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***Review title:***

**A cross-talk between fat and bitter taste modalities**

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**Running title:** Cross-talk between fat and bitter

**Abbreviations:** FA, fatty acid; TR, taste receptors; PROP, 6-n-propylthiouracil; PTC, phenylthiocarbamide

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## Abstract

The choice of food is governed largely by the sense of taste. To date, five basic taste modalities have been described; however, there is an increasing agreement on the existence of a 6<sup>th</sup> fat taste. The taste modalities might interact with each other and also with other senses. The advancements in cellular and molecular biology have helped the characterization of taste signaling mechanisms, down to the receptor level and beyond. CD36 and GPR120 have been shown to be involved in the detection of fat taste while bitter taste is perceived by a number of receptors that belong to a family of taste-type 2 receptors (T2R or TAS2R). Hence, the most common role is played by TAS2R16 and TAS2R38 in bitter taste perception in humans. Increasing evidences from behavioural studies suggest that fat and bitter taste modalities might interact with each other, and this interaction might be critical in obesity. In the current review, we will discuss the evidence from genetic and behavioural studies and propose the molecular mechanism of a cross-talk between fat and bitter tastes.

**Key words:** Bitter taste; fat taste; cross-talk; genetic polymorphism.

## 1. Introduction

Humans are omnivorous food-seeking species that have developed through evolution a sense of taste to survive in a complex environment. Taste is a sensory modality, involving the oral perception of food-derived chemicals that stimulate receptor cells within taste buds [1]. Taste not only helps decide whether a food is noxious or palatable but also prepares the gastrointestinal tract for post-ingestive metabolic events. The 5 basic taste modalities have been demonstrated. Simple carbohydrates are perceived as sweet, sodium salts and salts of few cations are perceived as salty, acids are perceived as sour while amino acids like glutamate and aspartate elicit a savoury taste [2]. Moreover, during the recent couple of years, there has been an increasing agreement that fatty acids might trigger a lipid taste [3]. Recent evidence indicates that CD36 and GPR120 might play a non-overlapping role in the detection of a fat taste [4].

The taste receptor (TR) cells are regrouped in taste buds which are the units of the papillae, distributed on the tongue. There are three kinds of papillae: fungiforme (localized in the frontal part of the tongue), foliate (localized in the lateral region of the tongue) and circumvallate (present on the anterior part of the tongue). There are three types of taste cells wherein type I cells are considered as supporting cells, type II cells respond to bitter, sweet and umami, and type III cells are involved in making synaptic junctions with afferent nerve fibres. In this review, we will not go into the details of perception of different taste modalities, as several recent review articles can be consulted on this subject [2,5-7]. Briefly, the heterodimeric T1R2/T1R3 detects the sweet taste whereas, the T1R1/T1R3 heterodimer is sensitive to umami taste [2]. Salt activates sodium channels, while the acidic compounds induce depolarization by blocking potassium channels [7]. TAS2R receptors have been shown to be involved in the perception of bitter taste. Bitter molecules belong to the largest family of tastants and humans possess more than 25 functional bitter taste receptor genes to interact with such large group of taste substances [1]. Therefore, most of the noxious and poisonous substances are experienced as bitter.

The majority of laboratory studies on taste perception are based on the use of candidate molecules. However, in the real world, food, most often, comprises of a mixture of agents that can trigger different taste sensations at the same time. The sense of taste can interact with other senses, and different taste modalities may interact with each other [8, 9]. For instance, salt taste has been shown to inhibit bitterness in food and enhances flavour [10, 11].

Similarly, salty and sour tastes have been shown to interact each other with the enhancement of their effect at low concentrations, while causing an inhibition or no effect at higher concentrations [12]. It is interesting to mention that some amino acids like L-arginine or L-lysine may modulate the oro-sensory perception of 5 taste modalities. The exogenous L-Arg was found to increase the perception of sucrose, umami, sodium chloride, salt and bitterness of caffeine only in tasters, and to decrease citric acid sourness [13]. Indeed, L-arginine has been considered as “carrier” as its addition to bitter molecules increases the bitterness as this agent makes hydrogen-bonded adducts that increase the solubility of PROP and its interaction with the receptor [14]. A detailed understanding of various taste interactions is out of the scope of the current appraisal and can be found elsewhere [12]. We will focus on the cross-talk between bitter and fat taste for the remaining part of this review.

## **2. Interaction between fat and bitter taste**

### *2.1. Evidence from behavioural studies*

To assess the bitter taste perception, the investigators have employed different agonists/agents like PROP (6-n-propylthiouracil), PTC (phenylthiocarbamide), quinine, caffeine etc. that elicit an unpleasant taste sensation [15]. On the basis of sensitivity to one of the bitter compounds, the researchers have classified the subjects as taster, non-taster or super taster. As regards fat taste perception, the fatty acids like oleic acid or linoleic acid or sometimes oils like canola oil or fat emulsions have been used in rodents and/or humans [16, 17]. In this review, we will employ a general term “fat taste perception” that would mean the use of one of hence-mentioned lipids/fatty acids in the studies.

There are several studies that have reported that fat and bitter tastes might interact with each other. Duffy and Bartoshuk [18] proposed that PROP supertasters may avoid high-fat food due to their intense sensations. Interestingly, PROP non-tasters were found to have high adiposity [19], and PROP phenotype can be used to discriminate different modalities of food preference including alcohol intake [20]. Tepper and Nurse [21] reported that bitter non-taster participants were unable to accurately distinguish fat content in high and low-fat Italian salad dressings. Nasser et al. [22] have shown that the majority of PROP non-tasters were also less sensitive in discriminating fatty acids in a high-fat food. Hayes and Duffy [23] demonstrated that PROP taste phenotype affects the nature of enhancement or suppression of creaminess in liquid fat/sugar mixtures.

On the contrary, eighty percent of the PROP tasters in this study correctly discriminated the sample containing the added free fatty acid. These observations suggest that bitter taste modality might interfere with lipid taste perception, though Drewnowski et al [24] proposed that PROP responsiveness was not associated with the presence of low dietary fat in tasting sessions. However, there are reports demonstrating that the presence of fatty acids in tasting-sessions influences oro-sensory perception of bitter compounds. Mattes et al. [25] reported that the perceived intensity of high concentration of caffeine was rated weak in the presence of linoleic acid. Koriyama et al. [26] reported that tauna oil suppressed bitter taste perception, though sweetness or saltiness remained unaffected. Pittman et al. [27] reported that the addition of linoleic and oleic acid to bitter taste solutions produced decreases in licking responses in rats when compared with the licking responses to the solutions in the absence of free fatty acids. Altogether, these studies indicate that bitter taste and fat taste might interfere with each other. A brief summary of the evident findings of the various studies cited above has been given in Table 1A.

## *2.2. Evidence from genetic polymorphism*

In humans, bitter taste receptors are encoded by at least 25 TAS2R-genes [1]. Some polymorphisms of these genes give rise to individual differences in bitter taste sensitivity. Genetic association of bitter taste came into notice, for the first time, in 1930 when Arthur Fox reported that PTC for some individuals was virtually tasteless [28, 29]. Afterwards, similar observations were also reported for PROP. The ability to taste bitter molecules containing a -N-C=S group “such as PTC and PROP” is inheritable. It is believed that PROP and PTC taste sensitivity follows a recessive Mendelian pattern of inheritance [30]. In 2003, Kim et al. identified, for the first time, a small region on chromosome 7q which contained a single gene that encoded a member of the TAS2R bitter taste receptor family [31]. The three single nucleotide polymorphisms (SNPs) give rise to 6 haplotypes (PAV, AVI, AAV, PAI and PVI) that are responsible for PTC and PROP sensitivity in the majority of population.

CD36 and GPR120 are two receptors that are implicated in the detection of fat taste in humans and rodents [4]. The CD36 gene spans 77 Kb (7q11.2–7q21.11) and is comprised of 9 alternatively spliced exons that are differentially regulated by several upstream promoters [32]. The CD36 SNP is associated with Alzheimer’s disease [33]. The team of Nada Abumrad reported, for the first time, the possible association of AA-genotype of CD36 rs1761667 with high detection thresholds for fatty acids in Afro-Americans subjects [34].

The same team further proposed that CD36 polymorphism is closely related to the disorders linked with excess of body lipids [35]. These studies have been confirmed in Algerian and Tunisian subjects by our team [36] wherein we have demonstrated that rs1761667-AA genotype is associated with obesity. It is noteworthy that rs1761667-AA genotype was also associated to *de novo* lipogenesis markers in obese subjects [37]. Interestingly, Plesnik et al. [38] reported that another variant of CD36, i.e., rs1527483 SNP, was associated with high body weight in young Czech participants.

The association between orosensory perception of oleic acid, rs1761667 SNP in the CD36 gene, and PROP tasting was, first time reported, by Melis et al. [39] who showed that bitter non-taster subjects were also hyposensitive to fat taste, and CD36 SNP appeared to play a decisive role. The individuals who show reduced oral fat perception may consume high fat foods and, consequently, are more prone to become obese [40]. The degree of decreased fat taste perception in PROP non-tasters had also been demonstrated in previous studies [23,41-44], but a correlation with CD36 SNP was demonstrated for the first time by Melis et al. [39]. The participants in this study were classified for their PROP taster status based on their ability to taste PROP, and genotyped for TAS2R38 locus, based on molecular analysis. TAS2R38 subjects (AVI/AVI) homozygous for the G-allele of the rs1761667 for CD36 had 11-fold lower detection threshold for oleic acid than subjects with the same TAS2R38 genotype (AVI/AVI), but with a homozygous AA genotype of the rs1761667 polymorphism. PROP non-tasters exhibited a higher threshold for oleic acid than super-tasters. Hence, AA genotype of rs1761667 appeared to be associated with increased BMI (body mass index) and decreased sensitivity to fat and bitter taste perception [39].

Our team has recently further investigated the association of PROP detection thresholds with CD36 and TAS2R38 genotypes in obesity in a Tunisian population [45]. We observed that all the genotypes of rs1761667 (CD36) and rs1726866 (TAS2R38) and rs10246939 (TAS2R38), except AV genotype of rs1726866, were associated with higher PROP detection thresholds and higher BMI in obese subjects than normal weight participants. The participants with AA genotype of rs1726866 had significantly higher BMI than the subjects with AV and VV genotypes. High PROP thresholds in VV genotype of rs1726866 may also participate in obesity as V-allele of this genotype has been shown to be associated with high plasma leptin and increased disinhibition [46]. Interestingly, the obese participants with VV genotype of rs10246939 exhibited higher thresholds for LA (linoleic acid) than normal weight controls, and these VV genotype subjects had significantly higher BMI than the participants with IV

and II genotypes. Also, the normal weight controls with VV genotype of rs10246939 showed significantly lower detection threshold than the control with II and IV genotypes. Hence, TAS2R38 variants rs1726866 and rs10246939 are associated with obesity. These SNP studies clearly suggest the relationship between fat and bitter taste perception in obesity.

### **3. Possible cross-talk between fat and bitter taste**

Whether TAS2R38 plays a role as sensor for textural clues or it also provides chemosensory signals and is involved in cross-talk between fat and bitter taste is yet to be determined. However, there are several reports that have shed light on the association between fat and bitter taste perception. Keller [47] suggested that TAS2R38 might be involved in the textural perception of dietary fat through its association with the PROP taster phenotype, whereas CD36 protein would influence chemosensory perception of fat. However, the density of taste papillae is also variable among individuals and might play a crucial role in taste sensitivity [48, 49]. Some studies have suggested that bitter and fat taste sensitivity might be related to the density of taste papillae and the number of taste bud cells [50, 51]. Hence, the subjects containing high density of taste papillae might be more sensitive to oro-sensory detection of bitter and fatty acids. However, the relationship between the numbers of papillae and the intensity of taste perception is, sometimes, debated. For example, Hayes et al. [52] very clearly demonstrated that an alteration between decreased bitter taste perceptions was not proportional to the density of fungiform papillae. The concept of “bitter-like fat taste” seems to be very complicated and might involve other components. Barbarossa et al. [28] have recently reported that the presence of very dilute concentrations of oleic acid in milk shakes was associated with perceived bitterness in nearly half of the subjects and this bitterness was blunted remarkably when subjects were asked to wear nose-clips. Hence, olfactory stimulation appeared to play a critical role in the perception of “bitter taste” of fatty acids. These investigators proposed that the variability in the perceived perception of bitterness among individuals was associated with the genetic variability in the expression of an olfactory binding protein (OBPIIa) expressed in the olfactory cleft with high affinity for long chain fatty acids. The subjects homozygous for the A-allele for a common single nucleotide polymorphism (rs2590498) in the OBPIIa gene were able to perceive bitterness of oleic acid in the absence of nose clips. Subjects homozygous for G-allele for rs2590498 or heterozygous were unable to perceive bitterness of fatty acids, even when nose clips were omitted. Moreover, subjects homozygous for A-allele were also more sensitive to PROP than homozygous G-allele or heterozygous. These findings suggest the novel implication of



olfaction in the cross talk-talk between bitter and fat tastes. Furthermore, a recent study by Lee et al. [53] has demonstrated that CD36 is expressed by olfactory receptor cells in mouse and plays a role in olfaction. It will be very interesting to investigate whether CD36 expressed on olfactory cells is also involved in the perception of a lipid taste through olfactory cues. Moreover, it will also be tempting to find whether a cross-talk exists between OBPIIa and CD36 expressed on olfactory cells. However, regardless of the mechanisms involved, the existence of an association between fat and bitter taste perception and obesity requires further alterations.

As for as the cellular and molecular interactions are concerned, we would like to state as follows. Both, fat (CD36 and GPR120) and bitter-taste receptors (TAS2Rs), are expressed on type-II cells which are gustducin-positive cells, suggesting that these cells might use gustducin for downstream signaling receptors [2, 54]. Binding of fat and bitter molecules to their respective receptors results in the activation of PLC $\beta$  which hydrolyses phosphatidylinositol 4, 5-bisphosphate (PIP<sub>2</sub>) to inositol trisphosphate (IP<sub>3</sub>). Subsequently, IP<sub>3</sub> binds to its receptor (IP<sub>3</sub>R) located on the endoplasmic reticulum (ER) and triggers the release of Ca<sup>2+</sup> (Figure 1). Hence, we can state that the common mechanism is “Ca<sup>2+</sup> - signaling” between the bitter and fat taste perception, though the later phenomenon is well-characterized at the molecular level, involving STIM1 and Orai1/3 Ca<sup>2+</sup> channels, for fat taste [55]. “The cross-talk” between the two taste modalities might also take place, downstream to Ca<sup>2+</sup> signaling via TRPM5 channels. Indeed, TRPM5 channels have been shown to be activated both in bitter and fat taste perception [56]. Opening of TRPM5 channels results in the entry of Na<sup>+</sup> ions and depolarization of cell. In either case, the resulting cell depolarization succeeding an increase in intracellular concentrations of cations would result in the release of neurotransmitters, notably ATP and serotonin at afferent nerve endings which then would carry the taste message to sensory areas of the brain, involved in taste perception (Figure 1). Some bitter tastants like quinine and divalent salts might also block K<sup>+</sup>-channels and result in depolarization of the gustatory cell. Although, both fat and bitter taste modalities seem to be involved in cross-talk with each other, it is not known exactly how fat-taste might inhibit the bitterness perception which has been reported in various studies. Nonetheless, TRPM5 channel is a good candidate. It has been reported that TRPM5 channels are activated by lower concentrations of free intracellular calcium while high calcium levels result in inhibition of these channels resulting in a bell shaped dose response curve [57]. We hypothesize that simultaneous administration of fat and bitter tasting agents

results in very high increases in  $[Ca^{2+}]_i$  due to the opening of store-operated calcium channels, following the activation of fat taste receptors. Such increases in  $[Ca^{2+}]_i$  much higher than required, may trigger inhibition of TRPM5 channels and, consequently, inhibition of the bitter-taste perception. However, this hypothesis needs experimental confirmations.

#### **4. Conclusions and perspectives**

Our short, but comprehensive review, sheds light on the interaction of “bitter taste” and “bitter taste of lipids”. However, there is a long way to better understand this interaction. The recent report on the involvement of olfaction in the perception of “fat bitterness” has twisted the story. In future, a number of behavioral and genetic studies are required to confirm this relationship in different populations of the world as by now only one study is available on this subject [28]. Besides, we have to explore the “cross-talk” between fat sensors like CD36 and GPR120 and olfactory receptors, both of nasal and buccal origins. Indeed, human taste bud cells have been found to express olfactory binding proteins (OBP) like OBPII (unpublished observations) which can via direct interaction, at the lingual papillae level, with CD36 or GPR120 might influence taste perception and feeding behavior. Furthermore, new studies are required to establish the implication of genetic polymorphism of OBPIIa, CD36/GPR120 and TAS2R receptors in obesity. Nonetheless, we should not ignore the environmental/social factors, beside genetic polymorphism, in the incidence of obesity. Indeed, Burd et al. [58] have very elegantly shown that two children populations with TAS216 SNP were susceptible to develop obesity, and the one that was residing in a low socio-economic area developed more incidence of obesity than the one that was in high posh area. The exploration of a cross-talk between fat and bitter tastes might find applications even in areas other than food industry such as in the pharmaceutical industry as reducing the bitterness of the medicaments is highly desirable to make them acceptable for the patients, particularly for young ones.

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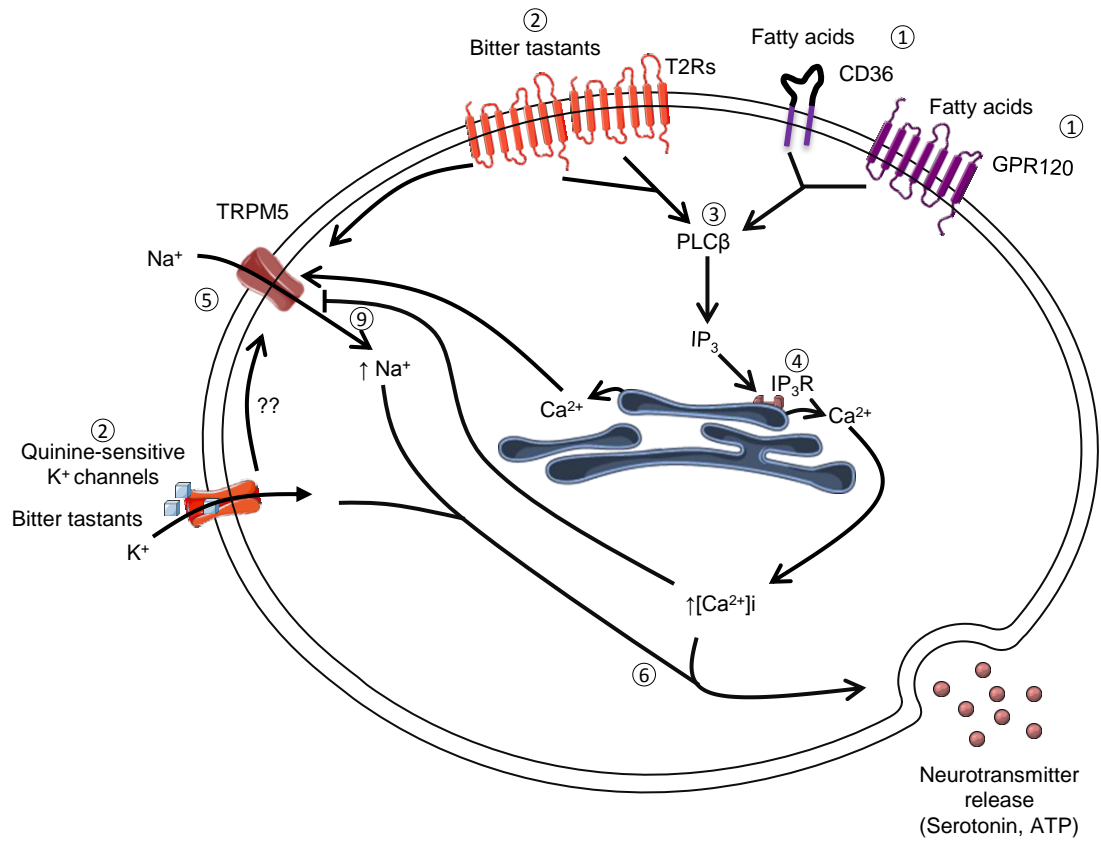
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**Figure legends**

Figure 1: Fatty acids bind to CD36 and GPR120 (1) while bitter molecules activate TAS2R receptors (2). This binding results in the activation of PLC $\beta$  which hydrolyses PIP<sub>2</sub> to give rise to IP<sub>3</sub> (3). Binding of IP<sub>3</sub> to IP<sub>3</sub>R on endoplasmic reticulum results in the release of calcium (4), which subsequently opens TRPM5 channels (5). An increase in the free intracellular concentrations of Na<sup>+</sup> following the opening of TRPM5 channels results in depolarization of the gustatory cell and the release of neurotransmitters, notably ATP and serotonin (6). Some bitter tastants like Quinine can bind directly and block potassium channels which in-turn results in depolarization and neurotransmitter release (2). Notably, very high increases in [Ca<sup>2+</sup>]<sub>i</sub> can inhibit TRPM5 channels which might explain the inhibition of bitter taste following the simultaneous administration of fat and bitter tastants. The interrogative marks (?) represent the possible direct interaction of K<sup>+</sup> channels and TRPM5 channels.



**Figure 1**

**Table 1:** Summary of studies highlighting the interaction between fat and bitter taste perception**A) Behavioural studies**

Study	Purpose	Sample	Findings
Duffy and Bartoshuk [18]	Association between genetic variation in taste and acceptance for sweet, high-fat, and bitter foods and beverages	n= (46, 24 female, 22 male; age (21± 6 years)	In women, liking for high-fat food decreased with increasing perceived bitterness of PROP. In men, liking for the same high-fat food increased but with increasing papillae densities.
Tepper and Nurse [21]	Relationship between papillae density, bitter taste and fat taste perception	Subjects were divided into 3 groups based on their sensitivity to PROP (n=25 for each group)	Bitter non-tasters were not able to discriminate between low and high fat content in salad dressings. Fat perception and preference is related to genetic and anatomical differences among individuals.
Nasser et al. [22]	To assess whether PROP tasters are sensitive to the presence of bitter-tasting fatty acids	n=37 (42 – 43 years old); The PROP tasters (7 males and 22 females); PROP nontasters (4 males and 4 females)	PROP tasters correctly discriminated the sample containing the added free fatty acids.
Hayes and Duffy [23]	Investigation of the influence of PROP phenotype on fungiform papillae density and sweet and creamy sensations	n=79 male subjects	The fungiform papillae density generally showed similar effects as PROP on sweetness and creaminess.
Drewnowski et al. [24]	Associations between PROP responsiveness, food choices, and dietary intakes	Female breast cancer patients (n=179) and cancer-free controls (n=179)	PROP responsiveness was not associated with diets lower in fat, more favourable plasma lipid profiles, or with lower body mass indexes.
Mattes et al. [25]	Investigation of the sensitization of taste receptors by fatty-acids through inhibition of delayed-rectifying potassium channels	PROP tasters (n=34, 17 male and 17 female)	Presence of fatty acids reduced the perception of highest concentrations of caffeine, a bitter tast ant, but not sweet, sour or salty ratings.
Koriyama et al. [26]	To elucidate the effects of oils on taste perception using oil in water emulsions and different tastants	A trained panel of 4 females and 5 males (25 to 45 years old) having previous experience in tasting emulsions	Tuna oil suppressed bitterness but not sweetness or saltiness.
Pittman et al. [27]	Investigation of the licking response of rats to different taste modalities in the presence of fatty acids	38 naive male Sprague–Dawley rats greater than 90 days old	Presence of fatty acids increased licking response to sweet taste solutions but inhibited for bitter tasting solution.



**B) Genetic polymorphism**

Study	Gene/Variant	Purpose	Sample	Findings
Melis et al. [39]	CD36: rs1761667	Investigation of the association of fat detection and preference with CD36 or 6-n-propylthiouracil (PROP) sensitivity	64 Caucasian (23 males 41 females)	Direct association exists between orosensory perception of fatty acid and PROP and CD36 polymorphism plays the crucial role.
Karmous et al. [45]	CD36: rs1761667 TAS2R38: rs1726866 rs10246939	Determination of fatty acid and bitter-taste thresholds in normal and obese individuals and correlation with fat and bitter taste receptor polymorphisms	Tunisian normal weight and obese adults (n=104, 33 males, 71 females)	Orosensory detection thresholds for fat and bitter taste are associated with BMI. PROP detection thresholds were higher for CD36 SNP (rs1761667) and TAS2R38 SNPs (rs1726866 and rs10246939) in obese participants compared to normal weight subjects.