3.13 Taste Genetics

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3.13.1 Abstract

The molecular mechanisms underlying taste perception are diverse and complex; however, they are unified in being genetically encoded. This provides a powerful route for dissecting taste systems' architecture, for not only do genes specify the basic structure and function of a protein, they can harbor mutational variation resulting in functional changes. The two key processes responsible for initiating taste responses are G protein coupled receptor (GPCR) signaling and ion channel signaling. The GPCR mediated tastes, sweet, bitter, and umami, are initiated by receptors encoded by the *TAS1R* and *TAS2R* gene families, which respond to sugars, L-glutamate, and numerous small molecules. GPCRs are also implicated in a newly recognized taste modality, fat taste, which appears to be initiated by free fatty acid receptors and scavengers encoded by the *FFAR1*, *FFAR4*, and *CD36* genes. Downstream components of the GPCR pathway that are genetically encoded include G protein subunits, intracellular receptors (encoded by *ITPR3*), phospholipase (*PLCB2*), phosphodiesterase (*PDE1A*), and protein kinase A (*PRK*s). The mechanisms initiating the ion channel mediated tastes, sour and salty, remain poorly understood; however, otopetrins (encoded by *OTOP1*) and ENaC (*SCNN1A*, *B*, and -G) channels are the primary candidates. Recent findings suggest that proteins secreted in saliva, including carbonic anhydrase (*CA6*) and a proline rich protein (*PRB1*) play important roles in perception, as well. Many of the genes encoding taste perception systems harbor mutational variants, suggesting that the proteins mediating taste sensations exhibit variable functionality resulting in variability in perception abilities. Such variability is well documented in the bitter (TAS2R) receptors and likely affects others, explaining differences in ingestive behaviors and possibly health among individuals and populations.

3.13.2 Introduction

Taste perception plays key roles in diet and health. By enabling us to evaluate the nutritional properties and safety of foods before they are consumed, it provides a powerful means of enhancing evolutionary fitness. For instance, bitter sensations, which are triggered by plant toxins, signal the presence of noxious components, allowing avoidance. Sweet sensations, which are triggered by sugars, signal carbohydrate richness. Salty, sour, and umami/savory sensations signal the presence of electrolytes, pH levels indicative of ripeness, and protein content. Together these modalities provide a chemical profile that shapes preferences and intake, with downstream consequences for nutrition and wellbeing.

The molecular mechanisms underlying taste perception are diverse and complex; however, they are unified in being genetically encoded. Like all metabolic systems, taste systems are composed of proteins, each of which is a gene product. This provides a powerful route for dissecting taste systems' architecture, for not only do genes specify the basic structure and function of a protein, they can

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harbor mutational variation resulting in functional changes. In the case of taste, such changes frequently explain differences in behavior and health among both individuals and populations. The aim of this chapter is to outline the molecular mechanisms underlying taste responses, the architecture and diversity of the genes that encode them, and their associations with preferences, behaviors, and health.

3.13.3 Sensing and Transduction

Taste perception systems are necessarily embedded in the organism as a whole and thus in a strict sense depend on the myriad aspects of physiology and anatomy. However, the mechanisms of principal interest lie at the interface between body and environment, where the molecular detection of tastants occurs and neural signaling begins.

The molecular pathways underlying taste responses originate in specialized receptor cells in the oropharyngeal cavity, particularly the epithelia of the tongue, soft palate, and larynx (Roper and Chaudhari, 2017). These cells are organized in clusters, taste buds, embedded beneath epithelial tissue. There, they face the interior of the oropharyngeal cavity through taste pores. These cells contain the molecular machinery for depolarizing in response to exposure to tastants, producing signals propagated to the central nervous system.

3.13.3.1 GPCR Signaling

Taste receptor cells targeted at bitter, sweet, and umami stimuli express two types of cell surface G protein-coupled receptor (GPCR), TAS1R and TAS2R. These combine to form three receptor types: bitter (TAS2R), sweet (TAS1R2+TAS1R3 heterodimer), and umami (TAS1R1+TAS1R3 heterodimer). When stimulated by agonists these activate a molecular cascade within the expressing cell (Margolskee, 2002; Roper, 2007; Kinnamon, 2009). Following stimulation by agonists, the TAS1Rs and -2Rs activate the principal G protein involved in taste signaling, gustducin, a heterotrimer composed of three subunits, Gα3, Gβ3, and Gγ13. When activated, gustducin separates into two main components, Gα3 and Gβ3 + Gγ13 dimer (Gβ3γ13). Gα3 and Gβ3γ13 proceed to trigger two pathways leading to increases in intracellular Ca^{2+} concentrations and, ultimately, depolarization of the receptor cell.

The primary depolarization pathway underlying GPCR mediated tastes is initiated by Gβ3γ13. Gβ3γ13 stimulates phospholipase Cβ2 (PLCβ2), catalyzing the production of inositol triphosphate (IP3). IP3 in turn stimulates IP3 receptor III (IP3R3) residing in the endoplasmic reticulum membrane, allowing escape of Ca^{2+}. The Ca^{2+} increase stimulates transient receptor potential cation channels TRPM4 and -5, allowing sodium influx that depolarizes the cell, triggering neurotransmitter release via a dimeric calcium homeostasis modulator, CALHM1/3 (Liman, 2007; Dutta Banik et al., 2018; Ma et al., 2018; Kashio et al., 2019). A secondary pathway is mediated by α-gustducin. α-gustducin stimulates phosphodiesterase (PDE1A), suppressing cAMP levels by catalyzing cAMP's decomposition to AMP (Ruiz-Avila et al., 1995; Margolskee, 2002). α-gustducin stimulates phosphodiesterase (PDE), suppressing cAMP levels by catalyzing cAMP's decomposition to AMP. The drop in cAMP deactivates protein kinase A (PKA), preventing its inhibition of K+ channels and allowing depolarization and, as with the Gβ3γ13 mediated pathway, ATP release via CALHM1/CALHM3 (Taruno et al., 2013).

The mechanisms underlying taste responses to fats remain poorly understood. However, three receptor candidates currently stand out: GPR40, GPR120, and CD36. Two, GPR40 and GPR120, are GPCRs. Both are responsive to free fatty acids and initiate signaling in response to fatty acid exposure, likely through pathways shared in whole or in part with the TAS1Rs and -2Rs (Liu et al., 2016). The third candidate CD36, is a surface expressed fatty acid scavenger. It natively responds to fatty acids and localizes to taste receptor cells, and knockout of the gene in rats and mice abolishes preferences for fat-containing solutions and foods (Laugerette et al., 2005; Martin et al., 2011). However, the downstream pathways through which it transmits taste signals remain speculative.

3.13.3.2 Ion Channel Signaling

Mechanisms underlying sour and salt tastes are not as well understood as those underlying bitter, sweet, and umami, partly because they do not rely on G protein signaling pathways, which are more thoroughly dissected (Roper and Chaudhari, 2017). The primary candidate receptors for compounds perceived as sour and salty are plasma membrane ion channels. In the case of sour tastes, acid-sensing ion channels (ASICs 1, -2, -3, and/or 4), hyperpolarization-activated cyclic nucleotide-gated channels (HCN1 and -4), polycystic kidney disease-like channels (a PKD1L3 and PKD2L1 dimer) and an inward-rectifier potassium channel (K_{IR} 2.1) are all candidates (Gilbertson et al., 1992; Stevens et al., 2001; Lin et al., 2002; Richter et al., 2004; Horio et al., 2011; Yee et al., 2011; Ye et al., 2016). Recent evidence implicates otopetrin proton channel 1 (OTOP1) as the canonical sour receptor (Tu et al., 2018; Saotome et al., 2019). OTOP1, which in taste buds only localizes to sour taste receptor cells, is selective to H^+ ions enriched in sour solutions, and H^+ conductance is abolished in mice harboring OTOP1 mutations. Nonetheless, fully rejecting the alternative receptors is difficult and they are not necessarily mutually exclusive. The pathways underlying salty tastes are least well understood. The ENaC channel is the primary receptor candidate, although some evidence suggests that TRPV1 may also initiate responses to salts (Chandrashekar et al., 2010; Dias et al., 2013; Roper, 2015).

3.13.3.3 Salivary Proteins

An often overlooked aspect of taste systems is the collection of mechanisms controlling the oropharyngeal environment itself. The potential importance of these was recognized in the earliest study of genetics of bitter taste by Fox (1932), who suggested that the solubility of tastants in saliva might vary from person to person. Proteomic inventories have revealed more than 1300 proteins in human saliva, which could play roles in taste (Guo et al., 2006). Two found at high concentrations in saliva and implicated in taste are carbonic anhydrase VI (CA6, also called gustin), a protein catalyzing the reversible hydration of carbon dioxide, and PRB1, a proline rich protein that undergoes proteolysis to form various active subproducts (Sly and Hu, 1995; Calo et al., 2011; Cabras et al., 2012; Manconi et al., 2016).

3.13.4 Taste Genes

The anatomy and physiology of taste mechanisms provide a framework for understanding the genetic basis of taste (**Tables 1** and **2**). Each of the proteins involved in surface sensing, the transduction cascade, and salivary secretions is encoded by a gene. This provides avenues for understanding because in addition to containing information about the primary structure of the encoded protein, genes contain information about the presence of mutational variation, which can account for similarities and differences in phenotype among individuals and populations.

Table 1 Taste genes, functions, and modalities.

	Gene	Protein Type/Function	Modality	Reference
Surface Sensors	*ASIC1*	Acid-sensing ion channel	Sour	Richter *et al.* 2004
	ASIC2	Acid-sensing ion channel	Sour	Richter *et al.* 2004
	ASIC3	Acid-sensing ion channel	Sour	Richter *et al.* 2004
	ASIC4	Acid-sensing ion channel	Sour	Richter *et al.* 2004
	CD36	Fatty acid translocase	Fat	Laugerette *et al.* 2005
	FFAR1	Free fatty acid receptor	Fat	Besnard *et al.* 2016
	FFAR4	Free fatty acid receptor	Fat	Besnard *et al.* 2016
	HCN1	Cyclic nucleotide-gated channel	Sour	Stevens *et al.* 2001
	HCN4	Cyclic nucleotide-gated channel	Sour	Stevens *et al.* 2001
	KCNJ2	Inward rectifier K+ channel	Sour	Ye *et al.* 2016
	OTOP1	Proton channel	Sour	Tu *et al.* 2018
	PKD1L3	Cation channel	Sour	Huang *et al.* 2006
	PKD2L1	Cation channel	Sour	Huang *et al.* 2006
	SCNN1A	Sodium channel α subunit	Salt (ENaC)	Chandrashekar *et al.* 2010
	SCNN1B	Sodium channel β subunit	Salt (ENaC)	Chandrashekar *et al.* 2010
	SCNN1G	Sodium channel γ subunit	Salt (ENaC)	Chandrashekar *et al.* 2010
	TAS1R (n = 3)	GPCR subunit	Sweet, umami	Nelson *et al.* 2001; Zhao *et al.* 2003
	TAS2R (n = 26)	GPCR	Bitter	Chandrashekar *et al.* 2000
	TRPV1	Nonselective cation channel	Salt	Dias *et al.* 2013
GPCR-Mediated Transduction	*GNAT3*	G protein α subunit (Gustducin)		Wong *et al.* 1996
	GNB3	G protein β subunit (Gustducin)		Huang *et al.* 2003
	GNG13	G protein γ subunit (Gustducin)		Huang *et al.* 1999
	ITPR3	Calcium channel		Clapp *et al.* 2001
	PDE1A	Phosphodiesterase		Ruiz-Avila *et al.* 1995
	PLCB2	Phospholipase		Zhang *et al.* 2003
	PRKACA	Protein kinase A catalytic subunit α (PKA types I and II)		Taskén and Aandahl 2004
	PRKACB	Protein kinase A catalytic subunit β (PKA types I and II)		Taskén and Aandahl 2004
	PRKACG	Protein kinase A catalytic subunit γ (PKA types I and II)		Taskén and Aandahl 2004
	PRKAR1A	Protein kinase A type I regulatory subunit α (PKA types I and II)		Taskén and Aandahl 2004
	PRKAR1B	Protein kinase A type I regulatory subunit β (PKA types I and II)		Taskén and Aandahl 2004
	PRKAR2A	Protein Kinase A type II regulatory subunit α (PKA types I and II)		Taskén and Aandahl 2004
	PRKAR2B	Protein Kinase A type II regulatory subunit β (PKA types I and II)		Taskén and Aandahl 2004
	CALHM1	Nonselective ion channel subunit (CALHM1/3 hexamer)		Kashio *et al.* 2019
	CALHM3	Nonselective ion channel subunit (CALHM1/3 hexamer)		Kashio *et al.* 2019
	TRPM4	Nonselective cation channel		Dutta Banik *et al.* 2018
	TRPM5	Nonselective cation channel		Pérez *et al.* 2002
Salivary Secreted	*CA6*	Carbonic anhydrase	Bitter, possibly others	Calo *et al.* 2011
	PRB1	Proline rich glycoprotein	Bitter, possibly others	Cabras *et al.* 2012

Table 2 Taste gene coordinates and structures.

	Gene	Location	Gene size (bp)	Exons	Protein size (aa)
Surface Sensors	*ASIC1*	chr12:50,058,767–50,081,649	22,883	11	574
	ASIC2	chr17:33,013,965–33,292,115	278,151	10	563
	ASIC3	chr7:151,048,886–151,052,747	3,862	10	543
	ASIC4	chr2:219,514,344–219,538,046	23,703	9	647
	CD36	chr7:80,646,741–80,674,147	27,407	12	472
	FFAR1	chr19:35,351,552–35,352,454	903	1	300
	FFAR4	chr10:93,566,721–93,587,609	20,889	3	361
	HCN1	chr5:45,261,921–45,696,093	434,173	8	890
	HCN4	chr15:73,322,481–73,368,270	45,790	8	1,203
	KCNJ2	chr17:70,175,040–70,176,323	1,284	1	427
	OTOP1	chr4:4,188,803–4,226,864	38,062	6	612
	PKD1L3	chr16:71,929,538–71,999,978	70,441	30	1,732
	PKD2L1	chr10:100,288,396–100,330,103	41,708	16	805
	SCNN1A	chr12:6,347,873–6,374,783	26,911	12	669
	SCNN1B	chr16:23,348,600–23,380,801	32,202	12	640
	SCNN1G	chr16:23,186,272–23,215,469	29,198	12	649
	TAS1R ($n = 3$)	chr1	~4000–20,000	6	~840
	TAS2R ($n = 26$)	chr1, 7, 12	~1 kb	1	~350
	TRPV1	chr17:3,566,815–3,592,350	25,536	15	839
GPCR-Mediated Transduction	*GNAT3*	chr7:80,458,671–80,511,926	53,256	8	354
	GNB3	chr12:6,841,288–6,846,898	5,611	9	340
	GNG13	chr16:798,719–799,077	359	2	67
	ITPR3	chr6:33,621,603–33,695,780	74,178	58	2,671
	PDE1A	chr2:182,147,079–182,522,376	375,298	14	545
	PLCB2	chr15:40,288,715–40,307,672	18,958	32	1,185
	PRKACA	chr19:14,093,112–14,117,547	24,436	10	351
	PRKACB	chr1:84,144,362–84,235,305	90,944	10	398
	PRKACG	chr9:69,013,037–69,014,092	1056	1	351
	PRKAR1A	chr17:68,515,400–68,530,449	15,050	10	381
	PRKAR1B	chr7:550,430–711,505	161,076	10	381
	PRKAR2A	chr3:48,751,585–48,847,596	96,012	11	404
	PRKAR2B	chr7:107,044,908–107,159,582	114,675	11	418
	CALHM1	chr10:103,455,262–103,458,751	3,490	2	346
	CALHM3	chr10:103,473,213–103,479,032	5,820	3	344
	TRPM4	chr19:49,157,867–49,211,498	53,632	25	1,214
	TRPM5	chr11:2,404,937–2,423,036	18,100	24	1165
Salivary Secreted	*CA6*	chr1:8,945,887–8,974,704	28,818	8	308
	PRB1	chr12:11,353,107–11,395,529	42,423	4	330

3.13.4.1 Surface Sensors

3.13.4.1.1 GPCRs

The gene family contributing the largest number of proteins mediating taste responses is the *TAS2R* family, which encodes the bitter receptors (TAS2Rs). In humans the *TAS2R* family is represented by approximately 26 loci residing in two main clusters, one on chromosome 7 and one on chromosome 12, and a single locus on chromosome 1. *TAS2R*s are roughly 1kilobase (kb) in length, with a single coding exon. Levels of genetic similarity among *TAS2R* genes are highly variable, with the most similar retaining >99% nucleotide identity and others diverging more than 60% (Shi et al., 2003). The genetic differences among *TAS2R* loci include extensive coding variation, resulting in considerable amino acid sequence variation in their encoded products (Kim et al., 2005).

Genetic differentiation among TAS2R loci produces receptors with highly divergent agonist specificities and affinities. As a result, TAS2Rs are responsive to a broad constellation of compounds (Meyerhof et al., 2010). In addition, TAS2Rs exhibit both many-to-one and one-to-many relationships with agonists: most TAS2Rs respond to more than one compound, and many compounds are agonists for more than one TAS2R. These patterns are exemplified by the results of an *in vitro* survey of the responses of 25 TAS2Rs to 104 bitter compounds performed by Meyerhof et al. (2010). Meyerhof et al. (2010) found that the number of compounds eliciting responses was highly variable across TAS2Rs, ranging from 0 to 32, with 20 of 25 receptors responding to at least one of the compounds tested. The number of receptors stimulated by a given compound was also highly variable, ranging from 0 to 15. Thus, the toxin warning system encoded by *TAS2R*s is capable of detecting a very large range of noxious substances.

A key feature of *TAS2R*s is that they exhibit extensive overlap in expression, with most bitter receptor cells expressing multiple *TAS2R*s simultaneously and the set of expressed *TAS2R*s varying from cell to cell (Behrens et al., 2007). These patterns suggest that responses to agonists may also vary from cell to cell. Whether these expression patterns result in differences in perception is not

known and will be technically challenging to clarify. The central issue is neural coding; in particular, it is not clear whether bitter cells expressing different subsets of *TAS2R*s convey information to the central nervous system via identical pathways (Mueller et al., 2005; Roper and Chaudhari, 2017). If they utilize identical pathways, then ability to distinguish bitter agonists by *TAS2R*-mediated signaling alone seems unlikely; if not, then ability to distinguish agonists is a possibility. The preponderance of current evidence is that the ability to distinguish bitter agonists is low. Thus, bitter pathways signal that noxious compounds are present, but not their identities. This pattern is consistent with TAS2Rs acting as generalized, as opposed to specifically targeted, toxin detectors warning against exposure.

*TAS2R*s, like most genes, are expressed in multiple tissue types, suggesting they may have multiple biological functions. Indeed, two extraoral functions of TAS2Rs are well established, and others seem likely. The best understood extraoral activity of *TAS2R*s is in gastrointestinal tissues. Expression of *TAS2R*s in the gut was first reported by Wu et al. (2002), who identified TAS2Rs in STC-1 enteroendocrine cells and found that exposure to bitter agonists resulted in Ca^{2+} release consistent with GPCR-mediated intracellular signaling mechanisms. Further, stimulation of STC-1 cells with bitter tastants stimulates release of cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1) (Rozengurt and Sternini, 2007). The importance of this role is exemplified by responses to gut exposure to bitter tastants in mice, which result in increases in ghrelin levels and food intake (Janssen et al., 2011). In addition, consistent with their role as toxin detectors, stimulation of cells expressing *TAS2R*s in the gut also alters the cellular absorption of TAS2R agonists. In particular, TAS2R signaling activates ATP-binding cassette B1 (ABCB1) in intestinal cells, resulting in increased efflux, limiting absorption (Jeon et al., 2011). Thus, TAS2Rs expressed in the gut, like those in orosensory cells, likely serve a protective function.

A second extraoral system expressing *TAS2R*s is the respiratory airway where they are found in airway smooth muscle, ciliated epithelial and brush cells, and solitary chemosensory cells (Dalesio et al., 2018). Remarkably, stimulation of TAS2Rs in airway smooth muscle causes relaxation and bronchodilation (Deshpande et al., 2010). This suggests the presence of a paradoxical, damaging feedback loop: inhalation of TAS2R agonists likely begets increased inhalation, increasing exposure rather than decreasing it. This action contradicts the assumption that TAS2Rs perform a uniformly protective role.

The TAS1R dimers initiating sweet and umami sensations are encoded by three genes, *TAS1R1*, *TAS1R2*, and *TAS2R3*. All are located on chromosome 1, and all are composed of 6 exons. The three genes differ dramatically in size, with *TAS1R1* and *TAS1R2* both 20 kb in length and *TAS1R3* 4 kb in length; however, their encoded products are similar in size, roughly 840 amino acids. This makes them substantially larger than TAS2Rs, which average roughly 350aa in length. The size difference is due to TAS1Rs' possession of a large extracellular domain at the N-terminus absent in TAS2Rs. A critical feature of TAS1Rs is that they are heterodimeric, with the functional receptor composed of conjoined TAS1R monomers. The mature umami receptor is composed of TAS1R1 and TAS1R3 while the mature sweet receptor is composed of TAS1R2 and TAS1R3. Thus, the sweet and umami receptors are structurally distinct but share a major subunit.

Like bitter receptors, sweet and umami receptors are responsive to a broad range of compounds. The sweet receptor is responsive to sugars such as sucrose and glucose, artificial sweeteners such as saccharin, aspartame, sucralose, and acesulfame potassium, and natural non-sugars, such as stevioside and mogroside v (Kim et al., 2017; Lee and Owyang, 2017) Agonists of the umami receptor are amino acid related compounds including individual amino acids such as L-glutamate and aspartate, variants such as monosodium glutamate and monoammonium glutamate, and some proteins (Li et al., 2002; Chaudhari et al., 2009). The incorporation of TAS1R3 into both the sweet and umami receptors suggests they may share specificity to some agonists, such that some compounds evoke sweet and umami sensations simultaneously. This phenomenon occurs with two compounds, cyclamate and lactisole. Interaction of cyclamate with TAS1R3 enhance both sweet and umami responses (Xu et al., 2004; Jiang et al., 2005a, 2005b). Conversely, of lactisole with TAS1R3 inhibit TAS1R1/3 and TAS1R2/3 receptor function, attenuating both sweet and umami responses (Xu et al., 2004; Jiang et al., 2005b).

The ability of the TAS1Rs to mediate two taste modalities is explained by their patterns of gene expression and neural coding. Unlike *TAS2R*s, which exhibit shared expression in cells with shared neural pathways, *TAS1R*s are differentially expressed in cells with different neural pathways. Two of the three *TAS1R* genes, *TAS1R1* and *TAS1R2*, are expressed in separate cell populations, producing subtypes; the third, *TAS1R3*, is expressed both subtypes. This produces cell populations responsive to two categories of agonist: sweet and umami. In addition, sweet and umami receptor cell populations operate through different neural pathways, allowing their responses to be distinguished at the level of the CNS (Zhang et al., 2003).

Like *TAS2R*s, *TAS1R*s are expressed and functional in numerous extraoral tissues (Laffitte et al., 2014). For instance, the sweet receptor is expressed in gut enteroendocrine cells, where stimulation by sweeteners triggers hormonal responses (Jang et al., 2007; Egan and Margolskee, 2008; Calvo and Egan, 2015). The most significant of these are the release of GLP-1 and gastric inhibitory peptide (GIP), which stimulate increases in insulin levels. Stimulation of gut sweet receptors is also accompanied by upregulation of sodium/glucose transporter genes (*SLGT*s). Thus, sweet receptor signaling enables different body systems to respond in concert to consumed nutrients, increasing the efficiency of caloric intake. The umami receptor is also expressed in endocrine cells in the gut, where stimulation triggers release of cholecystokinin (CCK) and ghrelin, hormones known to affect food intake, insulin release, and gastric motility (Daly et al., 2013; Vancleef et al., 2015; Behrens and Meyerhof, 2019). Thus, like the sweet receptor enables concerted responses to sugars in the mouth and gut, the umami receptor likely enables concerted responses to proteins.

The two GPCRs implicated in fat taste, GPR40 and GPR120, are encoded by single genes, *FFAR1* and *FFAR4* respectively. *FFAR1* is located on chromosome 19 and is quite small, a single exon 903 bp in length encoding a 300aa final product. *FFAR4* is substantially larger and more complex. It is 21 kb in length with three exons, and its product is 361aa in length. The third protein implicated in fat taste, CD36, is also encoded by a single gene, *CD36*, which is comprised of 12 exons in a 27 kb region, resides on chromosome

7. A remarkable feature of *CD36* is that it genomically spans *GNAT3* (which encodes α-gustducin). This has ramifications for efforts to identify associations between variation in the two genes and taste responses, because they may be correlated. It also raises questions about whether their expression is shaped by the same genomic factors.

3.13.4.1.2 Ion Channels

The receptor most strongly implicated in sour tastes, OTOP1, is encoded by a single gene, *OTOP1* (Tu et al., 2018). *OTOP1* is comprised of 6 exons spanning a 38 kb region on chromosome 4, which together produce a protein 612aa in length. The gene is expressed in numerous tissues in mice, including cells in the vestibular system (Tu et al., 2018). However, it is only expressed in one taste receptor cell type, sour, consistent with the hypothesis that OTOP1 is the canonical sour receptor.

The PKD2L1/PKD1L3 heterodimer implicated in sour taste is encoded by two genes, *PKD2L1* and *PKD1L3* (Wu et al., 1998; Huang et al., 2006; Ishimaru et al., 2006; Kawaguchi et al., 2010; Zheng et al., 2015). *PKD2L1* and *-1L3* are located on chromosomes 10 and 16 respectively, and are 42 kb and 70 kb in length, with 16 and 30 coding exons respectively. The product encoded by *PKD2L1* is 805aa in length while that encoded by *PKD1L3* is much larger, 1732aa.

PKD2L1 and *-1L3* are relatives of the *PKD1* and *-2* genes, which encode widely expressed polycystins present in renal epithelial cells, osteoblasts, and other cell and tissue types (Wilson, 2001; Dalagiorgou et al., 2010). However, unlike *PKD1* and *-2* genes, *PKD2L1* and *-1L3* are expressed in a limited number of types. In surveys across tissues, Huang et al. (2006) found that *PKD2L1* is present in type III taste receptor cells and spinal cord. Ishimaru (2009) found expression of *PKD2L1* and *-1L3* is expressed in the apexes of type III receptor cells, testes, and at low levels in other tissues. Thus, in addition to having the biochemical properties of acid sensors, *PKD2L1/1L3* exhibits localization consistent with participation in taste.

The other candidate initiators of sour tastes, ASIC, HCN, and K_{IR}, are encoded by three sets of genes. The ASIC channels are encoded by four genes, *ASIC1*, *ASIC2*, *ASIC3*, and *ASIC4*, which are located on chromosomes 12, 17, 7, and 2. The structures of the four genes vary substantially. The largest, *ASIC2*, is seventy times as large as the smallest, *ASIC3* (∼280 kb vs ∼4 kb). In addition, the genes are comprised of different numbers of exons: 11, 10, 10, and 9. However, their encoded products are similar in size, ∼550–700aa. The genes encoding the HCN channels implicated in sour taste, *HCN1* and *-4*, also vary substantially in size, with *HCN1* being roughly 10 times larger than *HCN4* (∼450 kb vs ∼45 kb). Again, however, their products are similar in size, ∼900aa and ∼1200aa. *KCNJ2*, which encodes K_{IR}2.1, has a relatively simple structure. It resides on chromosome 17, is ∼1.3 kb in size, has a single exon, and a product length of 427aa.

In contrast to *PKD2L1* and *-1L3*, *ASIC*s, *HCN*s, and *KCNJ2* are widely expressed and appear to perform multiple functions (Boscardin et al., 2016). *ASIC*s are highly expressed in the central and peripheral nervous system and are present at low levels in other tissues, where they are activated by low pH (Lingueglia, 2007). In addition to taste, the *ASIC*s have been implicated as components of sensory systems including nociception, photoreception, hearing, and mechanosensation (Lingueglia, 2007; Omerbasic et al., 2015; Vullo and Kellenberger, 2019). *HCN*s are widely expressed in the nervous system, including the hippocampus, cardiac Purkinje fibers, and cardiac myocytes, where they mediate pacemaker activity (Robinson and Siegelbaum, 2003). Like *HCN*s, *KCNJ2* is widely expressed in the peripheral nervous system, central nervous system, cardiac cells, and skeletal muscle (Hibino et al., 2010; Binda et al., 2018). The broad expression patterns of *ASIC*s, *HCN*s, and *KCNJ2* indicate that they are not dedicated solely to sour tasting, but play other roles as well.

Like sour tastes, salty tastes are not initiated by GPCRs, but by an ion channel or channels. The primary candidate salt receptor is ENaC (Epithelial Na Channel). ENaC is a heterotrimer encoded by three genes, *SCNN1A*, *SCNN1B*, and *SCNN1G*, which produce ENaC's α, β, and γ subunits. They are located on chromosomes 12, 16, and 16, and are relatively uniform in structure. Their genomic lengths vary from 27 kb (*SCNN1A*) to 32 kb (*SCNN1B*), and each is comprised of 12 coding exons. The lengths of their encoded products are commensurately similar, with SCNN1α, -β, and –γ all being ∼650aa in length. A second candidate salt receptor, TRPV1, is encoded by a single gene ∼25 kb in size, with 15 exons and an 839aa product.

ENaC is an essential mechanism for salt sensing a variety of body systems. In particular, it is expressed in kidney, lung, skin, reproductive and digestive tissues, where mediates Na^+ reabsorption in processes controlling fluid transport. ENaC is especially abundant in nephrons, where it participates in regulation of whole body Na^+ homeostasis (Boscardin et al., 2016). In taste buds, ENaC is found in a subset of receptor cells dedicated to salt tastes, which are distinct from those utilized for bitter, sweet, or umami sensing (Chandrashekar et al., 2010). Like ENaC, TRPV1 exhibits expression in many tissues and plays diverse physiological roles, including sensory functions such as heat detection and detection of chemical irritants such as capsaicin and allyl isothiocyanate (DeSimone and Lyall, 2006; Zhao and Tsang, 2017).

3.13.4.2 GPCR Signaling Cascade

The G protein activated by GPCR taste receptors, gustducin, is a heterotrimer encoded by three genes, *GNAT3*, *GNB3*, and *GNG13*, which specify its α, β, γ subunits. The three genes reside on chromosomes 7, 12, and 16. They are 53 kb, 7 kb, and 2.5 kb in length, and their products are 354aa, 340aa, and 67aa in length. *GNAT3*, which encodes α-gustducin, exhibits a relatively circumscribed expression pattern, mostly limited to cells participating in bitter, sweet, and umami sensing (Rozengurt et al., 2006). In addition to presence in tastes, it is found in extraoral tissues expressing the GPCR taste receptors, including enteroendocrine cells, pancreatic cells, and cells in the airway. This pattern is consistent with findings suggesting that α-gustducin is utilized principally for chemosensory signaling by TAS1Rs and -2Rs. Like that of *GNAT3*, *GNG13* expression is circumscribed, and highest in tissues utilizing taste and olfaction signaling pathways (Huang et al., 1999, 2003; Li et al., 2006). Unlike *GNAT3* and *GNG13*, whose function is largely

restricted to taste responses, *GNB3* participates in signaling by numerous GPCRs (Rosskopf et al., 2000). Hence, it is expressed in numerous tissues in addition to those dedicated to TAS1 and -2R mediated sensations. *GNB3*, for instance, is expressed in brain, colon, eye, gamete, and heart in addition to the tissues expressing *GNAT3* (Rosskopf et al., 2000; Schwindinger and Robishaw, 2001).

PDE, IP3R, and PLCβ2 are each encoded by single genes, *PDE1A*, *ITPR3*, and *PLCB2*. These reside on chromosomes 2, 6, and 15. *PDE1A* is large, 375 kb with 14 exons, yet it encodes a relatively small mature protein, 545aa in length. *ITPR3* is substantially smaller at 75 kb, but it is highly complex and encodes a far larger protein, with 58 exons together producing a molecule 2600aa in length. *PLCB2* is the smallest of the three, 19 kb in length, with 32 exons producing a protein 351aa in length.

The genetic encoding of PKA is highly complex (Taskén and Aandahl, 2004; Turnham and Scott, 2016; Soberg et al., 2017). It is comprised of seven genes: *PRKACA*, *PRKACB*, *PRKACG*, *PRKAR1A*, *PRKAR1B*, *PRKAR2A*, *PRKAR2B*. These encode PKA subunits that bond to form heterotetramers made up of two regulatory components (R1A and R1B or R2A and R2B) and two catalytic components (two of CA, CB, and CG), each of which is encoded by a different gene. The structures of the genes encoding these molecules vary greatly themselves in complexity. The smallest, *PRKACG*, is comprised of a single exon 1 kb in length, which produces a mature protein 351aa in length. The largest, *PRKARIB*, is composed of 10 exons and 160 kb in length. Nonetheless, its product is small as well, 381aa.

The intracellular components of the taste transduction cascade are broadly utilized by intracellular signaling mechanisms and are expressed in numerous tissues. For instance, in addition to being expressed in type 2 taste receptor cells, *ITPR3* is expressed in pancreatic cells, thymus, and vascular smooth muscle cells, where it participates in epithelial growth, apoptosis, and other processes (Taylor et al., 1999; Mendes et al., 2005; Mikoshiba, 2007; Ivanova et al., 2014). Similarly, *PDE1A* is expressed in kidney, liver, pancreas, and other tissues, where it regulates diverse processes. For instance it participates in regulation of vascular smooth muscle cell growth and apoptosis (Nagel et al., 2006). *PLCB2* and the *PKA* genes are similarly broadly expressed and participate in diverse signal dependent processes (Taskén and Aandahl, 2004; Taylor et al., 2004; Nakamura and Fukami, 2017).

The final stages of GPCR mediated taste responses are mediated by the ion channels, CALHM, TRPM4, and TRPM5. The CALHM receptor implicated in taste is encoded by two genes, *CALHM1* and *CALHM3*, whose products bond to form a CALHM/CALHM3 hexamer (Ma et al., 2018). *CALHM1* and *-3* are tandemly arranged 14 kb apart on chromosome 10, and each encodes a product ~354aa in length. However, their structures are different, with *CALHM3* being substantially larger than *CALHM1* (6 kb vs 3.5 kb), and encoded by three exons as opposed to *CALHM1*'s two. *TRPM4*, located on chromosome 19, has a highly complex structure. It more than 50 kb in length, with 25 exons, and encodes a protein 1,214aa in length. *TRPM5*, located on chromosome 11, has a structure similar to that of *TRPM4*, with 24 exons and a 1165aa product, but is smaller at 18 kb.

In addition to being expressed in type II taste receptor cells, *CALHM1* and *CALHM3* are widely coexpressed in tissues including nasal epithelia, bladder, and cerebral cortex where CALHM mediates ATP release in response to extracellular Ca^{2+} (Ma et al., 2012, 2016; Siebert et al., 2013; Kashio et al., 2019). *TRPM4* is similarly widely expressed in cells and is broadly used in signaling processes (Mathar et al., 2014). *TRPM5* expression is more circumscribed than that of *CALHM1*, *CALHM3*, or *TRPM4*. It is found predominantly in chemosensory cells in the olfactory epithelium, respiratory, and gastrointestinal tissues, where it likely participates in TAS1R and -2R initiated signaling (Kashio et al., 2019). However, it is also present in pancreatic β cells, suggesting that it may have signaling roles outside of taste (Prawitt et al., 2003).

3.13.4.3 Salivary Secreted Proteins

The *PRB1* gene, which occupies a 42 kb region of chromosome 12, is comprised of four exons and produces a protein 330aa in length. The *CA6* gene spans a 29 kb region of chromosome 1, is comprised of 8 exons and encodes a protein 308aa in length. Both are highly expressed in salivary glands, which secrete CA6 and PRB1 into the oropharyngeal environment. However, *CA6* is expressed in other tissues carrying out secretory processes as well, including mammary glands, gastric mucosa, and von Ebner's glands (Parkkila et al., 1997; Karhumaa et al., 2001; Leinonen et al., 2001).

3.13.5 Genetic Variation

In addition to encoding the basic proteins underlying taste mechanisms, taste genes harbor extensive allelic variation. This has potentially far reaching consequences for taste abilities and downstream phenotypes. For instance, if observed allelic variation affects protein function, then polymorphisms in taste genes may translate into variability in taste sensitivity, which could in turn result in variable preferences and, hence, health. In addition, genetic variation is often apportioned among human populations such that population differences in genotype frequencies emerge, which can translate into systematic differences in perception.

3.13.5.1 Diversity

Most research on genetic diversity in taste genes has focused on the *TAS2R*s, which were the first taste receptor genes to be discovered. Studies of *TAS2R*s have revealed extensive allelic variability including numerous nonsynonymous polymorphisms. In the first population genetic study of a *TAS2R*, Wooding et al. (2004) found five nucleotide substitutions in *TAS2R38*, all of which were nonsynonymous, in a panel of 165 subjects. In a subsequent study of *TAS2R38*, Campbell et al. (2012) found 61 substitutions in a panel

of 743 subjects, including 19 nonsynonymous changes in African subjects alone. The high levels of diversity in TAS2R38 extend to other *TAS2R*s, as well. In a survey of variation in 24 TAS2Rs in 55 subjects from worldwide populations, Kim et al. (2005) found amino acid substitutions producing 151 coding haplotypes, with an average of 6 per gene. Functional studies of nonsynonymous TAS2R variants have confirmed that most do indeed alter receptor affinity and specificity (Bufe et al., 2005; Roudnitzky et al., 2011; Behrens et al., 2013). The discovery that *TAS2R* genes harbor extensive variation affecting receptor function, together with evidence that most TAS2Rs are responsive to multiple compounds, suggests that humans vary in taste responses to myriad substances (Meyerhof et al., 2010).

Population genetic studies directed at taste genes other than *TAS2R*s remain scant, so the patterns of diversity they harbor remain largely unknown. However, in a survey of genes sequenced in 2504 subjects in 26 populations by the 1000 Genomes Project (1000 GP) we found that the coding regions of most taste genes, like *TAS2R*s, harbor substantial variability (**Table 3**) (The 1000 Genomes Project Consortium, 2015). The number of variable nucleotide positions (S) ranged from 10 (in *PRKACB*) to 242 (in *ITPR3*). The number of nonsynonymous substitutions, which is a key predictor of the extent of functional variation, also showed a broad range, with the smallest number found in *PRKARIA* ($S_n = 4$) and the largest in *TRPM5* ($S_n = 101$). These findings suggest that numerous functional variants do occur in most or all taste genes, which could drive variation in taste perception processes.

In addition to revealing overall levels of variation in taste genes, the 1000 GP data reveal varying levels of population structure, which likely underlie population level similarities and differences in taste abilities. Measures of population differentiation using the

Table 3 Genetic diversity in taste genes.

	Gene	*S(S$_s$,S$_n$)*	*D*	*F$_{ST}$*
Surface Sensors	*ASIC1*	35 (22, 13)	−2.26	0.08
	ASIC2	38 (18, 20)	−1.88	0.07
	ASIC3	75 (23, 52)	−2.41	0.03
	ASIC4	70 (28, 42)	−2.04	0.08
	CD36	85 (14, 71)	−1.87	0.08
	FFAR1	28 (8, 20)	−2.06	0.06
	FFAR4	36 (19, 17)	−1.99	0.09
	HCN1	34 (17, 17)	−2.43	0.06
	HCN4	111 (58, 53)	−2.14	0.08
	KCNJ2	34 (26, 8)	−2.26	0.12
	OTOP1	20 (5, 15)	−1.55	0.08
	PKD1L3	[b]	−1.66	0.08
	PKD2L1	102 (33, 69)	−1.95	0.08
	SCNN1A	81 (27, 54)	−1.83	0.09
	SCNN1B	64 (22, 42)	−1.99	0.11
	SCNN1G	55 (21, 34)	−1.85	0.07
	TAS1R ($n = 3$)[a]	92.3 (47.0, 88.3)	−1.97	0.11
	TAS2R ($n = 26$)[a]	29.3 (7.9, 21.4)	−1.47	0.13
	TRPV1	97 (40, 57)	−1.64	0.19
GPCR-Mediated Transduction	*GNAT3*	28 (13, 15)	−2.06	0.14
	GNB3	44 (19, 25)	−2.28	0.13
	GNG13	13 (6, 7)	−1.96	0.06
	ITPR3	242 (125, 117)	−1.79	0.11
	PDE1A	31 (11, 20)	−1.90	0.07
	PLCB2	98 (37, 61)	−2.11	0.10
	PRKACA	14 (9, 5)	−2.39	0.09
	PRKACB	10 (4, 6)	−2.23	0.04
	PRKACG	27 (11, 16)	−1.82	0.05
	PRKAR1A	16 (12,4)	−2.07	0.04
	PRKAR1B	47 (32, 15)	−2.10	0.06
	PRKAR2A	32 (10, 22)	−2.58	0.11
	PRKAR2B	19 (11,8)	−2.20	0.08
	CALHM1	58 (15,43)	−2.10	0.05
	CALHM3	30 (11,19)	−2.14	0.10
	TRPM4	129 (43, 86)	−1.88	0.07
	TRPM5	174 (73, 101)	−1.97	0.05
Salivary Secreted	*CA6*	48 (22, 26)	−1.73	0.07
	PRB1	37 (10, 27)	−1.89	0.06

Key: S, Segregating sites in coding regions; S_s, synonymous segregating sites; S_n, nonsynonymous segregating sites; D, Tajima's D (whole gene), FST, F_{ST}(whole gene).

[a]Averages given.

[b]Not annotated in reference genome.

F_{ST} statistic, which reflects the proportion of observed genetic variation attributable to differences between populations, reveals two important patterns (Slatkin, 1991). First, F_{ST} values across taste genes average 0.08, consistent with genome-wide studies, which typically yield F_{ST} values of ~0.10 (Sachidanandam et al., 2001). Thus, levels of variation are comparable to those found throughout the genome. Second, F_{ST} values vary, ranging from 0.03 (in *ASIC3*) to 0.19 (in *TRPV1*). Thus, variation in some genes, such as *ASIC3*, is distributed relatively homogeneously among the populations while variation in others, such as *TRPV1*, is more heterogeneous. These findings suggest that populations exhibit analogous homo- and heterogeneity in taste responses.

3.13.5.2 Natural Selection

Taste perception's role in enabling organisms to identify safe, nutrient rich foods is fundamentally important to organisms' survival and reproduction and, thus, evolutionary fitness. This suggests that the genes underlying taste perception are under selective pressure to optimize the ability of taste systems to identify safe, nutrient rich foods. However, the molecular mechanisms underlying taste perception are shared with other biological processes, particularly GPCR mediated signaling, and are undoubtedly under selective pressure to maintain function in those systems as well. Thus, taste genes are likely under multiple, perhaps countervailing, pressures simultaneously.

The first evidence that natural selection operates on taste genes was observed by Wooding et al. (2004). In an analysis of polymorphism in *TAS2R38* utilizing Tajima's D statistic, which assesses the relative abundance of alleles at different frequencies, Wooding et al. (2004) concluded that the gene accumulated high levels of amino acid variation as the result of balancing natural selection (Tajima, 1989). This is consistent with the hypothesis that the ability to detect a greater diversity of bitter compounds confers fitness advantages. Later studies of *TAS2R38* used similar methods but came to varying conclusions, perhaps reflecting the complexity of selective pressures (Campbell et al., 2012; Risso et al., 2016b). In a study of *TAS2R16* in African populations, Campbell et al. (2014) detected a different type of natural selection, positive selection, which is consistent with recent adaptations to the local environment. This illustrated that selective pressures are likely not uniform across taste genes, or even across *TAS2R*s, but vary. The first multi-gene study of selective pressures on bitter receptors by Kim et al. (2005), who analyzed the relative proportions of synonymous and nonsynonymous variants in 24 bitter receptor genes, confirmed this hypothesis. Kim et al. (2005) concluded that selective pressures vary among *TAS2R*s, but local adaptation has been a pervasive phenomenon. This is consistent with the notion that bitter receptors evolve to target those plant toxins most likely to be present in foods, which are those in the local environment.

Data from the 1000 GP shed light on selective process in taste genes other than *TAS1R*s and *-2R*s, as well. As shown in **Table 3**, patterns of diversity vary from gene to gene; however, all taste genes have highly negative values of Tajima's D (ranging from −1.55 to −2.58, with a mean of −1.89). Negative D values reflect an overabundance of rare alleles, which is a signature of purifying natural selection. This suggests that although taste genes harbor extensive variation, including large numbers of nonsynonymous substitutions, the accumulation of diversity over time has been restricted. This likely reflects the participation of most taste genes in more than one metabolic pathway, which places them under pressure to maintain constant function.

3.13.6 Genotype-Phenotype Associations

Statistical associations between allelic variation in taste genes and taste related phenotypes are well documented. The most evident associations are between variants in taste receptors and responses to specific tastants. However, associations between allelic variants and more complex traits are also found, such as between taste receptor alleles and food and drink preferences, as well as health variables such as body mass index. Allelic variants in taste genes are also often associated with catastrophic disorders, a pattern that seems not to be due to changes in taste sensitivity, but to the sharing of proteins utilized by the taste transduction cascade with other signaling systems.

3.13.6.1 Compound Specific Associations

The earliest evidence of associations between genetic variation and taste sensitivity emerged in the 1930s, shortly after Fox (1932) discovered variability in bitter perception of PTC, when Blakeslee and Fox demonstrated that inheritance of PTC sensitivity could be explained by the presence of "taster" and "non-taster" alleles (Blakeslee, 1932; Wooding, 2006). The specific gene accounting for the variation, *TAS2R38*, was mapped 75 years later by Kim et al. (2003), who found that polymorphism in *TAS2R38* accounts for more than 50% of phenotypic variance in threshold sensitivity to phenylthiocarbamide (PTC), which ranges nearly 10,000-fold among individuals. The functional basis of the polymorphism was established by Bufe et al. (2005), who identified relationships between specific amino acid substitutions, receptor function, and PTC perception. Later, Wooding et al. (2010) made the first identification of a compound found in foods, goitrin, and *TAS2R38* genotypes. This validated numerous previous studies linking PTC taste sensitivity and diet, particularly vegetable consumption, and justified numerous subsequent studies attempting to dissect the relationships between genes, taste, diet, and health (Sandell and Breslin 2006).

Tests for association between variation in GPCR taste genes and perception of specific substances have identified a number of relationships (**Table 4**). In addition to associating with PTC responses, *TAS2R38* genotypes associate with responses to two closely related synthetics, 6-*n*-propylthiouracil (PROP), and methimazole, both of which possess anti-thyroid properties similar to those of PTC and goitrin (Behrens et al., 2013). *TAS2R16* harbors variants associated with perception of salicin, a plant toxin (Campbell

Table 4 Associations between taste gene variation and perception of specific compounds.

Gene	*Compound*	*References*
CA6	PROP	Calò et al. (2011)
CD36	Linoleic acid	Karmous et al. (2018)
CD36	Oleic acid	Pepino et al. (2012)
CD36	Triolein	Pepino et al. (2012)
GNAT3	Sucrose	Fushan et al. (2010)
KCNJ2	Citric acid	Chamoun et al. (2018)
PRB1	PROP, NaCl	Cabras et al. (2012)
SCNN1B	NaCl	Dias et al. (2013)
TAS1R1	MSG	Shigemura et al. (2009)
TAS1R2	Sucrose	Fushan et al. (2009)
TAS1R3	Sucrose, MSG	Fushan et al. (2009), Shigemura et al. (2009)
TAS2R4	Stevioside	Risso et al. (2014)
TAS2R14	Stevioside	Risso et al. (2014)
TAS2R16	Salicin	Campbell et al. (2014)
TAS2R19	Quinine	Reed et al. (2010)
TAS2R31	Saccharin, acesulfame K, quinine	Roudnitzky et al. (2011), Hayes et al. (2015)
TRPV1	NaCl	Dias et al. (2013)
TAS2R38	PTC, PROP, goitrin, methimazole	Kim et al. (2003), Bufe et al. (2005), Wooding et al. (2010), Behrens et al. (2013)

et al., 2014). Compound specific genotype-phenotype associations are also found for TAS2R4 (stevioside), TAS2R14 (stevioside), TAS2R19 (quinine), and TAS2R31 (saccharin, acesulfame K, and quinine).

Variation in the *TAS1R*s is, as predicted, associated with perception of sweet and umami substances. Variants in *TAS1R1*, which encodes the umami-specific TAS1R1 monomer, is associated with recognition thresholds of monosodium glutamate, and MSG and inosine monophosphate mixtures (Shigemura et al., 2009), and *TAS1R2* harbors variants associated with suprathreshold sensitivity to sucrose (Dias et al., 2015). Also as predicted, *TAS1R3*, which encodes the monomer shared between sweet and umami receptors harbors variants associated with responses to both sucrose and MSG (Fushan et al., 2009; Shigemura et al., 2009).

Compound specific genotype-phenotype associations are also found in the non-GPCR taste sensors. Dias et al. (2013) found associations between variants in *SCNN1B* (which encodes the β subunit of ENaC), *TRPV1* and recognition thresholds for NaCl. Similarly, variation in the ion channel gene *KCNJ2* associates with the sourness of citric acid (Chamoun et al., 2018a). Associations are also found between variants in the CD36 scavenger receptor and the lipids linoleic acid, oleic acid, and triolein (Pepino et al., 2012; Karmous et al., 2018).

Of the many genes encoding intracellular components of GPCR mediated taste pathways only one, *GNAT3*, is known to harbor variants associated with taste responses to specific compounds. Variation in *GNAT3*, which encodes the alpha subunit of gustducin, is associated with sucrose perception (Fushan et al., 2010). However, associations with taste responses to specific compounds have not been reported for any genes listed in **Table 1** other than those cited in **Table 4**. This is likely the result of two factors. First, studies aimed at identifying variants accounting for perception of specific compounds have focused on those molecules most likely to be involved specifically in taste – the surface receptors. Second, the intracellular components of GPCR mediated transduction pathways frequently participate in signaling processes unrelated to taste. Because these proteins participate in more than one system, they are under added pressure from natural selection to keep their functions constant; hence, they are less likely to harbor functional variation.

Associations between variation in the salivary protein genes *CA6* and *PRB1* and taste sensitivity are also known. Variants in both *CA6* and *PRB1* covary with threshold and suprathreshold sensitivity to PROP, and variants in *CA6* are associated with salt perception (Calo et al., 2011; Cabras et al., 2012; Feeney and Hayes, 2014). The mechanisms underlying these associations are not yet known. However, some evidence suggests that *CA6* affects taste by shaping proliferation and metabolic activity in fungiform papillae (Melis et al., 2013).

3.13.6.2 Preferences and Behaviors

The notion that genetic variation in taste sensitivity likely translates to differences in food preferences dates back to at least 1954 (Fox, 1954). This was based on Blakeslee (1931)'s discovery that differences in PTC sensitivity, which were readily measured using simple methods, is highly heritable. Thus, while really a phenotypic measure, PTC sensitivity could serve as a surrogate genetic marker. It retained this use in human genetics for decades (Wooding, 2006). In the realm of taste genetics, PTC sensitivity, and later PROP sensitivity, were used to examine a range of associations between taste, preferences, and behaviors, particularly between taste and vegetable preferences. These were motivated by the chemical similarities between PTC PROP, and thiourea compounds actually found in vegetables (Drewnowski and Rock, 1995; Dinehart et al., 2006). Thus, while PTC sensitivity phenotype was not a perfect

genetic marker, it was a surrogate powerful enough to provide an important bridge between heritability and chemosensation (Wooding, 2006; Wooding et al., 2010).

As information about the genetic basis taste sensitivity has increased, so too has knowledge about associations with responses relevant to everyday behavior. To date, most research has continued to focus on the *TAS2R* genes, which are relatively simple in structure and function. Numerous studies of *TAS2R38* genotypes have been conducted, revealing associations with such diverse phenotypes as alcohol intake, feeding behavior in infants, eating disinhibitions, and vegetable and candy consumption (Duffy et al., 2004; Dotson et al., 2010; Hayes et al., 2013; Hoppu et al., 2015). The number of *TAS2R*s being studied has expanded, as well. For instance, Hayes et al. (2015) found that variation in two *TAS2R*s, *TAS2R19* and *-31*, associates with liking of grapefruit juice, and variants in *TAS2R16* associate with alcohol intake (Hayes et al., 2011). Given the large number of *TAS2R*s in the human genome, and the extensive variation they contain, it is likely that both individual and combinations of *TAS2R* polymorphisms are associated with many consumption behaviors. Evidence for associations with taste genes beyond TAS2Rs is emerging as well. For instance, variants in *TAS1R1* and *TAS1R3* is associated with food choices in buffet meal settings, and variation in *CD36* is associated with fat and sugar intake (Pioltine et al., 2016; Han et al., 2018).

3.13.6.3 Health Measures

The associations observed between taste genes and taste responses to specific compounds and consumption behaviors extend to health measures. As with preferences and consumption patterns, the earliest associations between taste genes and health measures were with the PROP/PTC phenotype. These confirmed the existence of associations between genes, diet, and health, and fostered the development of an extensive literature analyzing associations between bitter taste, particularly PROP/PTC perception, and health (Tepper, 1998). Indeed, the simplicity and convenience of PROP/PTC tasting has kept it in wide use for this purpose (Tepper et al., 2009).

Studies of specific mutational variants in taste genes has revealed a constellation of genotype-phenotype associations between taste and health (Dotson et al., 2012; Chamoun et al., 2018b). Again, *TAS2R38* has emerged as a dominant example (Tepper et al., 2014). The most readily explained and consistent associations are between *TAS2R38* variants, obesity, and body mass index, which are likely driven by food likings and ingestion behaviors (Ortega et al., 2016). *TAS2R38* also harbors variants associated with smoking behaviors, with alleles conferring higher taste sensitivity being associated with lower levels of smoking (Cannon et al., 2005; Risso et al., 2016a). Another compelling and relatively direct connection between variation in taste genes and health is between the sweet receptor monomer (*TAS1R2*) and risk of dental caries, which is hypothesized to result from variation in sugar consumption (Wendell et al., 2010; Robino et al., 2015).

Variation in taste genes associated with more complex health measures, as well. These associations are consistent with current knowledge about relationships between diet and health, but their mechanisms are not known. One of the most conspicuous associations is between variation in *TAS2R*s and gastrointestinal cancers. Again, variation in *TAS2R38* has emerged as important. It has been found to be associated with risk of gastric cancer, colorectal cancer, and development of colonic neoplasms (Basson et al., 2005; Carrai et al., 2011; Schembre et al., 2013; Choi et al., 2016; Choi and Kim, 2019). These associations are intriguing because the vegetables most strongly associated with *TAS2R38* variation are also well known for containing isothiocyanates with anti-cancer properties (Fahey et al., 1997; Shapiro et al., 2001). Thus, associations between variation in *TAS2R38* and susceptibility to cancer in the gastrointestinal tract might be explained by variation in consumption of these vegetables and, hence, to altered risk of cancer. Associations between *TAS2R38* variants and cancer are also found in tissues outside the gastrointestinal tract, notably thyroid adenoma and carcinoma (Choi et al., 2018).

A second trend in genotype-phenotype associations involving taste receptors is that many are endocrinological (Dotson et al., 2008; Keller et al., 2012; Calvo and Egan, 2015; Loper et al., 2015; Behrens and Meyerhof, 2019). This is consistent with the notion that consumed foods alter hormone states, such that variation in consumption due to variation in taste receptors could be causal. It is also consistent with the observation that the transductional mechanisms utilized in taste sensations are also utilized for hormonal signaling by endocrine cells in the gut (Egan and Margolskee, 2008). Thus, the action of taste receptors in the gut has potentially impactful and far reaching metabolic consequences. These patterns suggest that associations between variation in taste receptors and measures of obesity and cardiovascular health are driven simultaneously by taste receptors' effects on ingestive behaviors and their effects on endocrinological processes in the gut. This hypothesis is supported by several reported associations, including between *SCNN1B* variants and Liddle syndrome, between *CD36* variants and fatty acid metabolism, and between *TAS2R42* variants and thyroid function (Chang et al., 1996; Firsov et al., 1996; Clark et al., 2015; Melis et al., 2017).

Taste genes encoding components of the transduction cascade downstream of the surface receptors exhibit little evidence of being associated with taste responses. This is likely due to their being widely expressed and involved in multiple signaling systems, so variation results in catastrophic disorders. For instance, variants in PKA are implicated in disorders arising from dysregulation of cAMP signaling, including neurological disorders, anxiety behaviors, and cancers (Soberg et al., 2012; Wong et al., 2014; Keil et al., 2016; Turnham and Scott, 2016). Variants in the CALHM channels are implicated in the development of Alzheimer's disease, epilepsy, and Creutzfeldt-Jakob disorder (Dreses-Werringloer et al., 2008; Lv et al., 2011; Calero et al., 2012; Rubio-Moscardo et al., 2013; Lu et al., 2016). Variants in *KCNJ2* are implicated in the development of channelopathies resulting in cardiac rhythm, including both long- and short-QT syndrome (Tristani-Firouzi et al., 2002; Chun et al., 2004; Kimura et al., 2012). Mutations in *ITPR3* are associated with disorders arising from dysfunction in intracellular Ca^{2+} release, including some evidence of involvement in type 1 diabetes, apoptosis, and cancer (Roach et al., 2006; Shibao et al., 2010; Reddy et al., 2011). Thus, variants in these genes

that alter taste responses without causing disease are likely rare. Conversely, however, it may be that these disease causing variants result in alterations in taste sensitivity simultaneous with disease. This possibility remains poorly investigated.

3.13.7 Summary

The genetic encoding of taste perception systems, particularly of sensory proteins responsible for the earliest stages of response, provides a framework for understanding the molecular basis of taste. By enabling the perception of nutrients and other key aspects of the environment, these genes enable behavioral and metabolic reactions via mechanisms utilizing both shared and distinct molecular pathways, and mutational variation results in variable responses among individuals, resulting in variable behaviors and downstream health effects. Further dissecting these pathways will lead to a better understanding of the fundamentals of environmental response and shed new light on their biological significance.

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