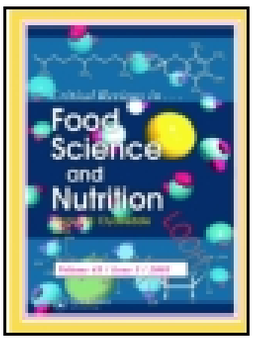

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A review of the associations between single nucleotide polymorphisms in taste receptors, eating behaviours, and health

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A review of the associations between single nucleotide polymorphisms in taste receptors, eating behaviours, and health

Elie Chamoun, David M. Mutch, Emma Allen-Vercoe, Andrea C. Buchholz, Alison M. Duncan, Lawrence L. Spriet, Jess Haines and David W.L. Ma*, on behalf of the Guelph Family Health Study

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Abstract: Food preferences and dietary habits are heavily influenced by taste perception. There is growing interest in characterizing taste preferences based on genetic variation. Genetic differences in the ability to perceive key tastes may impact eating behavior and nutritional intake. Therefore, increased understanding of taste biology and genetics may lead to new personalized strategies which may prevent or influence the trajectory of chronic diseases risk. Recent advances show that single nucleotide polymorphisms (SNPs) in the CD36 fat taste receptor are linked to differences in fat perception, fat preference, and chronic-disease biomarkers. Genetic variation in the sweet taste receptor T1R2 has been shown to alter sweet taste preferences, eating behaviours, and risk of dental caries. Polymorphisms in the bitter taste receptor T2R38 have been shown to influence taste for brassica vegetables. Individuals that intensely taste the bitterness of brassica vegetables ("supertasters") may avoid vegetable consumption and compensate by increasing their consumption of sweet and fatty foods, which may increase risk for chronic disease. Emerging evidence also suggests that the role of genetics in taste perception may be more impactful in children due to the lack of cultural influence compared to adults. This review examines the current knowledge of SNPs in taste receptors

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associated with fat, sweet, bitter, umami, and salt taste modalities and their contributions to food preferences, and chronic disease. Overall, these SNPs demonstrate the potential to influence food preferences and consequently health.

Keywords: biomarkers; bitter; fat; salt; single nucleotide polymorphisms; sour; sweet; taste receptor; umami.

1. Introduction

Similar to many species, humans are often driven to select foods based on their hedonic characteristics (Rolls, 2012; Turner-McGrievy, Tate, Moore, & Popkin, 2013). As such, the taste of food is an important factor when parents create dietary habits for themselves and their children (Kral & Rauh, 2010). In modern society, it is easy to gain access to large amounts of highly-palatable foods containing saturated fats and added sugars. Obesity, cardiovascular disease (CVD), type 2diabetes (T2D), and metabolic syndrome (MetS—may include dyslipidemia, elevated blood pressure, insulin resistance, abdominal obesity, and pro-inflammatory and thrombotic states) are chronic pathologies which have been partially attributed to adverse eating behaviours in humans compelled by the rewarding experience of taste perception (Rolls, 2012). A growing body of knowledge demonstrates the importance of understanding individual responses to medicine and nutrition (Gibney, McNulty, Ryan, & Walsh, 2014). Emerging research suggests that genetic predisposition and non-genetic factors such as life stage, eating behaviour, physical activity, and gut microbiota also determine taste perception differently for every individual (Fay & German, 2008; Grimm & Steinle, 2011). It is therefore possible that due to different perceptions of taste, individual food preferences are important determinants of chronic disease risk.

Taste receptors on the tongue can be characterized in terms of their genetic variation to determine their contributions to specific eating behaviours and potentially the development of chronic diseases. Variations in receptor function for sweet, fat, and bitter tastes form much of the basis for the known inter-individual differences in taste perception (Mennella, Pepino, & Reed,

2005). The putative fat taste receptor cluster determinant 36 (CD36), the sweet taste receptors type 1 member 2 (T1R2) and T1R3, the bitter taste receptor T2R38, the umami fat taste receptors T1R1 and T1R3, and the salt taste receptors epithelial sodium channel (ENaC) and transient receptor potential cation channel subfamily V member 1 (TRPV1) contain single nucleotide polymorphisms (SNPs) which may alter taste perception, food preference, and consequently metabolic and health outcomes. Polymorphisms in this review will be stated with their unique SNP identifier and, where available, the minor allele frequency (MAF) in the CEU population from the International HapMap Project is indicated (2003). The aim of this review is to summarize current knowledge of SNPs in taste receptors associated with fat, sweet, bitter, umami, and salt taste modalities and their contributions to food preferences and chronic disease.

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2. Brief overview of human taste perception

Taste or gustatory perception is one of the five traditional senses. Humans are able to taste food and other substances with the tongue papillae, which each consist of hundreds of taste buds (Daniel D.Chiras, 2005). Between 2000 and 5000 taste buds exist along the surface of the front and back of the tongue, and each taste bud is lined with 50-100 taste bud cells (TBCs) (Daniel Schacter, 2009). Nutrients dissolved in saliva interact with taste receptors located at the apical side of a TBC.

Taste bud cells can be separated into four morphological subtypes: Types I, II, III and IV (Chaudhari & Roper, 2010) (Table 1). It is thought that Type I cells play a supporting role for

other TBCs, similarly to glial cells of the central nervous system. As such, Type I cells express proteins capable of clearing or degrading neurotransmitters following a synaptic event (Bartel, Sullivan, Lavoie, Sevigny, & Finger, 2006). Additionally, the Type I cells comprise membrane ion channels that allow for the perception of salty taste from sodium chloride (Chandrashekar et al., 2010; Vandenbeuch, Clapp, & Kinnamon, 2008; Yoshida et al., 2009). Type II cells can be further categorized based on the expression of sweet, bitter and umami taste receptors (Adler et al., 2000; Nelson et al., 2001). These receptors are seven-transmembrane G-protein coupled receptors (GPCR). Sweet taste is elicited by a heterodimer of T1R2 and T1R3, whereas umami taste is elicited by a heterodimer of T1R1 and T1R3. Bitter taste can be initiated by a number of T2R proteins, depending on the particular bitter substance consumed. All Type II cells are thought to express the signaling enzymes phospholipase C β2 and transient receptor potential channel M5 downstream of the GPCRs, while only a subset express the G protein subunit α-gustducin (Yarmolinsky, Zuker, & Ryba, 2009). Type II taste cells do not form traditional synapses with afferent nerve fibers. However, Type III cells do display presynaptic features including synaptic vesicles and vesicle fusion machinery such as synaptosomal-associated protein 25 (e.g., (Clapp, Medler, Damak, Margolskee, & Kinnamon, 2006; DeFazio et al., 2006)). Some Type III cells are sensors for sour taste (Huang et al., 2006a). Type IV cells are basal cells which have been suggested to contain precursor populations that can differentiate into other TBC types (Sullivan, Borecki, & Oleskevich, 2010). It is not known which TBC types contain the putative fat taste receptor CD36, but it has been hypothesized that Type II and/or Type III cells contain this receptor (Simons, Kummer, Luiken, & Boon, 2011). One study used

the cell culture method to determine that CD36 is expressed in a taste bud cell line (HTC-8) similar to Type II cells (Hochheimer et al., 2014).

Small molecule neurotransmitters signal between taste cells and/or between taste cells and intragemmal nerve fibers. These molecules and their functions in taste perception have been reviewed in detail by Chaudhari and Roper (Chaudhari et al., 2010). As mentioned, Type II cells do not exhibit typical synapses. Instead, Type II cells respond to stimuli by releasing adenosine triphosphate (ATP) and acetylcholine through hemichannels (Dando & Roper, 2009; Finger et al., 2005; Huang et al., 2007; Romanov et al., 2007) which, in turn, activate purinergic receptors on cranial nerve fibers (Bo et al., 1999; Dando & Roper, 2012; Ogura, 2002; Yang, Montoya, Bond, Walton, & Kinnamon, 2012). Type III cells, however, respond to stimulation by releasing serotonin, norepinephrine and L-aminobutyric acid (Cao, Zhao, Kolli, Hivley, & Herness, 2009; Dvoryanchikov, Huang, Barro-Soria, Chaudhari, & Roper, 2011; Huang, Dando, & Roper, 2009; Huang, Maruyama, & Roper, 2008; Huang, Maruyama, Stimac, & Roper, 2008; Huang, Pereira, & Roper, 2011; Obata, Shimada, Sakai, & Saito, 1997). The primary neurotransmitter that allows for taste cells to associate with afferent nerves appears to be ATP (Finger et al., 2005), while other neurotransmitters may mediate important taste cell functions through autocrine and paracrine signaling. Thus, other neurotransmitters may also contribute to the output of the taste bud (Chaudhari et al., 2010). Fatty acids, sugars/sweeteners, bitter compounds, sodium chloride, monosodium glutamate, and protons are examples of stimuli which have the potential to initiate synaptic events leading to the sensation of taste.

3. Eating behaviour may differ in children and adults

The maturation of taste and its consequences on eating behaviour appear to be influenced early in life by genetics, as well as by environmental and cultural experiences. In adulthood, environmental and/or cultural experiences rather than genetic predisposition appear to be more correlated to taste perception and eating behaviour (Connors, Bisogni, Sobal, & Devine, 2001; Drewnowski, Henderson, Levine, & Hann, 1999; Drewnowski & Specter, 2004; Monge-Rojas, Mattei, Fuster, Willett, & Campos, 2014; Scheibehenne, Miesler, & Todd, 2007). While not consistently reported, several studies on the genetics of taste suggest that learned behaviours can override genetic predisposition. This may explain, for example, why adults consume bitter vegetables which confer health benefits despite the bitter taste that instinctively promotes avoidance (Forrai & Bankovi, 1984; Glanville EV & Kaplan AR, 1965; Jerzsa-Latta, Krondl, & Coleman, 1990; Kulkarni et al., 2013; Lucas & Bellisle, 1987; Mattes & Labov, 1989; Mattes, 1985; Niewind A., Krondl M., & Shrott M., 1988; Rodin, Moskowitz, & Bray, 1976; Sharma & Kaur, 2014; Zeinstra, Koelen, Kok, & de, 2007).

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Twin studies provide evidence that eating behaviour in adults is contributed in part by environment and genetics. In a longitudinal adult study investigating eating styles in 39 female and 45 male monozygotic Finnish twin pairs discordant for obesity or overweight, normal-weight twins were observed to have different eating styles than their obese siblings. Specifically, the normal-weight twins were less likely to report restrictive eating, overeating, and unhealthful food choices (Keski-Rahkonen et al., 2007). In contrast, a Swedish adult male twin study demonstrated that the heritability of eating behaviour such as cognitive restraint, emotional eating, and uncontrolled eating were 59%, 60%, and 45% respectively (Tholin, Rasmussen, Tynelius, & Karlsson, 2005). Similarly, another adult male twin study from the United Kingdom

and Finland showed that the heritability of cognitive restraint, emotional eating, and uncontrolled eating were 26-63%, 9-45%, and 45-69% respectively (Keskitalo et al., 2008). It is important to note that the heritability of obesity in these discordant twin studies does not refer to the heritability of specific genes, such as taste receptor genes (Keski-Rahkonen et al., 2007; Keskitalo et al., 2008; Tholin et al., 2005). None of the heritable factors investigated in the twin studies have been attributed to specific polymorphic variations in taste receptors. Therefore, future studies in twins discordant for obesity should explore taste receptor genetic variation as a heritable factor which influences eating behaviour. Furthermore, no genetic analyses have been done in elderly participants in association with taste perception, taste preferences, nutritional status, or health outcomes. The reason for the lack of genetics studies could be that the loss of taste sensitivity, as a result of reduced TBC regeneration, in the elderly would strongly confound genetic components of taste as causes of change in taste outcomes and health outcomes (Fukunaga, 2005).

In children, studies examining the association between genetics of taste and eating behaviour are limited and may not be generalized from adult studies. Compared to studies with adults, research with children show stronger correlation between genetic predisposition for certain eating behaviours and their actual consumption patterns (Sharma et al., 2014). This relationship is especially pronounced in the tasting of bitter compounds by young children. It is thought that aversion to bitter taste by young children is an evolutionary adaptation to prevent the ingestion of toxic plant compounds or other harmful bitter substances which occur in nature (Zeinstra et al., 2007). These few observations present a potential new line of investigation to

explore ways to develop positive eating habits in children through a better understanding of the genetics of taste on eating behavior (Sharma et al., 2014; Zeinstra et al., 2007).

4. Fat taste

Oleogustus is the most recently identified taste modality (Running, Craig, & Mattes, 2015). The taste perception of long-chain fatty acids (LCFA) was previously thought to only be dependent on the texture of the lipid, and the olfactory stimulus to a lesser extent (Greenberg & Smith, 1996; Ramirez, 1993; Tepper & Nurse, 1997). There is now an abundance of evidence supporting taste as a method of oral detection of dietary fat, including saturated fat (Table 2) (Fukuwatari et al., 2003; Mattes, 2009; Running et al., 2015). LCFA provide this stimulus in both rodents (Takeda, Imaizumi, & Fushiki, 2000; Tsuruta, Kawada, Fukuwatari, & Fushiki, 1999) and in humans (Chale-Rush, Burgess, & Mattes, 2007). In the mouse, knockout experiments for LCFA receptor genes such as CD36 indicated a decrease in the spontaneous attraction for fat-enriched foods (Laugerette et al., 2005; Sclafani, Ackroff, & Abumrad, 2007).

The fatty acid translocase CD36 has been the subject of much of the research related to LCFA taste perception. CD36 is expressed in human TBCs (Simons et al., 2011), and has a strong affinity for LCFA (Baillie, Coburn, & Abumrad, 1996). CD36 knockout mice have been shown to lack the ability to detect LCFA in behavioral tests (Laugerette et al., 2005; Sclafani et al., 2007). The oral perception of linoleic acid (an n-6 polyunsaturated fatty acid), α-linolenic acid (an n-3 polyunsaturated fatty acid), and oleic acid (an n-9 monounsaturated fatty acid) have been attributed to the CD36 TBC receptor (Hochheimer et al., 2014; Keller et al., 2012b). Additionally, a GPCR has been found to bind LCFA and influences the perception of lipids in

the oral cavity. GPCR120-null mice show decreased preference for LCFA-enriched solutions in eating behavioral tests compared to wild type (Cartoni et al., 2010). Thus, LCFA as gustatory stimuli are more complex than initially understood.

The consumption of energy-dense foods may be linked to enhanced palatability of dietary fats which predispose individuals to metabolic complications (Liang et al., 2012; Stewart, Feinle-Bisset, & Keast, 2011). The relationship between sensory fat perception and predisposition to weight gain has been shown in recent adult human studies (Liang et al., 2012; Stewart et al., 2010; Stewart et al., 2011). This relationship outlines the remarkable difference in obese and lean subjects with respect to fat intake and taste sensitivity. In an obese rat model, an inverse correlation between gustatory sensitivity to LCFAs and dietary preference for fat was observed (Gilbertson, Liu, York, & Bray, 1998). Correspondingly, a higher sensitivity to tasting LCFA has been correlated to reduced fat intake, total caloric intake, and body mass index (BMI) (Stewart et al., 2010). Similarly, a high-fat diet decreased the taste sensitivity to oleic acid in lean, but not obese patients (Stewart & Keast, 2012). These observations suggest that a lack of sensitivity to fat taste increases fat intake, and may partly explain why obese adult individuals seem to consume fatty foods more frequently than lean patients (Liang et al., 2012; Stewart et al., 2011). Therefore, the implications of these findings on eating behaviour and health have potential significance.

A study by Ma et al. investigated associations between common SNPs in the CD36 gene, lipid and glucose metabolism, and risk for cardiovascular disease (Ma et al., 2004). This group genotyped 21 polymorphisms which evenly spanned the CD36 gene, revealing 2 linkage

disequilibrium (LD) blocks represented by a haplotype. The haplotype comprised the following five SNPs: 1) -33137A/G (rs1984112; MAF=0.3468), 2) -31118G/A (rs1761667; MAF=0.3904, 3) 25444G/A (rs1527483; MAF=0.1018), 4) 27645 deletion /insertion (del /in) (rs3840546; MAF not reported) and 5) 30294G/C (rs1049673; MAF=0.3832). In a population of adults of European descent, the 30294C polymorphism was significantly associated with higher plasma free fatty acids (FFA), with a stronger association among men compared to women. A similar increase in plasma FFA levels was seen in men carrying the -33137A and -31118G polymorphisms. In the order of SNPs listed above, the haplotype of an individual can be represented by sequentially naming the nucleotide bases. Men with the AGGIG haplotype had 31% higher FFA and 20% higher plasma triglycerides (TG) than non-carriers. The AGGIG haplotype was also correlated to an increased risk of coronary artery disease in T2D American participants (n=197) and Italian participants (n=321). In the scope of this study by Ma et al., CD36 modulated lipid metabolism and CVD risk in adults of European descent. However, it is unclear whether this modulation occurred at the level of taste perception or metabolism. Further research is required to discern the effects of taste perception and lipid transport on the levels of FFA and TG in the plasma, or if this modulation would also be seen in other ethnicities.

CD36 plays an important role in lipid metabolism and polymorphisms within the CD36 gene have been linked to CVD risk factors (Noel et al., 2010). The relationship between genotypes and haplotypes of five SNPs in the CD36 gene (-33137G, -31118A, -22674C (rs2151916; MAF=0.3339), 27645 del/ins and 30294C) with lipid levels have been examined in young normal-weight subjects (Ramos-Arellano et al., 2013). High-density lipoprotein cholesterol (HDL-C) levels were lower in -22674C carriers than -22674T carriers, and TT

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homozygotes had lower oxidized low-density lipoprotein cholesterol (LDL-C) levels compared to -22674C allele carriers. LDL-C levels were higher in carriers of the CC genotype for the 30294C polymorphism compared to non-carriers. Subjects carrying the AATDC haplotype had 3.2 times higher risk of LDL-C > 100 mg/dL than those carrying the AGTIG haplotype, whereas subjects carrying the AATIC haplotype had 2.0 times higher risk of total cholesterol > 200 mg/dL than the AGTIC haplotype. Therefore, genetic variation in CD36 may modulate CVD risk by affecting lipid metabolism.

Single nucleotide polymorphisms in the CD36 gene have also been associated with metabolic disorders related to excess fat depots in adult populations (Corpeleijn et al., 2006; Lepretre et al., 2004b; Lepretre, Cheyssac, Amouyel, Froguel, & Helbecque, 2004a; Love-Gregory et al., 2008; Ramos-Arellano et al., 2013), and a (TG)-repeat in intron 3 has been linked to elevated BMI in Korean patients with coronary heart disease (Yun, Song, Song, Song, & Kim, 2007). Bokor et al. assessed the link between CD36 SNPs and the risk of obesity in a case–control study comprising 307 obese (age = 15.0 ± 1.1 years) and 339 normal-weight (age = 14.6 ± 1.1 years) adolescents (Bokor et al., 2010). Four SNPs (rs3211867, rs3211883, rs3211908, and rs1527483) were associated with increased obesity risk, higher BMI, and higher percent body fat. A haplotype consisting of the minor alleles of these SNPs was also linked to obesity and excess adiposity (i.e., higher BMI and percent body fat).

Studies examining correlative relationships between genetic variations in CD36 and chronic disease have focused on predispositions to specific eating behaviours (Table 3). Three CD36 gene polymorphisms (-31118A and 25444A and 27645ins), which correspond to part of

the haplotype studied by Ma et al., were investigated for their associations with changes in fat taste perception (Keller et al., 2012b). Homozygotes for the A allele at locus -31118 reported greater perceived creaminess, independently of fat concentration of salad dressings and higher mean acceptance of added fats and oils compared to other CD36 genotypes. Participants with the CT or TT genotypes at 25444 also perceived greater fat content in the salad dressings, regardless of actual fat concentration. 27645 deletion homozygotes had higher waist circumference and BMI than ins/del or ins/ins individuals ($P < 0.001$, n=2), however this particular observation requires further replication due to small sample size. Furthermore, Pepino et al. reported findings on the -31118A SNP and fat preference (Pepino, Love-Gregory, Klein, & Abumrad, 2012). Twenty-one obese participants with the locus variations AA (n=6), AG (n=7), and GG (n=8) were studied with respect to oleic acid and triolein orosensory detection thresholds. The major and minor alleles of this SNP vary depending on the population. In populations with African ancestry, the G allele is minor, whereas the opposite is true in individuals of European descent. G allele homozygotes had 8-fold lower oral detection thresholds (i.e. higher sensitivity) for oleic acid and triolein than the A allele which was associated with a decrease in CD36 expression. Intermediate thresholds were observed in heterozygotes. Higher fat taste sensitivity is associated with a decrease in fat preference (Stewart et al., 2010). However, these findings conflict with other studies on the effect of the -31118 SNP on CD36 expression and function. For instance, Ma et al. hypothesized that the G homozygosity for the -31118 SNP is associated with decreased CD36 function, along with the other associated SNPs in LD (Ma et al., 2004). This was hypothesized due to higher plasma FFA and TG in the presence of normal glucose and insulin levels in G allele homozygotes. Higher plasma FFA are indicative of defective CD36 due to the

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role of this receptor to translocate FFA into the muscle and other tissues from the plasma (Febbraio et al., 1999). The increased FFA in the plasma is redirected to the liver which takes up FFAs independently of CD36 (Goudriaan et al., 2003). The liver can then synthesize TGs and release them into the plasma, which may also explain why TGs are high in G allele homozygotes. If the G allele of -31118 is associated with decreased function in the skeletal muscle, and the SNP is located in the promoter of the gene, one would hypothesize that the decreased function might be the result of a decreased expression of the receptor in skeletal muscle. Decreased expression of CD36 on the tongue should lead to decreased taste sensitivity to fat, hence an increase in fat intake and higher plasma FFAs and TGs. However, the oral fat perception studies which have examined the -31118 SNP have associated the A allele, not the G allele, with decreased fat taste sensitivity and greater preference for fat. This apparent discrepancy could be due to differences in CD36 promoter activity between skeletal muscle and tongue. This difference can be investigated in the future by assessing the expression of CD36 in these tissues in a group of individuals genotyped for the -31118 SNP as well as other associated SNPs in LD. This information would be useful in consolidating current studies on CD36 genetic variation and its effects on fat taste perception and metabolic profile. It would also serve to inform individuals on how they can optimize their diets to improve their metabolic profile based on their CD36 genetic profile (Madden et al., 2008).

Lean mice and humans can be more sensitive to LCFA-rich foods such as butter, oil, and fatty meat while obese individuals have decreased taste sensitivity to fatty acids due to particular CD36 variants. Therefore, CD36 genetic variation may have the potential to influence fat intake and weight gain by decreasing the oral taste sensitivity of LCFAs in individuals. CVD and

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dyslipidemia may result from this eating behaviour associated with fat overconsumption, especially when the dietary fat predominantly consists of saturated fats (Colin-Ramirez et al., 2014). Although studies to date are limited, they provide promising data on the link between genetics, fat perception, and fat preference. It is important to characterize genetic variations in putative fat taste receptors in order to more clearly understand the role of fat taste perception in the development of chronic metabolic disease.

5. Sweet taste

The only receptors known to be involved in the perception of sweet taste are T1R2 and T1R3, which form a heterodimer (Li et al., 2002). These transmembrane proteins allow humans to taste a variety of sweet substances such as naturally occurring sugars (glucose, sucrose, fructose and sugar alcohols), D-amino acids (D-tryptophan and D-phenylalanine) and glycosides (stevioside and glycyrrhizin), as well as alternative sweeteners such as sucralose, aspartame, neotame, saccharin sodium, acesulfame potassium, and cyclamate (Chandrashekar, Hoon, Ryba, & Zuker, 2006). Moreover, naturally occurring sweet proteins, such as brazzein, thaumatin, and monellin, and naturally occurring taste-modifying proteins, such as neoculin and miraculin, also bind to T1R2 and T1R3 (Cui et al., 2006; Jiang et al., 2004; Nakajima et al., 2006; ssadi-Porter et al., 2010; Temussi, 2002; Walters & Hellekant, 2006). Although both receptors are needed to elicit sweet taste, T1R2 is the subunit specific to sweet taste perception because T1R3 is also involved in the detection of the umami taste when it dimerizes with T1R1 (Nelson et al., 2002).

Genetic variations in T1R2 and T1R3 are important to characterize because they pertain to changes in taste sensitivity to sugar (Drayna, 2005; Keskitalo et al., 2007b; Keskitalo et al.,

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2007a; Keskitalo et al., 2008; Kim, Breslin, Reed, & Drayna, 2004; McDaniel & Reed, 2003; Reed, Bachmanov, Beauchamp, Tordoff, & Price, 1997; Reed, Li X, Bachmanov AA, Mascioli K, & Beauchamp GK, 2003; Reed & McDaniel, 2006; Reed, Tanaka, & McDaniel, 2006), summarized in Table 4. In African, Asian, European and Native American populations, all three T1R genes have a multitude of polymorphisms. These SNPs include non-synonymous SNPs which are located in the N-terminal extracellular domain, the part of the receptor where ligands for taste are thought to bind. Being particularly polymorphic in comparison with other human genes, T1R2 is within the top 5–10% of all human genes with regards to the reported number of polymorphisms. This increased polymorphic rate was hypothesized to be associated with variations in sweet taste perception (Kim, Wooding, Riaz, Jorde, & Drayna, 2006). One study sought to determine whether Ile191Val variations in T1R2 were linked to differences in the consumption of sugars in 1037 diabetes-free young adults, and 100 individuals with T2D. (Eny, Wolever, Corey, & El-Sohemy, 2010). They demonstrated an association between the Ile191Val SNP (rs35874116; MAF=0.2670) in T1R2 and BMI in individuals with a BMI $\geq$25. In the diabetes-free individuals, Val carriers (homozygous or heterozygous) consumed significantly fewer sugars compared to homozygous Ile carriers. This finding was consistent in T2D individuals where Val carriers also consumed significantly less sugar compared to Ile homozygotes. Genetic variation in the other half of the heterodimer, T1R3, was explored in a separate study by Fushan et al. They showed that intronic SNPs in the T1R3 promoter were linked to sucrose taste sensitivity in humans by altering T1R3 transcription levels (Fushan, Simons, Slack, Manichaikul, & Drayna, 2009). These SNPs accounted for 16% of the population's variability in sweet perception (Fushan et al., 2009). The associations between

genetic variations in sweet taste receptors and consumption of sweet foods are important findings for individuals who are at risk for metabolic complications due to their eating behaviour.

In children, the risk for developing dental caries is associated with the consumption of sweet foods (WEISBERGER, 1950). One study has investigated an association between the prevalence of dental caries and the Ile191Val polymorphism (T1R2) in 80 young adults of European descent (Kulkarni et al., 2013). Val carriers of the T1R2 SNP, i.e., individuals who have been shown to have lower consumption of sweet foods, had lower risk of developing dental caries. A similar finding was observed in a study conducted in schoolchildren. A significant association between total caries was observed with the Ile191Val (T1R2) and the rs307355 SNPs (T1R3). Moderate number of caries (4-7 caries) was observed in rs307355 (MAF=0.2364) heterozygotes, while high-risk caries (>8 caries) was observed in Val homozygotes of the T1R2 SNP (Haznedaroglu et al., 2015). Therefore, individuals who are genetically predisposed to prefer sweet foods should also consider that their eating behaviour influences not only metabolic risk factors, but also dental health. The profundity of those implications must be verified with more studies which consider this T1R2 SNP and other polymorphisms in sweet-sensing genes. Nevertheless, these findings suggest a highly relevant outcome in children as well as young adults.

6. Bitter taste

Bitter and sweet taste profiles interact together to affect eating behavior, and this phenomenon is seen especially in children (Mennella et al., 2005). High concentrations of bitter substances generally result in food rejection, which corresponds to an evolutionary adaptation to

avoid toxic substances such as rancid fat, hydrolyzed protein and plant alkaloids (Glendenning JI, 1994; Hladik CM & Simmen B, 1996). Higher sensitivity to bitter taste may cause individuals to avoid consuming vegetables rich in anti-tumour and anti-oxidant compounds and may, consequently, lead to a higher consumption of sweet and fatty foods as substitutes. This eating behaviour has the potential to increase the risk of CVD, obesity, and cancer (Goldstein, Daun, & Tepper, 2005).

Although there are 25 different types of T2Rs for bitter taste perception on Type II TBCs (Dong, Jones, & Zhang, 2009), only T2R38 has been associated with a genetically predetermined bitter taste status (Kim et al., 2003). Kim et al. identified the bitter receptor T2R38 as being responsible for tasting phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) (Kim et al., 2003). Three common SNPs were found in this gene which results in 3 amino acid substitutions at residues P49A (rs713598; MAF=0.4952), A262V (rs1726866; MAF=0.4255) and V296I (rs10246939; MAF=0.4794). The bitter-tasting phenotype is attributed to a combination of these three SNPs resulting in a PAV amino acid haplotype, while non-tasters carry the AVI amino acid haplotype (Bufe et al., 2005). Homozygosity for the PAV haplotype is considered to be a marker of “supertaster” status while those who are homozygous for the AVI haplotype are considered “non-tasters”, and heterozygotes have an intermediate phenotype. This phenotype is also observable by simply assessing the intensity (or lack thereof) of the bitter taste impregnated on a strip of filter paper covered in PTC.

A supertaster is a person who experiences the sense of bitter taste with far greater intensity than average (Bartoshuk, Duffy, & Miller, 1994). This amplified oral perception

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appears to have a biological basis rather than being the result of response bias or a scaling artefact (Turner-McGrievy et al., 2013). The underlying cause of this relatively heightened oral response is not known, although it is thought to be due to both an increased number of fungiform papillae and the T2R38 phenotype (Bufe et al., 2005; Duffy et al., 2004); however, those factors do not completely explain the supertasting phenomenon as it may be attributed to other orosensory phenotypes (Hayes, Bartoshuk, Kidd, & Duffy, 2008). Among adults, the T2R38 genotype has been linked to avoidance of alcoholic beverages (Duffy et al., 2004), increased prevalence of colon cancer through inadequate vegetable consumption (Glendenning JI, 1994), avoidance of cigarette smoking (Cannon et al., 2005), and a preference for sweetness (discussed in detail below).

A variety of studies, summarized in Table 5, have linked PTC taste status with eating behaviour. Two studies involving young, healthy women observed an inverse relationship between bitter sensitivity and an acceptance of brassica vegetables, spinach, coffee, and tart citrus flavours (Drewnowski et al., 1999; Drewnowski, Henderson, Shore, & Barratt-Fornell, 1998). Furthermore, supertaster women showed a decreased acceptance of sweet and fatty foods (Duffy & Bartoshuk, 2000). T2R38 taster status has also been associated with a preference for sweet-tasting foods in children, but not adults (Mennella et al., 2005; Ooi, Lee, Law, & Say, 2010; Timpson et al., 2005); however, this result was not replicated in another study examining children (O'Brien, Feeney, Scannell, Markey, & Gibney, 2013). Bitter tasters ate fewer soy products and drank less green tea, and rated these foods to be more bitter than non-tasters (Gayathri, Henderson, & Drewnowski, 1997). These eating behaviors, which are influenced by the T2R38 phenotype, can lead to adverse health effects (Goldstein et al., 2005). However, a

study by Choi et al. did not observe any differences in food preference with varying bitter taste status based on a questionnaire (Choi, 2014).

Turner McGrievy et al. investigated the relationship of supertasting (bitter) and sweet preference with MetS and dietary intake (Turner-McGrievy et al., 2013). In this study, 38% of the participants met criteria for MetS. After classifying adult study participants with respect to sweet liking (SL) or supertasting (ST), the study found a correlation between the combination of SL and ST statuses (SL+ST) and higher incidence of MetS. Participants who were either SL or ST had a significantly reduced risk of MetS compared to those who were SL and ST. In addition, those who were SL and ST consumed less fiber than SL + non-ST individuals. This study highlights an interaction between SL and ST statuses that may be linked with MetS. This is not the only study to indicate a possible relationship between taster status and weight. Indeed, Tepper et al. showed that those who are STs have a lower BMI than nontasters (Tepper, 2008) while another study observed that mean stature of adult PTC non-tasters was higher than that of tasters, and tasters had higher body fat % than non-tasters (Sharma et al., 2014).

Taken together, studies on bitter tasting phenotype suggest a complex relationship with other taste modalities. Despite the evidence presented thus far, the association between taster profile and health outcomes, weight, and dietary intake has been mixed, with studies showing variable results (Drewnowski, Henderson, & Cockroft, 2007; Tepper et al., 2008; Tepper & Nurse, 1998). Given that certain adverse eating behaviours may result from having a supertaster phenotype, further characterizing the effect of bitter taste receptor variation on food preferences has implications for metabolic and health outcomes.

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7. Umami taste

The name "umami" originates from the Japanese language which means "delicious savory taste" (Ikeda, 2002). The GPCR heterodimer complex of T1R1 and T1R3 elicits the umami taste when interacting with amino acids, typically mono-sodium glutamate (MSG), and this interaction occurs synergistically with 5'ribonucleotides guanosine monophosphate (GMP), inosine monophosphate (IMP), and adenosine monophosphate (AMP) (Nelson et al., 2002). The TBC receptors metabotropic glutamate receptor 1 (mGluR1) and mGluR4 have also been implicated in this taste modality (Toyono et al., 2002; Toyono et al., 2003).

Perception of umami serves as an indicator of purine-rich foods, in particular, the purine-derived metabolite uric acid. Elevated serum urate (a salt derived from uric acid) has previously been considered benign except for carrying an increased risk for gout (varez-Lario & arron-Vicente, 2010). However, serum urate has recently been linked to a multitude of biologic effects including high blood pressure, increased hepatic lipogenesis, and insulin resistance (Baldwin et al., 2011; Lanaspa et al., 2012). These adverse health effects suggest that the consumption of certain umami tasting foods, similar to sweet and fatty foods, may increase metabolic disease risk.

There is evidence that differences in the perception of umami are common among individuals with taste threshold concentrations of umami stimuli varying up to 5 fold (Lugaz,

Pillias, & Faurion, 2002). Similar to bitter taste perception, a fraction of the population may carry a "nontaster" phenotype for umami (Lugaz et al., 2002), but more research is needed to characterize this phenotype. Despite the lack of research linking differences in umami taste sensitivity to health outcomes, some studies have correlated certain SNPs in umami taste receptors to differences in taste perception (Table 6). One such study was conducted where 17 T1R1 and T1R3 SNPs were examined in Japanese adults (Shigemura, Shirosaki, Sanematsu, Yoshida, & Ninomiya, 2009). The purpose of the study was to demonstrate a link between SNPs and detection thresholds for IMP and MSG. Taste thresholds for three common SNPs: Gln12His (rs75881102; MAF=0.0114) and Ala372Thr (rs34160967; MAF=0.1354) in T1R1 and Arg757Cys (rs307377; MAF=0.0481) in T1R3 were investigated. The T1R1 SNP Ala372Thr (rs34160967) appeared to be non-synonymous as the Thr allele was associated with increased sensitivity to umami. This association was significant for MSG as well as a mixture of MSG and IMP, but not for IMP alone. The T1R3 SNP Arg757Cys also appeared to be non-synonymous for all umami tasters, as the Cys757 allele yielded a reduced sensitivity for umami taste. Therefore, it is possible that the T1R1 and T1R3 heterodimer have separate binding sites for IMP and MSG, and the T1R3 757 and T1R1 372 SNPs are located in the active sites for IMP and MSG binding, respectively. Shigemura et al. have also shown that that these two SNPs are not in LD, but that their functions may overlap to a certain degree. Thus, having the T1R1 Thr372 SNP and the T1R3 Arg757 SNP causes an overall decrease in umami taste threshold, and having the T1R1 Ala372 SNP and the T1R3 Cys757 SNP causes an overall increase. This was confirmed in another study where the Cys757 variant reduced stimulation of the heterodimer by MSG (Raliou et al., 2011). More research is needed to better understand the influence of genetics on the

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preference or intake of MSG-rich foods. Further characterization of the genetic variation implicated in this taste modality would allow individuals to determine their predisposition to preferring umami foods. This knowledge may prove to be important given that moderating the consumption of umami foods may reduce the risk for metabolic complications.

8. Sour taste

Taste receptor function for sour tasting, which involves GPCR-mediated signaling, is not well-characterized. Studies on the variation at the genetic loci for taste receptor genes involved in sour taste have yet to be undertaken—however, some important advances have been made with regards to this taste modality in a thorough and recent review by Garcia-Bailo et al. (Garcia-Bailo, Toguri, Eny, & El-Sohemy, 2009). Major findings were related to the biology of sour taste perception and the palatability of sour foods (Huang et al., 2006b; Ishimaru et al., 2006; Kim et al., 2004; LopezJimenez et al., 2006; Richter, Caicedo, & Roper, 2003). In general, sour taste perception is thought to be elicited upon the stimulation of taste buds by acidic substances, leading to depolarization of TBCs. Many animals find mildly acidic foods to be palatable, but most mammals reject strong sour stimuli as a means to avoid the consumption of spoiled foods. Putative sour taste receptors PKD2L1 and PKD1L3 belong to the polycystic kidney disease-like (PKDL) subfamily of transient receptor potential ion channels and function as a heteromer to elicit sour taste. The PKD2L1 and PKD1L3 genes carry coding SNPs which may influence sour taste perception. Exploring the effect of these SNPs on sour taste perception and subsequent food choices are important future directions for this taste modality.

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9. Salt taste

Salt taste perception influences sodium intake, the excess for which corresponds to a major public health concern due to the risk of developing hypertension. Excessive sodium consumption may be attributed to greater individual preferences for salty foods, which may be linked to genetic factors such as salt taste receptor function. However, the source of inter-individual differences in salt preferences is controversial as environmental influences, such as dietary salt intake, may be more important than genetic predisposition to salt preference (Bertino, Beauchamp, & Engelman, 1982; Wise, Hansen, Reed, & Breslin, 2007). Thus, salt preference may be due to sensory habituation to high sodium foods and a subsequent increase in the preference of these foods. Similar to sour taste, salt taste receptors have yet to be characterized in sufficient detail to draw definitive conclusions about differences in salt taste receptor function and possible implications for differences in eating behaviour and health outcomes. Due to the fundamental importance of electrolyte consumption for mammalian physiology, the desire to consume sodium-rich foods could be attributed to physiological factors rather than to the search for the sensory pleasure of salt taste (Wald & Leshem, 2003). The physiological basis for seeking electrolytes is supported by periodic fluctuations which occur in women more than men, likely due to hormonal cycling (Hayes, Sullivan, & Duffy, 2010).

ENaC and TRPV1 are the two putative salt taste receptors (Dias et al., 2013). Studies have shown that nerve fibers responding to sodium can be classified according to their sensitivities to the ENaC blocker, amiloride, which distinguishes amiloride-sensitive (AS) and

amiloride-insensitive (AI) groups (Yoshida et al., 2009). The AS fibers respond specifically to sodium chloride (NaCl) whereas AI fibers respond broadly to various electrolytes including NaCl. It has been proposed that while the AS mechanism of salt detection is dependent on ENaC, the AI mechanism is mediated by the function of TRPV1. Thus, it has been suggested that the appealing taste of sodium, representative of a lower taste concentration threshold, is mediated by the AS fibers and hence the ENaC protein while aversive reactions to tasting high concentrations of sodium are mediated by the AI fibers using TRPV1 (Yoshida et al., 2009). These data suggest that at least two different systems exist to facilitate salt taste transduction in taste cells via AS and AI fibers.

In a study by Dias et al., SNPs in ENaC and TRPV1 receptors were associated with differences in salt taste perception among adults (Dias et al., 2013). In the ENaC gene, two intronic SNPs modified salt taste sensitivity. Homozygotes for the A allele of rs239345 (A/T) (MAF=0.2642) and the T allele of rs3785368 (C/T) (MAF=0.1899) perceived salt solutions less intensely than carriers of the other respective alleles, ($P = 0.02$; $P = 0.03$, respectively). In the TRPV1 gene, the Val585Ile polymorphism rs8065080 (C/T) (MAF=0.3177) modified taste sensitivity where carriers of the T allele were significantly more sensitive to salt solutions than the CC genotype ($P = 0.008$). These findings suggest that genetic variation in the ENaC and TRPV1 genes may contribute to inter-individual differences in salt taste perception.

Altogether, environmental influences and genetic factors play a role in defining a salt-preferring phenotype, but environmental influences may have a more dominant role. Nevertheless, new genetic findings associating TRPV1 and ENaC to salt preference suggests

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that there is more to learn about genetic influences (Dias et al., 2013) (Table 7). Due to the novelty of this type of research, the extent to which such variation influences preference or intake of salty foods is unknown. Future studies are needed to investigate the role of salt taste receptor SNPs in sodium consumption and across the lifespan.

10. Summary and conclusion

The relatively new and active field of taste research shows great promise to enhance our fundamental understanding of how taste receptors SNPs contribute to eating behaviour, health and disease. For illustrative purposes, a single candidate SNP is used to demonstrate the effect of genetic variation on taste perception, dietary intake and health outcomes (Figures 1-6). In particular, genetic variation in the CD36 LCFA receptor (Figure 1), the T1R2 sweet taste receptor (Figure 2), and the T2R38 bitter taste receptor (Figure 3) has important health implications because they may predispose individuals to the over-consumption of unhealthy foods and the under-consumption of healthy foods. Investigation into the roles of SNPs in taste receptor genes for umami, sour, and salt tastes (Figures 4-6) is also warranted due to their potential to influence taste preference, dietary intake, and health. An important consideration in future research requires attention to taste-driven food preferences in children and adults, which may be genetic in origin in children but uncoupled in adults due to cultural influences. Additional studies on taste preferences in children are needed, which may help establish healthy eating habits unique to every child (Nielsen & El-Sohemy, 2014; Nielsen, Shih, & El-Sohemy, 2014). As food palatability often involves a combination of different types of taste, such as salt and fat, studies examining combinations of SNPs across different taste modalities are warranted.

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Sex-specific differences in various ethnicities are also important factors to be considered in future studies. Overall, new research in taste may aid in tailoring food choices and reducing the risk for obesity, T2D, CVD, and other chronic diseases.

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Abbreviations

The following abbreviations are used in this manuscript:

SNP: Single nucleotide polymorphism

CVD: Cardiovascular disease

T2D: Type II diabetes

MetS: Metabolic syndrome

CD36: Cluster determinant 36

T1R2: Type 1 receptor member 2

T2R38: Type 2 receptor member 38

ENaC: Epithelial sodium channel

TRPV1: Transient receptor potential cation channel subfamily V member 1

MAF: Minor allele frequency

TBC: Taste bud cell

GPCR: G-protein coupled receptors

ATP: Adenosine triphosphate

LCFA: Long-chain fatty acid

BMI: Body mass index

LD: Linkage disequilibrium

FFA: Free fatty acids

TG: triglycerides

HDL-C: High-density lipoprotein cholesterol

LDL-C: Low-density lipoprotein cholesterol

PTC: phenylthiocarbamide

PROP: 6-n-propylthiouracil

ST: Supertaster

SL: Sweet liker

MSG: mono-sodium glutamate

GMP: 5'ribonucleotides guanosine monophosphate

IMP: inosine monophosphate

AMP: adenosine monophosphate

mGluR1: Metabotropic glutamate receptor type 1

PKDL: polycystic kidney disease-like

AS: Amiloride-sensitive

AI: Amiloride-insensitive

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Table 1 Three types of taste bud cells and their known functions.

	Type I **Glial-like Cell**	**Type II** **Receptor Cell**	**Type III** **Presynaptic Cell**
Function	Neurotransmitter clearance Ion redistribution and transport	Taste Transduction: • T1Rs, T2Rs, mGluRs (GPCRs) • Gα-gus and Gγ13 (G protein subunits) • PLCβ2 (Synthesis of IP3) • TRPM5 (Depolarizing cation current) Excitation and transmitter release	Surface glycoproteins and ion channels Excitation and transmitter release Neurotransmitter synthesis
Taste Modality	Salt	Sweet Bitter Umami Fat?	Sour

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Table 2

Taste as a method of oral fat detection and the role of CD36

Study subjects	Outcome	Reference
Anosmic rats	Rat recognizes oleate by a gustatory cue and fatty acids are important for gustatory recognition of fat.	(Fukuwatari et al., 2003)
Wistar rats	Rats select LCFA from olfactory or gustatory cues that are related to both the carbon chain and carboxylate group.	(Tsuruta et al., 1999)
Mice	Mice find vegetable oils to be as palatable as sucrose solutions.	(Takeda et al., 2000)
Humans	Linoleic, oleic, stearic, and oxidized linoleic acids are detectable in the oral cavity of humans with minimal input from the olfactory, capsaicin, and viscosity-assessing tactile systems.	(Chale-Rush et al., 2007)
Rats	Comparison of CD36 with that of human muscle fatty acid binding protein suggested that a potential binding site for the fatty acid on CD36 may exist in its extracellular segment between residues 127 and 279.	(Baillie et al., 1996)
Humans and pigs	CD36 is the putative orosensory receptor for dietary LCFA in humans and may be involved in the preference for fatty foods.	(Simons et al., 2011)
Mice and rats	CD36 is involved in oral LCFA detection and raises the possibility that an alteration in lingual fat perception may be linked to feeding dysregulation.	(Laugerette et al., 2005)
Mice	CD36 deletion decreased fat consumption and enhanced the ability of the mice to compensate for the calories provided by their optional fat intake.	(Sclafani et al., 2007)
Mice (GPR40 and GPR120 KOs)	GPR40 and GPR120 play a role mediating fatty acid taste.	(Cartoni et al., 2010)

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Table 3

Associations between CD36 gene SNPs fat taste, eating behavior, and health outcomes

SNP Type	Polymorphism	SNP ID	Outcome	Reference
Intronic	-33137A > G	rs1984112	Common CD36 SNPs are related to oral fat sensitivity in an obese population, MetS in a Puerto Rican population, lipid levels in young normal-weight subjects, fat ingestive behaviours in African Americans, and lipid metabolism in individuals of European descent.	(Keller et al., 2012a; Ma et al., 2004; Noel et al., 2010; Pepino et al., 2012; Ramos-Arellano et al., 2013)
	-31118G > A	rs1761667		
	25444G > A	rs1527483		
	22674 C > T	rs2151916		
	30294G > C	rs1049673		
	71670C > T	rs3211931		
	27645del > ins	rs3840546		
	73946T > G	rs3211938	CD36 variants may impact MetS pathophysiology and HDL-C metabolism in African Americans and French individuals of European descent, both predictors of the risk of heart disease and T2D.	(Lepretre et al., 2004b; Lepretre et al., 2004a; Love-Gregory et al., 2008)
	32307A > G	rs10499859		
	35721C > T			
	61882G > A	rs13438282		
	58439T > C	rs1358337		
	48952A > C	rs1054516		
	67612T > C	rs1049654		
	56820A > G	rs3211909		
	68101A > G	rs3211849		
	80248C > G	rs3211913		
	59347T > C	rs13246513		
	60706C > T			
	56133G > A	rs3173798		
	36498C > T	rs3211870		
	60519T > C	rs3211842		
	-178 A > C	rs9784998		

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	rs3211868
	-

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Table 4

Associations between T1R2/T1R3 gene SNPs and sweet taste, eating behavior, and health outcomes

SNP Type	Polymorphism	SNP ID	Outcome	Reference
Non-synonymous	18854899T > C (Ile191Val)	rs35874116	Genetic variation in T1R2 is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. T1R2 is also associated with dental caries in 21-32 year-old individuals of European descent and 184 schoolchildren aged 7-12 years.	(Eny et al., 2010; Haznedaroglu et al., 2015; Kulkarni et al., 2013)
Intronic	-1572C > T -1266C > T	rs307355 rs35744813	Two SNPs are linked to human sucrose taste sensitivity. The T allele of each SNP results in reduced promoter activity in comparison to the C alleles. A distal region of the T1R3 promoter has a strong silencing effect on promoter activity. rs307355 was linked to dental caries in 184 schoolchildren aged 7-12 years.	(Fushan et al., 2009; Haznedaroglu et al., 2015)

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Table 5

Associations between T2R38 gene SNPs and bitter/sweet taste, eating behavior, and health outcomes

SNP Type	Polymorphism	SNP ID	Outcome	Reference
Non-synonymous	145G > C (A49P)	rs713598	A direct molecular link between heritable variability in bitter taste perception to non-synonymous T2R38 variations.	(Bufe et al., 2005)
			Greater propylthiouracil (PROP) sensitivity was associated with lower acceptance of coffee, cruciferous vegetables, tart citrus fruit, dark breads, soy products, green tea, and selected fats.	(Drewnowski et al., 1999; Drewnowski et al., 1998; Gayathri et al., 1997)
	785T > C (V262A)	rs1726866	In women, preference of sweet and high-fat food and beverage groups decreased with increasing perceived bitterness of PROP. In men, preference of these foods and beverages increased with increasing papillae densities.	(Duffy et al., 2000)
	886T > C (I296V)	rs10246939	T2R38 variations accounted for a major portion of individual differences in PROP bitterness perception in both children and adults, as well as a portion of individual differences in preferences for sweet flavors in children but not in adults.	(Mennella et al., 2005)
			TAS2R38 status was not an important determinant of CHD, related risk factors, or eating behavior in the British Women's Heart and Health Study sample	(Timpson et al., 2005)

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			The P49A SNP of T2R38 could not serve as a predictor of anthropometric measurements and aversion to vegetables or sweet/fat foods in Malaysian subjects.	(Ooi et al., 2010)
SNP Type	**Polymorphism**	**SNP ID**	**Outcome**	**Reference**
Non-synonymous	145G > C (A49P) 785T > C (V262A) 886T > C (I296V)	rs713598 rs1726866 rs10246939	Neither PROP taster status nor T2R38 genotype alone had significant impact on bitter vegetable preference or intake.	(O'Brien et al., 2013)
			Perceived bitterness of PTC/PROP thresholds were significantly and negatively correlated with body height and fat-free mass.	(Sharma et al., 2014)
			No significant differences in the PROP status distribution between African Americans and Asian Americans and in food preferences between tasters and nontasters. Significant differences in fat foods, sugar, and black coffee preference were observed among African Caribbean, African black, East Asian, and South Asian groups.	(Choi, 2014)
			There was a significant interaction between ST and SL status as associated with MetS. This interaction was also significantly associated with fiber and caloric beverage intake. Participants who were only an ST or SL appeared to have a decreased risk of having MetS compared with those who have a combination or are neither taster groups (P =	(Turner-McGrievy et al., 2013)

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	0.047) and that SL + ST consumed less fiber than SL + non-ST (P=0.04).	
	Medium tasters and supertasters could discriminate differences in fat content between 40% fat and 10% fat salad dressings ($p < 0.005$), but the non-tasters could not.	(Tepper et al., 1998)

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Table 6

Associations between T1R1 and T1R3 gene SNPs and umami taste perception

SNP Type	Polymorphism	SNP ID	Outcome	Reference
Non-synonymous	A372T	rs34160967	The 372Thr allele was linked to increased sensitivity to umami. This association was significant for MSG and a mixture of MSG and IMP, but not for IMP alone.	(Shigemura et al., 2009)
	R757C	rs307377	The Cys757 allele yielded a reduced function and is necessary for IMP interaction.	(Shigemura et al., 2009)

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Table 7

Associations between ENaC and TRPV1 gene SNPs and salt taste perception

SNP Type	Polymorphism	SNP ID	Outcome	Reference
Intronic	A > T	rs239345	The A allele carriers perceived salt solutions less intensely than carriers of the T allele. (P=0.02)	(Dias et al., 2013)
	C > T	rs3785368	T allele perceived salt solutions less intensely than carriers of the C allele. (P=0.03)	(Dias et al., 2013)
Non-synonymous	V585I (C > T)	rs8065080	Carriers of the T allele were significantly more sensitive to salt solutions than the CC genotype. (P=0.008)	(Dias et al., 2013)

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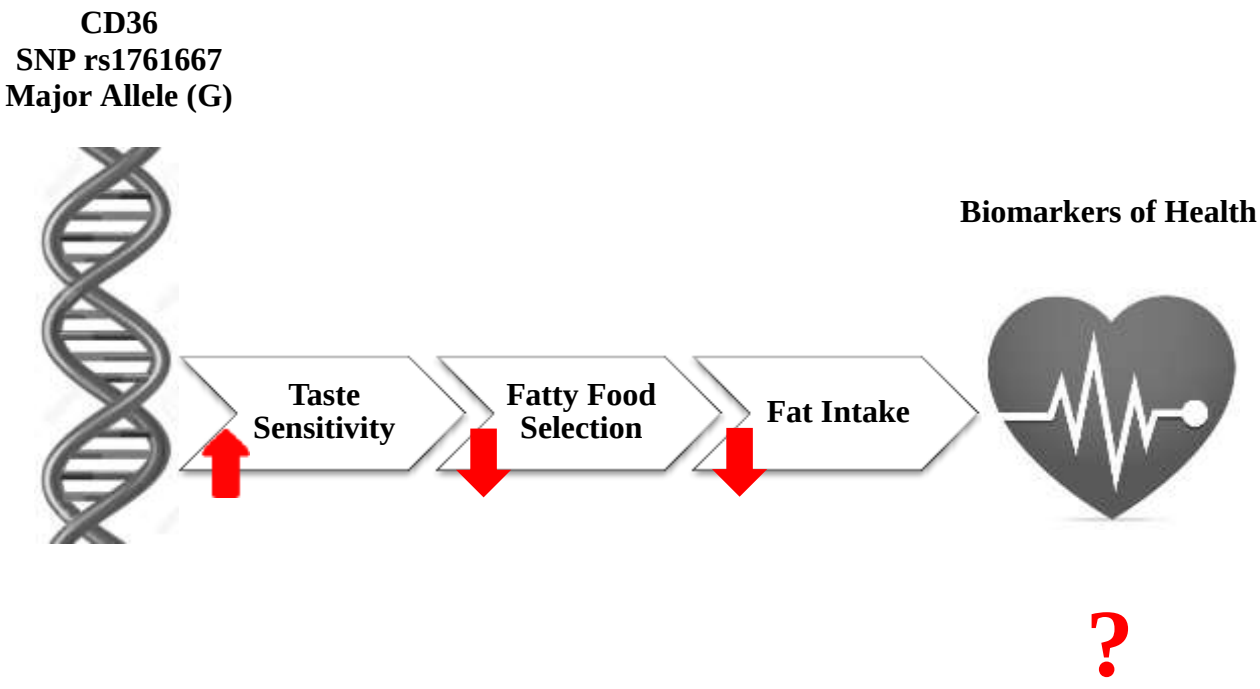

Figure 1 Schematic representation of the effect of the rs1761667 SNP in the CD36 fat taste receptor gene on fat taste perception, fatty food selection, fat intake, and biomarkers of health such as blood TG levels, cholesterol levels, and anthropometrics. The effect of the G allele on CD36 function in the tongue as a fat taste receptor and in the muscle as a fatty acid transporter is controversial. While taste perception studies have been able to consistently show that G allele homozygotes have higher taste sensitivities to fatty acids due to the increased expression of the receptor, others have suggested that the G allele is associated with decreased function in the muscle as a fatty acid transporter. Therefore, there is a discrepancy between the expected decrease in plasma TGs due to taste effects and the observed increase in plasma TGs due to the lack of FA transport into the muscle.

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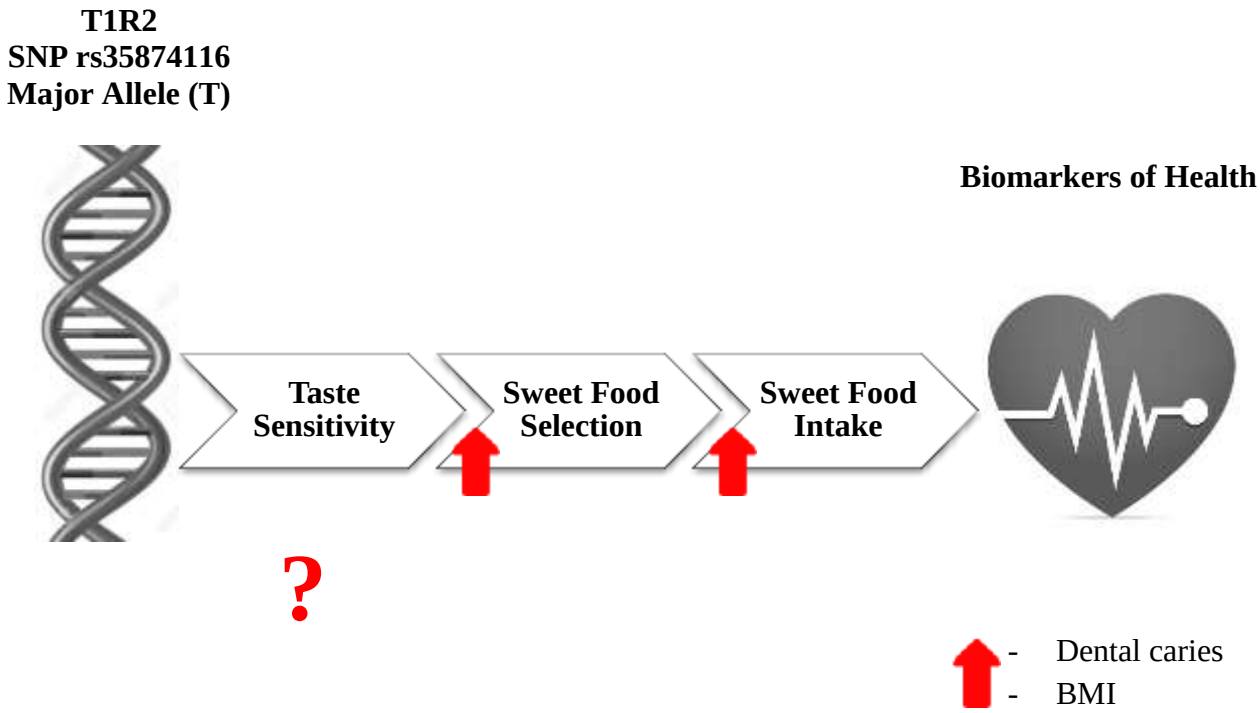

Figure 2 Schematic representation of the effect of the T allele in the rs35874116 SNP in the T1R2 sweet taste receptor gene on sweet taste perception, sweet food selection, sugar intake, and biomarkers of health such as dental caries and BMI. While this SNP has been related to increased preference as well as intake of sweet foods, the effect of the SNP on taste sensitivity has not been elucidated. This SNP has been linked to increased dental caries, and individuals with increase sweet preference and intake were also more likely to have higher BMIs. Importantly, a different SNP in the T1R2 sweet taste receptor (rs12033832) was found to be associated with altered sweet taste sensitivity.

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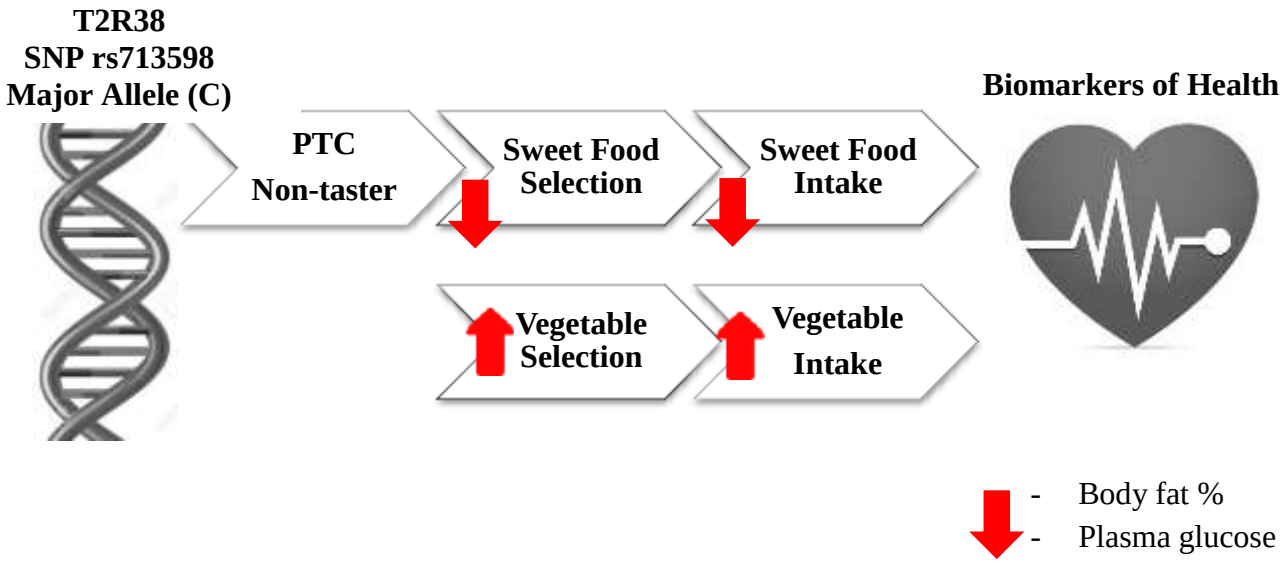

Figure 3 Schematic representation of the effect of the C allele in the rs713598 SNP in the T2R38 bitter taste receptor gene on bitter taste perception, bitter and sweet food selection, sugar, fruit, and vegetable intake, and biomarkers of health such as body fat % and plasma glucose. The C allele of this SNP is well established to be part of a haplotype which causes the PTC non-taster phenotype. This phenotype, unlike the 'supertaster' phenotype, is not prone to decreased vegetable preference and consumption or a compensatory increase in the preference and consumption of sweet food.

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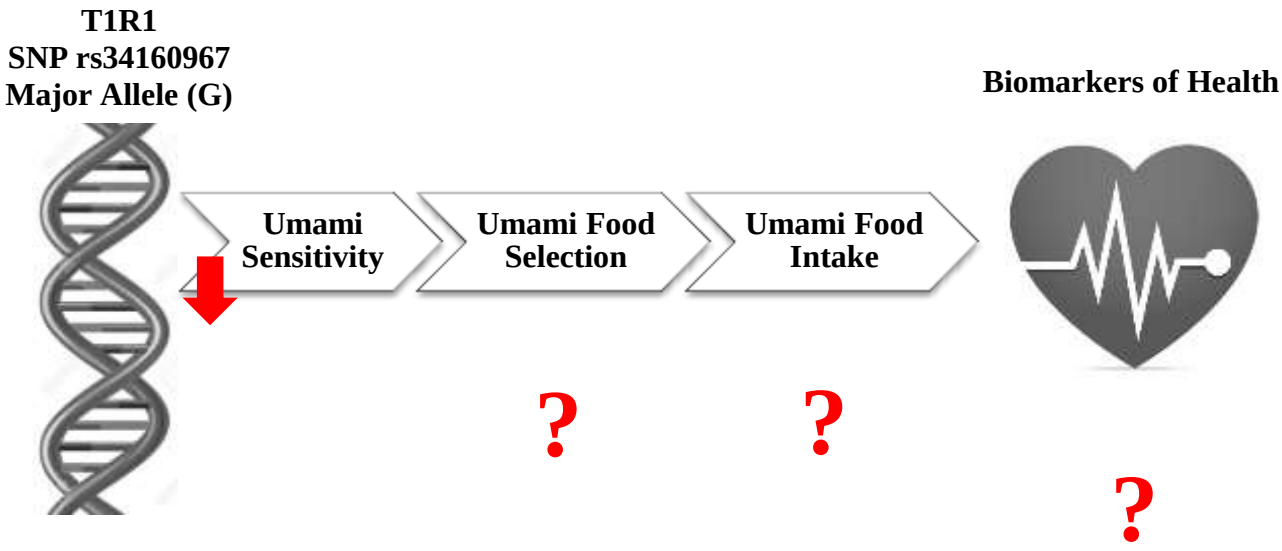

Figure 4 Schematic representation of the effect of the G allele in the rs34160967 SNP in the T1R1 umami taste receptor on umami taste perception, umami food selection, umami food intake, and biomarkers of health.

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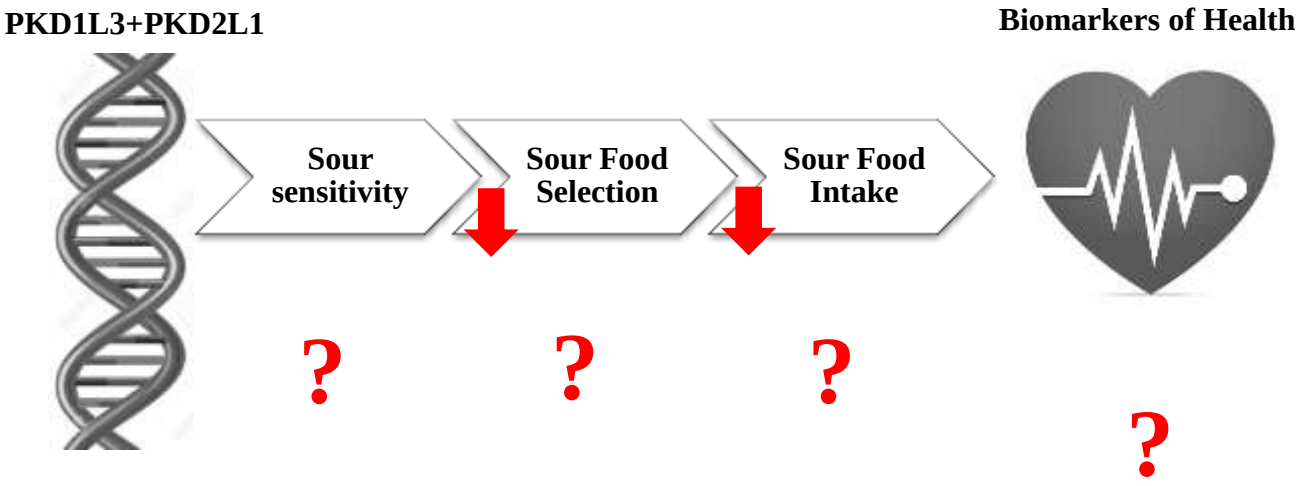

Figure 5 Schematic representation of the potential effect of the PKD1L3+PKD2L1sour taste receptor gene on sour taste perception, sour food selection, sour food intake, and biomarkers of health.

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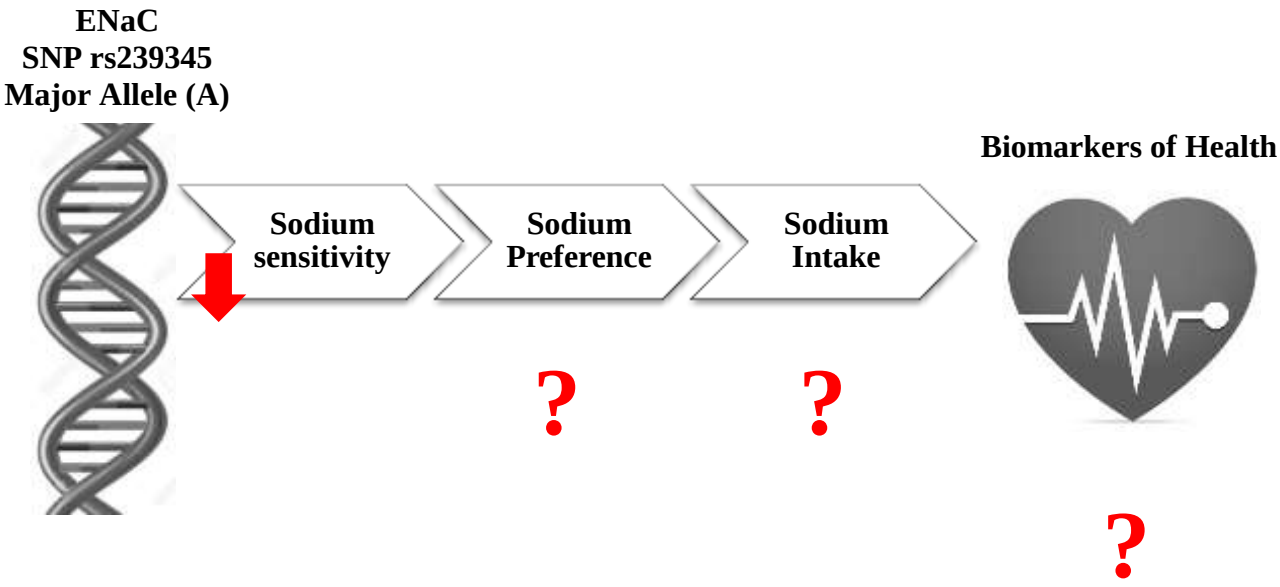

Figure 6 Schematic representation of the effect of the A allele in the rs239345SNP in the ENaC salt taste receptor gene on salt taste perception, salty food selection, salt intake, and biomarkers of health.

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