a change in the amino acid sequence. When such changes are inherited, and are consistently found in the population, they may be referred to as a single nucleotide polymorphism (SNP; pronounced snip). That is, a polymorphism (from Greek, meaning `many forms') is a specific location in DNA where more than one stable form exists across the population. The less common form is called the minor allele, and the proportion with which it occurs is known as the minor allele frequency (MAF). When there is linkage disequilibrium (LD) across multiple SNPs (see previous section), small groups of alleles may be inherited together such that the probability of having one allele is not statistically independent of the probably of having another nearby allele. When groups of alleles on a single strand are inherited this way, it is known as a haplotype. As DNA is double stranded, a pair of haplotypes forms a diplotype, much in the same way a pair of alleles form a genotype.

Depending on where in a codon the change is found, SNPs may result in the translation of a different amino acid. (A SNP does not always lead to an amino acid change, due to redundancy in amino acid coding. When this occurs, it is called a synonymous SNP; conversely, when a nucleotide change results in an amino acid change, it is termed a non-synonymous SNP.) The incorporation of a different amino acid in a polypeptide sequence can alter the function of the resultant protein in several different ways. If the change occurs in the binding pocket, this can affect the ability of the receptor to bind to the chemical (ligand). In the case of taste receptor proteins, the function of the receptor may be reduced or enhanced in different people (e.g., (Bufe, et al., 2005; Duffy, et al., 2004)).

SNPs in noncoding regions, such as promoter regions, can also affect receptor function. One example of this is the differential variation in sweet taste perception that is attributed to SNPs located in the promoter region of the TAS1R1 gene (Fushan, Simons, Slack, Manichaikul, & Drayna, 2009). There is also evidence suggesting SNPs within the promoter region of the gustducin gene (*GNAT3*) are responsible for some of the variation in sweet perception, although this is yet to be confirmed (Fushan, Simons, Slack, & Drayna, 2010).

Copy number variation (CNV) is another way in which the expression levels of genes and their resultant proteins can vary. Defined as sections of DNA longer than 1kb that are present in variable copies in a genome versus a reference genome, CNVs are stable, inheritable variations that occur when sections of DNA are repeated or deleted, (CNVs can arise through a variety of processes (reviewed by (Hastings, Lupski, Rosenberg, & Ira, 2009)). These can occur in a segment of a gene, one gene or multiple genes. In the case of chemoreceptors, variations in copy numbers can lead to differential expression of receptors, and variation in an individual's capability of detecting the sensation. A high degree of the variation in copy number (as much as 68%) occurs in areas encoding chemoreceptors (Wong, et al., 2007). This estimate suggests that copy number variations may be an important source of individual differences in chemosensation. Indeed, much of the variation in odor receptor (OR) genes are CNVs, and these can differ greatly from person to person. One recent investigation into CNV and smell demonstrated that the person with the greatest number of odorant receptors had 77 more receptors than the person with the fewest (Waszak, et al., 2010) (cited in Keller, 2011). Evolutionary biologists have theorized that the large variation in copy number in OR genes may have arisen from an initial expansion of the repertoire in response to the movement from sea to land, in order to detect air-borne odorants. Then, following the development of trichromatic vision, the sense of smell became less important, lowering the functional constraint on the OR genes, and thus humans have fewer intact copies than a number of other mammals. It appears humans may have undergone two separate `relaxation of constraint' events: old world monkeys and primates (trichromatic vision) have more pseudogenes than new world monkeys (Gilad et al 2004, Liman, 2012), and humans have more pseudogenes than old world monkeys and apes (Gilad et al 2003, Liman, 2012). However, individual differences in copy number variation are an area that has not generally been well-studied, and very few CNVs have been functionally characterized. Thus, the remainder of the text below will primarily focus on other polymorphisms, mostly SNPs, that have been shown to influence chemosensation.

The following sections summarize some of the current knowledge on genetic variation in chemosensation with a particular emphasis on taste, as it is the best studied and understood to date.

4. Bitter Taste Differences

Variable bitter taste perception is the best-known example of genetic variation in oral sensation. In this section, we review the prototypical example as it relates to ingestive behavior, and then discuss several other more recent findings.

4.1 TAS2R38

The genetic basis for variability in the perception of bitterness was first demonstrated over 8 decades ago (Blakeslee, 1932). The idea that this variation might be driven by natural selection to avoid ingestion of bitter plant toxins is almost as old (see (Wooding, 2006; Wooding, et al., 2010) for reviews). A putative association between human food choice and genetic variation came later (e.g. (Fischer, Griffin, & Kaplan, 1963; Glanville & Kaplan, 1965)). In 2003, the molecular genetics underlying this long studied trait were finally uncovered (Kim, et al., 2003), and influences on ingestive behavior were documented almost immediately (Duffy, et al., 2004). Comprehensive reviews have recently been published on *TAS2R38* variation and food choice (Feeney, 2011; Tepper, 2008) so we will only present a few examples here.

4.1.1 Molecular Genetics of TAS2R38—In 2003, Kim and colleagues mapped the ability to detect the thiourea (N-C=S) drug phenylthiocarbamide (PTC) to the *TAS2R38* gene (HGNC: 9584; formerly *PTC*) on chromosome 7 (Kim, et al., 2003). They reported 3

SNPs that form two common haplotypes (Proline–Alanine–Valine, and Alanine–Valine–Isoleucine), and associate with individual differences in detection thresholds. These haplotypes are named for the amino acid substitutions Ala49Pro, Val262Ala, and Ile296Val. The PAV haplotype is ancestral, conferring the ability to detect thiourea (N-C=S) compounds while the AVI variant is less functional. Shortly thereafter, this finding was extended to beyond threshold phenotyping to include suprathreshold bitterness of propylthiouracil (PROP) (Duffy, et al., 2004), the other thiourea compound commonly used in taste research. Subsequently, the ability of PROP to activate hT2R38 was demonstrated *in vitro*, and differences in suprathreshold bitterness were confirmed *in vivo* (Bufe, et al., 2005). For a discussion on the difference between threshold and suprathreshold measurement and their respective phenotypes, see (Duffy, Hayes, Bartoshuk, & Snyder, 2009; Hayes & Keast, 2011).

The concept of supertasting is thoroughly intertwined with PROP bitterness, both in the public consciousness, and in the scientific literature (e.g (Bartoshuk, Duffy, & Miller, 1994)). However, it is important to note that elevated chemosensory response across diverse stimuli – the modern understanding of supertasting – can be separated from the definition based on PROP bitterness (Hayes & Keast, 2011). Critically however, *TAS2R38* variation does *not* explain supertasting (Hayes, et al., 2008). Thus, it is inappropriate to talk about `genetic supertasters', either in reference to PAV homozygotes or in general. Detailed discussion of generalized supertasting (hypergeusia) (Hayes & Keast, 2011) and the influence of supertasting on ingestive behavior are beyond the scope of this review, and can be found elsewhere (see (Duffy, 2007; Feeney, 2011)). In the following section, we focus on *TAS2R38* gene data as it relates to ingestive behavior.

4.1.2 TAS2R38 variation and alcohol use—The first evidence that *TAS2R38* variation associates with alcohol intake came in 2004, when Duffy and colleagues reported annual alcohol intake (based on a summed quantity-frequency measure) associated with *TAS2R38* diplotype in a cohort of primarily European ancestry (Duffy, et al., 2004). Specifically, PAV homozygotes consumed less alcohol than heterozygotes, who consumed less that AVI homozygotes, Notably, intake was heteroscedastic across the groups as *TAS2R38* diplotype appeared to provide a ceiling, but not a floor; some individuals consumed little or no alcohol regardless of diplotype, but the heaviest drinking PAV homozygote still consumed far less than the heaviest drinking AVI. This finding was generally confirmed in a separate cohort of European-Americans when Hayes et al. reported that both intake frequency of alcoholic beverages and total alcohol intake differed by *TAS2R38* diplotype (Hayes, et al., 2011). However, unlike the earlier cohort described by Duffy and colleagues, the intake of heterozygotes was not intermediate between the two homozygous groups. Thus, it is unresolved as to whether the effect of *TAS2R38* variation on alcohol intake is dominant or additive. In a cohort of head and neck cancer patients who were predominantly white (presumably European American ancestry), Dotson and colleagues (Dotson, Wallace, Bartoshuk, & Logan, 2012) found the Ala49Pro SNP rs713598 was associated with frequency of consuming drinks containing alcohol and heavy drinking (defined as 6 or more drinks in a day), but not number of typical drinks consumed on a drinking day.

4.1.3 TAS2R38 variation and alcohol misuse and abuse—Wang and colleagues (Wang, et al., 2007) explored *TAS2R38* diplotype as a predictor of Maxdrinks in the Collaborative Study of the Genetics of Alcoholism (COGA) cohort. COGA is a large family based study consisting of alcoholics, their family members, and controls from the community (Edenberg & Foroud, 2006). In contrast to the retrospective frequency (Hayes, et al., 2011) and quantity-frequency (Duffy, et al., 2004) measures described above, the Maxdrinks phenotype is assessed by asking "What is the largest number of drinks you have

ever had in a 24-hour period?'). Thus, Maxdrinks is a quantitative trait measuring alcohol misuse rather than habitual use or a clinical diagnosis of dependence. In the COGA cohort, *TAS2R38* diplotype associated with Maxdrinks in African-Americans but not European-Americans (Wang, et al., 2007). Because Maxdrinks measures the heaviest lifetime consumption rather than typical alcohol intake, a failure to observe an effect among European-Americans does not directly contradict the results of Duffy et al. (2004) and Hayes et al. (2011). It is also worth noting however that environment can severely attenuate genetic influences on alcohol intake (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001), which suggests unmeasured environmental factors may partially explain differences across studies.

4.1.4 TAS2R38 variation and vegetable bitterness, liking and intake—Reports
linking *TAS2R38* variation to vegetable intake are mixed. In 2006, Sandell and Breslin reported glucosinolate-containing vegetables evoked more bitterness for PAV homozygotes than for heterozygotes, who reported more bitterness than AVI homozygotes (Sandell & Breslin, 2006), although they did not measure liking or intake. Since increased vegetable bitterness associates with lower intake (e.g.(Dinehart, Hayes, Bartoshuk, Lanier, & Duffy, 2006), it is not surprising three subsequent studies found significant relationships between *TAS2R38* variation and vegetable intake. In the Italian arm of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, PA_ carriers (heterozygotes and PA_ homozygotes) ate less cruciferous vegetables than AV_ homozygotes (Sacerdote, et al., 2007). In young adults in the Northeastern United States, Duffy and colleagues found *TAS2R38* haplotype associated with differences in intake across multiple assessment methods (Duffy, et al., 2010). Regardless of whether vegetable intake was estimated via 5 nonconsecutive food records, or a retrospective food frequency questionnaire, the PAV carriers consumed fewer vegetable servings and ate vegetables less often than AVI homozygotes. Likewise, in an outpatient study of older postmenopausal Brazilian women, Pro49 allele homozygotes were more likely to be non-consumers of bitter vegetables like chard and arugula (Colares-Bento, et al., 2012). However, not all studies support an association between *TAS2R38* variation and vegetable intake (Gorovic, et al., 2011; Timpson, et al., 2005); the reasons for these null findings are unknown, but may relate to cultural foodways and habits that override genetic influences of liking and intake. Notably, there is a gap in the literature regarding hedonic response: no one has tested whether *TAS2R38* variation explains differences in *liking* of sampled vegetables. However, this would seem to be a reasonable assumption, given the large body of evidence linking vegetable bitterness, liking and intake with thiourea phenotypes (see (Feeney, 2011) for a review).

4.2 TAS2R16

4.2.1 Evolutionary basis and molecular genetics of TAS2R16 variation—
Receptors encoded by the *TAS2R16* gene (HGNC: 14921) are relatively narrowly tuned, responding primarily to compounds containing a beta-glucopyranoside moiety such as salicin, amygdalin and other similar plant derived compounds (Bufe, Hofmann, Krautwurst, Raguse, & Meyerhof, 2002; Meyerhof, et al., 2010). Plants that produce cyanogenic glucosides do so to protect themselves against herbivores, as enzymatic cleavage of these compounds liberates cyanide. Presumably, there was strong evolutionary pressure to detect beta-glucopyranoside containing compounds. The human *TAS2R16* gene contains several polymorphic loci, two of which give rise to nonsynonymous amino acid substitutions; critically, one of these altered residues enhances receptor activation *in vitro* (Soranzo, et al., 2005). The Lys172 variant is more responsive to natural plant-derived toxins than the ancestral Asn172 variant, suggesting positive selection may have occurred to help early humans avoid cyanogenic toxins (Soranzo, et al., 2005). Notably, the less responsive

Asn172 is more common in individuals of African ancestry compared to those of European or Asian ancestry, the vast majority of whom carry the Lys172 allele. Similar small changes in *TAS2R16* also explain differences in beta-glucopyranoside response across species (Imai, et al., 2012).

4.2.2 TAS2R16 variation and alcohol intake in humans—In addition to differential response to beta-glycopyranosides *in vitro* and *in vivo*, clinical and laboratory data have implicated polymorphisms in or near *TAS2R16* in alcohol use and abuse. *TAS2R16* is proximal to a region on chromosome 7 repeatedly implicated in alcohol dependence in the Collaborative Study of the Genetics of Alcoholism (COGA) cohort via genome wide association. Given this proximity, Hinrichs and colleagues explored whether *TAS2R16* contains additional loci associated with alcohol dependence (Hinrichs, et al., 2006). They found the coding SNP rs846664, which results in the Asn172Lys substitution described above, associates with alcohol dependence across multiple diagnostic criteria. As the minor allele frequency of Asn172Lys varies dramatically across ancestry (MAF of 0.6% for European-Americans versus 26% for African-Americans), the clinical relevance of this SNP is mostly restricted to those of African ancestry, although non-African individuals who carry the Asn172 allele are also at higher risk for alcohol dependence. Subsequent analysis extended this association to include the Maxdrinks phenotype (see section 4.1.3), which is a separate phenotype based on alcohol use history rather than a diagnosis of dependence (Wang, et al., 2007).

Associations between alcohol abuse and variation in bitter taste are presumably due to protective effects on habitual intake, and these effects may transient, operating only during critical developmental windows. For example, phenotypic markers of TAS2R variation predict beer intake, but only during the first year of drinking (Intranuovo & Powers, 1998). Likewise, modeling of gene-gene interactions suggest bitter taste genes may act as a stage gate for other genetic risk factors; that is, if you never learn to drink alcohol because of an aversive taste, other risk alleles may be largely irrelevant (Mustavich, Miller, Kidd, & Zhao, 2010). Thus, our group and others have explored the potential role of other SNPs near this region as predictors of alcohol use, rather than abuse. Unlike the rs846664 SNP described above, the rs846672 SNP has a much higher Minor Allele Frequency in European-Americans (28%), and is located 4.5 kilobases downstream from *TAS2R16*. In a laboratory study where self reported alcohol intake was collected using a validated semiquantitative food frequency questionnaire, this SNP was a significant predictor of both intake frequency and overall intake in a cohort of primarily European ancestry (Hayes, et al., 2011). The high intake group drank alcohol twice as frequently as the low intake group. Although rapid progress has been made on the structure function relationships for hT2R16 and its' ligands in the past 5 years (eg (Meyerhof, et al., 2010; Sakurai, Misaka, Ishiguro, et al., 2010; Sakurai, Misaka, Ueno, et al., 2010)), the basis for these behavioral data are unknown, as ethanol has not been tested as an agonist in cultured cell expression systems.

4.3 TAS2R31

4.3.1 Bitterness of sulfonyl amide sweetners—In spite of strong consumer demand for sweetness in the absence of calories, the utility of non-nutritive sweeteners is often impaired by undesirable side tastes. The sulfonyl amide sweeteners saccharin and acesulfame potassium (AceK) have a concentration-dependent bitter side taste that varies across individuals (Horne, Lawless, Speirs, & Sposato, 2002; Schiffman, Booth, Losee, Pecore, & Warwick, 1995; Schiffman, Reilly, & Clark, 1979). As might be expected, this variable bitterness predicts acceptability (Kamerud & Delwiche, 2007).

4.3.2 Variation in TAS2R31 and sweetener bitterness—The genes *TAS2R31* (HGNC: 19113; formerly *TAS2R44*) and *TAS2R43* (HGNC: 18875) are part of a highly related subfamily of 5 *TAS2Rs* located on chromosome 12. Their role in perception of saccharin and AceK bitterness was first identified in 2004 (Kuhn, et al., 2004). Expressing these genes in embryonic kidney cells resulted in calcium influx when the cells were treated with saccharin, AceK, and aristolochic acid, a purely bitter toxin found in plants in the Birthwort family (Kuhn, et al., 2004). Using saccharin and aloin (from aloe), Pronin and colleagues demonstrated the presence of Tryptophan at amino acid residue 35 in hT2R31 (Arg35Trp) associates with increased receptor activation *in vitro* and lower recognition thresholds *in vivo* (Pronin, et al., 2007). Subsequently, Roudnitsky and colleagues explored these genes and other related *TAS2Rs* on chromosome 12, generating long-range haplotypes across these genes (Roudnitzky, et al., 2011). One common haplotype (out of seven common haplotypes) associated with the bitterness of AceK and saccharin. By mutating individual amino acid residues in artificial chimeric receptors *in vitro*, they demonstrated the Arg35Trp (R35W) polymorphism in *TAS2R31* was causal. Notably, however, they also found that other mutations in *TAS2R31* abolished the ability of hT2R31 to respond to AceK and saccharin, even when tryptophan was present at position 35. Notably, the studies described above generally (but not exclusively) use threshold methods to define human taste phenotypes. Data from our laboratory confirms that polymorphisms in *TAS2R31* also explain differences in the perceived intensity (suprathreshold bitterness) elicited by AceK (Allen, McGeary, Knopik, & Hayes, 2013), but not RebaudiosideA (Allen, McGeary, & Hayes, 2013).

Other compounds known to activate hT2R31 in functional expression systems include amarogentin, arborescin, arglabin, caffeine, chloramphenicol, falcarindiol, grossheimin, helicin, quinine, cromolyn, denatonium benzoate, and diphenidiol (Meyerhof, et al., 2010). However, just because a compound is known to activate hT2R31 receptors encoded by *TAS2R31* does not imply perception of these compounds will vary across individuals, as the 25 *TAS2Rs* found in humans appear to include substantial functional redundancy. For example, diphenidiol activates 15 different hT2Rs and quinine activates 9. Thus, individuals who express low-functioning hT2R31 variants may still have a normal phenotype if functional recovery is provided by another redundant receptor. The question of whether *TAS2R31* variation predicts the acceptability of sulfonyl amide-sweetened beverages remains untested. Such studies will require large sample sizes and whole gene sequencing of multiple TAS2Rs to deal with the potential for functional recovery discussed above, and to account for a loss of function due to rare variants in *TAS2R31.*

4.4 A multigene haplotype on chromosome 7

4.4.1 Coffee Bitterness varies with a haplotype across TAS2R3, TAs2R4, and TAS2R5—Coffee bitterness appears to vary across a haplotype on *TAS2R3, TAS2R4* and *TAS2R5* (HGNC: 14910, 14911, and 19912, respectively), which are located close to each other on chromosome 7. In this region (7q31.3–q32), four SNPs (rs765007, rs2234001, rs2227264, rs2234012) form three common haplotypes: CCGT homozygotes (26% of individuals), heterozygotes (41%) and homozygotes TGAG (22%) (Hayes, et al., 2011). The TGAG homozygotes report twice as much bitterness as the CCGT homozygotes, and the heterozygotes also report significantly greater bitterness than CCGT homozygotes (Hayes, et al., 2011).

4.4.2 Coffee Liking and Intake may not vary with genetics—Notably, this haplotype did not predict coffee liking or intake among a cohort that was predominantly middle aged, presumably due to postingestive conditioning/learning over many years. The causal SNP for this variation in bitterness is unknown: two of the SNPs result in amino acid

substitutions (rs2234001 in TAS2R4, Val96Leu; and rs2227264 in TAS2R5, Ser26Ile) while the other two rs765007 (TAS2R3) and rs2234012 (TAS2R5) occur in the 5' untranslated region (5' UTR), potentially altering protein expression (Calvo, Pagliarini, & Mootha, 2009). Also, in the absence of *in vitro* verification that these SNPs are functional, it is possible none of them are causal, and are merely in linkage disequilibrium with an unknown causal polymorphism that is nearby. Given the absence of an effect on liking, one would not expect effects on intake; however, there is no data formally testing this relationship to date. Alternatively, this variation might predict liking and/or intake, but only in individuals that have not yet been conditioned to like coffee via repeated exposure to the positive post-ingestive effects associated with coffee intake (e.g. young adults who are still learning to drink coffee).

4.5 TAS2R19 polymorphisms appear to be functional

4.5.1 The rs10772420 SNP in TAS2R19 associates with quinine bitterness, grapefruit bitterness and grapefruit liking—Evidence that *TAS2R19* (HGNC: 19108; formerly *TAS2R48*) contains a functional polymorphism first emerged in 2009 when Duffy and coworkers (Duffy, Hayes, Sullivan, & Faghri, 2009) reported liking ratings for grapefruit juice in surveyed liking ratings for grapefruit juice varied with a SNP in *TAS2R48*. Subsequently, genome wide association by Reed and colleagues showed that the same SNP (rs10772420) explained variation in the bitterness of quinine (Reed, et al., 2010). The resulting amino acid substitution, Arg299Cys (rs10772420) accounted for a small but significant amount of the trait variance in the genome wide analysis, and the A allele (Cys299) was associated with greater quinine bitterness (perceived suprathreshold intensity) for both discovery and replication cohorts.

Subsequent evidence extended these findings to include sampled unsweetened white grapefruit juice (Hayes, et al., 2011). The Cys299 homozygotes (AA individuals) reported much greater bitterness than either heterogyzotes (AG individuals) or Arg299 homozygotes (GG individuals), who did not differ from each other. As would be expected from mixture suppression (Lawless, 1979), sweetness showed the reverse pattern, although the differences were not significant. This pattern of increased bitterness and decreased sweetness also had the expected effect on liking: the Cys299 homozygotes had significantly lower liking ratings that the Arg299 homozygotes. This is wholly consistent with prior work showing endogenous sweetness and bitterness make statistically independent contributions to grapefruit juice liking (Lanier, Hayes, & Duffy, 2005). However, it remains unknown whether these phenotypic differences are sufficient to influence the consumption of quinine containing beverages (i.e. tonic water), grapefruit or grapefruit juice.

Moreover, these data are somewhat complicated by evidence that neither quinine nor the grapefruit bitterants limonin and naringin activate hT2R19 receptors in functional expression assays in vitro (Meyerhof, et al., 2010). As is true with any association design, significant associations may result from linkage disequalibrium with other unmeasured polymorphisms. For example, Roudnitzky et al. (2011) recently demonstrated that while 30 SNPs across 5 distinct TAS2R genes all associated with AcesulfameK thresholds, this variation can be attributed to a single allele in a single gene (Arg35Trp in *TAS2R31*). Thus, it is possible the rs10772420 SNP in *TAS2R19* is not causal, but is merely acting as a tag SNP for another causal SNP on a nearby gene.

4.5.2 Recent molecular data provide new insights into older psychophysical data—Prior to the discovery of the *TAS2R* genes and their receptors, several studies explored the relationship between grapefruit bitterness and the bitter probe propylthiouracil (PROP), with conflicting results (Drewnowski, Henderson, & Shore, 1997; Smagghe &

Louis-Sylvestre, 1998). Drewnowski and colleagues found liking for grapefruit juice (surveyed) and sampled naringin (the predominant bitter flavonoid found in grapefruit) in water was significantly lower in those who found PROP to be the most bitter (Drewnowski, et al., 1997). As expected, the naringin bitterness-liking relationship and the PROP bitterness-liking relationship were both negative and significant, while the relationship between naringin liking and PROP liking was significant and positive. At the time, this led to the conclusion that the liking for grapefruit (and naringin) is therefore related to genetics underlying PROP variation. However, it is difficult to reconcile these data with modern molecular evidence. Specifically, PROP does not activate *TASR19* (Meyerhof, et al., 2010) and grapefruit juice bitterness does not differ by *TAS2R38* genotype (Figure 1; unpublished data from (Hayes, et al., 2011)). It may be that the relationship observed by Drewnowski and colleagues reflects some sort of generalized supertasting (i.e. hypergeusia; see (Hayes & Keast, 2011) rather than a specific effect of *TAS2R38* variation. Indeed, PROP bitterness (i.e., the phenotype) captures variation in suprathreshold intensity across qualities even after controlling for *TAS2R38* genotype (Hayes, et al., 2008). Notably, naringin has not been shown to activate *TAS2R19 in vitro* (Meyerhof, et al., 2010) but this may be due to technical difficulties with naringin as a ligand in heterologous expression systems, or the *TAS2R19* SNP acting as a tag SNP for another polymorphism.

In direct contrast to the Drewnowski data, Smagghe and Louis Sylvestre (Drewnowski, et al., 1997; Smagghe & Louis-Sylvestre, 1998) reported those who were less sensitive to PROP (via detection thresholds, not suprathreshold intensity) reported greater suprathreshold bitterness from sampled naringin. At the time, Bartoshuk speculated this paradoxical finding was due to a reversal artifact based on the choice of psychophysical scale (Bartoshuk, 2000). However, insight from modern molecular data provides another alternative explanation for these conflicting accounts; in the Smagghe study, the numbers of PROP tasters and nontasters phenotyped for naringin bitterness were quite small (n=20 in each group). If Cys299 carriers were overrepresented among the PROP nontaster group by random chance, this could have driven a spurious, `paradoxical' relationship with PROP. Ironically, had the situation been reversed (with Cys299 carriers being overrepresented in the PROP taster group, again by chance), this would have been seen as support for the prevailing paradigm at the time (that PROP bitterness should predict grapefruit bitterness). Collectively, this suggests earlier work on correlations between various bitter compounds in studies with small sample sizes need to be carefully reconsidered in light of strong evidence that bitter response/sensitivity to real foods is not a monolithic up or down trait (Hayes, et al., 2011), as illustrated by the data described throughout this section

5. Sweet taste Differences

Sweetness, like bitterness, is transduced via G-protein coupled receptors (GPCRs). The sweet receptor is a heterodimer formed from the protein products of two genes, *TAS1R2* and *TAS1R3*. Since the first sweetener-binding model was proposed in 1914, many different models of sweet receptor and ligand interactions have been proposed, which have evolved over time as the knowledge in this area has grown (See (DuBois, 2011; Hayes, 2008) for comprehensive reviews). The advancement of x-ray crystallography allowed molecular docking models and site-directed mutagenesis to identify three potential ligand-binding sites within the sweet receptor (Cui, et al., 2006). The most current model builds on these data, suggesting that 5 receptor sites within the T1R2/T1R3 dimer exist, for different structural classes of sweetener (Morini, Bassoli, & Temussi Piero, 2008). This model would also explain synergistic effects noted in some sweetener interactions (DuBois, 2011; Hayes, 2008).

SNPs in the genes encoding these binding-site regions could potentially affect receptor function, although no empirical evidence of this has been reported to date. However, as noted above, perceptual differences are not limited to SNPs within protein-coding regions of the genes, as recent evidence suggests that SNPs in the promoter regions of some genes may also affect the perception of sucrose.

5.1 TAS1R3 promoter SNPs may predict discriminability between low concentrations of sucrose

Fushan and colleagues (Fushan, et al., 2009) examined sucrose perception, asking 144 participants to rank the intensity a series of 9 sucrose solutions in an R-index task. Genetic analyses suggested that SNPs within the promoter regions of the *TAS1R3* gene (rather than the sequence associated with one of the ligand binding regions of the receptor) were associated with the measured phenotype (Fushan, et al., 2009). Specifically, two C/T SNPs (rs307355 and rs35744813) in the promoter region (situated at -1572 and -1266 upstream of the coding sequence respectively) were associated with altered sweetness perception. Individuals with T alleles at both loci had reduced sweetness perception compared to those who were homozygous for the C allele at both loci. The authors noted the two lower-sensitivity T alleles are more prevalent in African populations, and postulated a link with geographical location and availability of carbohydrate-rich plants in the survival of early humans. Plants such as sugar cane are more likely to grow in tropical climates, so higher sensitivity to sucrose may not have been as important for survival to these populations as to Europeans living in colder climates, where the sensitive form of the allele is more common. However, this work has not been replicated (Hayes, McGeary, Grenga, & Swift, 2010), and it remains to be determined whether this variation may influence liking or intake of sweet foods.

5.2 GNAT3 and sucrose intensity

Gustducin is a G-protein involved in the signaling of sweet, bitter and umami tastes; its release is thought to be triggered by tastant binding, to either hT1R or hT2Rs (Chandrashekar, Hoon, Ryba, & Zuker, 2006). *GNAT3*, located on chromosome 7, encodes a subunit of gustducin, and a number of SNPs have been identified within it that have been linked to differences in sucrose perception (Fushan, et al., 2010). This report, based on the same cohort and phenotyping strategy as their earlier 2009 report (144 participants and ROC analysis of scores of ranked sucrose solutions), suggests that in addition to the variation in sweet perception explained by SNPs in *TAS1R3*, additional variation can be explained by eleven SNPs in the gustducin gene. The most individually significant of these SNPs is rs7792845; because it is located 10 kb upstream of the coding region, it presumably modifies the promoter region of the gene. Again, there remains a knowledge gap as to whether this variation is sufficient to influence food liking or consumption of sweet foods.

5.3 Heritability of Variation in Sweet liking

Liking for sweetness is thought to be innate, not learned, as evidence shows that newborns increase their suck rate in response to increased sucrose concentrations, and young children relax in the presence of strange adults when sucrose is given (Maller & Desor, 1973). Although this preference for sweetness is instinctive, perception of sweetness can vary across people (e.g.(Hayes & Duffy, 2007), as can the level of sweetness that is preferred (e.g., (Hayes & Duffy, 2008; Lundgren, et al., 1978). Multiple studies suggest preference for sweet stimuli is heritable in both children and adults. Mennella and colleagues (2005) examined heritability of sweet preference in children and their parents and found that preference for sweet foods (cereals and beverages) was heritable, although they failed to observe a heritable component for sucrose solutions tested in the laboratory. In 4–7 year old children, a strong genetic component was found in the preference for different sweetened

grape solutions (Bretz, et al., 2006), while Keskitalo and coworkers (Keskitalo, Tuorila, et al., 2007) found roughly half of the variation in hedonic scores for a 20% w/v sucrose solution in adults aged 17–80 was attributable to genetic factors. However, the molecular basis of this heritability remains unknown, precluding the sorts of candidate gene and candidate SNP studies described above for bitterness. Notable, a region on chromosome 16 has been implicated in sweet preferences (Keskitalo, Knaapila, et al., 2007), but a specific gene was not identified and this region does not contain any genes known to be involved in taste.

5.4 Intake of Sweet Foods and Sugar

A strong genetic component has also been implicated in the consumption of sweet foods (Keskitalo, Knaapila, et al., 2007), and variations in non-oral chemoreceptors have been implicated in dietary intakes of sugar. For example, variation in *GLUT2*, a glucose transporter gene involved in glucose sensing in the brain, has been liked to sugar intakes (Eny, Wolever, Fontaine-Bisson, & El-Sohemy, 2008). However, only one report to date has linked variation in a sweet taste receptor to sugar intake. Eny and colleagues (Eny, Wolever, Corey, & El-Sohemy, 2010) examined dietary intakes in relation to two common SNPs in the sweet receptor subunit gene *TAS1R1*: Ile191Val (a variation in a potential ligand binding pocket) and Ser9Cys (a variation in a region believed to be important for signaling). They observed Ile191Val variation associated with dietary sugar intake in overweight individuals, with Val191 individuals consuming less daily sugar than their Ile191 counterparts. The mechanism through which this SNP is associated with intake is not yet known; one possibility is that this is a tag SNP, and simply linked to the functional SNP of interest. Alternatively, it is possible this SNP leads to a reduction in receptor function, requiring increased intake in order to get the same sugar `hit' as individuals with the fully functional receptor. Additional work is needed to both replicate these findings and to work out the putative mechanism by which they influence intake.

6. Influence of Polymorphisms on Umami Savory Sensations

Umami, from the Japanese word for deliciousness, describes the savory, meaty taste elicited by *L*-glutamate, first isolated from seaweed in 1908. The taste receptor for umami is a heterodimer encoded by the *TAS1R1* and *TAS1R3* genes (the hT1R3 protein is shared by the sweet and umami heterodimer complexes). The hT1R1/hT1R3 dimer is also stimulated by 5' ribonucleotides, and is therefore believed to have evolved as an indicator of dietary sources of amino acids. Evidence suggests that inter-individual perceptual differences exist for umami, with taste thresholds differing up to 5 fold (Lugaz, Pillias, & Faurion, 2002), and, similar to bitter taste perception, a fraction of the population can be described as `taste blind' to umami. Lugaz and colleagues (2002) estimate the prevalence to be approximately 4%, although this estimate should be used cautiously, as this is still a poorly studied trait. Shigemura and colleagues (Shigemura, Shirosaki, Sanematsu, Yoshida, & Ninomiya, 2009) examined 17 *TAS1R1* / *TAS1R3* SNPs in 254 Japanese subjects in relation to the detection thresholds for IMP (a purine nucleomonophosphate) and MSG, compounds known to elicit umami tastes. Eight of these SNPs were previously reported (Kim, Wooding, Ricci, Jorde, & Drayna, 2005), while 9 were new polymorphisms identified by Shigemura and coworkers. Of these, three SNPs, at amino acid residue 12 and 372 in *TAS1R1* and 757 in *TAS1R3* were deemed to be `common' and were investigated in relation to recognition thresholds. The *TAS1R1* SNP at position 12 was not significantly associated with umami perception, while the *TAS1R1* Ala372Thr SNP (rs34160967) appeared to be functional, with the 372Thr allele conferring increased sensitivity to umami. (This relationship was only significant for MSG and a mixture of MSG and IMP, but not for IMP alone). The *TAS1R3* Arg757Cys SNP (rs307377) also appeared to be functional for all umami tastants, with the Cys757 allele resulting in reduced function (higher thresholds). Considered together, these results led the

authors to conclude that the TAS1R1/R3 heterodimer may have separate binding areas for IMP and MSG, and that the *TAS1R3* 757 SNP may lie in the area for IMP while the *TAS1R1* 372 SNP may be important for MSG binding.

In Figures 2 and 3 data from Shigemura et al. are reanalyzed in `Low' and `High' threshold groups for MSG. In Figure 2, individuals with one or two copies of the Cys757 variant are over represented among the insensitive (high threshold) individuals. In Figure 3, Thr372 homozygotes are overrepresented in the MSG sensitive (low threshold) individuals. Moreover, it appears that these two SNPs are not in linkage disequilibrium, and they appear to have offsetting effects. That is, having the *TAS1R1* Thr372 (low) SNP and the *TAS1R3* Arg757 (normal) SNP pulls an individual's threshold down, while having the *TAS1R1* Ala372 (normal) SNP and the *TAS1R3* Cys757 (high) SNP pulls an individual's threshold up. Raliou *et al.*, (2011) confirmed this role of the Arg757Cys SNP in umami perception, via a heterologous system, and observed that the Cys757 variant reduced activation of the heterodimer in response to MSG. As with many of the examples detailed above, it is still unknown whether this variation is sufficient to influence liking or intake of glutamate rich foods.

7. Salty and Sour Taste – Minimal Evidence to Date

Variation in the perception of sour and of salt taste have not received the same degree of attention as the three GPCR mediated prototypical tastes. Twin studies suggest salt perception appears to be more dependent on environmental influences than genetic factors (Wise, Hansen, Reed, & Breslin, 2007). Additionally, salt preferences are strongly influenced by physiological state (Wald and Lesham 2003), and are more variable in women than men (Hayes, Sullivan, & Duffy, 2010), presumably due to hormonal cycling. Other studies have demonstrated that sensory habituation to high sodium levels may increase the liking of high-sodium foods (Bertino, Beauchamp, & Engelman, 1982; Blais, et al., 1986). Collectively, difficulty in defining a stable phenotype for salt taste or preference impairs the ability to explore genetic variation, and it suggests any genetic influences on ingestive behavior may be swamped by environmental factors. Indeed, previous twin studies have failed to observe any heritablity for either salt taste or preference (Greene, Desor, & Maller, 1975). Nonetheless, very recent data suggest that variations in *TRPV1* and *SCNN1B* may influence the perception sodium chloride (Dias, et al., 2013). This is a very new area of research and if replicated, it is unknown whether such variation is sufficient to alter liking or intake of salty foods.

Likewise, relatively little is known about genetic influences on sour taste perception, or differences in liking or intake of sour foods. Twin studies suggest a substantial amount of the variance in citric acid thresholds can be attributed to genetic factors (Wise, et al., 2007); whether this is due to receptor differences, or other factors like salivary buffering capacity is unknown. Also, sour taste liking is quite variable, but there does not appear to be a strong relationship between sourness intensity and affective response to sour foods (Liem, Westerbeek, Wolterink, Kok, & de Graaf, 2004; Tornwall, et al., 2012). A candidate sour receptor PKD2L1 has been identified (Ishimaru, et al., 2006), but knocking out the PKD2L1 gene in mice reduces but does not eliminate sour taste response (Horio, et al., 2011), suggesting other unknown receptors also play a role in mammaliam sour taste.

8. SNPs in the Gustin (CA6) gene may have non-quality specific effects on taste

Gustin, a zinc metalloprotein, is thought to be a trophic factor involved in the development of taste buds (Henkin, Martin, & Agarwal, 1999). Variations in the gustin gene *CA6* were

recently reported to associate with some of the bitterness of PROP (Calo, et al., 2011). As mentioned above in section 4, most of the observed variation in PROP bitterness can be explained by variation in the *TAS2R38* gene (Bufe, et al., 2005; Kim, et al., 2003; Prodi, et al., 2004); the remainder of the unexplained variation may be due to other unknown factors that may or may not have a genetic basis. Some authors have postulated that either the density or total number of fungiform papillae may account for the remainder of the unexplained variation, but reports have been inconsistent. Recent work by Calo and colleagues (Calo, et al., 2011) revisits the idea that differences in tongue anatomy are involved in differences in taste perception. They observed a SNP within the gustin (*CA6*) gene (HGNC: 1380) were also associated with PROP bitterness intensity. An A>G substitution at base pair 31479 (rs227433) explained additional variance in PROP bitterness after accounting for effects of *TAS2R38*; the major allele `A' was associated with PROP sensitivity, and the `G' was associated with nontasting. When both *TAS2R38* haplotypes and the gustin SNP were combined, they accounted for just under 60% of the variation in PROP response in their sample, suggesting additional unknown factors still play a role. It is thought that the variation in this gene affects the zinc-binding capacity in the resultant protein (Padiglia, et al., 2010) and thus the AA form allows zinc to fully bind. An individual's nutritional status in relation to zinc is a possible regulatory factor that could also potentially explain some of the variation in PROP response.

Because the putative nature of this link with taste perception occurs via a mechanism is not limited to bitterness alone, variations in the gustin gene could be important for taste function in general. More work is needed to determine whether gustin SNPs associate with variation in fungiform papillae density, or with the perceived intensity of other tastants. Further research is also needed to determine whether variation in the gustin gene influences food liking or intake.

9. Tactile Sensations

9.1 Creaminess perception

Creaminess is an important quality in many types of foods, and these sensations can arise from varying levels of fat or starch in a food. Chocolate and ice cream are two highly liked foods, and part of their appeal has been linked to their dynamic texture as they melt in the mouth (Hyde & Witherly, 1993). As they melt, they decrease in oral viscosity, and the degree of this `thinning' in viscosity is linked to their perceived creaminess and to consumer sensory acceptance (Prindiville, Marshall, & Heymann, 1999; Prindiville, Marshall, & Heymann, 2000).

9.1.1 Copy number variation in the salivary amylase gene—Differences in perceived creaminess have been associated with levels of salivary alpha amylase. The glucose monomers in starch are connected by 1,4- glycosidic bonds, which are cleaved by amylase while food is chewed. Salivary alpha amylase (a protein) is encoded by the *AMY1* gene, and there is substantial variation in the number of copies of this gene an individual has, ranging from 2 – 15 diploid copies. The concentration of oral salivary amylase is proportional to the number of copies, and it is hypothesized that the greater the enzyme concentration in saliva, the faster these bonds are broken. This copy number variation appear to have arisen in evolutionary response to differing levels of starch in the diet of different populations (Perry, et al., 2007). Subsequently, Mandel and co-workers ((Mandel, Peyrot des Gachons, Plank, Alarcon, & Breslin, 2010) demonstrated that individuals with copy number variation (CNV) of the *AMY1* gene had different levels of salivary amylase present, and that perception of viscosity thinning of an oral starch sample over time was related to the level of oral amylase, although they were unable find evidence directly associating the number of copies of the *AMY1* gene. As with any meditational variability, the lack of a

direct effect may simply result from a lack of power. The degree to which CNV in *AMY1* associates with liking of creamy starch based foods, or selection of a diet high in starchy foods remains unknown, and requires further study.

9.1.2 TAS2R38 variation and creaminess—Other genetic factors may also be involved in creaminess perception. For example, is evidence that fungiform papillae density, which can vary from person to person, plays a role in perceived creaminess from different foods, such as salad dressing (Tepper & Nurse, 1997). Because papillae density associates with PROP bitterness, and PROP bitterness associates with *TAS2R38* genotype, this has led some investigators to suggest potential associations between creaminess perception and variation in *TAS2R38*. However, more recent data indicate that fungiform papillae density is independent of *TAS2R38* (Hayes, et al., 2008), suggesting that reports linking creaminess and PROP bitterness (Hayes & Duffy, 2007; Tepper & Nurse, 1997) may have been due to PROP being a marker for overall taste intensity (hypergeusia) (Hayes & Keast, 2011), and not due to variation in *TAS2R38*. This is an important illustration of the distinction between genotype and phenotype, raised in section 2.1. Many studies indicate elevated PROP bitterness associates with perceived creaminess, and many other studies indicate PROP bitterness is largely (but not entirely) determined by *TAS2R38* genotype. However, hT2R38 is a narrowly tuned bitter taste receptor, so there is no simple, biologically plausible mechanism by which *TAS2R38* genotype should influence creaminess perception. Thus, the ability of PROP bitterness (the phenotype) to predict creaminess is likely due to other factors independent of *TAS2R* genetics.

9.2 Astringency

Astringency is a sensation described as a drying and/or puckering of the mouth, often caused by consumption of the naturally-occurring plant flavonoid phenols such as tannins (Lee & Lawless, 1991), which are present in many common beverages like tea, coffee, wine and beer. When such beverages are consumed, the tannins bind to salivary proteins within the mouth, causing aggregation, and leading to the perception of a dry mouth (Kallithraka, Bakker, & Clifford, 1998). This sensation can lead to the rejection of beverages in some consumers (Lesschaeve & Noble, 2005).

9.2.1 Differences in salivary protein content influences astringency perception and liking of high tannin foods—Individuals may differ in their levels of salivary protein, which affects the amount of astringency they perceive from tannic acid (Horne, Hayes, & Lawless, 2002). The degree of perceived astringency may be a strong driver of preference and liking in many cases. Dinella and colleagues (Dinnella, Recchia, Tuorila, & Monteleone, 2011) grouped individuals into low, medium and high responders, based on their salivary protein content, and the high responder group reported significantly more astringency from apple, grape and carrot juices containing added tannic acid, compared to the low and medium responders. Across all three juices, liking scores also differed by responder group. Nor were differences limited to sampled beverages with manipulated tannin content; in the same study, preference for raw chicory was also lower in the high responder groups, and food such as ripe pear and banana, which elicit less astringency, were more liked.

Critically, the mechanisms underlying these differences in astringency perception may be genetic; a recent Finnish study in monozygotic and dizygotic twins measured salivary protein levels, and sensory responses to tannic acid spiked and control (unspiked) apple juice (Tornwall, et al., 2011). Their data suggest the level of salivary protein is genetically determined, and liking and frequency of use of astringent foods are heritable. Notably, they used naïve assessors and ask them to rate the `intensity' of a tannic spiked apple juice versus

unspiked juice; the term `astringency' was not mentioned or defined for participants. Presumably, similar results would be obtained from assessors trained to evaluate astringency. Unfortunately, as with any twin design, the biological basis of this variation is unknown, and no candidate genes have been identified thus far.

Astringency perception may also be dependent on salivary flow rates, which also vary across individuals (Horne, Hayes, et al., 2002; Lesschaeve & Noble, 2005). For example, individuals with low salivary flow rates rated wine as more intensely astringent, and found that the astringency lasted for a longer time than high-salivary flow individuals for the same wine samples. Although other studies have shown similar results in red (Ishikawa & Noble, 1995) and white wine (Fischer, 1994), not all studies agree (e.g (Guinard, Zoumas-Morse, & Walchak, 1997)). It is possible that these different results could stem from a lack of a clear, universal definition of astringency. Methodological issues in the measurement of astringency pose a further problem, as this sensation builds up over time during sampling. Furthermore, astringency from beverages depends on the food with which they are eaten (Less & Noble, 2005). This emphasizes highlights the point that high quality psychophysics are needed to define phenotypes, and that subtle variation across labs can potentially obscure effects. It remains unknown whether salivary flow rates are heritable, and if it is, what the genetic basis of this variation is. Given observed differences in perception as a function of flow rates, this would seem to be a fruitful area for future research.

10. Odor

Neurons that are present in the olfactory epithelium transmit electrical impulses when the receptors they express are stimulated (Hasin-Brumshtein, Lancet, & Olender, 2009). Each neuron expresses one odorant receptor (OR) gene, monoallelically (Chess, Simon, Cedar, & Axel, 1994). These are transmitted to synaptic complexes, and each stimulus (odorant) is a unique combination of activated units (Hasin-Brumshtein, et al., 2009). Early work hypothesized that smells were interpreted through a `primary' or fundamental odor system (Amoore, 1977). Today, it is apparent that the relationship between odorants and ORs is complex (multiple ORs bind can recognize one odorant molecule, and multiple molecules can be recognized by one OR). Due to the complicated nature of this relationship, current data supports a cross fiber patterning model, which suggests primary odors do not exist (Niimura, 2012).

Although the pathway of odor perception has not yet been fully elucidated, it is clear that sensory `blindness' to certain compounds is not limited to taste; some compounds which are strong-smelling to some individuals appear odorless to others. This phenomenon has been termed `specific anosmia' (Amoore, 1977), and is known to exist for a variety of different stimuli. Early evidence for this came from Blakeslee, who showed that when presented pink and red verbena flowers, approximately 1/3 of those tested could smell only the pink flowers, while the remainder could only smell the red flowers (Blakeslee, 1918). Another, somewhat infamous, example is that of the smell from butyl mercaptan, a compound similar to that of the foul-smelling odor emitted by a skunk, which is odorless to a fraction of the population (Gates, 1946, cited in (Patterson & Lauder, 1948). Initial genetic studies indicated that specific anosmias were hereditary, and they were inherited as a recessive characteristic (they also suggested a second type of anosmia, `delayed onset', which appeared to be inherited as a dominant trait) (Patterson & Lauder, 1948). The genetic basis for specific anosmia may arise from mutations in receptor genes involved in the different odors, although to date, only few examples have been characterized.

Odorant receptors are encoded by a superfamily of OR genes, one of the largest gene repertoires in the human genome. To date, 851 OR genes have been identified in humans, of

which just approximately 384 are known to be functional (Zhang & Firestein, 2009). The remainder are pseudogenes: pseudogenes are genetic sequences which have most of the characteristics of a gene but which have a disabling feature such as a frameshift or stop codon in the coding sequence, or are missing a promotor region. They are generally believed to be genes which have lost their function over time due to relaxation of selective pressure. In ORs, these loss-of-function events are thought to have occurred relatively recently, and thus, there is substantial variation in the level of inter-individual OR gene functionality (Menashe, Man, Lancet, & Gilad, 2003; Zhang & Firestein, 2009). That is, the number of psuedogenes may vary from person to person – currently at least 60 loci known to exist, the true number is likely to be higher and will be determined as further individual genomes are sequenced. Although it is currently unknown if differences in pseudoegenization lead to differential olfactory sensitivity, phenotypic variation in the sense of smell is commonplace. This may be driven by Copy Number Variation, which is particularly high in the OR gene family compared to the rest of the genome and is responsible for most of the inter-individual *genomic* variation. Because these patterns are observed in mammals with trichromatic vision, this has lead to speculation that this is an evolutionary relic from the corresponding reduction in the functional constraint on the sense of smell. That is, as color vision evolved, smell became less important for survival.

Few CNVs have been functionally characterized in relation to olfactory ability and as such, SNP variations account for some of the classic examples of olfactory anosmia (e.g., OR7D4 and androstenone) (Keller, et al., 2007). Another classic example is the perception of methanethiol, an odorous metabolite found in the urine of some individuals after asparagus consumption. Detection of this compound is associated with a SNP near the odor receptor gene OR2M7 (Eriksson, et al., 2010). Other specific anosmias are thought to have a genetic basis, but here we focus on several examples especially relevant to food. Data on isovaleric acid (cheesy) and urinary metabolites of asparagus are reviewed elsewhere (Newcomb, Xia, & Reed, 2012).

10.1 Androstenone and OR7D4

Androstenone is a steroid derived from testosterone, which elicits a strong odor in some individuals. The ability to smell androstenone varies across people; some describe it as `foul smelling', `urinous' and `sweaty', while others report it is `sweet-smelling' or `floral', and finally, to some, it is undetectable. Early work showing differences in androstenone detection thresholds between monzygotic and dizygotic twins suggested this was a genetically determined trait (Wysocki & Beauchamp, 1984). A recent study in a sample of Finnish twins examined responses to a range of odors, which included androstenone and isovaleric acid, along with chocolate, cinnamon, turpentine, and isovaleric acid (Knaapila, 2008). Their data suggest the environmental factors influencing odor perception (of the tested odorants) was stronger than the genetic component. However, all the odors were lumped together in this model, and this approach does not speak to individual genes or polymorphisms, which are the primary focus of this review.

Conversely, a GWAS approach conducted in 2007 indicated that SNPs in the OR receptor gene OR7D4 are partly responsible for differential ability to smell androstenone (Keller, et al., 2007). Two amino acid changes within OR7D4, R88W and T133M, alters the ability to detect androstenone, and a closely related compound, androstatiedone. The `R' form at position 88 and the `T' form at position 133 are associated with normal perception, while the `W' and `M' forms respectively are associated with impaired androstenone detection. Together, these substitutions account for approximately 40% of variation in the ability to smell androstenone.

Of specific relevance to food, androstenone is produced by male pigs (boars), and is often present in their skin, leading to a pork defect known as ` boar taint', where the androstenone odor has been described as `sweaty, `ammonia', `dirty', `silage' and `acrid', among others. In one recent study, anstrostenone-containing meat was found to be less acceptable to subjects with two copies of the RT variant of the OR7D4 receptor, indicating that this genetic variation affects food preferences (Lunde, et al., 2012). The existence of this taint in pork is already a particular problem for pork producers, and one that may become may become more worrisome in Europe, where a proposed ban on pig castration due to animal cruelty issues could lead to a rise in androstenone levels in pork, and subsequently reduce consumer acceptance. In Norway for example, approximately 40% of the population is sensitive to this odor (Lunde, et al., 2012). It is unclear whether the proportion of androstenone-sensitive individuals varies in different countries, but if so, it may impact the areas from which pork products are imported to different countries, with consequential economic considerations (Lunde, et al., 2012).

10.2 Cis-3-hexen-1-ol, green/grassy odors, and food acceptability

Cis-3-hexen-1-ol (C3HEX) is the prototypical odorant associated with `green' or `grassy' odors, and C3HEX is present in a range of fruit and vegetables. Differences in C3HEX detection thresholds span two orders of magnitude, and this variation has been associated with polymorphisms in *OR2J3*. The amino acid substitutions T113A and R226Q, are associated with in an impaired ability to smell C3HEX and may account for a quarter of the variation *in vivo*. (However, the haplotypes do not respond *in vitro* to C3HEX, so they may merely be in linkage disequilibrium with the causal SNPs).

More critically, variation in the ability to detect C3HEX is linked to food preferences. In a comprehensive investigation, Jaeger and colleagues demonstrated that this variation was important for preference using a range of foods including tomato juice, hummus, and Japanese green tea (Jaeger, et al., 2012). Samples spiked with C3HEX received lower acceptability ratings than the `normal' samples, and the degree of the negative response was higher in those who were C3HEX-responsive. As C3HEX is found in a vast array of plant-derived foods, this has wide implications for the food industry in terms of inter-individual food preferences. The challenge for the next phase of this area of research will be not only to elucidate the other functional genetic variations in chemosensory receptors but also to examine how these variations interact, to determine the effect on eating behavior.

10.3 Cilantro Aversions

Cilantro (also known as coriander leaf) has been described as `polarizing', as some individuals have an extreme dislike for this herb. Flavor descriptions range from `fragrant' and citrussy' to `soapy' and `insect or bug-like' (Mauer & El-Sohemy, 2012). The idea that the variation in the `soapy' character from cilantro is genetically-determined is not new (e.g. (Hertz, 2004). Recent GWAS have attempted to identify the SNPs involved. Data from the Toronto Nutrigenomics and Health study in 316 females indicates a role for both an odorant receptor variant (rs7277172 in *OR4N5*) and a SNP in a bitter taste receptor (rs427871 near TAS2R1), as 75% of participants who were homozygous for the minor alleles of both SNPs reported disliking cilantro, while none of those who homozygous for the major alleles reported disliking this herb (Mauer 2011, Master's thesis, available online). However, more recent evidence in a much larger group of subjects (11,851) suggests that a genetic variation (rs7921001) in the odorant receptor gene *OR6A2* on chromosome 11 may be responsible for the detection of soapiness and disliking of cilantro (Eriksson et al, 2012). As food preferences are influenced by a wide range of factors, including exposure and cultural influences, this may account for some of the differences in these two reports. Future

research using all of these putative SNPs may further ascertain their role in cilantro flavor and preference.

11. Summary and Conclusions

Biological differences in chemosensory ability from SNPs and CNVs are both commonplace and highly variable from person to person. This appears to be partly a result of evolutionary processes that have driven us to detect a vast array of potential toxins as well as potential foodstuffs, through both gustation, olfaction, and oral somatosensation. This is exemplified by the fact that although many SNPs are associated with differences in perception across multiple taste qualities, by far the most diverse is the variation in bitter taste receptor genes, likely due to the increased selective advantage in the conferred ability to discriminate a wide range of potential toxins at low levels. This discriminatory facility is strengthened by the fact that single compound can contain multiple distinct moieties that bind to separate TAS2Rs. For example, allylglucosinolate (also called sinigrin) contributes to the bitterness of brassica vegetables such as Brussels sprouts and cauliflower (Engel, Baty, Le Corre, Souchon, & Martin, 2002; van Doorn, et al., 1998). Critically, allylglucosinolate contains both a beta-glucopyranoside ring and a thiourea moiety (N-C=S), which activate hT2R16 and hT2R38 respectively (Meyerhof, et al., 2010). This demonstrates both the diversity of bitter tastants within food and how individuals may perceive a range of bitter tastes differently depending on different genetic variations. As such, the historical treatment of `bitter' as a uniform trait exemplified by a single compound is no longer tenable, and should not be used as strategy to screen sensory panelists. Instead, we suggest that sensory practitioners use the actual food of interest be used for panelist screening; hops for studies on beer, cocoa polyphenols for chocolate, etc.

Further, the influence of genetic variation on food sensations, liking and intake are not limited to bitterness. Nor are these effects limited to taste; recent data suggest differences in olfactory ability may also impact food preference, and should be considered, particularly where volatile compounds are important in the flavor aspect of a food product. This is an emerging area of research, and more work is needed; it will be interesting to see how the next challenges will be met.

In conclusion, inter-individual genetic differences have arisen in response to the changing environment as part of the evolutionary process. In the modern world, such variations affect how the surrounding environment is perceived, and have important implications for individual food preference and intake. The challenge that now lies ahead for sensory researchers is to establish how various combinations of chemosensory differences may interact to both influence and predict food choice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Genetic variation in chemosensation is more common than previously thought

- This variation is known to alter sensations from and preference for food

- Recent data suggests these differences extend beyond taste to include odor and touch

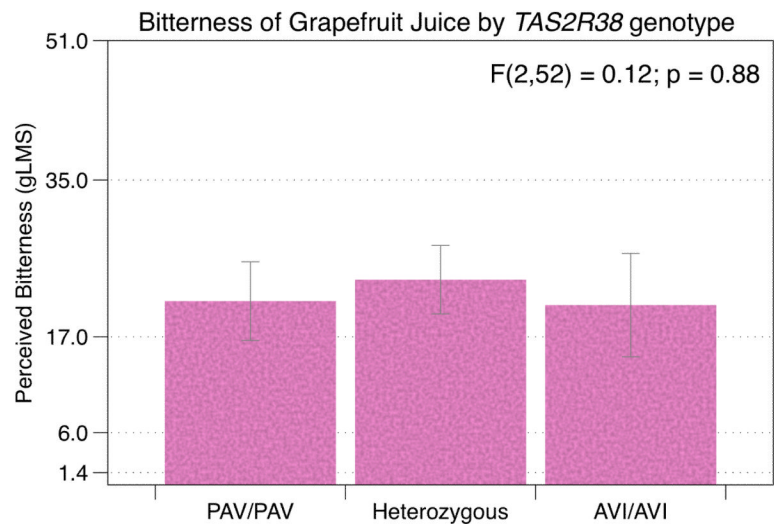- We summarize current knowledge, emphasizing human behavioral data

Figure 1.
Unpublished data from Hayes et al. 2011 showing that the bitterness of unsweetened grapefruit juice does not vary by *TAS2R38* genotype.
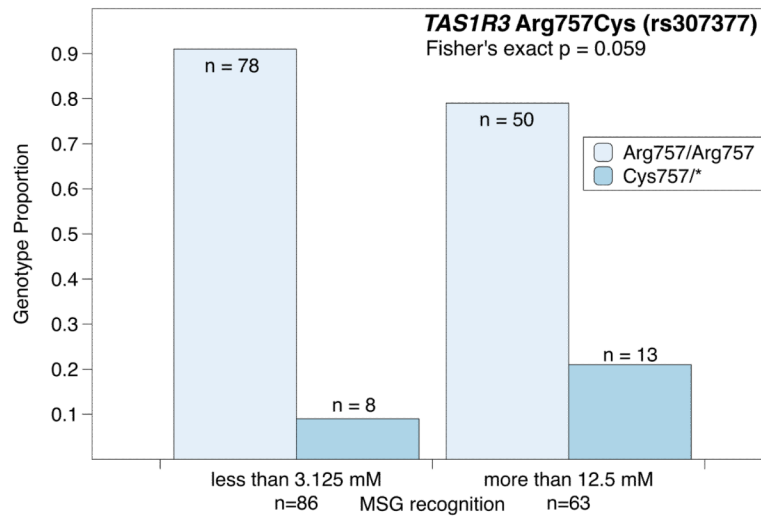
Figure 2.
Reanalysis of data from Shigemura et al 2009 indicates Cys757 carriers for the *TAS1R3* SNP (rs307377) may be overrepresented among those with elevated MSG recognition thresholds.
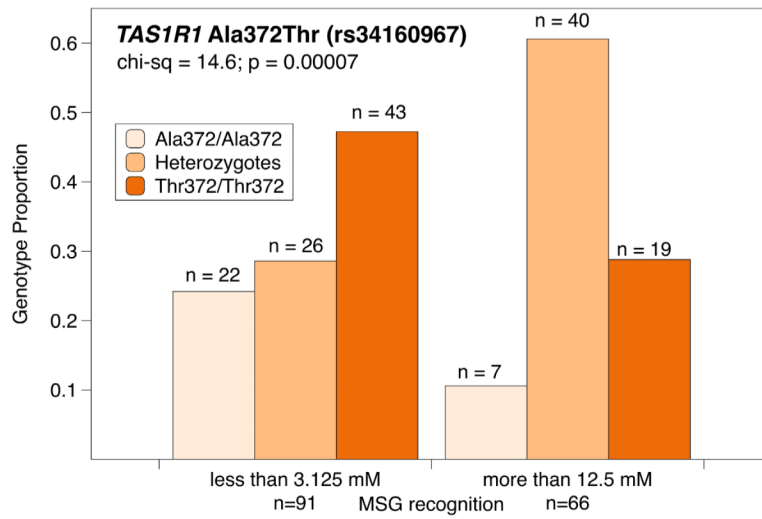
Figure 3.
Data from Shigemura also show Thr372 homozygotes (G/G) for the *TAS1R3* SNP (rs34160967) are overrepresented in the group with low MSG recognition thresholds.