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Taste, olfactory and texture related genes and food choices: implications on health status

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Abstract. – OBJECTIVE: The food choices are due to a mixture of sensory signals including gustatory, olfactory, and texture sensations. The aim of this quality review was to update data about studies concerning genetics of taste, olfactory and texture receptors and their influence on the health status in humans.

MATERIALS AND METHODS: An electronic search was conducted in MEDLINE, Pubmed database and Scopus, for articles published in English until December 2018. Two independent researches selected the studies and extracted the data.

RESULTS: The review confirms the importance of inter-individual variations in taste, olfactory and texture related genes on food choices and their implications in the susceptibility to nutrition-related conditions such as obesity, dental caries, diabetes, cardiovascular disease, hypertension, hyperlipidemia and cancer.

CONCLUSIONS: The knowledge of variants in taste, olfactory and texture related genes can contribute to the prevention of diseases related to unhealthy nutrition. Further studies would be useful to identify other variants in the genes involved in these systems.

Key Words
Taste receptors, Olfactory receptors, Texture sensations, Obesity.

Introduction

The genes and the food choices are closely connected. It is conceivable that taste and olfaction receptors have progressed together during vertebrate evolution. The high frequency of genetic variations within taste and olfactory receptors is unique in the human genome[1,2]. Therefore, variations in these two perceptions may be considered as a landmark of human evolution[3]. Texture sensations, detected by receptors located in the mouth mucous membranes[4], represent a component of food flavour, which contributes greatly to palatability[5]. The high palatability of foods detected by texture perceptions is the principal characteristic of obesogenic foods[6,7]. Genetic variations in taste and olfactory receptors, palatability of foods and environmental factors may

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influence food intake and, therefore, influence risk for nutrition-related conditions such as obesity, but also diabetes, cardiovascular diseases, hypertension, hyperlipidemia and cancer[8]. This review focuses on genetics of taste, olfactory and texture receptors and their implications on the health status.

Materials and Methods

This paper is a "qualitative review". Information for the drafting of this paper was retrieved from original papers and reviews. An electronic search was conducted in MEDLINE, PubMed database and Scopus, using different combinations of the search terms "taste system", "taste receptors", "olfactory system", "olfactory receptors", "texture". Articles published in English were included if they presented detailed data on a large cohort of patients, model animals and *in vitro* results. Screening process was conducted independently and in duplicate. The bibliographies of all articles selected for inclusion were examined to include as many studies as possible and a comprehensive and systematic manual search of journals identified as potentially important for this review was conducted. Subsequently, the reviewers performed the assessment of the full-text articles. Any disagreements were solved through discussion until consensus. Our final search was conducted until December 2018.

Results

Taste System

Humans are able to distinguish five flavors: bitter, sweet, sour, salty and umami. Sweet and umami taste can indicate the presence of essential and energy-rich nutrients and salt taste induces the ingestion of essential minerals for the ion and water homeostasis. In contrast, bitter taste can alert for the presence of potential toxins in foods and sour taste can indicate food spoilage[9,10]. Recently, additional taste modalities for the perception of calcium and lipids have been evidenced[11,12]. The perception of different tastes occurs through receptors on the surface of specialized epithelial cells called taste receptor cells (TRCs), which are bundled in taste buds. The taste buds are small neuroepithelial structures located on the upper surface of the tongue, in the upper larynx and at the back of the oropharynx[13]. The taste receptors are expressed not only in the oral cavity, but also in several extra-oral tissues. The basic function of the taste receptor cells is to perceive the flavors of ingested foods when the substances that make up the food are in an aqueous solution in the saliva and can reach the taste buds. Between 2000 and 5000 taste buds exist along the surface of the front and back of the tongue, and each taste bud is lined with 50-100 taste bud cells[14]. The moment of life in which an individual has the highest number of taste buds is down to 6 years of age due to their continuous renewal. Taste buds are formed at the beginning of the third trimester of embryonic development, and for this reason the fetus is already able to perceive the taste of the nutrients contained in the amniotic fluid[15]. Generally, women have a higher number of taste buds. It cannot be ruled out that this difference is aimed at the survival of the species by controlling edibility and toxicity of the food to be offered to children[16]. Each gustative quality is detected through a different molecular mechanism of transduction. In particular, salty and acid act directly on the ionic membranes, while sweet, umami and bitter use transduction mechanisms mediated by taste receptors associated with G proteins[17]. Taste buds exhibit different cell types with different functions[18]. Approximately 50% of the total number of cells are type I, whose role is to maintain the supporting structure of the taste buds. Type I "glial-like" cells are involved in terminating synaptic transmission and restricting the spread of transmitters[19]. Type I cells may exhibit ionic currents implicated in salt taste transduction[20]. Amiloride-sensitive sodium channel subunit α (channel α-ENaC) is expressed on type I cells and is considered to be the major mediator of perception of low salt. Many studies suggested that there are at least two transduction pathways for salty taste. The first one is based on theamiloride, a potassium-sparing diuretic, able to block ENaC. The amiloride-sensitive mechanism is cation (Na^+ and Li^+) selective; on the other hand, the amiloride-insensitive mechanism is cation nonselective and can be activated by sodium and non-sodium salts[21]. TRPV1 was proposed to function as an amiloride-insensitive salt taste receptor in mouse[22]. Probably, TRPV1 contributes to oral chemosensory responses to salts in trigeminal nerve endings, and not only in taste bud cells[23,24]. Another candidate for amiloride-insensitive salt taste receptor is TRPML3[25].

Type II taste cells express all elements of the taste transduction cascade for sweet, umami and

bitter[26]. Sweet and umami tastants are sensed by a family of three receptors: taste receptor type 1 member 1 (TAS1R1), taste receptor type 1 member 2 (TAS1R2) and taste receptor type 1 member 3 (TAS1R3). Heterodimeric receptors of TAS1R1 and TAS1R3 subunits are activated by umami tastants and heterodimeric receptors of TAS1R2 and TAS1R3 subunits are activated by sweet tastants[27,28]. It is known that the expression of fat sensors in type II taste bud cells (TBCs), such as *GPR120* and *CD36*, detect long-chain fatty acids[29]. Type III taste cells express synaptic proteins and are implicated in transmission of information to the nervous system[26]. Similar to neurons, these cells contain voltage-gated Ca^{2+} channels and release vesicular serotonin, acetylcholine, norepinephrine and γ-aminobutyric acid (GABA) when depolarized[30]. Moreover, these cells also respond directly to sour taste stimuli and carbonated solutions and are presumably the cells responsible for signaling these sensations[31]. TRCs make synapses with primary sensory axons that run in the three cranial nerves, VII (facial), IX (glossopharyngeal), and X (vagus), which innervate the taste buds[32]. Small molecule neurotransmitters signal between taste cells and between taste cells and intragemmal nerve fibers, which carry taste information to the central nervous system. ATP is the primary neurotransmitter allowing taste cells to associate with afferent nerves, while other neurotransmitters mediate the taste cell functions through autocrine and paracrine signals and contribute to the output of the taste bud[33,34]. Various hormones are expressed in taste buds: CCK and Y-family peptides, glucagon GLP-1 and GLP2, VIP peptides, ghrelin, oxytocin, galanin and leptin. The hormones that are expressed in the gut and that are also present in the cells within taste bud in the tongue modify the intensity of taste perception. In the taste bud cells, NPY functions antagonistically to CCK with downregulation of signalling in response to sweet and umami tastants and amplification of perception of bitter taste; glucagon causes an increase of taste responses to both calorie-containing (sucrose) and artificial (sucralose) sweeteners and a decrease of the sensitivity to umami taste perception; VIP peptides reduce perception of sweet and bitter tastants; ghrelin enhances perception of salty and sour tastes; oxytocin regulates salt appetite and galanin increase preferences for fatty foods. Finally, leptin is a key hormone that is involved in regulating energy expenditure, bodyweight, fat mass and feeding behaviour. Leptin modifies neurological hedonic responses to eating and the intensity of sweet perception[35].

Genetic Variations in Taste Receptor Genes and Food Choices

The taste receptors are encoded by more than 50 coding regions distributed in clusters over most chromosomes in mammals[36]. Taste receptors are conserved among vertebrates. Their respective genes and proteins are orthologs, and originated from common ancestral genes. Taste perception varies between individuals in function of genetic variation in the genes encoding taste receptors[37], a variability that has been well documented in humans. The allelic variations can affect food perception, choice, and consumption, thus influencing nutrition and susceptibility to certain diseases[38]. BitterDB (http://bitterdb.agri.huji.ac.il) was introduced as a central resource for information on bitter-tasting molecules and their receptors[39]. There are numerous genes that code for receptors of bitter taste of T2R family (GPRs). In particular, in humans a family of 25 genes, T2Rs or TAS2Rs, mapped on chromosomes 12, 7 and 5 has been identified[40-42]. Several variations have been observed in the T2R gene family encoding for bitter receptors[43]. Multiple non-synonymous single nucleotide variations of the *TAS2R38* gene have been the most widely studied and are associated with differences in the ability to perceive compounds containing the thiocyanate group (NC = S) responsible for bitter taste, such as phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP)[44,45]. This chemical group is also present in glucosines and goitrines, substances commonly found in cruciferous plants and other plants in the Brassicaceae family, such as broccoli, cabbage and cauliflower[46]. There are two different forms of *TAS2R38*, namely the PAV form and the AVI form (Proline–Alanine–Valine, and Alanine–Valine–Isoleucine), which differ in three single nucleotide polymorphisms. The PAV form is ancestral and specific for the taster phenotype and the AVI form is specific for the non-taster phenotype. About 75% of the Caucasian population is sensitive and able to perceive PTC and PROP, while about 25% are non-tasters[47]. However, the genetic variations in TAS2R38 gene, explain about the 80% of the sensitivity to PTC/PROP[48]. In numerous studies the ability to perceive the bitter taste of PTC or PROP, mediated by the *TAS2R38* gene, has been associated with differences in the preference for different types of foods, such as vegeta-

bles, coffee, beer, grapefruit, chili, fats, alcohol consumption[49-53]. The *T2R43* and *T2R44* genes are responsible for increased sensitivity to the bitterness of saccharin[54]. The sweet and umami tastes are perceived by receptors belonging to the T1R or TAS1R family. This family of GPCRs includes T1R1, T1R2 and T1R3, encoding by *TAS1R1*, *TAS1R2*, and *TAS1R3* genes located on chromosome 1[55]. In particular, the receptor for sweet taste consists of the dimer formed by T1R2 and T1R3[56], while T1R1 combined with T1R3 forms the dimer responsible for the perception of umami taste[57]. Variants in the *TAS1R3* gene promoter regions situated at position 1266 and 1572 have been associated with a reduction of the ability to perceive sweet taste[58]. Similarly, it was reported that genetic variations of *TAS1R3* gene are related to a reduced sensitivity to umami, while variations in the *TAS1R1* gene to an increased sensitivity to umami[59]. Humans have four ENaC channel subunits (α, β, γ, δ) encoded by *SCNN1A, SCNN1B, SCNN1G* and *SCNN1D* genes[60]. Variations in SCNN1A, SCNN1B and SCNN1G have been associated to the change of perception of salty taste[61-63]. Taste receptors for sour tasting, not well-characterized; variants in *PKD2L1* and *PKD1L3* genes may influence sour taste perception[64]. Recently, it has been proposed that our taste is mediated by the potassium ion channel $K_{IR}2.1$ encoded by the *KCNJ2* gene[65]. The rs236514 and rs173135 variations in the *KCNJ2* gene were significantly associated with sour preference[63]. Variants at the *CD36* gene are considered responsible for differences in the ability to perceive and recognize the molecules of fat contained in foods[66-68].

Influence of Genetic Variations of Taste Genes on Health Status

Genetic variations of taste genes cause differences in taste perception that influence food choices and the risk of developing diet-related diseases such as obesity, cardiovascular disease (CVD), type 2 diabetes (T2D), and metabolic syndrome[69]. An increase in our knowledge of taste genetics is very important because it could lead to new personalized therapeutic strategies for the prevention of disease risk. *TAS2R38* gene is broadly tuned to the perception of the bitter taste in vegetables and other foods with purported health benefits, such as green tea and soya, with consumption promoting intake of dietary fibres and thiamine, vitamin B6 and folate, or factors indicative of healthy eating[70]. Variations in this gene contribute to three thiourea taster groups of people: supertasters, medium tasters and nontasters. Higher sensitivity to bitter taste may cause individuals to avoid consuming vegetables rich in anti-tumor and anti-oxidant compounds, and may lead to a higher consumption of fatty and sweet foods as substitutes. This eating behavior has the potential to increase the risk of obesity but also of CVD and cancer[50,71,72]. In fact, the risk of colon cancer, partly mediated by diet, has been also linked to genetic variations in the *TAS2R38* gene[73] interestingly, colon cancer may also be the cause of weight gain[74]. Moreover, variants in the *TAS2R43* gene have been associated with the perception of caffeine and the preference for coffee[75] and have been linked to avoidance of cigarette smoking[76], which can have repercussions on health. Finally, the risk of developing dental caries, presumably like consequence of greater preference for sugar containing food, has been associated with variations in bitter taste perception[77]. The Lys172 variant of *TAS2R16* gene is responsive to natural plant-derived toxins suggesting positive selection may have occurred to help early humans avoid cyanogenic toxins[78]. Variations in *TAS2R16* gene also explain differences in beta-glucopyranoside response across species[79]. Furthermore, the Asn172Lys substitution in *TAS2R16* has been associated with alcohol use and abuse[80]. Genetic variations the *T1R2* gene, responsible for perception of sweet taste, have been associated with differences in the consumption of sugars in overweight and obese subjects[81], to alcoholism[82] and to the development of caries[83]. Analyzing the variants Ala372Thr (rs34160967) in T1R1 and Arg757Cys (rs307377) in T1R3, it has been demonstrated that having the variants Thr372 in T1R1 and the Arg757 in T1R3 causes an overall decrease in umami taste threshold, and having the variants Ala372 in T1R1 and Cys757 in T1R3 causes an overall increase in umami taste threshold[59]. The perception of umami is an indicator of purine-rich foods, in particular, the purine-derived metabolite uric acid. The elevated serum urate, derived from uric acid, is responsible of an increased risk for gout, high blood pressure, increased hepatic lipogenesis and insulin resistance. Then, the consumption of certain umami tasting foods may increase metabolic disease risk[84]. The rs4790522 variant in *TRPV1* was found to be significantly associated with preference for salt in children. Sodium intake plays a role in the development of hypertension that is a risk factor for the development of cardiovascular disease[64]. Variations in *CD36* and *GNAT3* genes are associated with different sensitivity to fatty

foods[85]. Many variants in CD36 have a consequent impact on the body mass index (BMI) and the risk of developing obesity[86,87], on triglycerides and free fatty acids levels[88] and metabolic syndrome[85]. Ma et al[89] have associated common variations in *CD36* gene with lipid and glucose metabolism and also with risk for cardiovascular disease. In this study, two linkage disequilibrium blocks represented by a haplotype have been identified by the genotyping of 21 variants. This haplotype comprises five variants: 33137A/G (rs1984112), 31118G/A (rs1761667), 25444G/A (rs1527483) 27645 del / ins (rs3840546), and 30294G/C (rs1049673). The 30294G/C, 33137A/G and 31118G/A variants have been significantly associated with higher plasma free fatty acids (FFA). The haplotype of an individual can be represented by sequentially naming the nucleotide bases in the order of variants listed. Individuals with the AGGIG haplotype have an increased risk of coronary artery disease, 31% higher FFA and 20% higher plasma triglycerides (TG) than non-carriers[89]. Genetic variation in *CD36* may modulate the lipid metabolism. In a study of the relationship between genotypes and haplotypes of the five variants listed in *CD36* gene, it has been shown that subjects carrying the AATDC haplotype had 3.2 times higher risk of LDL- C>100 mg/dL than those carrying the AGTIG haplotype, whereas subjects carrying the AATIC haplotype had 2.0 times higher risk of total cholesterol>200 mg/dL than the AGTIC haplotype[86]. In *GNAT3* gene rs11760281 variant and rs1194197 were associated with metabolic syndrome[85]. Table I summarizes the main variations of taste genes that have impact on health status.

Olfactory System and Nutrition

Odours are detected through the orthonasal pathway, which involves odours that are sniffed in through the nose, and the retronasal pathway which connects the top of the throat to the nasal cavity. The retronasal pathway detects aromas that are contained in the foods. In humans, the olfactory area contains about 50 million receptor cells with 8-20 cilia in a layer of mucus[127]. The olfactory chemoreceptors include olfactory receptors (ORs), vomeronasal receptors, and trace amine associate receptors that detect respectively smells, pheromones, and volatile amines. These receptors are G-protein coupled receptors (GPCRs), and as such, have structural features that are shared with other chemosensory genes such as sweet and bitter taste receptors[128]. In particular, the ORs can detect multiple odorant molecules of foods and each odorant molecule can bind to multiple ORs with different binding affinities to discriminate diverse and complex odors[129]. Like the taste receptors, also the ORs are expressed in different locations including gut[130], pancreas[131], liver[132], kidney[133], lung[134] and human spermatozoa[135] with different functions[136]. Anyway, in the olfactory epithelium the principal function of the ORs is to influence appetite by changes in secretion of neuropeptides and in the activity of the gastric vagal nerves[137]. Humans have about 400 olfactory receptors proteins. However, human olfaction can detect numerous odorant molecules with a small number of receptors by means of accessory functions gained during evolution. Reduced number of genes for olfactory receptors is also compensated by the great capacity of human brain processing compared to other mammals that have more than a thousand genes for olfactory receptors[138]. The activity of the olfactory system is influenced by hormonal (e.g. orexins A and B and leptin), nutritional, and metabolic factors that influence food preference and food intake[139,140]. The vomeronasal receptors (V1Rs, V2Rs) and trace ammine associated receptors (TAARs) detect pheromones and volatile amines including certain pheromones that among the many actions play an important role in nutrition[141,142]. The interaction between olfactory and visual information contributes to an effective perception of odours. The processing of visual stimuli occurs through the piriform cortex, which is part of the primary olfactory cortex. Recently, it has been demonstrated that the piriform cortex pre-processes emotional visual information prior to olfactory stimulations whose emotional connotation is subsequently integrated into an extended olfactory network for olfactory processing[143].

Genetic variations in olfactory genes and food choices

The OR genes are the largest gene superfamily in vertebrates, being distributed among 51 different loci on 21 human chromosomes. The OR genes can be found at many chromosomal loci, but highly related ORs often reside at the same locus[144]. It was demonstrated that loss of function in OR7D4, OR11H7P, OR6A2, OR2J3 and OR5A1 leads to altered detection of the respective agonists androstenone, isovaleric acid, cilantro, cis-3-hexen-1-ol and β-ionone. The mechanism of smell is complex and implies many olfactory receptors.

The olfactory system uses a mixed system in which many receptors encode a given odorant

Table I. The main variations of taste genes that impact health status.

Gene (OMIM ID)	Variant	Rs ID	Taste modality and associated variant outcome	References
T2R38 (OMIM: 607751)	NM_176817.4: c.145G>C (A49P)	rs713598	This variation is associated with high sensitivity to bitter taste of the compound phenylthiocarbamide (PTC) and similar molecules in foods (like cabbage and raw broccoli) or drinks (like coffee and dark beers) and it is causative of metabolic diseases and coronary heart disease.	45,46,90,91
	NM_176817.4: c.785T>C (V262A)	rs1726866	This variation is associated with high sensitivity to bitter taste of the compound phenylthiocarbamide (PTC) and similar molecules in foods (like cabbage and raw broccoli) or drinks (like coffee and dark beers) and it is causative of metabolic diseases and coronary heart disease.	45,46,90
	NM_176817.4: c.886A>G (I1296V)	rs10246939	This variation is associated with high sensitivity to bitter taste of the compound phenylthiocarbamide (PTC) and similar molecules in foods (like cabbage and raw broccoli) or drinks (like coffee and dark beers) and it is causative of metabolic diseases. It is correlated with aging.	45,46,92,93
T1R2 (OMIM: 606226)	NM_152232.2: c.571A>G (I191V)	rs35874116	This variation is associated with high sensitivity to sweet taste and it is causative of obesity and dental caries.	81,83,94, 95,96
	NM_152232.2: c.26C>G (Ser9Cys)	rs9701796	This variation is associated with high sensitivity to sweet taste, a higher chocolate intake and an increased risk of obesity.	97
T1R3 (OMIM: 605865)	NM_152228.2: c.-1572T>C	rs307355	This intronic variant is linked to human sucrose taste sensitivity and it result in reduced promoter activity. This variant has been associated to dental caries.	58,94
	NM_152228.2: c.-1266T>C	rs35744813	This intronic variant is linked to human sucrose taste sensitivity.	58,94, 96
	NM_152228.2: c.2269C>A (R757C)	rs307377	This variation is associated with low sensitivity to umami taste.	59
T1R1 (OMIM: 606225)	NM_138697.3: c.1114G>A/ c.1114G>C (A372T)	rs34160967	This variation is associated with high sensitivity to umami taste.	13,59,98
	NM_177540.2: c.329C>T (A110V)	rs41278020	This variation is associated with low sensitivity to umami taste.	59
T2R16 (OMIM: 604867)	NM_016945.2: c.516T>G (N172L)	rs846664	This variation is associated with low sensitivity to bitter taste and alcohol dependence.	78,80
	NM_016945.2: c.-212A>C	rs978739	This variation is associated with low sensitivity to bitter taste alcohol dependence; association with the and aging process.	80,93
SCNN1A (OMIM: 600228)	NM_000336.2: c.-8-13975T>A	rs239345	This variation is associated with high sensitivity to salt risk of hypertension and cardiovascular disease.	61,99,100
	NM_001159575.1: c.-2018A>G	rs11064153	This variation is associated with high sensitivity to salt; risk of hypertension.	62

Continued

Table I (Continued). The main variations of taste genes that impact health status.

Gene (OMIM ID)	Variant	Rs ID	Taste modality and outcome	References
SCNN1B (OMIM: 600760)	NM_000336.2: c.-9+7022G>A	rs3785368	This variation is associated with high sensitivity to salt; risk of hypertension.	61
	NM_000336.2: c.-8-13975T>A	rs239345	This variation is associated with low sensitivity to salty taste.	61,99
SCNN1G (OMIM: 600761)	NM_001039.3: c.1078-3669C>G	rs4401050	This variation is associated with high sensitivity to salt; risk of hypertension.	62
TRPV1 (OMIM: 602076)	NM_018727.5: c.*256T>G	rs4790522	This variation is associated with preference for salt in children and cardiovascular risk disease.	64
	NM_018727.5: c.1753A>G	rs8065080	This variation is associated with preference for salt in Caucasians; risk of hypertension.	61
CD36 (OMIM: 173510)	NM_001001547.2: c.-184+11225A>G	rs1984112	This variation is associated with high sensitivity to fat foods. It is related to lipid metabolism, type 2 diabetes and cardiovascular disease risk.	101,102,103,104
	NM_001001547.2: c.-184+13244G>A	rs1761667	This variation is associated with greater perceived creaminess and higher acceptance of added fats and oils with ethnic-specific effects, this variant is associated with higher BMI; risk of metabolic syndrome and type 2 diabetes mellitus.	68,102,105,106,107,108,109
	NM_000072.3: c.1125+144G>A	rs1527483	This variation is associated with high sensitivity to fatty foods and it is associated to obesity.	68,87,105,110
	NM_001001547.2: c.-184+21688T>A	rs2151916	This variation is associated with high sensitivity to fatty foods and it is associated to obesity and high triglycerides levels.	86, 110
	NM_001001548.2: c.*572G>A	rs7755	This variation is associated with high sensitivity to fatty foods. It has been associated to type 2 diabetes mellitus.	110
	NM_001001548.2: c.*651C>G	rs1049673	This variation is associated with high sensitivity to fat foods. It has been associated to obesity, hypertension, type 2 diabetes mellitus and premature coronary heart disease.	96,97,105
	NM_000072.3: c.*238_*253del16	rs3840546	This variation is associated with high sensitivity to fat foods it has been associated to obesity and type 2 diabetes mellitus.	105,114
	NM_001001547.2: c.975T>G	rs3211938	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	114-116
	NM_001001547.2: c.-183-16594A>G	rs10499859	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	105
	NM_001001547.2: c.281+924C>A	rs3211867	This variation is associated with high sensitivity to fatty foods. It has been associated to obesity.	105,117
	NM_001001547.2: c.282-1336A>T	rs3211883	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	105,117,118

Continued

Table I (Continued). The main variations of taste genes that impact health status.

Gene (OMIM ID)	Variant	Rs ID	Taste modality and outcome	References
CD36 (OMIM: 173510)	NM_001001547.2: c.121-6T>C	rs3173798	This variation is associated with high sensitivity to fatty foods. It has been associated to obesity and metabolic syndrome.	115,119
	NM_001001547.2: c.282-10A>G	rs3211892	This variation is associated with high sensitivity to fatty foods. It has been associated to obesity and metabolic syndrome.	115,119
	NM_001001547.2: c.-183-2836T>A	rs1527479	This variation is associated with high sensitivity to fatty foods. There are secondary associations between this variant and fasting lipid parameters, body composition and cardiovascular disease.	102,104,12
	NM_001001547.2 c.701+103C>T	rs3211908	This variation is associated with high sensitivity to fatty foods. It has been associated: to obesity and diabetes.	87,117,118,121
	NM_001001547.2: c.282-1994G>A	rs1358337	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	115
	NM_001001547.2: c.121-914T>C	rs1054516	This variation is associated with high sensitivity to fatty foods. It has been associated to high levels of triglyceride and metabolic syndrome.	115,122
	NM_001001547.2: c.-132A>C	rs1049654	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	115
	NM_001001547.2: c.701+302T>C	rs3211909	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	115
	NM_001001547.2: c.121-2533A>G	rs3211849	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome and high levels of triglycerides.	115,123,124
	NM_001001547.2: c.121-80248C>G	rs13246513	This variation is associated with high sensitivity to fatty foods. It has been associated obesity and metabolic syndrome.	115,123,125,126
	NM_001001547.2: c.121-3220G>A	rs3211842	This variation is associated with high sensitivity to fatty foods. It has been associated obesity and metabolic syndrome.	115,123
GNAT3 (OMIM: 139395)	NC_000007.13: g.80175606A>G	rs1194197	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	92
	NM_001102386.2: c.462-854T>C	rs11760281	This variation is associated with high sensitivity to fatty foods. It has been associated to metabolic syndrome.	92

and a single receptor can have a large influence on the perception of an odorant[145]. There are various genetic variations in OR genes which influence olfactory function and food choices[146]. Androstenone is a steroid derived from testosterone, which is detected as a strong odour from some individuals and it is described as 'foul smelling', 'urinous' and 'sweaty' or alternately as 'sweet-smelling' and 'floral'. Androstenone is produced by male pigs and it is often present in their skin. Two variants in OR7D4, R88W and T133M, are associated with the ability to detect androstenone. The meat pork from uncastrated male pigs containing androstenone is less acceptable from subjects with two copies of the RT variant of the *OR7D4* gene, indicating that this genetic variation affects food preferences[147]. The perception of the isovaleric acid odor emanating from the cheese may be conditioned by c.679C>T (G227=) variant in the *OR11H7P* gene. Individuals with two copies of the defective form of OR11H7P are less likely to be able to detect the strong cheesy smell and to prefer this food[148]. Cilantro is an aromatic herb suitable for different food uses. The aromatic herbs can play a significant role in improving health, helping to reduce sodium, calories and fat and making healthy eating more attractive[149]. Cilantro dislike may stem from genetic variants in olfactory receptors. In particular, the variant rs72921001 in *OR6A2* gene has been detected as an element of cilantro aversion[150]. Cis-3-hexen-1-ol, which smells of freshly cut grass, is a flavor compound for foods such as fruits, vegetables, white wine and processed foods. The genetic variations T113A and R226Q of OR2J3 are associated with an altered capacity to perceive the Cis-3-hexen-1-ol odor[151]. The Table II summarizes the main variations of olfactory genes that influence the foods choices.

Implications of the Olfactory System on Obesity

Specific odorants can activate ORs in the olfactory epithelium to influence animal appetite, food choices and food consumption[152]. Therefore, the smell perception can influence eating behaviors and lead to overeating and overweight[153,154]. Moreover, high BMI appears to be associated with olfactory dysfunction[155]. The olfactory sense may play a large role in the development of obesity and the resistance to weight loss methodologies because the odor can modify both preparatory and satiety-related components of ingestion[156]. In a study by Choquette et al[157] the variations in the *OR* gene have been associated with eating behavior traits such as cognitive dietary restraint, disinhibition and hunger having a role in adiposity. In particular, the rs2878329 variant in *OR7D4* gene has been associated with cognitive dietary restraint, susceptibility to hunger and reduced levels of adiposity, while the rs61729907 and rs5020278 have been associated with abdominal fat. Moreover, a variant in *OR7G3* gene (rs10414255, M29V) was associated with lower cognitive dietary restraint, higher levels of hunger, high body max index and percentage of body fat, a variant in *OR7G1* gene (rs7246980, A156V) was associated with visceral adipose tissue area and a variant *OR7E24* (rs2240927, S208S) was

Table II. The main variations of olfactory genes that influence food choices.

Gene (OMIM ID)	Variant	Rs ID	Odor Outcome	References
OR7D4 (OMIM: 611538)	NM_001005191.2: c.262C>T (R88W)	rs61729907	Androstenone (meat pork. truffles)	147
	NM_001005191.2: c.398C>G (T133M)	rs5020278	Androstenone (meat pork, truffles)	147
OR11H7P	NM_001348273.1: c.679C>T (G227=)	rs1953558	Cheesy	148
OR6A2 (OMIM: 608495)	NM_001004460.1: c.-1338C>A	rs72921001	Cilantro	150
OR2J3 (OMIM: 615016)	NM_001005216.3: c.337A>G T113A	rs28757581	Cis-3-hexen-1-ol (fruits, vegetables, white wine and processed foods)	151
	NM_001005216.3: c.677G>A (R226Q)	rs3749977	Cis-3-hexen-1-ol (fruits, vegetables, white wine and processed foods)	151

correlated with obesity-related phenotypes. However, the mechanisms linking genetic variation in OR genes with eating behaviours and adiposity are not fully understood[157]. Olfactory receptors expressed in the liver and adipose tissue regulates cellular energy metabolism and obesity. The activation of OLFR544 in mouse models of obesity reduced adiposity and improved glucose tolerance. Therefore, OLFR544 can be a potential anti-obesity therapeutic target[158,159].

Somatosensorial System and Impact of Genetic Variations on Texture Sensations

The somatosensory system comprises nerves under the skin's surface that send information to the central nervous system and peripheral nervous system sub serving the sensations of touch, pain, pressure, temperature and proprioception[160]. Oral touch sensations are generated by pressoreceptors, mechanoreceptors and thermoreceptors sensory cells of the oral cavity. Receptors localized in the mucosa of the buccal cavity and pharynx responsible for the perception of the granulometry of food and receptors located in the jaw and teeth that act in the perception of the consistency of food are key receptors of the texture perception of sensory tasting. Through these receptors it is possible to perceive texture sensations, such as creaminess, astringency, temperatures, greasiness, succulence, etc. The proprioceptive system also provides information about the shape, size and texture of foods during oral exploration by the tongue[161]. Particularly, various associations between flavor and shape have been demonstrated[162,163]. Interactions between viscosity and flavor have also been identified[164,165]. Texture plays a key role in the perception of a flavor of a food; the perception of taste components within flavour can be altered by cross-sensory manipulations in texture[166]. Even the exposure of food to the hands can be influential. In fact, it has been observed in children that playing with food increases the acceptance of food and could help increase the variety of food intake[167]. Creaminess is a sensory feature that has an important influence on preferences of foods. The sensory creaminess matched with viscosity can be detected using texture but also taste and smell perceptions. Coffee, chocolate, ice cream and dairy products are examples of highly liked foods for their creaminess[168]. In particular, the presence of cream in espresso coffee has been associated with the release of pleasant volatile elements. For consumers, the cream on top of an espresso is highly appreciated as part of the coffee experience, regardless of the quality of the coffee[169]. The use of hydrocolloids in foods is due to their ability to modify two basic properties of food system: viscosity and texture. Various foods such as sauces, gravies, soups, toppings, Ketchup, ice-crams, jams, cakes and candies use hydrocolloids as additives. An example of a hydrocolloid is the cellulose. The gelling action of cellulose when combined with water, similar to an emulsion, provides both thickening and stabilization of the food. Cellulose allows for the production of thick and creamy food items[170]. The fast-food industry has elaborated numerous strategies to increase the palatability of foods. The frequency of the consumption of products of the fast food industry which uses these strategies has been associated with higher weight and less healthy eating habits[171]. Differences in perception of creaminess have been associated with levels of salivary alpha amylase that cleaves glucose during the chewing of food. Salivary alpha amylase is a protein encoded by *AMY1* gene. The concentration of oral salivary amylase is proportional to the number of copies of this gene, ranging between 2-15 diploid copies. Probably, the copy number variation is the evolutionary response to differing levels of starch in the diet of different populations[170]. The number of fungiform papillae that is associated with PROP bitterness has been correlated with creaminess perception[171]. However, it has also been shown that PROP is a marker for the intensity of taste in general and therefore the perception of creaminess should not be strictly related to variations in *TAS2R38* gene[172]. Astringency is a sensation described as a drying and puckering of the mouth and it is an attribute of wines, beer, coffee, tea, fruit juices and chocolate, which contain polyphenolic, compounds that bind salivary proteins[173]. This sensation can lead to the rejection of beverages in some consumers[174]. Differences in salivary protein content due to genetic factors influences astringency perception, but the genes involved have not been identified[175,176]. Astringency perception may also be dependent on salivary flow rates[177].

Conclusions

The senses of taste, olfaction and texture yield information about nutrients, influence pal-

atability and foods preferences. Many studies have been carried out for the discovery and characterization of mammalian taste, olfactory and texture receptors by animal models or receptor-expressing cells. Variations in chemosensory perception may be attributed to genetic variations that can be analysed by quantitative and molecular genetics approaches. In particular, twin studies provide a quantitative genetic estimate of a trait that is attributable to genetic influences, while studies of molecular genetics allowed the identification of genes and SNPs that are responsible of a different perception of the foods[178]. In commerce edible taste strips for testing genetically linked taste ability are available. The development of these taste strips for threshold and suprathreshold studies allows for the rapid and efficient evaluation of taster status in large populations[179]. Examining genetic variations in taste receptors will help establish the association between food intake behaviours and risk of chronic disease. Therefore, the knowledge of the genetical basis of foods choices can promote health and wellness. The creation of foods high in sugar, fat, salt and glutamate with nice smells and pleasant textures that are hyper-appealing can cause obesity and malnourishment from lack of micronutrients and intake of insulin-dependent macronutrients[180]. Obesity is very widespread in westernized societies caused by genetic susceptibility and environmental influences and, in turn, it causes a high risk of cardiometabolic disease, osteoarthritis, and different types of cancer[181]. The effects of wrong dietary behaviors can be immediate and overt, such as the vitamin deficiency diseases, or complex and less immediate, as the predisposition to dental caries, obesity, type 2 diabetes, cardiovascular risk and other metabolic chronic diseases[8]. There may be many more genetic variants in taste and odor genes yet to be discovered that could contribute to the prevention of diseases related to unhealthy diet. Finally, the study of the variations in taste receptors may have broader effect on the clinical practice for different reasons. Studies in mice highlighted the overlap among taste signal transduction and the signalling related to the vision mechanisms[182]. α-gustducin (highly expressed in the tongue for sweet and bitter perception) knockout mice show an overexpression of the α-transducin (highly expressed in the rod) in the tongue[182]. Furthermore, in cellular models has been demonstrated that the activation of the sweet taste receptor T1R3 by sucralose attenuates the VEGF-induced retinal endothelial blood vessel formation (a typical mechanism associated with diabetic retinopathy)[183].

Contributions

MB conceived the study; VP, SP, EM and MB collected information; VP wrote the manuscript; VP, TB, LS, MB, SP, EM, GADM, BF, VU, MB reviewed and edited the text; MB supervised the work.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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