# Taste perception and expression in stomach of bitter taste receptor tas2r38 in obese and lean subjects

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ABSTRACT

Differences in taste perception have been related to eating behavior, nutritional status, and diseases. Recently, taste receptors have been identified in several extra-oral tissues, such as the gastrointestinal tract, where they seem to influence processes like digestion, sense of satiety as well as energy balance and intraluminal changes occurring in obesity.

Our study aims to analyze differences in taste perception among 42 obese patients (OB) and 41 normal-weight subjects (LEAN). Polymorphisms in the gene codifying for the bitter taste receptor TAS2R38 and its expression on the surface of the gastric mucosa were tested and compared among OB and LEAN.

Taste intensity of PROP (6-*n*-propylthiouracil), quinine, sucrose, citric acid and NaCl were measured on a labeled magnitude scale. DNA from peripheral whole blood was extracted and three polymorphisms in the *TAS2R38* gene (rs713598, rs1726866, rs10246939) analyzed. Gastric biopsies were collected during bariatric surgery in OB and during endoscopy in LEAN. RNA was extracted and TAS2R38 gene expression assessed by RT-Real-Time qPCR. Anamnestic and anthropometric data were recorded in all participants during baseline visits.

Logistic regression analysis showed that OB perceives sweet (sucrose) and bitter (PROP or 6-*n*-propylthiouracil) taste more intensely than LEAN (p-value = 0.02 and p-value = 0.005, respectively). While polymorphisms in *TAS2R38* gene did not differ among OB and LEAN, we observed a significant increase of TAS2R38 mRNA levels in the stomach of OB compared to LEAN (p = 0.01).

Our results provide new evidence of a link between obesity and altered taste perception as well as TAS2R38 expression in the stomach.

## 1. Introduction

Obesity is one of the emerging problems regarding Global Health, due to the increased risk of chronic and degenerative conditions, which can affect duration and quality of life (Kolotkin & Andersen, 2017). Obesity is not only an aesthetic problem but, most importantly, is a health issue since it is associated with cardiovascular disease, type 2 Mellitus diabetes, strokes, Obstructive Sleep Apnea Syndrome (OSAS), non-alcoholic fatty liver disease (NAFLD) and cancer (Csige et al., 2018; Flegal, Kit, Orpana, & Graubard, 2013; Li, Li, & Lu, 2018; Salaün, Thariat, Vignot, Merrouche, & Vignot, 2017).

The development of obesity is multifactorial with both environmental and genetic factors involved. Evidence suggests a possible influence of taste perception. The gustatory system allows to detect some nutrients and toxins in food, and taste is one of the most important factors affecting food choices. However, there is a large interindividual variability in taste perception. Sex and age differences are among the factors responsible for this variability (Barragán et al., 2018; Guido

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et al., 2016; Martin & Sollars, 2017; Tepper et al., 2017a, 2017b), but it may partly be explained also by genetic polymorphisms in taste receptor genes (Bachmanov et al., 2014; Chamoun et al., 2018; Diószegi, Llanaj, & Ádány, 2019).

Differences in taste perception have been also related to eating behavior and nutritional status; moreover, they may in turn have possible implications for health outcomes. For example, the link between taste perception and obesity or other parameters to classify weight status, such as BMI (Body Mass Index) or waist circumference, have been investigated (Coltell et al., 2019; Fernandez-Garcia et al., 2017; Miller, Polgreen, Segre, & Polgreen, 2020; Sharafi, Rawal, Fernandez, Huedo-Medina, & Duffy, 2018). A large research has focused on sweet sensitivity (Bartoshuk, Duffy, Hayes, Moskowitz, & Snyder, 2006; Hardikar, Höchenberger, Villringer, & Ohla, 2017; Hwang et al., 2016; Pepino, Finkbeiner, Beauchamp, & Mennella, 2010), while other taste qualities such as salty and sour perception have been less explored. Extensive studies have also been conducted on the bitter taste of 6-*n*-propylthiouracil (PROP), a compound that some individuals (called tasters) perceive as bitter, while others (called non tasters) can detect only at high concentrations or not at all (Fox, 1932; Guo & Reed, 2001).

Although research findings are controversial (Catanzaro, Chesbro, & Velkey, 2013; Drewnowski et al., 2007a; Wijtzes et al., 2017), differences in food preferences and intake among tasters and non-tasters have been reported in some works (Bajec & Pickering, 2010; Dinehart, Hayes, Bartoshuk, Lanier, & Duffy, 2006; Feeney, O'Brien, Scannell, Markey, & Gibney, 2011; Robino et al., 2014; Tepper, 2008; Tepper, Neilland, Ullrich, Koelliker, & Belzer, 2011). Studies have also reported higher BMI in PROP non tasters, specifically in women (Goldstein et al., 2005, 2007; Tepper & Ullrich, 2002). However, since mixed results have been reported (Bajec & Pickering, 2010; Dinehart et al., 2006; Drewnowski et al., 2007b), this relationship remains still to be elucidated.

The capacity to perceive PROP taste is genetically determined and the *TAS2R38* gene is considered the major responsible of individual differences in PROP perception. Three single nucleotide polymorphisms (SNPs) account for three amino acid substitutions at residues P49A, A262V, V296I and their combination results in two main haplotypes: AVI and PAV (Bufe et al., 2005; Guo & Reed, 2001). Homozygous AVI individuals are mainly non tasters (Kim & Drayna, 2005). The possible effect of genetic variants in *TAS2R38* gene (rs713598, rs1726866, rs10246939) on obesity and BMI has been also investigated; however, this relationship is still controversial and past studies mainly showed weak (Tepper et al., 2008) or no association (Keller et al., 2013; Ooi, Lee, Law, & Say, 2010; Timpson et al., 2005).

More recently, taste receptors, including TAS2R38, have been identified in several extra-oral tissues, such as the upper and lower gastrointestinal tract where they seem to regulate many gastrointestinal functions (food intake, appetite, gut motility, hormone secretion, etc) (Calvo & Egan, 2015; Dotson, Geraedts, & Munger, 2013; Janssen et al., 2011; Loper, La Sala, Dotson, & Steinle, 2015). A difference in TAS2R38 receptor expression among obese and lean subjects has been also reported in the human colonic mucosa, suggesting an involvement in increased energy balance and intraluminal changes occurring in obesity (Latorre et al., 2016).

Since literature data on the relationship between taste perception and obesity remain contradictory, the present study analyzed differences in taste perception for different compounds (PROP, quinine, sucrose, citric acid, NaCl) among obese patients and normal-weight subjects. Moreover, polymorphisms in the gene codifying for the bitter taste receptor TAS2R38 and its expression on the surface of the gastric mucosa were tested and compared.

## 2. Methods

### 2.1. Study participants

This study was carried out between February 2017 and September 2018. The patients enrolled in the study were divided into two groups: obese patients eligible for bariatric surgery (OB group) and non-obese patients (LEAN group) undergoing the upper gastrointestinal endoscopic procedure (Gastroscopy *or* Endoscopic retrograde cholangiopancreatography -ERCP).

The OB group inclusion's criteria were obese patient eligible for bariatric surgery in according with international guidelines: well-informed and motivated patients with acceptable surgical risk, failure of previous non-surgical weight loss treatments, patients who accept periodical medical exams, age between 18 and 65 y/o and BMI (Body Mass index, Kg/m$^2$) over 40 kg/m$^2$ or over 35 kg/m$^2$ with comorbidities related to obesity. In the OB group, the surgical intervention performed were Sleeve gastrectomy (SG) and Gastric by-pass (GBP) and all patients eligible for bariatric surgery underwent pre-operative gastroscopy with gastric mucosa biopsy.

In LEAN group were enrolled normal-weight subjects undergoing upper gastrointestinal endoscopic procedures for no-neoplastic diseases.

The exclusion criteria in OB group were: patients suffering from diseases with reduced life expectancy or with major psychiatric disorders, patients unable to take care of themselves in the absence of adequate family support.

Exclusion criteria in LEAN group were patients suffering from neoplastic disease and age <18 y/o.

Patients unable to express valid informed consent were excluded from the study.

From all study participants, anamnestic and smoking habit were recorded during baseline visits. Moreover, height (centimeters, cm) and body weight (kilograms, kg) on a digital weighing scale were taken and body mass index was calculated (BMI, kg/m$^2$).

To define the individual differences in the taste perception, we tested the perceived intensity of 5 filter papers impregnated with different compounds: PROP (50 mmol/l), quinine (0.0024 g/ml), NaCl (1.0 mol/l), citric acid (0.165 g/ml) and sucrose (0.2 g/ml) (Catamo, Tornese, Concas, Gasparini, & Robino, 2020; Zhao, Kirkmeyer, & Tepper, 2003). Subjects were examined in a room without odors, visual or auditory distractions and were asked not to eat or brush their teeth beforehand. Subjects also received detailed instructions by an expert administrator. Briefly, each subject was asked to place the paper on the tongue until it is wet and rate the intensity on labeled magnitude scale (LMS) ranging from 0 (barely detectable) to 100 (strongest imaginable) (Green et al., 1996). Between the different strips, a pause of 120 s was done, and in the meanwhile patients had rinsed their mouth with bottled mineral water. Each compound was evaluated once.

All subjects gave their written informed consent before participating in this study, approved by protocol N. 16637 Local Ethical Committee (Comitato Etico Regionale Unico, FVG, SSN).

### 2.2. DNA extraction and TAS2R38 genetic analysis

In the OB group, DNA was extracted from a blood sample obtained before surgery. In LEAN group, DNA samples were taken rubbing a swab (Isohelix, Cell Projects, Kent, UK) against the inside of the cheek for 2 min on each side.

Three SNPs (rs1726866, rs713598, and rs10246939) located within the TAS2R38 gene were analyzed in both OB and LEAN subjects using the TaqMan probe-based assays (Applied Biosystems, Foster City, CA, USA). PCR primers and TaqMan probes were designed by Applied Biosystems. The PCR was conducted in 96-well PCR plates with 10 μl in each well and a final concentration of 20 ng genomic DNA. The TaqMan PCR was carried out in an automatic thermal cycler (7900HT Fast-Real-Time PCR System) under the following conditions: 95 °C for 10 min (initial step), 40 cycles of 95 °C for 15 s (denature) and 60 °C for 1 min (anneal/extend). The system software records the results of the genotyping run on a scatter plot of Allele 1 versus Allele 2. Based on the results on the three SNPs, all participants were classified into heterozygous PAV/AVI, homozygous PAV/PAV and homozygous AVI/AVI.

### 2.3. RNA extraction, quantification, and retrotranscription

In LEAN group and OB subjects who underwent GBP, the expression of *TAS2R38* gene was analyzed on a gastric mucosa biopsy performed during the upper gastrointestinal endoscopic procedure. In patients who underwent SG, the analysis of *TAS2R38* was performed on a surgical gastric biopsy obtained by the removed stomach.

Stomach tissues were lysed with TRI Reagent® (T9424 Sigma-Aldrich) following manufactures' instructions for the total RNA extraction. Quantification was performed spectrophotometrically at 260 nm in a *Beckman DU 640B spectrophotometer*, using quartz cuvettes. The RNA purity was evaluated by measuring the ratio A260/A280, considering RNA with appropriate purity those showing values between 1.8 and 2.0; its integrity was evaluated by gel electrophoresis. The integrity of RNA was assessed on standard 1% agarose/formaldehyde gel. Isolated RNA was suspended in RNAse free water and stored at −80 °C until analysis. Total RNA (1 μg) was reverse transcribed using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's instructions. Retro transcription was performed in a Thermal Cycler, following temperature protocol proposed by manufacturers: 10 min at 25 °C (annealing), 120min at 37 °C (cDNA synthesis), 5 min at 85 °C (enzyme denaturation).

### 2.4. Gene expression analysis by Real Time RT-PCR

cDNA samples obtained from RT-PCR were used in the Real Time quantitative PCR to determine gene expression in both experimental groups. PCR amplification was carried out in 15 μL reaction volume containing cDNA, 1x iQ SYBR Green Supermix and specific sense and anti-sense primers. All primer pairs used for Real Time PCR were designed using the software Beacon Designer 8.10 and they were synthesized by ®Metabion international AG. Primer sequences, concentrations, and ng of cDNA used are reported in Table 1. Standard curves were prepared using a "calibrator" cDNA for each target and reference gene. To verify the specificity of the amplification, a melt curve analysis was performed, immediately after the amplification protocol. Non-specific products of PCR were found in any case. The relative quantification was made using the Pfaffl modification of the ΔΔCt equation (Pfaffl, 2001), taking into account the efficiencies of individual genes. The results were normalized to β-actin and 18S used as reference genes. The data were analyzed using iQ5™ optical system software version 2.0 (Bio-Rad). Each sample was analyzed in triplicate.

### 2.5. Statistical analysis

Percentages, means and range were used to represent descriptive statistics.

To assess the relationship between perception for each taste quality and obesity linear regression analyses were performed. Taste intensity (quantitative variable) was used as an outcome, while obesity (dichotomic variable) as a predictor.

A logistic regression model was used to test the effect of *TAS2R38* haplotype on obesity.

Finally, to analyze the association between obesity (predictor) and TAS2R38 expression in the stomach (outcome) a linear regression model was performed.

In all models, gender and age were used as covariates.

Statistical significance was set at p-value $< 0.05$. All statistical analyses were performed with R software (www.r-project.org).

## 3. Results

### 3.1. Sample characteristics

41 LEAN and 42 OB subjects participated in the study. The OB group was composed of 25 females and 17 males with a mean age of 43.8 (range:19–61) and a mean BMI of 45.9 kg/m2 (range:32.6–64.6). The LEAN group comprised 24 females and 17 males, with a mean age of 41.2 (range:18–68) and a mean BMI of 22.4 kg/m2 (range:17–28).

No gender and age differences emerged between OB and LEAN subjects.

In 13 OB (31%) the surgical intervention performed were GBP, while in 29 OB (69%) SG.

### 3.2. Taste perception in OB and LEAN subjects

Linear regression analysis showed a significant association between obesity and sucrose and PROP taste perception (p-value = 0.02 and p-value = 0.03, respectively). As shown in Fig. 1, higher taste intensity perception emerged in obese patients compared to lean subjects.

For quinine and citric acid p-value was close to significance (p-value = 0.06 and p-value = 0.05, respectively), while for NaCl no significant results emerged (p-value = 0.11).

### 3.3. TAS2R38 haplotype in OB and LEAN subjects

Both OB and LEAN subjects were classified in homozygous AVI/AVI, heterozygous AVI/PAV and homozygous PAV/PAV based on the 3 SNPs in the *TAS2R38* gene.

In our sample, 27% of subjects were AVI/AVI, 47% were AVI/PAV and 26% PAV/PAV. As expected, a strong association between *TAS2R38* haplotype and PROP intensity emerged in our sample (p-value<0.0001), while no association with other taste qualities were found ($p > 0.05$) (Table S1).

No difference emerged in terms of *TAS2R38* haplotype frequencies among obese and lean subjects (p-value = 0.9) (Table 2).

### 3.4. TAS2R38 gene expression in OB and LEAN subjects

TAS2R38 is expressed along the gastrointestinal tract, being highly expressed in terms of mRNA in the small intestine, and, in a lesser extent, in the stomach (The Human Protein Atlas., 2019). Tacking advantage of the available material during the esophagogastroduodenoscopy and surgical biopsy, we analyzed the expression of this gene in stomach tissue collected from OB and LEAN subjects. Data showed that the OB group presented an up-regulation in the gene expression of TAS2R38 (median 179, percentile range 18.32–13081) vs the LEAN control group (median 22, percentile range 5.05–92.37) ($p = 0.01$) (Fig. 2).

## 4. Discussion

In the present study, we compared the perception of bitter, sour, salty and sweet taste in lean and obese subjects. We found that obese subjects are more sensitive to taste than lean ones. Specifically, a significant difference emerged for the sweet and bitter perception of PROP. For quinine and citric acid, our results are close to statistical

**Table 1**
Primer pair sequences and experimental concentrations.

| Genes | Accession number | Forward | Reverse | Primer (nM) | cDNA (ng) |
|---|---|---|---|---|---|
| 18S | NR_003286.2 | TAACCCGTTGAACCCATT | CCATCCAATCGGTAGTAGCG | 250 | 25 |
| β-actin | NM_001101.3 | CGCCGCCAGCTCACCATG | CACGATGGAGGGGAAGACGG | 100 | 25 |
| TAS2R38 | NM_176817 | GAATAACAATACAAGGCTCAACT | GGCACAGACCACAGATAG | 250 | 25 |

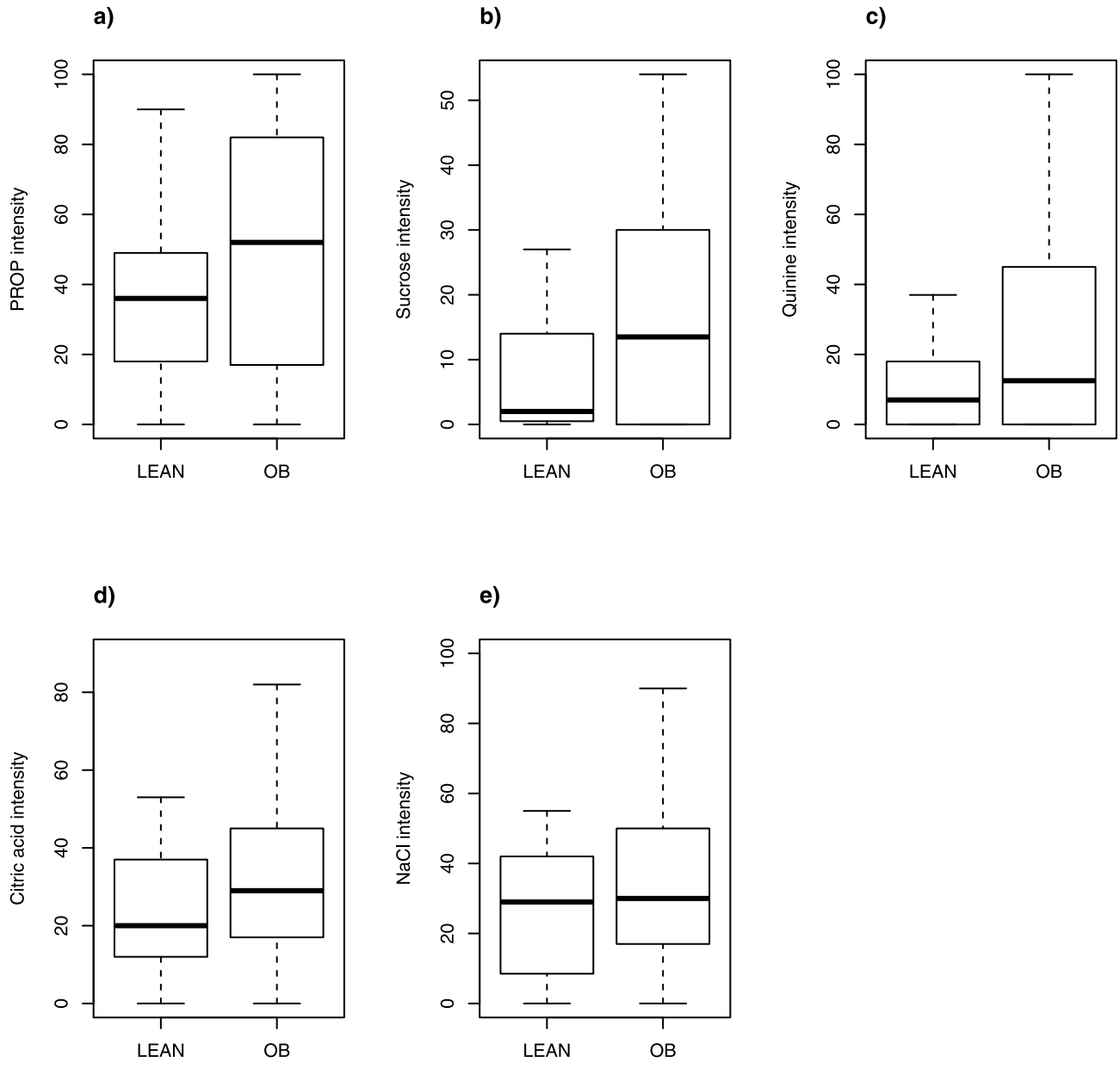


**Fig. 1.** Taste perception among OB and LEAN subjects for PROP (a), Sucrose (b), Quinine (c), Citric acid (d), NaCl (e).

**Table 2**
TAS2R38 haplotype frequencies.

| *TAS2R38* Haplotype | All | Obese | Lean |
|---|---|---|---|
| AVI/AVI | 27.0% | 28.5% | 25.0% |
| AVI/PAV | 47.5% | 47.5% | 47.5% |
| PAV/PAV | 25.5% | 24.0% | 27.5% |

significance, while we did not find a significant difference for salty taste perception.

Very controversial results have emerged from past studies on the relationship between obesity and taste perception. Some studies have found no differences (Martinez-Cordero, Malacara-Hernandez, & Martinez-Cordero, 2015), others lower taste sensitivity (Overberg, Hummel, Krude, & Wiegand, 2012; Proserpio, Laureati, Bertoli, Battezzati, & Pagliarini, 2015; Simchen, Koebnick, Hoyer, Issanchou, & Zunft, 2006; Skrandies & Zschieschang, 2015) while others a higher taste sensitivity in obese subjects (Hardikar et al., 2017; Pasquet, Frelut, Simmen, Hladik, & Monneuse, 2007). Our results agree with findings reporting higher taste intensity in obese participants.

The inconsistency of the existing results could reside in the difference in the method used to measure taste sensitivity across studies (e.g. whole mouth or localized stimulation; use of different concentrations and scales; etc.). These methodological differences may contribute making difficult the comparison among the current findings. Although we found comparable results to past works (Hardikar et al., 2017; Pasquet et al., 2007), the methodology we used to assess taste perception differs. For example, while we analyzed taste strips, in other works taste solutions at different concentrations were tested to determine taste perceived intensities and the visual analogue scales (VAS) or 9-point scale were used (Hardikar et al., 2017; Pasquet et al., 2007). Moreover, several confounding factors such as gender, age or ethnicity (Simchen et al., 2006; Tepper et al., 2017a, 2017b) may modulate the complex relationship between taste perception and obesity and could also be responsible for this variability. For example, past studies have already reported gender differences in chemosensory perception, showing that women were more sensitive than men (Pasquet et al., 2007; Tepper et al., 2017a,

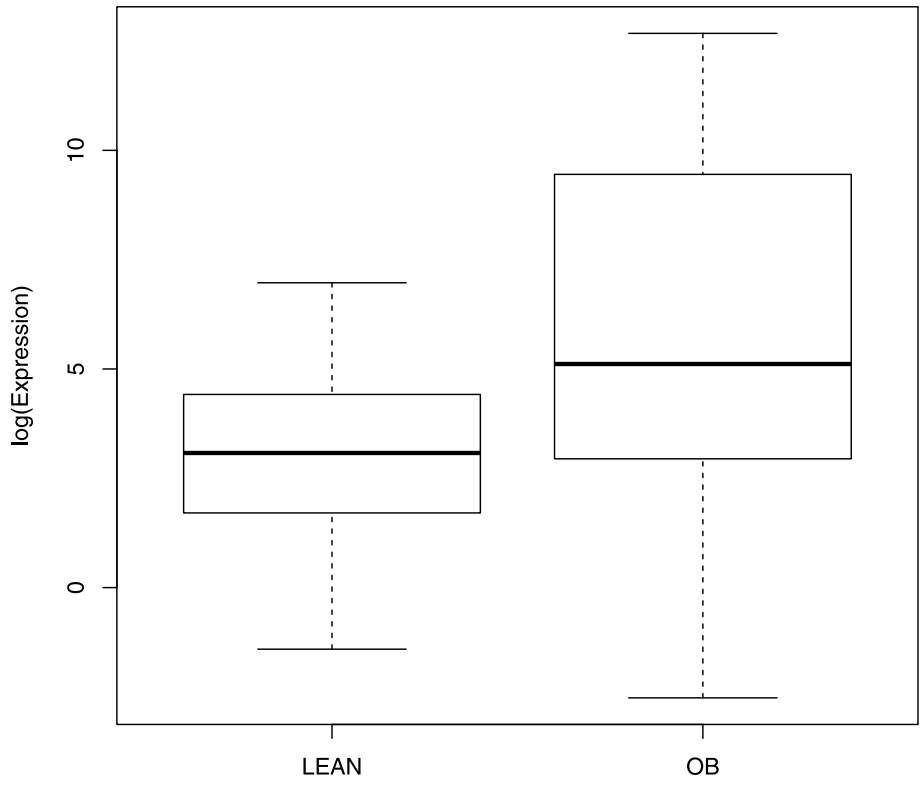


**Fig. 2.** Gene Expression analysis of TAS2R38 in OB and LEAN subjects.

2017b). Moreover, gender-specific associations between taste perception and body weight have been showed in some works (Feeney, O'Brien, Scannell, Markey, & Gibney, 2017; Keller & Tepper, 2004; Pasquet et al., 2007; Tepper et al., 2008). Finally, discrepant results can also be linked to the weight of the study subjects. Indeed, in line with our findings, previous work reported higher taste sensitivity in massively obese adolescents compared to control subjects (Pasquet et al., 2007).

While we found a significant difference in PROP taste perception among OB and LEAN individuals, no difference emerged comparing *TAS2R38* haplotype frequencies between the two groups. TAS2R38 polymorphisms, determining the ability to detect bitter taste, were previously associated with food intake and eating behavior (Dotson, Shaw, Mitchell, Munger, & Steinle, 2009; Tepper, 2008). However, controversial findings have emerged about their possible influence on obesity-related traits such as BMI. As stated above, differences in weight status of the participants may influence this association and may be responsible of the discrepancy of the existing findings. Our results agree with studies reporting no relationship between TAS2R38 variants and adiposity measures (Coltell et al., 2019; Keller et al., 2013; Ooi et al., 2010; Timpson et al., 2005). However, it should be noted that there are significantly differences in the mean BMI of participants across these studies. Moreover, while we have compared massively obese and non-obese subjects, past studies analyzed the association between *TAS2R38* polymorphisms and BMI used as quantitative trait.

Finally, in the present work, we compared TAS2R38 expression in the stomach of OB and LEAN individuals and found a significant upregulation of TAS2R38 mRNA in the OB group. Interestingly, these findings support previous data showing that TAS2R38 is expressed in enteroendocrine cells of the human colonic mucosa and that is upregulated in overweight and obese subjects compared to lean ones (Latorre et al., 2016). The same authors have previously shown in animal models that different types of diet, included a long-term high fat diet, may induce in several regions of the gut intraluminal changes that in turn alter the expression of TAS2R receptors (like TAS2R138) (Vegezzi et al., 2014). Thus, they also suggested that in human the up-regulation of TAS2R38 in colon mucosa might represent adaptation to intraluminal changes induced by increased food intake and obesity (Wijtzes et al., 2017). Similarly, in our work, the observed upregulation of TAS2R38 mRNA in the OB group might be linked to changes in luminal content of the stomach and possibly also of other regions of the gastrointestinal tract. Further studies analyzing other districts of the gut and a larger sample are needed to confirm our results.

This study has some limitations, including the selection of the lean group that includes subjects with other digestive pathologies (i.e. dyspepsia, gastroesophageal reflux, epigastric pain). However, the need to perform a gastric biopsy have reduced the possibility of choosing normal-weight participants. Moreover, although gender adjustment was performed, the present work did not evaluate males and females separately; thus, it is not able to support earlier studies that have observed gender-specific associations between taste perception and body weight. Finally, the study did not include food preferences or intake data, that could explain the observed taste-adiposity associations. Their associations should be examined in future research.

In conclusion, our findings provide further evidence of a link between obesity and taste perception, showing in obese subjects higher sweet and bitter taste perception as well as an increased TAS2R38 expression in the stomach compared to lean individuals. Overall, the present results may represent a step toward to better understand the role of genetic predisposition in obesity and the mechanisms underlying changes occurring in obese subjects.

## Declaration of competing interest

The authors declare that they have no conflict of interest.

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The authors wish to thank all the participants.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.appet.2021.105595.

## Author contribution

AR, NR, SP designed research; AR, NR, PJG, SP conducted research; AR, NP, PJG, MLB analyzed data or performed statistical analysis; MG, PC, BC, CT, FM data collection; AR, NR, CT, PG, NdM, SP writing and editing of the manuscript; all authors read and approved the final manuscript.


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## Ethical statement

The study was approved by the Regional Ethical Committee (N. 16637). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Data and code availability

Data and material will be made available upon request.

The lead author has full access to the data reported in the manuscript.

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