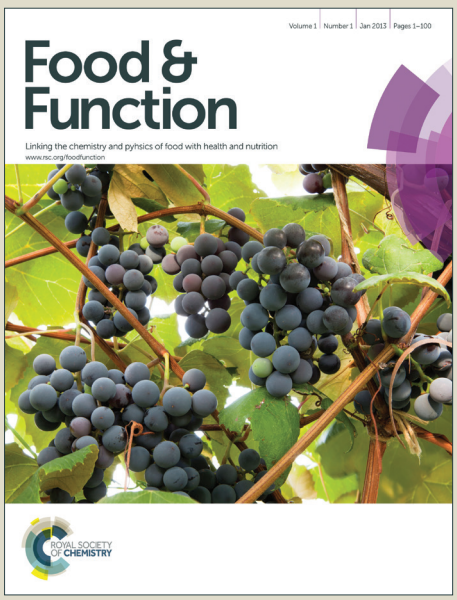
# Food & Function

Accepted Manuscript




This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/foodfunction

# Bitter Taste Genetics- the relationship to tasting, liking, consumption and health

**Emma L Beckett[1,2], Charlotte Martin[1], Zoe Yates[3], Martin Veysey[4], Konsta Duesing[2] and Mark Lucock[1]**

[1]School of Environmental and Life Sciences, University of Newcastle, Brush Rd, Ourimbah, NSW, 2258, Australia. [2]CSIRO Animal, Food and Health Sciences, North Ryde, NSW, 2113, Australia, [3] School of Biomedical Sciences and Pharmacy, University of Newcastle, Brush Rd, Ourimbah, NSW, 2258, Australia, [4]Teaching and Research Unit, Central Coast Local Health District, PO Box 361, Gosford, 2250, Australia.

**Corresponding Author:** A/Prof Mark Lucock, PhD. School of Environmental and Life Sciences, University of Newcastle, Brush Rd, PO Box 127, Ourimbah, NSW, 2258, Australia. Phone: (02) 4348 4109. Fax: (02) 4348 4145. Email: mark.lucock@newcastle.edu.au.

## Abstract

Bitter is the most complex of human tastes, and is arguably the most important. Aversion to bitter taste is important for detecting toxic compounds in food; however, many beneficial nutrients also taste bitter and these may therefore also be avoided as a consequence of bitter taste. While many polymorphisms in TAS2R genes may result in phenotypic differences that influence the range and sensitivity of bitter compounds detected, the full extent to which individuals differ in their abilities to detect bitter compounds remains unknown. Simple logic suggests that taste phenotypes influence food preferences, intake and consequently health status. However, it is becoming clear that genetics only plays a partial role in predicting preference, intake and health outcomes, and the complex, pleiotropic relationships involved are yet to be fully elucidated.

## Introduction

Taste is one of our most important senses. It allows the assessment of the nutritional value, safety and quality of our food. Consumption of foods is vital, but can also pose risks. Taste is vital for preventing intake of toxic substances and indigestible materials, ensuring adequate

intake of energy and providing enjoyment in food. However, there is significant variability in how effectively individuals can detect toxins, and modulate preferences for fruits and vegetables or high calorie foods[1-3].

Humans possess 5 basic tastes; salty, sour, sweet, umami and bitter. Sweet, umami and salt (low concentrations) are appetitive tastes, which are involved in the detection of the "desirable" components of food. Salt (high concentrations), sour and bitter are aversive tastes, and are important for defensive eating[4, 5]. Humans detect "tastants" (chemicals stimulating the sense of taste) via stimulation of taste receptors on taste receptor cells, which cluster in taste buds. These cells are found in the soft palate, pharynx, larynx, epiglottis, and on the gustatory papillae on the tongue. Sour and salt receptors are channel type receptors[6-10], while sweet, umami and bitter are all detected by G-protein coupled receptors (GPCRs)[11]. Two classes of GPCRs have been identified in taste receptor cells, the TAS1R family of receptors detect sweet and umami[12] and TAS2Rs detect bitter compounds[13, 14].

Salt and sour tastes are triggered by elements or ions, and thus are referred to as mineral tastes[15]. Sour taste is responsible for the detection of unripe or spoiled foods and can be triggered by extracellular acidic pH and by organic acids that penetrate the cell membrane[16, 17]. However, the precise contribution of each is not yet fully elucidated. Several cellular sour taste receptors have been proposed, including acid sensing ion channels[18, 19], HCNs[20], potassium channels[21, 22], transient receptor potential channels (PKD2L1 and PKD1L3)[10, 23]. Salt receptors are important in the assessment of electrolyte and mineral content, and are dependent on concentration, and can be appetitive or aversive[24, 25]. Appetitive salt receptors include the sodium specific amiloride sensitive epithelia channel (ENaC)[24] and non-specific amiloride-insensitive channels[26]. Aversive salt taste is modulated by sour and bitter taste mechanisms[25].

The expression of 3 TAS1R genes combine to form heterodimers which detect sweet and umami [12, 21]. The TAS1R2/TAS1R3 heterodimer detects sweet, while the TAS1R1/TAS1R3 detects umami[12]. The major role of both is to indicate the caloric content of food. Umami is responsible for savoury flavour in foods and is triggered by protein content, mainly L-amino acids[12, 27], while sweet receptors are triggered by sacchrides[12]. However, calorie free artificial sweeteners and amino acids with little caloric content can also activate these receptors[28, 29].

Bitter taste, the focus of this review, is important in detection of potentially toxic compounds, bacterial metabolites and protein products of spoilage and/or food aging[5, 30-32]. Bitter taste receptors are also activated by some artificial sweeteners, resulting in a bitter after-taste[33, 34], and contribute to the aversive response to high salt concentrations[25]. Twenty five functional TAS2R genes have been identified in humans[13, 35], named numerically from TAS2R1 to TAS2R64, with gaps in the numbering due to non-existent genes, pseudogenes or proposed genes which are yet to be annotated. While all TAS2Rs are believed to detect bitter compounds, several receptors are yet to be deorphaned[13, 14, 36] (Table 1).

The tasting experience is complex, interacting with olfaction, the detection of fats and oils, temperature, and the common chemical sense, which is responsible for irritation from chemicals substances (for example, capsaicin in chillies). Visual cues, touch, cultural and social norms, personality, and health attitudes can also impact upon food choices, in concert with the aforementioned 5 basic tastes[1, 37].

## Bitter taste

Bitter taste is arguably the most important, and certainly the most complex and sensitive of all the taste types. There are more unique receptors dedicated to bitter than any other taste, and bitter molecules are able to be detected at much lower thresholds than others, up to 1000 times lower in some cases[31]. Bitter taste is generally thought to have evolved to protect humans from the consumption of toxic compounds[36].

Copious natural sources of bitter tasting compounds exist in nature. The substances are structurally and functionally diverse, and many are potentially toxic. Plants may produce bitter compounds as a defence mechanism against herbivores, and bitter taste receptors may have in turn evolved to protect herbivores against consumption of these toxins[5, 11, 38]. Many bitter compounds are harmful and therefore need to be avoided. Common toxins in plant products include progoitrin (found in turnips), cyanide (found in cassava), saponin (found in soy beans). Interestingly, bitter substances such as denatonium benzoate are often added to consumer products to discourage accidental poisoning[39].

Whilst many bitter compounds are toxic if consumed in sufficient quantity, several also have beneficial nutritional or pharmaceutical properties[40-43]. Bitter tasting foods include highly

nutritious vegetables such as spinach, turnip, soy products and cruciferous vegetables (broccoli, bok choy, kale, cauliflower, rocket). Bitterness can be an acceptable or even desirable property in some foods, such as sharp cheeses, coffee, beer and tea[44-46] and fermented food products[47]. These foods contain a range of different bitter tasting chemicals such as isothiocyanates, polyophenols, methylxanthines, isoflavones, sulfamides, phenols, flavonoids, and catechins[37, 38, 48, 49]. Bitter taste can also be imparted in food following heating and food degradation[31]. The bitter components of fermented foods come from protein breakdown, although bitterness is desirable in some contemporary foods, this may additionally act as an effective deterrent against the consumption of decayed food[47].

TAS2R receptors are low affinity compared to other families of GPCRs, with a functional detection range of high μM to mM, however, this is similar to the concentration of most nutrients in food[50]. All TAS2Rs are coupled to the same intracellular signalling molecules, with receptor activation leading to the activation of the heterotrimetric G protein, which consists of α, β and γ subunits[51, 52]. The α-gustducin sub-unit activates a phosphodiesterase and is involved in the regulation of intracellular cAMP levels[51, 52]. The β and γ subunits activate phospholipase $CB_2$ ($PLC\beta_2$), leading to the generation of inositol phosphate ($IP_3$), which mediates the release of intercellular calcium stores and the activation of the monovalent selective cation channel, TrpM5[53, 54]. From the taste buds, three branches of three cranial nerves (CNVII, IX and X) then conduct these signals to the medulla[55]. In addition some TAS2Rs require interaction with auxillary proteins for the receptor transport protein (RTP) and receptor expression enhancing protein (REEP) families[56].

TAS2R expression is not limited to the taste buds. TAS2R expression has been demonstrated in a range of cell types including, solitary chemosensory cells, endocrine cells, epithelial cells[57] and smooth muscle cells, in the airways[58], gastrointestinal tract[59], pancreas[60], reproductive organs[61], and the brain[62]. The signalling pathways activated by TAS2Rs are conserved in different tissues. This implies that TAS2Rs not only respond to xenobiotics, but may also have physiological agonists[63].

Expression of TAS2Rs in non-gustatory tissues implies roles for these receptors in processes other than concious taste perception. Tastants may play a role in the regulation of digestion and metabolic processes following ingestion[64-66]. Functions may include modulation of cholesterol[65] and insulin levels[67] and regulation of gastric emptying[68-72]. Interestingly,

intragastrically administered mixtures of bitter compounds has been shown to trigger some of the same centres in the brain stem as oral taste receptors[66].

In the airways TAS2Rs are thought to detect bitter metabolites produced by microorganisms and may act as a defence mechanism against the inhalation of irritants[73]. TAS2R stimulation has been shown to have anti-inflammatory properties[74], and asthmatic children have been shown to exhibit increased TAS2R expression in peripheral blood cells[75]. Paradoxically, activation of TAS2Rs has been shown to induce relaxation of smooth muscle cells, however, this was found to occur in a compound and species dependent manner[58, 76].

Multiple TAS2Rs are expressed on each taste receptor cell[77, 78]. One TAS2R may be activated by several ligands, and the same ligand may activate multiple TAS2Rs[36, 79]. Hundreds of molecules (for example; isothiocyanates, quinine, caffeine, strychnine, acesulfame K and erythromycin) have been described as TAS2R ligands (Table 1)[36, 63, 80]. The tuning of TAS2Rs varies dramatically. Some are highly selective or narrowly tuned and only detect one or a limited number of bitter compounds. Others are broadly tuned and can detect a wide range of molecules (Table 1). TAS2R10, 14 and 46 are so broadly tuned, that combined, they have been suggested to detect half of the bitter compounds known[36]. Sensitivity of bitter taste receptors also varies widely, with the EC50 values varying widely from the mid nM range to the low mM range[80].

## Modulation of bitter taste by gene polymorphisms

A significant degree of variance exists in the TAS2R genes. Genetic polymorphisms have been identified and validated in nearly all of the intact and functional TAS2R genes (Table 2). The functional consequences of a majority of these polymorphisms are yet to be elucidated.

### *TAS2R38 variants and PTC/PROP tasting*

The best studied of the TAS2R genes is *TAS2R38*. The TAS2R38 receptor detects compounds with thiocyanate moiety (N-C=S), including phenylthiocarbamide (PTC) and 6-n-propyl-2-thiouracil (PROP)[81], the two most common compounds used in bitter taste research. Whilst neither of these compounds is known to occur naturally in foods, several related

compounds do occur naturally and activate the same receptor. This includes isothiocyanates, which are formed in cruciferous vegetables when glucosinolates are hydrolysed[82].

Threshold tasting of PROP or PTC is often used as a surrogate marker for bitter taste in general. PROP/PTC tasting phenotypes are divided into non-tasters who are blind to the bitterness of PTC/PROP and tasters who find PTC/PROP bitter. Tasters can further be divided into medium tasters and supertasters, with supertasters finding PTC/PROP intensely bitter. PTC has been commonly used in laboratory studies, however, due to its slightly sulphurous odour[83] and reports of its toxicity[84], PROP has now become more common in laboratory studies. A very high degree of correlation has been demonstrated between PTC and PROP perception, although they do not completely match[85, 86].

13 non-synonymous single-nucleotide polymorphisms (SNPs) have been validated in the *TAS2R38* gene (http://www.ncbi.nlm.nih.gov/snp, 1000 genome project validated only, accessed May, 2014). Three of the SNPs (rs713598; rs1726866 and rs10246939; Table 3), resulting in three amino acid substitutions (A49P, A262V, V2961), have been identified as being primarily responsible for the variation in PTC/PROP tasting status. Despite the number of potential haplotypes, two common haplotypes Ala-Val-Ile (AVI) and Pro-Ala-Val (PAV)[87, 88], account for more than 90% of the Caucasian population [87]. The V262A and V291I polymorphisms are in perfect linkage disequilibrium, therefore some studies only assay the AV and PA sites. Other rare haplotypes (AAV, PVI and AAI) have been identified, but only occur in specific populations. The AAI haplotype is limited to sub-Saharan Africans[89].

There is a strong correlation between PAV/AVI status and sensitivity to PTC/PROP tasting[90]. The PAV haplotype is associated with the PTC/PROP tasting phenotype and the AVI haplotype is associated with the non-tasting phenotype. The AAI haplotype has shown intermediate responses in *ex vivo* studies[88]. AAV has been shown to have intermediate sensitivity *in vivo*[88]. PAI responses are similar to PAV, and PAI may represent a rare secondary taster allele[63, 88]. Percentages of PAV/PAV, PAV/AVI and AVI/AVI are similar to those of super tasters (30%), medium tasters (50%) and non-tasters (20%), respectively[88, 91, 92]. However, proportions differ between populations around the world; in west Africa, only 3% of the population are non-tasters; in China the frequency of non-tasters ranges from 6-

23%; in India the incidence of non-tasters have been reported to be as high as 40%[93, 94]; in Georgia, the frequency of non-tasters is more than 50%[95].

However, genotype and tasting phenotype do not overlap completely. The PAV and AVI diplotypes account for 45-80% of the variance of taste sensitivity to thiocyanate containing chemicals[87, 96]. Additional variation may be explained by other SNPs in *TAS2R38*, SNPs in other TAS2R genes[97, 98] or other modifying mechanisms, such as epigenetics and influences due to age[99], and sex[93].

***TAS2R38 variants and broader bitter taste***

Numerous psychophysiological studies have suggested that *TAS2R38* genotype and PTC/PROP tasting phenotype also correlate with sensitivity to a range of bitter compounds that are structurally unrelated to PTC or PROP. These include caffeine[100, 101], naringin[100, 102], isohumulones[103, 104], L-phenylalanine[100], epicatechins[100], salicin, methimazole[63], and, to a lesser extent, quinine[100, 101, 105]. This is used to justify the use of PTC and PROP as markers of bitter taste in general. However, the strength of these relationships varies significantly between compounds and concentrations. Negative findings have also been reported for caffeine[106, 107] and quinine[107-109], and no clear pattern has been demonstrated between goitrin and singrin[63]. The rare haplotypes (PVI, AAI, AAV) have displayed unexpectedly heterogeneous profiles in response to bitter stimuli, dependent on the stimulus used. The rare haplotypes match PAV in responses to methimazone, goitrin, singrin, and PTC, but not PROP[63]. This suggests that minor differences in structure may translate into major differences in receptor affinity.

***TAS2R38 variants and general taste acuity***

Increased sensitivity to bitter tastants has been hypothesised to correlate with greater taste sensitivity to other tastants. PROP tasters have been shown to have heightened response to sweet[110-114] and salty stimuli[115, 116]. Oral irritation to capsaicin, ethanol and carbonation are also heightened amongst tasters[111, 117]. Tasters also show increased responses to olfactory cues[118] and to viscous substances such as fats and thickeners [111, 119, 120].

PROP tasting status and sensitivity to thermal taste have been proposed to serve as markers of enhanced global sensitivity[121, 122]. This has been suggested to have an anatomical basis, as general taste acuity, PROP intensity and TAS2R38 genotype correlate with density of

fungiform papillae on the tongue[105, 110, 119, 123, 124]. However, the relationship is complex and remains unclear. In TAS2R38 heterozygotes fungiform papillae density does not seem to predict PROP intensity[85]. Others have found no correlation between PROP intensity, creaminess perception and fungiform papillae density[125]. It has been suggested that differences in central nervous system processing are more important than fungiform papillae density[126]. Additional studies are required to resolve the exact nature of the contribution of fungiform papillae density to bitter taste.

***Other TAS2R variants and bitter taste***

While TAS2R38 is the most studied of the bitter taste genes, others have been identified that contribute phenotypic variance in bitter taste. The TAS2R16 receptor is sensitive to Beta-glucopyranosides, a family of compounds that include salicin, a natural analgesic found in the bark of the willow[80]. Polymorphisms in this gene are associated with subtle differences in bitter taste[127]. The non-synonymous *TAS2R16* polymorphism, K172N (rs846664), confers significant phenotypic variance *in vitro*, with the N172 (common) allele conferring 2 fold greater sensitivity to salicin, arbutin (found in berries) and amygdalin (found in bitter almonds)[127].

Missense polymorphisms in the *TAS2R9* gene (rs3741845; V187A), and the *TAS31R31* gene (rs10772423; V240I) are significantly associated with the perceived bitterness of Acesulfame K, with the polymorphisms explaining 7% and 8.7% of the variance, respectively[33]. *TAS2R31* polymorphisms are also associated with differential bitterness of aristolochic acid and saccharin[33]. *In vitro* assays have confirmed the functional importance of four *TAS2R31* mutations, which had independent effects on receptor response[128].

Recently, it has been demonstrated that variants in the α-gustin gene further explain the variations in PROP tasting across individuals[129]. Identification of additional variants in the intracellular signalling pathways of TAS2Rs may further explain the variance in bitterness perception, beyond the variation in the receptor alone.

## Bitter compounds contained in foods

***Influence of taster status on the detection of bitter compounds in food***

Bitter compounds are not consumed in isolation, but in foods. In laboratory testing, bitter compounds are often dissolved in aqueous solutions or delivered on impregnated filter paper,

but consumption of bitter compounds in actual food may not always have the same response. Also, bitterness of foods can be altered dependent on season, cultivar, growth conditions, and food storage and preparation methods[1]. These factors may confound results and complicate the analysis of associations.

Greater sensitivity to PROP has previously been associated with increased bitterness perception from glucosinolate and singrin containing vegetables , but not from non-glucosinolate producing vegetables[130]. This demonstrates the detection of bitter compounds in whole food. However, the other components of the food may interact to mask or heighten tastes.

PROP tasters have also been shown to be more sensitive to the addition of the bitter compound caffeine to foods and beverages. PROP supertasters are better able to discriminate added caffeine in orange juice, and tasters were better able to detect caffeine in cream cheese than non-tasters[131]. While tasters were more likely to detect added caffeine in solution than not tasters, interestingly, addition of non-nutritive sweetener decreased bitterness intensity in both groups by similar degrees[132].

PROP taster status has been shown to influence the bitterness perception of black coffee (containing caffeine)[100]. Additionally, a haploblock across TAS2R3, TAS2R4, and TAS2R5 (rs765007, rs2234001, rs2234012, rs2227264) explains some variability in the bitterness of espresso coffee[133]. PROP taster status also influences bitterness perception of dark chocolate (containing epicatechin)[100].

Conversely, others have reported no differences between PROP tasters and non-tasters in sensory responses to white, milk or dark chocolate[132]. Furthermore, no association was found between PROP taster status and bitter perception of white grapefruit (containing naringin)[100]. However, a mutation in the TAS2R19 gene (rs10772420, resulting in the substitution of Arg for a Cys at amino acid position 299 appears to influence grapefruit juice bitterness[133] and accounting for this variation may account for the null result found when only considering PROP taster status.

***Influence of TAS2R genotype and tasting status on "liking" of bitter foods***

Taste sensitivity is logically hypothesised to play a role in food preferences[38, 134]. Taste is arguably the most important determinant of food choices[38, 135, 136] and genetics is powerfully positioned to influence intake[137]. It has been reported that dislike of bitter taste is one of the primary reasons cited by consumers for rejecting certain foods, such as fruits, vegetables, whole grain products and soy[138]. It is a logical hypothesis that those insensitive to bitter compounds would have less aversion to bitter foods, than those who find them more bitter. As many healthy vegetables have bitter components, this hypothesis has been extended to suggest that non-tasters would eat more healthy vegetables and therefore experience better health outcomes. Despite the neatness of this hypothesis, clear relationships between taste sensitivity and "liking" of bitter foods has not been consistently demonstrated[111, 130, 139], and has even been directly contradicted[140]. Genetically mediated differences in bitter perception may not be sufficient alone to alter food acceptance, as bitterness perception is only one facet of the complex sensory profile of food. The extent to which genetic variance in taste receptors influences preference and intake is contentious. Genes that involve metabolism and satiety may also be involved[141].

In children, taste perception strongly influences food preferences, and in this age group taste is one of the strongest mediators of fruit and vegetable consumption[142, 143]. It has been demonstrated that non-taster children prefer sucrose less than those with the taster allele, however, the same association was not found to continue in adults[112]. Similarly to children, adolescent PTC tasters had lower preference for raw cruciferous vegetables and other bitter tasting foods, but had a higher preference of sweet tasting foods[144].

In adults, it has been reported that PROP tasters have reported lower preference for a range of vegetables including brussel sprouts, cabbage, spinach[29], asparagus and kale[139]. Conversely, two studies have shown no correlation between PROP status and the liking of broccoli[44, 145]. In young women, a similar inverse correlation was demonstrated between PROP sensitivity and acceptance of tart citrus fruit, cruciferous vegetables, spinach, and coffee[29, 146]. Female PROP tasters also show a decreased acceptance of sweet and fatty foods[46].

Interestingly, despite adults demonstrating no difference between tasters and non-tasters in the sensitivity of detection of bitterness in white grapefruit[100], PROP sensitivity correlated with a lower preference for grapefruit juice[102] and other citrus fruits[146]. Furthermore, taster

children were observed to give a lower hedonic rating to a grapefruit/orange juice blend in a 3:1 ratio, compared to the same juices mixed in a 1:1 ratio[147]. Similarly, supertasters gave a lower hedonic rating than non-tasters to naringin solutions sweetened with 4% sucrose[102].

However, despite reported differences in sensitivity of taste perception to black coffee and dark chocolate, PROP taste status and TAS2R38 genotype were not shown to correlate with reported "liking" of these foods[119]. This may be because coffee and dark chocolate also include chemicals that enhance feelings of well-being[148]. Studies have shown that pairing flavours with caffeine consumption can result in increased liking of those flavours. Liking of a tea spiked with caffeine was increased compared to the same tea when spiked with quinine, which affords similar bitterness, but lacks the stimulation of caffeine[149].

In the genetically and geographically isolated village of Carlantino in Italy, the community as a whole reports a high liking of vegetables in general, and degree of reported liking did not vary by PROP taster status. It may be that the high cultural acceptance of vegetables overrides that contribution of genetics or the cooking styles of this culture may reduce bitterness acceptability among all taster groups[100]. In the same population, supertasters expressed a lower degree of liking of pungent and spicy foods and alcoholic beverages than non-tasters[100].

Different variants of the TAS2R43 gene have been associated with coffee liking, The TAS2R43 receptor is sensitive to caffeine. Possession of the wild-type allele, coding for the functional variant of the gene, was found to have a higher association with coffee liking, while the H212R polymorphism had an inverse association with coffee liking [150]. Interestingly, this SNP has been shown to reduce function of the expressed protein *in vitro* [114].

In fitting with increased general taste acuity; PROP tasting adults report a lower liking for salad dressing[94] sweetened milks[85], pungent foods[151], alcoholic beverages[152] and sweet taste[113]. However, in terms of sweet preference, children show the reverse response, with PROP tasting children preferring sweets[112, 153]. This suggests that the psychophysiological response to tastants may evolve over time.

***Influence of TAS2R genotype and tasting status on food intake patterns***

Nutrients such as glucosinolates, isoflavones, phytonutrients are bitter tasting compounds found in health foods to which PROP tasters may be more sensitive. Therefore, PROP sensitive individuals may be more sensitive to the bitter tastes of "healthy" foods, which may influence health status[29, 30, 138, 147]. However, although bitter taste sensitivity can affect the acceptance and liking in some foods, it appears to have a mixed influence on intake. Additional factors may alter how these factors relate to actual food intake. Influence may include cooking approaches and seasoning methods, health attitudes, personality traits, social and cultural influences, age and sex[1, 95, 144, 154, 155].

Several investigators have reported that adult PROP tasters and those with the PAV haplotype, consume fewer vegetables[48, 139, 156-158] and fruit[124]. Interestingly this has been shown not to be restricted to vegetables that are predominantly bitter[158]. The AVI variation (non-taster) of the gene was associated with nutrient intake pattern indicative of healthy eating[96]. PROP tasters have also been shown to eat fewer fats than non-tasters[147]. However others have shown no relationship between vegetable intake and TAS2R38 genotype or taster status[159-161].

In a multifactorial study of vegetable intake, sensitivity to bitter and sweet tastes, and reported preferences, it was found these factors only partially predicted intake. A small, but direct, relationship with age was also found[139]. A similar analysis found that PROP taster status, TAS2R38 genotype, sweetness perception, fungiform papillae density, age and sex all combine as a significant predictor of vegetable preference and explained 15.3% of the variation in males and 18.9% of the variation in females, with taster status and age being the most significant variables[96].

In a group of young women, perceived PROP bitterness was not associated with the frequency of consumption of 22 bitter foods[162]. Conversely, in a group of young males undergoing colonoscopy screening, those with the highest PROP sensitivity ate the least vegetables[48]. A similar link between PROP sensitivity and cruciferous vegetable intake was found in an Italian population[156]. However, in an Australian cohort it was found that *TAS2R38* diplotype did not predict intake of folic acid (methylfolic acid, pteroylmonoglutamic acid or total folic acid) or intake of vitamin C, which would be expected to be elevated with higher vegetable intake[160].

Taster children have been reported to eat less vegetables[163] and more sweets when offered a range of foods[164]. When given the choice of snacks, taster children consumed approximately half as many vegetables as non-taster children. Furthermore, 32% of taster children consumed no fruit and vegetables at all during the experiment, compared to 8% of non-taster children[163]. However, other studies have reported no association between PROP status and either liking or intake of vegetables in children[49, 165].

Vitamin $B_6$, thiamine and folate intake were significantly higher and B12 intakes were significantly lower in women with the non-taster phenotype or AVI/AVI diplotype. This suggests that non-tasters consume more green leafy vegetables and fortified cereals (the main sources of dietary folate) and less animal products (the main source of $B_{12}$)[96]. Similar patterns of dietary intake between tasters and non-tasters have been described elsewhere[166]. However, there were no significant differences in vitamin C, carotene or biotin[96] which would be expected if fruit and vegetable intakes differed considerably. A weak inverse correlation between TAS2R50 (rs1376251) C allele and the intake of dietary fibre and vegetables, has also been demonstrated[159]. Super tasters have shown lower acceptance to whole grain breads[167].

Other genetic factors involved in these relationships may yet be defined. Modest linkage has been identified between TAS2R38 polymorphisms and other markers on chromosome 16p[98]. The peak association score being at the gene encoding Gγ13, one of the intracellular signalling molecules of TAS2Rs[168].

Alcohol consumption is complex and influenced by polymorphisms in a number of TAS2R genes. Taster phenotype and genotype are a significant predictor of alcohol consumption [111, 133], Non-tasters consume alcoholic beverages more frequently[111, 133, 152]. A polymorphism in the TAS2R16 gene (rs846672) significantly influenced consumption of alcohol beverages, with the minor allele homozygotes consuming twice as many alcoholic beverages[133]. The same pattern was found for another polymorphism in the same gene (rs1308724). An additional polymorphism in the TAS2R13 gene (rs1015443 [C1040T, Ser259Asn]) showed a significant association with alcohol consumption, with those homozygous for the minor allele consuming the least alcohol[169].

Energy intake has been observed to be higher in those with the non-taster phenotype[170]. In a study of young Japanese women, AI (non-tasters) had higher energy and carbohydrate intakes than the tasters. Neither vegetable nor dairy product intake was different between the homozygotes with AI haplotype and the carriers of PV haplotype[161]. In Amish women, those with the non-taster genotype displayed increased disinhibition of eating[171]

Individuals can modify the bitterness of foods with additives (e.g. adding milk and sugar to coffee) or cooking methods. There is strong motivation for food and pharmaceutical industries to control the bitterness of their products in order to increase acceptance[172]. This may be through a variety of mechanisms, including selective plant breeding, use of encapsulation, additional of salt, sweeteners and other flavours[138]. Unfortunately, these methods may reduce the health value of some bitter foods. Addition of bitter taste receptor antagonists is a novel and innovative field of research, however the consequences of the mechanisms of action at play here are not yet clear[100, 173].

## The links between bitter taste perception and health and disease

*TAS2R38* mutations, and bitter taste responses have been linked to several adverse health events, such as alcoholism, smoking, and a range of chronic conditions including obesity, thyroid function and colon polyps[38, 46, 111, 133, 137, 139, 174-176]. The simple logic is that increased sensitivity to bitterness, leads to an alteration in preferences and aversions, which in turn alters dietary choices and habits. Furthermore, it is thought that dietary habits subsequently influences nutritional status, predicting long term health and chronic disease risk. However, the interactions between taste and other dietary influences are complex and the complete nature of the interactions is yet to be fully elucidated.

It has often been hypothesised that individuals with increased bitter taste sensitivity might have lower health outcomes due to the avoidance of bitter tasting antioxidant and nutrient rich foods, resulting instead in increased consumption of sweet, fatty and nutrient poor foods, leading to a greater risk of cardiovascular disease[37]. However, it appears that those with high sensitivity to bitter taste have heightened taste acuity in general, resulting in a parallel reduction in intake of sugars and fats[86, 110, 111]. Non-tasters who are less sensitive to bitter vegetables, may eat more vegetables, but are also more likely to be "sweet likers"[177] and to

prefer high fat foods[94]. This suggests that increased taste acuity may prevent over-consumption in all food groups. These relationships complicate the potential interactions between bitter taste and health.

**Bitter taste and Body Mass**

Several authors have suggested that bitter taste perception might alter body mass[30, 153, 178, 179]. In the 1960's it was demonstrated that those with the lowest thresholds for PROP and quinine tasters were more likely to be Sheldonian ectomorphs (thinner), whilst those with the highest thresholds were more likely to be endomorphs (heavier)[180]. This was replicated in a study of young Japanese females, where those with the taster haplotype were shorter and thinner than those with the non-taster haplotype[161].

Several studies have observed an increased Body Mass Index (BMI) in female PROP non-tasters[30, 94, 96, 181, 182]. Similar patterns have been seen with overweight (but not obese) middle age and elderly subjects tasting PROP as less bitter than those of normal weight[30, 96, 111, 152, 181]. However, this relationship was not maintained when genotype status replaced phenotype in the analysis[30, 96]. Overall, no direct relationship was demonstrated between genotype, consumption and BMI in large epidemiological studies[49, 165] or genome wide association studies[141, 183]. This suggests phenotype is more influential than genotype in BMI, and it appears sex plays a role in the strength of this association.

In children, non-tasters tend to be heavier, but the effects are small[153]. Others have shown an association only in girls, with non-tasters having higher BMIs and higher body fat[184]. In a longitudinal study PTC taster girls had a higher bodyweight than non-tasters at age 11, but at 18 years this difference was lost[144]. Additionally, non-taster children have been shown to be at higher risk of developing dental caries[185, 186]. This may be due to increased preference for sweet foods, or due to decreased sensitivity to oral bacteria, resulting in a decreased drive for teeth brushing[186].

A history of middle ear infection, which has the capacity to cause damage to the chorda tympani nerve, and a reduction in taste acuity, is associated with obesity in adults[187] and children[188]. Past damage leading to non-tasting could result in a greater preference for intake of sweets[177], fats[46, 111, 119] and alcoholic beverages[176, 189].

**Bitter taste and Metabolic Disorders**

Metabolic disorders often have dietary links, and so logically the role of bitter taste genes has been considered. Functional variants of the TAS2R9 have been associated with metabolic disorders, the inactive variant of the gene has been associated with impaired glucose homeostasis [64]. The non-taster AVI/AVI genotype was associated with a slightly lower risk of diabetes, in a study of post-menopausal women. This suggests that these women may have consumed a more prudent diet over their lifetimes[49]. However, no direct link between diet and TAS2R38 genotype were found. Importantly, this observation may be explained by changes in diet over time[49], which are not easily captured in cross-sectional studies, particularly as taste acuity has been shown to diminish with age[190, 191].

PTC non-tasters are at higher risk of thyroid disease than tasters[38]. This may be due to increased intake of bitter thiocyanate compounds, which are dietary goitrogens, that can inhibit the amount of biologically available iodine, and can effect energy balance[192, 193].

**Bitter taste and cardiovascular disease**

A link between polymorphisms in the TAS2R50 gene and risk of myocardial infarction has been identified[194-197], however no investigation of the link to dietary habits for this polymorphism have yet been undertaken. Conversely, others have found no link between *TAS2R38* genotypes and risk of cardiovascular disease[49].

**Bitter taste and colon cancer**

The findings into the relationship between colon polyps and PTC/PROP taster status have been mixed. Basson *et al.,*[48] found a weak but positive correlation between tasters and the number of colon polyps detected. Conversely, Carra *et al.*,[198] found that the AVI/AVI (non-taster) diplotype was associated with an increased risk of colon cancer. The authors hypothesised that rather than a dietary link existing, the AVI/AVI serves as a biomarker for impaired function of the gastrointestinal tract, resulting in slower elimination of toxins from the gut. However, Schembre *et al.,*[159] investigated colon cancer risk by polymorphisms in TAS2R38, TAS2R16 and TAS2R50 and found no significant relationships. Furthermore, Lucock *et al.*,[160] found that taste diplotype alone did not influence polyp risk, but red cell folate status did interact with bitter taste diplotype to predict polyp risk. The conflicting nature of these results means the relationship between bitter taste genotype, tasting phenotype and colon cancer are still unclear.

**Bitter taste, alcoholism and smoking**

PROP non-tasters also taste alcoholic beverages as less bitter, consume alcoholic beverages more frequently[152], and have a higher risk of alcoholism. As such, bitter tasting may protect against some forms of alcoholism[176, 199-201]. Polymorphisms in the TAS2R38 and TAS2R16 receptors are associated with alcohol dependence[133, 199, 201].

Smoking has long been associated with PROP/PTC tasting. Chronic smokers are more likely to be non-tasters[202, 203]. In African American smokers, those with the non-taster haplotype smoked significantly more than those with the taster haplotype[204]. This may be because bitter chemicals are less offensive to non-tasters.

**Bitter taste and affective disorders**

Level of sensitivity to bitter tastants has been linked to levels of serotonin and noradrenaline. Enhancing noradrenaline levels significantly lower the tasting thresholds of quinine. In addition, anxiety level positively correlates with bitter taste thresholds. This suggests a level of plasticity to tasting parameters and may explain the relationship between affective disorders and diet[205]. Leptin has been shown to modulate sweet taste and alcohol intake, in mice[206, 207], but this has not been demonstrated for bitter taste directly.

## The evolution of bitter taste

From an evolutionary point of view, it is interesting that there are considerably more receptors dedicated to detecting bitter than the other tastes. Just 3 genes have been identified in the TAS1R family, which are responsible for both sweet and umami taste, but for bitter taste humans have at least 25 intact TAS2R genes and several pseudogenes, making it the largest family of taste receptors. TAS2R genes are clustered together on chromosomes 5, 7 and 12[13, 208, 209]. On average, species that eat plants (herbivores and omnivores) have more TAS2Rs than carnivores[210]. Despite an increased number of receptors, behavioural studies have shown that plant eaters, are less sensitive to quinine hydrochloride (a natural bitter compound)[210]. This suggests that although herbivores can detect a larger number of bitter compounds, they can tolerate them better, perhaps because plant eaters cannot afford to reject bitter foods[211]. Herbivores may also have developed additional mechanisms for detoxification, such as fermentation by microbes[212].

The high sequence homology (30-70%) between TAS2R genes[213] suggests that the high number of TAS2R genes seems to have evolved from gene duplication events that expanded the range of bitter compounds to which humans are sensitive[69]. A conspicuous feature of the TAS2R genes is an absence of introns[13, 208, 209].

Even subtle genetically determined differences can have several selective advantages that only become visible over evolutionary time spans[127]. Taste is one of the primary means of determining the acceptability of foods, and might have been critical in the survival of early humans[30]. Bitter taste is innate, and is present at birth in humans and other primates, and does not need to be learnt[138, 211]. Great apes have a clearly identifiable TAS2R38 orthologue, although it contains several differences from the human gene. The few individual animals sequenced to date, are all homozygous for an allele containing a proline at position 42, an alanine at positon 262 and a valine at position 296 (analogous to the major PAV taster allele in humans)[87, 214].

It may be logical to assume that more sensitive versions of the *TAS2R* genes would improve avoidance of toxins, and therefore would confer an evolutionary advantage. However, as PTC/PROP non-tasters are found in almost all human populations, this may be evidence that this polymorphism has been subject to "balancing selection" or selection for heterozygous individuals in the population[89, 215]. Under balancing selection, both alleles are maintained in the population because they are both useful and heterozygosity may allow detection of a wider range of compounds[83]. Non-tasting variants of TAS2R genes are more common in African populations in areas where Malaria is endemic. It has been suggested that lower sensitivity to bitter tastes allows increased consumption of bitter plant compounds that have antimalarial properties[127].

TAS2R genes show remarkable variation across species. For example, the human TAS2R38 gene shows only a 65% amino acid identity to the most closely related gene in the mouse[216]. Given that the human taster and non-taster alleles of these genes are 99% identical at the amino acid level, it is possible that the most closely related gene in mice does not serve to detect PTC and its relatives at all. This may not be surprising, given the differences in the diet between the two species[93].

## External influences on taste

The lack of concordance between the results of tasting studies suggests that the link between genetics, tasting, liking and consumption is complex, and not yet fully understood. Eating is a complex behaviour with multiple determinants, including age, sex, prior experiences, social and cultural norms, body, and health and weight attitudes. Few studies have factored all the these determinants into one study, but those that have done have generally found interesting associations[85, 147, 151].

### Food Adventurousness

Only limited studies have investigated the role of personal characteristics in the relationships between taster status and food intake. "Food adventurousness" (the self-reported frequency of trying new foods) helped to clarify this relationship. PROP tasters who rated themselves as adventurous, liked more food per food group (fruits, vegetables, alcohol, non-fat condiments) than those who rated themselves as non-adventurous. However, in the non-taster group, adventurousness did not influence food liking[151]. In a study of Finnish twins those who rated themselves as adventurous expressed higher liking for sour and spicy foods, and fruit and vegetables. The adventurous group also had more tolerance for capsaicin burn in the sensory-hedonic test[217].

In the elderly, it is suggested that environmental factors are more important than genetic influences in food preferences. Instead, the elderly may be more inclined to try and accept novel foods because of diet-related attitudes and beliefs that are formulated throughout the years[190].

### Age, sex and environmental influences

Age, sex, morphology and environment interact to produce major differences in bitter taste perception among individuals[110]. In fact, genetic predisposition may be outweighed by environmental influences. In one study taster status, age, and sex were found to be the most significant influences on food preferences, while genotype was less important[96]. TAS2R38 status is not sufficient to explain PROP bitterness perception, particularly at suprathreshold levels, suggesting other environmental or genetic mechanisms may play a role[85, 88].

Taste changes across individual lifespans result from gene-environment interactions; genetic predispositions are modified with exposure to pathogens, medications or changes in hormonal

status. Bitterness and general taste acuity may show loss with aging. As previously discussed, tasting and liking of bitter substances appear to be more heavily influenced by genetics in children than in adults[99, 112, 142, 143]. In the elderly, intensity of taste is reduced relative to young adults[218]. This may be due to decreased olfactory senses influencing taste or reduction in fungiform papillae density in the elderly[190, 219].

Sex specific differences in influence of TAS2R38 genotype of bitter taste phenotype have been noted in both children[179] and adults[46, 96]. Furthermore, the influence of gender on bitter taste perception may vary throughout the life cycle. Young women are more likely to be supertasters than young men[110], and this may advantageously contribute to the avoidance of ingestion of toxins, tetratogens and abortifacients[220]. During pregnancy, bitter perception peaks during the first trimester and is lowest in the third trimester[221]. Bitterness may decline in women following menopause and with aging in general – offering a potential advantage for the acceptance of bitter and nutrient rich food among the elderly[137].

Maternal diet may influence the tasting status of the fetus in later life. In rats, maternal consumption of ethanol led to increased acceptability of ethanol and quinine, but not sucrose in the offspring. This suggests that exposed offspring taste ethanol as less bitter[222]. Another study showed that offspring of mothers who ate more fruit during lactation were more likely to accept peaches than babies fed formula. However, the mothers consumption of string beans did not have the same effect[223]. It has also been demonstrated that there is a sensitive period of exposure after birth in which exposure can alter perception. Infants fed bitter protein hydrolysates in their formula, led to a learned acceptance of the bitter flavour[224].

Although it has not been directly demonstrated, it is likely that such early life programming occurs via epigenetic mechanisms. Significant variation in RNA expression levels of *TAS2R38* have been demonstrated to correlate with bitter taste detection and diet[225]. The mechanisms controlling this variation are yet to be identified.

## Conclusion

Historically, the investigation of bitter taste genetics has focused on TAS2R38, the so called PTC gene. The improvement in genomic technologies in recent years has led to a dramatic increase in the number of TAS2R gene variants that have been identified and validated.

However, the functional significance of the majority of these polymorphisms are yet to be elucidated. Additionally, some TAS2R receptors remain as orphans, with no functional ligands identified.

It has long been hypothesised that TAS2R genotype and resulting taster phenotype would influence food preference, dietary intake and consequently health and disease. Despite the neatness of this logic, this relationship is yet to be completely understood. While it is clear that TAS2R genotype and taster phenotype contribute to food preference and choices of dietary intake, it is clear that other factors play a significant role. These additional factors include age, "food adventurousness", gender, fungiform papillae density and social and cultural influences. All these factors may also interact with genetic and epigenetics to alter outcomes.

Unravelling the interaction between these factors is complex, and at times data appear inconsistent. However, it is important to note that studies examining differences in perception and liking use a diverse array of methods to determine taster status, making it sometimes difficult to make comparisons across studies. Also, some studies rely on genotyping or PROP/PTC tasting alone, whilst others combine the two assessments to determine taster status. Another issue is that studies that examine differences in tasting, preference and intake often focus on specific population subsets, which though informative, do not reveal a true representation of the population as a whole.

Failure in earlier investigations to take into account the complexities of taste preference, intake and health outcomes may be limiting our understanding of the genetic contribution to these parameters, where pleiotropic effects are clearly present. Care should be taken to address this in future studies into bitter taste genetics.

| Receptor | Breadth of Tuning | Examples of Ligands |
|---|---|---|
| TAS2R1 | Intermediate[226] | Bitter Peptides[226], Humulones, Picrotoxinin[36] |
| TAS2R3 | Narrow[36] | Chloroquine[36] |
| TAS2R4 | Intermediate[14] | PROP, denatonium benzoate[14], Epicatechin[227], quinine[36] |
| TAS2R5 | Narrow[36] | 1,10-phenanthroline[36], Epicatechin[227] |
| TAS2R7 | Intermediate[228] | Caffeine[63], Strychinine[80], cromolyn[36], malvidin-3-glucoside[227] |
| TAS2R8 | Narrow[14] | chloramphenicol and denatonium benzoate[14] |
| TAS2R9 | Narrow-Intermediate[64] | Ofloxacin, procainamide and pirenzapine[64] |
| TAS2R10 | Broad[229] | Caffeine[63], Strychinine[80], Chloroquine, denatonium benzoate[229], erythromycin, quinine[36] |
| TAS2R13 | Narrow[36] | Denatonium Benzoate, Diphenidol[36] |
| TAS2R14 | Broad[229] | Caffeine[63], Alpha-thujone[230], absinthin, quinine, aristolochic acid[36] |
| TAS2R16 | Broad[80] | B-D-glucopyranoside group, eg salicin[87] and amygdalin[36] |
| TAS2R19 | | Orphan |
| TAS2R20 | | Orphan |
| TAS2R30 | Intermediate[231] | Denatonium benzoate, Picrotoxinin[63] |
| TAS2R31 | Intermediate[34] | Saccharin[34] |
| TAS2R33 | | Orphan |
| TAS2R38 | Broad[87, 88] | Isothiocyanates (including PROP and PTC)[87 88] |
| TAS2R39 | Intermediate[36] | Epicatechin[227], Colchicine, denatonium benzoate[36] |
| TAS2R40 | Intermediate[232] | Quinine, Chlorpheniramine[36], Humulone isomeres[36, 232] |
| TAS2R41 | Narrow[233] | Chloramphenicol[233] |
| TAS2R42 | | Orphan |
| TAS2R43 | Intermediate[34, 231] | Sulfonyl amide sweetners[34], Caffeine[63], Sacchrin (Pronin et al, 2004 |
| TAS2R44 | Intermediate[36] | Quinine, Acesulfame K, Saccharin[36] |
| TAS2R45 | | Orphan |
| TAS2R46 | Broad[36, 229] | Qunine, Caffeine, Denatonium Benzoate,Hydrocortisone, Strychnine[36, 229] |
| TAS2R47 | Broad[36] | Denatonium Benzoate, Diphenidol, Artemorin, Absinthin[36] |
| TAS2R48 | | Orphan |
| TAS2R49 | Narrow[36] | Cromolyn[36] |
| TAS2R50 | Narrow[234] | Amarogentin, Andrographolide[36] |
| TAS2R60 | | Orphan |

**TABLE 1:** *Functional TAS2R receptors, their breadth of tuning, and some examples of ligands.*

| Gene | # Non synonymous variants |
|---|---|
| ***TAS2R1*** | 15 |
| ***TAS2R3*** | 8 |
| ***TAS2R4*** | 14 |
| ***TAS2R5*** | 17 |
| ***TAS2R7*** | 20 |
| ***TAS2R8*** | 18 |
| ***TAS2R9*** | 18 |
| ***TAS2R10*** | 16 |
| ***TAS2R13*** | 11 |
| ***TAS2R14*** | 12 |
| ***TAS2R16*** | 7 |
| ***TAS2R19*** | 15 |
| ***TAS2R20*** | 16 |
| ***TAS2R30*** | 8 |
| ***TAS2R31*** | 20 |
| ***TAS2R33*** | 0 |
| ***TAS2R38*** | 13 |
| ***TAS2R39*** | 8 |
| ***TAS2R40*** | 8 |
| ***TAS2R41*** | 9 |
| ***TAS2R42*** | 0 |
| ***TAS2R43*** | 15 |
| ***TAS2R44*** | 20 |
| ***TAS2R45*** | 0 |
| ***TAS2R46*** | 7 |
| ***TAS2R47*** | 8 |
| ***TAS2R48*** | 15 |
| ***TAS2R49*** | 16 |
| ***TAS2R50*** | 14 |
| ***TAS2R60*** | 30 |

**TABLE 2:** Number of non-synonymous nucleic acid variants in each intact and functional TAS2R gene. Only variants validated by the 1000 genomes project were included. Retrieved May 2014 from http://www.ncbi.nlm.nih.gov/snp

| Reference SNP ID | Alleles | MAF | Variant Amino Acid Position | Alleles |
|---|---|---|---|---|
| rs713598 | C/G | C=0.4692 | 49 | Proline/Alanine |
| rs10246939 | C/T | T=0.4509 | 262 | Alanine/Valine |
| rs1726866 | G/A | A=0.4082 | 296 | Valine/Isoleucine |

**TABLE 3:** *Common and rare variants in the TAS2R38 gene (ref: http://www.ncbi.nlm.nih.gov/snp) MAF; minor allele frequency*

## References


1. D. R. Reed and A. Knaapila, *Prog Mol Biol Transl Sci*, 2010, 94, 213-240.
2. D. Drayna, *6*, 2005.
3. F. Li, *Mol Hum Reprod*, 2013, 19, 349-360.
4. J. Berg, J. Tymoczko and L. Stryer, *Biochemistry. 5th edition.*, New York:, 2002.
5. U. K. Kim, P. A. Breslin, D. Reed and D. Drayna, *J Dent Res*, 2004, 83, 448-453.
6. A. Bigiani, V. Ghiaroni and F. Fieni, *Prog Biophys Mol Biol*, 2003, 83, 193-225.
7. Y. Ishimaru, H. Inada, M. Kubota, H. Zhuang, M. Tominaga and H. Matsunami, *Proc Natl Acad Sci USA*, 2006, 103, 12569-12574.
8. D. Stevens, R. Seifert, B. Bufe, F. Muller, E. Kremmer, R. Gauss, W. Meyerhof, U. Kaupp and B. Lindemann, *Nature*, 2001, 413.
9. A. Huang, X. Chen, M. Hoon, J. Chandrashekar, W. Guo, D. Tränkner, N. Ryba and C. Zuker, *Nature.*, 2006, 442, 934-938.
10. N. Horio, R. Yoshida, K. Yasumatsu, Y. Yanagawa, Y. Ishimaru, H. Matsunami and Y. Ninomiya, *PLoS One.*, 2011, 6, e20007.
11. J. Chandrashekar, M. Hoon, N. Ryba and C. Zuker, *Nature*, 2006, 444, 288-294.
12. X. Li, L. Staszewski, H. Xu, K. Durick, M. Zoller and E. Adler, *Proc Natl Acad Sci USA*, 2002, 99, 4692-4694.
13. E. Adler, M. Hoon, K. Mueller, J. Chandrashekar, N. Ryba and C. Zuker, *Cell Biochem Biophys*, 2000, 100, 693-702.
14. J. Chandrashekar, K. Mueller, M. Hoon, E. Adler, L. Feng, W. Guo, C. Zuker and N. Ryba, *Cell*, 2000, 100, 703-711.
15. E. R. Liman, Y. V. Zhang and C. Montell, *Neuron*, 2014, 81, 984-1000.
16. V. Lyall, R. I. Alam, D. Q. Phan, G. L. Ereso, T. H. Phan, S. A. Malik, M. H. Montrose, S. Chu, G. L. Heck, G. M. Feldman and J. A. DeSimone, *American journal of physiology. Cell physiology*, 2001, 281, C1005-1013.
17. T. A. Richter, A. Caicedo and S. D. Roper, *The Journal of physiology*, 2003, 547, 475-483.
18. R. B. Chang, H. Waters and E. R. Liman, *Proc Natl Acad Sci U S A*, 2010, 107, 22320-22325.
19. S. Shimada, T. Ueda, Y. Ishida, T. Yamamoto and S. Ugawa, *Archives of histology and cytology*, 2006, 69, 227-231.
20. D. R. Stevens, R. Seifert, B. Bufe, F. Muller, E. Kremmer, R. Gauss, W. Meyerhof, U. B. Kaupp and B. Lindemann, *Nature*, 2001, 413, 631-635.
21. W. Lin, C. A. Burks, D. R. Hansen, S. C. Kinnamon and T. A. Gilbertson, *Journal of neurophysiology*, 2004, 92, 2909-2919.
22. T. A. Richter, G. A. Dvoryanchikov, N. Chaudhari and S. D. Roper, *Journal of neurophysiology*, 2004, 92, 1928-1936.
23. H. Kawaguchi, A. Yamanaka, K. Uchida, K. Shibasaki, T. Sokabe, Y. Maruyama, Y. Yanagawa, S. Murakami and M. Tominaga, *J Biol Chem*, 2010, 285, 17277-17281.
24. J. Chandrashekar, C. Kuhn, Y. Oka, D. A. Yarmolinsky, E. Hummler, N. J. Ryba and C. S. Zuker, *Nature*, 2010, 464, 297-301.
25. Y. Oka, M. Butnaru, L. von Buchholtz, N. J. Ryba and C. S. Zuker, *Nature*, 2013, 494, 472-475.
26. M. J. Kim, H. J. Son, Y. Kim, H. J. Kweon, B. C. Suh, V. Lyall and M. R. Rhyu, *PLoS One*, 2014, 9, e89062.
27. P. A. Temussi, *Trends Biochem Sci*, 2009, 34, 296-302.
28. G. Nelson, M. A. Hoon, J. Chandrashekar, Y. Zhang, N. J. Ryba and C. S. Zuker, *Cell*, 2001, 106, 381-390.
29. A. Drewnowski, *Eur J Clin Nutr.* , 1999, 53, 757-763.
30. B. J. Tepper, *Annu Rev Nutr*, 2008, 28, 367-388.
31. W. Meyerhof, *Rev Physiol Biochem Pharmacol*, 2005, 154, 37-72.
32. B. Meyers and M. Brewer, *J Food Sci.*, 2008, 73, R81-90.
33. A. L. Allen, J. E. McGeary, V. S. Knopik and J. E. Hayes, *Chem Senses*, 2013, 38, 379-389.

34. C. Kuhn, B. Bufe, M. Winnig, T. Hofmann, O. Frank, M. Behrens, T. Lewtschenko, J. Slack, C. Ward and W. Meyerhof, *J Neurosci.* , 2004, 24, 10260-10265.
35. M. Behrens, S. Foerster, F. Staehler, J. D. Raguse and W. Meyerhof, *J Neurosci*, 2007, 27, 12630-12640.
36. W. Meyerhof, C. Batram, C. Kuhn, A. Brockhoff, E. Chudoba, B. Bufe, G. Appendino and M. Behrens, *Chem Senses*, 2010, 35, 157-170.
37. A. El-Sohemy, L. Stewart, N. Khataan, B. Fontaine-Bisson, P. Kwong, S. Ozsungur and M. C. Cornelis, *Forum Nutr*, 2007, 60, 176-182.
38. A. Drewnowski and C. L. Rock, *Am J Clin Nutr*, 1995, 62, 506-511.
39. J. Sibert and N. Frude, *Arch Emerg Med.*, 1991, 8, 1-7.
40. R. Liu, *J Nutr.*, 2004, 134, 3479S-3485S.
41. J. Weisburger, *Nutrition*, 2000, 16, 767-773.
42. L. Bravo, *Nutr Rev* 1998, 56, 317-333.
43. J. A. Mennella, A. C. Spector, D. R. Reed and S. E. Coldwell, *Clin Ther*, 2013, 35, 1225-1246.
44. J. Anliker, L. Bartoshuk, A. Ferris and L. Hooks, *Am J Clin Nutr.* , 1991, 54, 316-320.
45. A. Drewnowski, *Nutr Rev*, 2001, 59, 163-169.
46. V. Duffy and L. Bartoshuk, *J Am Diet Assoc*, 2000, 1006647-55.
47. K. Maehashi and L. Huang, *Cell Mol Life Sci*, 2009, 66, 1661-1671.
48. M. Basson, L. Bartoshuk, S. Dichello, L. Panzini, J. Weiffenbach and V. Duffy, *Dig Dis Sci.*, 2005, 50, 438-439.
49. N. Timpson, M. Christensen, D. Lawlor, T. Gaunt, I. Day, S. Ebrahim and G. Davey Smith, *Am J Clin Nutr.*, 2005, 81, 1005-1011.
50. A. A. Bachmanov and G. K. Beauchamp, *Annu Rev Nutr*, 2007, 27, 389-414.
51. S. K. McLaughlin, P. J. McKinnon, A. Robichon, N. Spickofsky and R. F. Margolskee, *Ciba Found Symp*, 1993, 179, 186-196; discussion 196-200.
52. R. Margolskee, *Bioessays.* , 1993, 15, 645-650.
53. M. Gees, Y. Alpizar, T. Luyten, J. Parys, B. Nilius, G. Bultynck, T. Voets and K. Talavera, *Chem Senses.*, 2014, 39, 295-311.
54. T. Clapp, L. Stone, R. Margolskee and S. Kinnamon, *BMC Neurosci.*, 2001, 2, Epub 2001 Apr 2023.
55. M. Kapsimali and L. Barlow, *Semin Cell Dev Biol.*, 2013, 24, 200-209.
56. H. Saito, M. Kubota, R. Roberts, Q. Chi and H. Matsunami, *Cell.*, 2004, 119, 679-691.
57. A. Shah, Y. Ben-Shahar, T. Moninger, J. Kline and M. Welsh, *Science.* , 2009, 325, 1131-1134.
58. D. Deshpande, W. Wang, E. McIlmoyle, K. Robinett, R. Schillinger, S. An, J. Sham and S. Liggett, *Nat Med.*, 2010, 16, 1299-1304.
59. K. Iwatsuki, R. Ichikawa, A. Uematsu, A. Kitamura, H. Uneyama and K. Torii, *Acta Physiol (Oxf).* 2012, 204, 169-177.
60. C. Dotson, S. Vigues, N. Steinle and S. Munger, *Curr Opin Investig Drugs.*, 2010, 11, 447-454.
61. J. Xu, J. Cao, N. Iguchi, D. Riethmacher and L. Huang, *Mol Hum Reprod.*, 2013, 19, 17-28.
62. N. Singh, M. Vrontakis, F. Parkinson and P. Chelikani, *Biochem Biophys Res Commun.*, 2011, 406, 146-151.
63. M. Behrens, H. C. Gunn, P. C. Ramos, W. Meyerhof and S. P. Wooding, *Chem Senses*, 2013, 38, 475-484.
64. C. D. Dotson, L. Zhang, H. Xu, Y. K. Shin, S. Vigues, S. H. Ott, A. E. Elson, H. J. Choi, H. Shaw, J. M. Egan, B. D. Mitchell, X. Li, N. I. Steinle and S. D. Munger, *PLoS One*, 2008, 3, e3974.
65. T. Jeon, B. Zhu, J. Larson and T. Osborne, *J Clin Invest.*, 2008, 118, 3693-3700.
66. S. Hao, M. Dulake, E. Espero, C. Sternini, H. Raybould and L. Rinaman, *Am J Physiol Regul Integr Comp Physiol.*, 2009, 296, R528-536.
67. S. Straub, J. Mulvaney-Musa, H. Yajima, G. Weiland and G. Sharp, *Diabetes.*, 2003, 52, 356-364.

68. T. Little, N. Gupta, R. Case, D. Thompson and J. McLaughlin, *Am J Physiol Regul Integr Comp Physiol.*, 2009, 297, R632-639.
69. I. Kaji, S. Karaki, Y. Fukami, M. Terasaki and A. Kuwahara, *Am J Physiol Gastrointest Liver Physiol.*, 2009, 296, G971-981.
70. S. Janssen, J. Laermans, P. Verhulst, T. Thijs, J. Tack and I. Depoortere, *Proc Natl Acad Sci U S A.*, 2011, 108, 2094-2099.
71. D. Wicks, J. Wright, P. Rayment and R. Spiller, *Eur J Gastroenterol Hepatol.* , 2005, 17, 961-965.
72. J. Glendinning, Y. Yiin, K. Ackroff and A. Sclafani, *Physiol Behav.* , 2008, 93, 757-765.
73. M. Tizzano, B. Gulbransen, A. Vandenbeuch, T. Clapp, J. Herman, H. Sibhatu, M. Churchill, W. Silver, S. Kinnamon and T. Finger, *Proc Natl Acad Sci U S A.*, 2010, 107, 3210-3215.
74. A. James, K. Daham, B. Dahlen, G. Hedlin, J. Kere, J. Konradsen, B. Nordlund, A. Lindeberg, E. Melen, C. Orsmark-Pietras, C. Söderhäll, V. Pulkkinen and S. E. Dahlen, *Am J Respir Crit Care Med* 2012, 1185, A6752.
75. C. Orsmark-Pietras, A. James, J. R. Konradsen, B. Nordlund, C. Soderhall, V. Pulkkinen, C. Pedroletti, K. Daham, M. Kupczyk, B. Dahlen, J. Kere, S. E. Dahlen, G. Hedlin and E. Melen, *Eur Respir J*, 2013, 42, 65-78.
76. C. H. Zhang, L. M. Lifshitz, K. F. Uy, M. Ikebe, K. E. Fogarty and R. ZhuGe, *PLoS Biol*, 2013, 11, e1001501.
77. K. Mueller, M. Hoon, I. Erlenbach, J. Chandrashekar, C. Zuker and N. Ryba, *Nature*, 2005, 434, 225-229.
78. R. Yoshida, A. Miyauchi, T. Yasuo, M. Jyotaki, Y. Murata, K. Yasumatsu, N. Shigemura, Y. Yanagawa, K. Obata, H. Ueno, R. Margolskee and Y. Ninomiya, *J Physiol.*, 2009, 587, 4425-4439.
79. M. Behrens and W. Meyerhof, *Results Probl Cell Differ*, 2009, 47, 203-220.
80. B. Bufe, T. Hofmann, D. Krautwurst, J. Raguse and W. Meyerhof, *Nat Genet.*, 2002, 32, 397-401.
81. H. Harris and H. Kalmus, *Ann Eugenics London* 1949, 15, 32-45.
82. J. Fahey, A. Zalcmann and P. Talalay, *Phytochemistry.*, 2001, 56, 5-51.
83. D. R. Reed, T. Tanaka and A. H. McDaniel, *Physiol Behav*, 2006, 88, 215-226.
84. P. Wheatcroft and C. Thornburn, *Nat New Biol.*, 1972, 235, 93-94.
85. J. E. Hayes, L. M. Bartoshuk, J. R. Kidd and V. B. Duffy, *Chem Senses*, 2008, 33, 255-265.
86. W. Chang, J. Chung, Y. Kim, S. Chung and H. Kho, *Arch Oral Biol.*, 2006, 51, 427-432.
87. U. K. Kim, E. Jorgenson, H. Coon, M. Leppert, N. Risch and D. Drayna, *Science*, 2003, 299, 1221-1225.
88. B. Bufe, P. A. Breslin, C. Kuhn, D. R. Reed, C. D. Tharp, J. P. Slack, U. K. Kim, D. Drayna and W. Meyerhof, *Curr Biol*, 2005, 15, 322-327.
89. S. Wooding, U. K. Kim, M. J. Bamshad, J. Larsen, L. B. Jorde and D. Drayna, *Am J Hum Genet*, 2004, 74, 637-646.
90. N. H. Khataan, L. Stewart, D. M. Brenner, M. C. Cornelis and A. El-Sohemy, *J Nutrigenet Nutrigenomics*, 2009, 2, 251-256.
91. U. Kim, S. Wooding, D. Ricci, L. B. Jorde and D. Drayna, *Hum Mutat*, 2005, 26, 199-204.
92. U. K. Kim and D. Drayna, *Clin Genet*, 2005, 67, 275-280.
93. S. W. Guo and D. R. Reed, *Ann Hum Biol*, 2001, 28, 111-142.
94. B. Tepper, *Am J Hum Genet.*, 1998, 63, 1271-1276.
95. N. Pirastu, A. Robino, C. Lanzara, E. Athanasakis, L. Esposito, B. J. Tepper and P. Gasparini, *J Food Sci*, 2012, 77, S413-418.
96. E. Feeney, S. O'Brien, A. Scannell, A. Markey and E. R. Gibney, *Proc Nutr Soc*, 2011, 70, 135-143.
97. D. Reed, L. Bartoshuk, V. Duffy, S. Marino and R. Price, *Chem Senses.* , 1995, 20, 529-533.

98. D. Drayna, H. Coon, U. Kim, T. Elsner, K. Cromer, B. Otterud, L. Baird, A. Peiffer, M. Leppert and U. G. R. Project., *Hum Genet.* , 2003, 112, 576-572.
99. J. Mennella, M. Pepino, F. Duke and D. Reed, *BMC Genet.*, 2010, 11, doi: 10.1186/1471-2156-1111-1160.
100. B. J. Tepper, E. A. White, Y. Koelliker, C. Lanzara, P. d'Adamo and P. Gasparini, *Ann N Y Acad Sci*, 2009, 1170, 126-139.
101. J. Hansen, D. Reed, M. Wright, N. Martin and P. Breslin, *Chem Senses.*, 2006, 31, 403-413.
102. A. Drewnowski, S. Henderson and A. Shore, *Am J Clin Nutr.* , 1997, 66, 391-397.
103. J. Guinard, D. Hong, C. Zoumas-Morse, C. Budwig and G. Russell, *Physiol Behav.*, 1994, 56, 1257-1263.
104. D. Mela, *Chem. Senses*, 1990, 15, 485-490.
105. J. Delwiche, Z. Buletic and P. Breslin, *Physiol Behav.* , 2001, 74, 329-337.
106. E. Leach and A. Noble, *Chem Senses*, 1986, 11, 339-345.
107. D. Mela, *Chem Senses*, 1989, 14, 131-135.
108. Schifferstein HN and J. Frijters, *Percept Psychophys.*, 1991, 49, 1-9.
109. Y. Yokomukai, B. Cowart and G. Beuchamp, *Chem Senses*, 1993, 18, 669-681.
110. L. M. Bartoshuk and G. K. Beauchamp, *Annu Rev Psychol*, 1994, 45, 419-449.
111. V. B. Duffy, *Appetite*, 2004, 43, 5-9.
112. J. Mennella, M. Pepino and D. Reed, *Pediatrics*, 2005, 115, e216-222.
113. M. Yeomans, B. Tepper, J. Rietzschel and J. Prescott, *Physiol Behav.*, 2007, 91, 264-273.
114. A. Pronin, H. Xu, H. Tang, L. Zhang, Q. Li and X. Li, *Curr Biol.*, 2007, 17, 1403-1408.
115. L. Bartoshuk, Duffy VB, L. Lucchina, J. Prutkin and K. Fast, *Ann N Y Acad Sci.* , 1998, 855, 793-796.
116. J. Hayes, B. Sullivan and V. Duffy, *Physiol Behav.* , 2010, 100, 369-380.
117. J. Prescott and N. Swain-Campbell, *Chem Senses.*, 2000, 25, 239-246.
118. G. Pickering, *J Anim Physiol Anim Nutr (Berl).* 2009, 93, 52-60.
119. B. Tepper and R. Nurse, *Physiol Behav.*, 1997, 61, 949-954.
120. J. Hayes and V. Duffy, *Chem Senses.* , 2007, 32, 225-236.
121. D. Reed, *Chem Senses.*, 2008, 33, 489-491.
122. M. Bajec and G. Pickering, *Physiol Behav.*, 2008, 95, 581-590.
123. G. Essick, A. Chopra, S. Guest and F. McGlone, *Physiol Behav.*, 2003, 80, 289-301.
124. C. Yackinous and J. Guinard, *Appetite.* , 2002, 38, 201-209.
125. J. Lim, L. Urban and B. Green, *Chem Senses*, 2008, 33, 493-501.
126. B. Green and P. George, *Chem Senses*, 2004, 29, 617-628.
127. N. Soranzo, B. Bufe, P. Sabeti, J. Wilson, M. Weale, R. Marguerie, W. Meyerhof and D. Goldstein, *Curr Biol.* , 2005, 15, 1257-1265.
128. N. Roudnitzky, B. Bufe, S. Thalmann, C. Kuhn, H. Gunn, C. Xing, B. Crider, M. Behrens, W. Meyerhof and S. Wooding, *Hum Mol Genet.*, 2011, 20, 3437-3449.
129. C. Calò, A. Padiglia, A. Zonza, L. Corrias, P. Contu, B. Tepper and I. Barbarossa, *Physiol Behav.*, 2011, 104, 1065-1071.
130. M. Sandell and P. Breslin, *Curr Biol.* , 2006, 16, R792-794.
131. J. Prescott, J. Soo, H. Campbell and C. Roberts, *Physiol Behav.* , 2004, 82, 459-469.
132. A. Ly and A. Drewnowski, *Chem Senses.*, 2001, 26, 41-47.
133. J. E. Hayes, M. R. Wallace, V. S. Knopik, D. M. Herbstman, L. M. Bartoshuk and V. B. Duffy, *Chem Senses*, 2011, 36, 311-319.
134. B. Garcia-Bailo, C. Toguri, K. M. Eny and A. El-Sohemy, *OMICS*, 2009, 13, 69-80.
135. K. Glanz, M. Basil, E. Maibach, J. Goldberg and D. Snyder, *J Am Diet Assoc.* , 1998, 10, 1118-1126.
136. A. Leterme, L. Brun, A. Dittmar and O. Robin, *Physiol Behav.*, 2008, 93, 994-999.
137. V. B. Duffy, *Curr Opin Gastroenterol*, 2007, 23, 171-177.
138. A. Drewnowski and C. Gomez-Carneros, *Am J Clin Nutr.*, 2000, 72, 1424-1435.

139. M. Dinehart, J. Hayes, L. Bartoshuk, S. Lanier and V. Duffy, *Physiol Behav.*, 2006, 87, 304-313.
140. R. Mattes, ed., *6-n-propylthiouracil taster status; Dietary modifier, marker, or misleaders?* , New York, 2004.
141. F. Bauer, C. Elbers, R. Adan, R. Loos, N. Onland-Moret, D. Grobbee, J. van Vliet-Ostaptchouk, C. Wijmenga and Y. van der Schouw, *Am J Clin Nutr.*, 2009, 90, 951-959.
142. M. Rasmussen, R. Krølner, K. Klepp, L. Lytle, J. Brug, E. Bere and P. Due, *Int J Behav Nutr Phys Act*, 2006, 3, 22.
143. E. Bere, J. Brug and K. Klepp, *Public Health Nutr.*, 2008, 11, 321-325.
144. K. Sharma and G. K. Kaur, *Ann Hum Biol*, 2014, 41, 29-39.
145. B. Turnbull and E. Matisoo-Smith, *Am J Clin Nutr.*, 2002, 76, 1101-1105.
146. A. Drewnowski, S. Henderson, A. Shore and A. Barratt-Fornell, *Ann N Y Acad Sci.*, 1998, 855, 797-801.
147. K. Keller, L. Steinmann, R. Nurse and B. Tepper, *Appetite.*, 2002, 38, 3-12.
148. R. Mattes, *Physiol Behav.*, 1994, 56, 1229-1236.
149. M. Yeomans, S. Mobini and L. Chambers, *Physiol Behav.* , 2007, 92, 831-839.
150. N. Pirastu, M. Kooyman, M. Traglia, A. Robino, S. M. Willems, G. Pistis, P. d'Adamo, N. Amin, A. d'Eustacchio, L. Navarini, C. Sala, L. C. Karssen, C. van Duijn, D. Toniolo and P. Gasparini, *PLoS One*, 2014, 9, e92065.
151. N. Ullrich, R. Touger-Decker, J. O'sullivan-Maillet and B. Tepper, *J Am Diet Assoc.*, 2004, 104, 543-549.
152. S. Lanier, J. Hayes and V. Duffy, *Physiol Behav.* , 2005, 83, 821-831.
153. K. Keller and B. Tepper, *Obes Res.*, 2004, 12, 904-912.
154. O. Laaksonen, J. Ahola and M. Sandell, *Appetite*, 2013, 61, 85-96.
155. R. Negri, M. Di Feola, S. Di Domenico, M. G. Scala, G. Artesi, S. Valente, A. Smarrazzo, F. Turco, G. Morini and L. Greco, *J Pediatr Gastroenterol Nutr*, 2012, 54, 624-629.
156. C. Sacerdote, S. Guarrera, G. Smith, S. Grioni, V. Krogh, G. Masala, A. Mattiello, D. Palli, S. Panico, R. Tumino, F. Veglia, G. Matullo and P. Vineis, *Am J Epidemiol.*, 2007, 166, 576-581.
157. M. Jerzsa-Latta, M. Krondl and P. Coleman, *Appetite.*, 1990, 15, 127-134.
158. V. Duffy, J. Hayes, A. Davidson, J. Kidd, K. Kidd and L. Bartoshuk, *Chemosens Percept.* , 2010, 3-148, 137.
159. S. Schembre, I. Cheng, L. Wilkens, C. Albright and L. Marchand le, *Nutr Cancer.*, 2013, 65, 982-990.
160. M. Lucock, X. Ng, L. Boyd, V. Skinner, R. Wai, S. Tang, C. Naylor, Z. Yates, J. Choi, P. Roach and M. Veysey, *Food Funct.*, 2011, 2, 457-465.
161. H. Inoue, K. Yamakawa-Kobayashi, Y. Suzuki, T. Nakano, H. Hayashi and T. Kuwano, *J Nutr Sci Vitaminol (Tokyo).* , 2013, 59, 16-21.
162. L. Kaminski, S. Henderson and A. Drewnowski, *Physiol Behav.*, 2000, 68, 691-697.
163. K. Bell and B. Tepper, *Am J Clin Nutr.* , 2006, 84, 245-251.
164. K. Keller, A. Olsen, T. Cravener, R. Bloom, W. Chung, L. Deng, P. Lanzano and K. Meyermann, *Appetite.* , 2014, 77, 115-123.
165. A. Drewnowski, S. Henderson and J. Cockroft, *J Am Diet Assoc.*, 2007, 107, 1340-1348.
166. A. Olsen, J. Halkjaer, C. van Gils, B. Buijsse, H. Verhagen, M. Jenab, M. Boutron-Ruault, U. Ericson, M. Ocké, P. Peeters, M. Touvier, M. Niravong, M. Waaseth, G. Skeie, K. Khaw, R. Travis, P. Ferrari, M. Sanchez, A. Agudo, K. Overvad, J. Linseisen, C. Weikert, C. Sacerdote, A. Evangelista, D. Zylis, K. Tsiotas, J. Manjer, B. van Guelpen, E. Riboli, N. Slimani and S. Bingham, *Eur J Clin Nutr.*, 2009, 63, S122-149.
167. A. Bakke and Z. Vickers, *J Food Sci.* , 2007, 72, S473-480.
168. L. Huang, Y. Shanker, J. Dubauskaite, J. Zheng, W. Yan, S. Rosenzweig, A. Spielman, M. Max and R. Margolskee, *Nat. Neurosci.*, 1999, 2, 1055–1062.
169. C. Dotson, M. Wallace, L. Bartoshuk and H. Logan, *Chem Senses.* , 2012, 37, 731-744.
170. B. Tepper, M. Neilland, N. Ullrich, Y. Koelliker and L. Belzer, *Appetite.* , 2011, 56, 104-110.

171. C. D. Dotson, H. L. Shaw, B. D. Mitchell, S. D. Munger and N. I. Steinle, *Appetite*, 2010, 54, 93-99.
172. M. Nagtegaal, J. Swen, L. Hanff, K. Schimmel and H. Guchelaar, *Pharmacogenomics.*, 2014, 15, 111-119.
173. T. Greene, S. Alarcon, A. Thomas, E. Berdougo, B. Doranz, P. Breslin and J. Rucker, *PLoS One.*, 2011, 6, e20123.
174. D. Cannon, T. Baker, M. Piper, M. Scholand, D. Lawrence, D. Drayna, W. McMahon, G. Villegas, T. Caton, H. Coon and M. Leppert, *Nicotine Tob Res.* , 2005, 7, 853-858.
175. B. Tepper and N. Ullrich, *Physiol Behav.*, 2002, 75, 305-312.
176. V. Duffy, J. Peterson and L. Bartoshuk, *Physiol Behav.*, 2004, 82, 435-445.
177. H. Looy and H. Weingarten, *Physiol Behav.* , 1992, 52, 75-82.
178. J. Lumeng, T. Cardinal, J. Sitto and S. Kannan, *Obesity (Silver Spring).* 2008, 16, 1522-1528.
179. K. Keller, A. Reid, M. MacDougall, H. Cassano, J. Song, L. Deng, P. Lanzano, W. Chung and H. Kissileff, *Obesity (Silver Spring).* 2010, 18, 1194-1200.
180. R. Fischer, F. Griffin and M. Rockey, *Perspect. Biol. Med.* , 1966, 9, 549-577.
181. G. Goldstein, H. Daun and B. Tepper, *Obes Res.*, 2005, 13, 1017-1023.
182. V. Andreeva, C. Martin, S. Issanchou, S. Hercberg, E. Kesse-Guyot and C. Méjean, *Appetite* 2013, 67, 53-60.
183. C. Willer, E. Speliotes, R. Loos, S. Li, C. Lindgren, I. Heid, S. Berndt, A. Elliott, A. Jackson, C. Lamina, G. Lettre, N. Lim, H. Lyon, S. McCarroll, K. Papadakis, L. Qi, J. Randall, R. Roccasecca, S. Sanna, P. Scheet, M. Weedon and E. Wheeler, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burtt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P, Kuokkanen M, Kuusisto J, Laitinen J, Lakatta EG, Luan J, Luben RN, Mangino M, McArdle WL, Meitinger T, Mulas A, Munroe PB, Narisu N, Ness AR, Northstone K, O'Rahilly S, Purmann C, Rees MG, Ridderstråle M, Ring SM, Rivadeneira F, Ruokonen A, Sandhu MS, Saramies J, Scott LJ, Scuteri A, Silander K, Sims MA, Song K, Stephens J, Stevens S, Stringham HM, Tung YC, Valle TT, Van Duijn CM, Vimaleswaran KS, Vollenweider P, Waeber G, Wallace C, Watanabe RM, Waterworth DM, Watkins N; Wellcome Trust Case Control Consortium, Witteman JC, Zeggini E, Zhai G, Zillikens MC, Altshuler D, Caulfield MJ, Chanock SJ, Farooqi IS, Ferrucci L, Guralnik JM, Hattersley AT, Hu FB, Jarvelin MR, Laakso M, Mooser V, Ong KK, Ouwehand WH, Salomaa V, Samani NJ, Spector TD, Tuomi T, Tuomilehto J, Uda M, Uitterlinden AG, Wareham NJ, Deloukas P, Frayling TM, Groop LC, Hayes RB, Hunter DJ, Mohlke KL, Peltonen L, Schlessinger D, Strachan DP, Wichmann HE, McCarthy MI, Boehnke M, Barroso I, Abecasis GR, Hirschhorn JN; Genetic Investigation of ANthropometric Traits Consortium., *Nat Genet.*, 2009, 41, 25-34.
184. S. Bouthoorn, F. van Lenthe, J. Kiefte-de Jong, H. Taal, A. Wijtzes, A. Hofman, V. Jaddoe, M. Glymour, F. Rivadeneira and H. Raat, *Int J Obes (Lond).* 2013, doi: 10.1038/ijo.2013.1141. [Epub ahead of print].
185. R. Pidamale, B. Sowmya, A. Thomas and T. Jose, *Indian J Hum Genet.* , 2012, 18, 101-105.
186. S. Rupesh and U. Nayak, *J Indian Soc Pedod Prev Dent.*, 2006, 24, 63-68.
187. L. Bartoshuk, V. Duffy, J. Hayes, H. Moskowitz and D. Snyder, *Philos Trans R Soc Lond B Biol Sci.* , 2006, 361, 1137-1148.
188. M. Tanasescu, A. Ferris, D. Himmelgreen, N. Rodriguez and R. Pérez-Escamilla, *J Nutr.*, 2000, 130, 1734-1742.
189. V. Duffy, A. Davidson, J. Kidd, K. Kidd, W. Speed, A. Pakstis, D. Reed, D. Snyder and L. Bartoshuk, *Alcohol Clin Exp Res.*, 2004, 28, 1629-1637.
190. A. Navarro-Allende, N. Khataan and A. El-Sohemy, *J Nutr Elder*, 2008, 27, 267-276.
191. D. Whissell-Buechy, *Chem. Senses*, 1990, 15, 39-57.

192. R. Lakshmy, P. Rao, B. Sesikeran and P. Suryaprakash, *Horm Metab Res.* , 1995, 27, 450-454.
193. S. Wooding, H. Gunn, P. Ramos, S. Thalmann, C. Xing and W. Meyerhof, *Chem Senses*, 2010, 35, 685-692.
194. W. Koch, P. Hoppmann, A. Schömig and A. Kastrati, *Int J Cardiol.*, 2011, 147, 38-41.
195. B. Horne, J. Carlquist, J. Muhlestein, Z. Nicholas, J. Anderson and I. H. C. S. Group., *Am Heart J.*, 2007, 154, 969-975.
196. R. Zee, S. Michaud, H. Hegener, K. Diehl and P. Ridker, *J Thromb Haemost.* , 2006, 4, 2093-2095.
197. J. van der Net, D. Oosterveer, J. Versmissen, J. Defesche, M. Yazdanpanah, B. Aouizerat, E. Steyerberg, M. Malloy, C. Pullinger, J. Kastelein, J. Kane and E. Sijbrands, *Eur Heart J.*, 2008, 29, 2195-2201.
198. M. Carrai, V. Steinke, P. Vodicka, B. Pardini, N. Rahner, E. Holinski-Feder, M. Morak, H. Schackert, H. Görgens, S. Stemmler, B. Betz, M. Kloor, C. Engel, R. Büttner, A. Naccarati, L. Vodickova, J. Novotny, A. Stein, K. Hemminki, P. Propping, A. Försti, F. Canzian, R. Barale and D. Campa, *PLoS One.*, 2011, 6, e20464.
199. A. L. Hinrichs, J. C. Wang, B. Bufe, J. M. Kwon, J. Budde, R. Allen, S. Bertelsen, W. Evans, D. Dick, J. Rice, T. Foroud, J. Nurnberger, J. A. Tischfield, S. Kuperman, R. Crowe, V. Hesselbrock, M. Schuckit, L. Almasy, B. Porjesz, H. J. Edenberg, H. Begleiter, W. Meyerhof, L. J. Bierut and A. M. Goate, *Am J Hum Genet*, 2006, 78, 103-111.
200. M. Pelchat and S. Danowski, *Physiol Behav.* , 1992, 51, 1261-1266.
201. J. C. Wang, A. L. Hinrichs, S. Bertelsen, H. Stock, J. P. Budde, D. M. Dick, K. K. Bucholz, J. Rice, N. Saccone, H. J. Edenberg, V. Hesselbrock, S. Kuperman, M. A. Schuckit, L. J. Bierut and A. M. Goate, *Alcohol Clin Exp Res*, 2007, 31, 209-215.
202. S. Snedecor, C. Pomerleau, A. Mehringer, R. Ninowski and O. Pomerleau, *Addict Behav.*, 2006, 31, 2309-2312.
203. D. Peterson, L. Lonergan and M. Hardinge, *Arch Environ Health*, 1968, 16, 219-222.
204. J. Mangold, T. Payne, J. Ma, G. Chen and M. Li, *J Med Genet.*, 2008, 45, 578-582.
205. T. Heath, J. Melichar, D. Nutt and L. Donaldson, *J Neurosci.*, 2006, 26, 12664-12671.
206. Y. Blednov, D. Walker and R. Harris, *Alcohol Clin Exp Res.*, 2004, 28, 1683-1692.
207. R. Yoshida, T. Ohkuri, M. Jyotaki, T. Yasuo, N. Horio, K. Yasumatsu, K. Sanematsu, N. Shigemura, T. Yamamoto, R. Margolskee and Y. Ninomiya, *Proc Natl Acad Sci U S A.*, 2010, 107, 935-939.
208. C. Conte, M. Ebeling, A. Marcuz, P. Nef and P. J. Andres-Barquin, *Cytogenet Genome Res*, 2002, 98, 45-53.
209. H. Matsunami, J. Montmayeur and L. Buck, *Nature.*, 2000, 404, 601-604.
210. D. Li and J. Zhang, *Mol Biol Evol*, 2014, 31, 303-309.
211. J. Glendinning, *Physiol Behav.*, 1994, 56, 1217-1227.
212. W. Freeland and D. Janzen, *Am Natur*, 1974, 108, 269-289.
213. M. Behrens and W. Meyerhof, *Cell Mol Life Sci*, 2006, 63, 1501-1509.
214. Y. Go, Y. Satta, O. Takenaka and N. Takahata, *Genetics.*, 2005, 170, 313-326.
215. S. Wooding, *Curr Biol*, 2005, 15, R805-807.
216. C. Conte, M. Ebeling, A. Marcuz, P. Nef and P. J. Andres-Barquin, *Physiol Genomics*, 2003, 14, 73-82.
217. O. Törnwall, K. Silventoinen, T. Hiekkalinna, M. Perola, H. Tuorila and J. Kaprio, *Appetite.*, 2014, 75, 1-10.
218. J. Mojet, J. Heidema and E. Christ-Hazelhof, *Chem Senses.*, 2003, 28, 397-413.
219. P. Pavlidis, H. Gouveris, A. Anogeianaki, D. Koutsonikolas, G. Anogianakis and G. Kekes, *Chem Senses.* , 2013, 38, 35-43.
220. S. Flaxman and P. Sherman, *Q Rev Biol.*, 2000, 75, 113-148.
221. V. Duffy, L. Bartoshuk, R. Striegel-Moore and J. Rodin, *Ann N Y Acad Sci.*, 1998, 30, 805-809.
222. S. Youngentob and J. Glendinning, *Proc Natl Acad Sci U S A.* , 2009, 106, 5359-5364.

223. C. Forestell and J. Mennella, *Pediatrics.*, 2007, 120.
224. J. Mennella, L. Lukasewycz, S. Castor and G. Beauchamp, *Am J Clin Nutr.*, 2011, 93, 1019-1024.
225. S. Lipchock, J. Mennella, A. Spielman and D. Reed, *Am J Clin Nutr.*, 2013, 98, 1136-1143.
226. K. Maehashi, M. Matano, H. Wang, L. Vo, Y. Yamamoto and L. Huang, *Biochem Biophys Res Commun*, 2008, 365, 951-955.
227. S. Soares, S. Kohl, S. Thalmann, N. Mateus, W. Meyerhof and V. De Freitas, *J Agric Food Chem.* , 2013, 61, 1525-1533.
228. E. Sainz, M. Cavenagh, J. Gutierrez, J. Battey, J. Northup and S. Sullivan, *Biochem J.*, 2007, 403, 537-543.
229. A. Brockhoff, M. Behrens, A. Massarotti, G. Appendino and W. Meyerhof, *J Agric Food Chem.*, 2007, 55, 6236-6243.
230. M. Behrens, A. Brockhoff, C. Kuhn, B. Bufe, M. Winnig and W. Meyerhof, *Biochem Biophys Res Commun.*, 2004, 319, 479-485.
231. A. Pronin, H. Tang, J. Connor and W. Keung, *Chem Senses.* , 2004, 29, 583-593.
232. D. Intelmann, O. Demmer, N. Desmer and T. Hofmann, *J Agric Food Chem.* , 2009, 57, 11014-11023.
233. S. Thalmann, M. Behrens and W. Meyerhof, *Biochem Biophys Res Commun*, 2013, 435, 267-273.
234. M. Behrens, C. Reichling, C. Batram, A. Brockhoff and W. Meyerhof, *Ann N Y Acad Sci*, 2009, 1170, 111-115.