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Association between variants of neuromedin U gene and taste thresholds and food preferences in European children:

Results from the IDEFICS study

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ABSTRACT (max 280 words- *Appetite*)

Aim: The neuropeptide neuromedin U (NMU) known for its role in appetite, feeding and energy balance could be involved in the control of food choice and taste sensitivity. We examined the association between *NMU* polymorphisms/haplotypes and taste thresholds and food preferences in a population of European children.

Methods: A total of 578 subjects from the IDEFICS study (mean age 7.5±0.8 SD, boys 53.6%) with *NMU* genotype data and food preference (salty, fatty, sweet, flavour and umami food) and taste threshold (salt, fat, sweet, umami) tests available were analysed. Three single nucleotide polymorphisms (SNPs; rs6827359, T:C; rs12500837, T:C; rs9999653, C:T) of *NMU* gene were analyzed and five major haplotypes were inferred. The associations between genotypes and food preferences or taste thresholds were investigated (odds ratios –OR, adjusted for age, sex and country). A $p<0.05$ after false discovery rate adjustment (pFDR) was considered statistically significant.

Results: The association between *NMU* genotypes and food preference showed two *NMU* SNPs associated with preference for food containing sodium glutamate (umami taste; rs6827359C, OR=1.61, 95% confidence interval (CI):1.20-2.17; rs9999653T, OR=1.59, 95%CI:1.18-2.13). In the haplotype analysis, the CTT haplotype showed an OR of 1.70 (95%CI:1.16-2.5) for the umami food preference, while CCT haplotype showed an OR of 1.63 (95%CI:1.11-2.40), compared to the most frequent haplotype (TTC). Carriers of CCT/CCT vs subjects with no CCT haplotype showed an OR of 4.78 (95%CI:1.86-12.30). Umami food preference was associated with low values of BMI *z*-score, arm circumferences, skinfolds and fat mass (pFDR<0.05). No association between *NMU* genetic variants and taste thresholds was found.

Conclusions: This study shows for the first time in children an association between preference for umami food and a *NMU* haplotype, previously found associated with low BMI values.

Keywords: *food preferences; umami; neuromedin U; neurology; genetics; obesity*

INTRODUCTION

Taste sensing influences food preference, appetite and satiety, thereby regulating diet quality and total food intake and, as a result, weight maintenance (Dotson 2012). Five taste qualities can be perceived by humans: sweet, salty, bitter, sour and umami. The ability of discriminate between tastes has shown to be the result of evolution, to avoid hazardous compounds while searching for nutrients important for life and development.

In children, food preferences are often guided by taste alone. Specifically, preferences for sugar and fat may be acquired early in life, as children learn to prefer those flavors that are associated with high energy density and fat content, with higher risk of developing overweight (Drewnowski 1997). In line with that, several studies showed that food preferences and taste sensitivity differ between obese and non-obese children (Overberg 2012; Wardle 2001).

The mechanisms behind the regulation of food preferences and taste perception has only been partially revealed (MacLean 2017). Recent findings suggested that genetics plays an important role, since high heritability levels were found for both food preferences and taste perception (Tornwall 2015). Genetic studies of taste variability have focused on a number of candidate genes encoding the taste receptors, hormones and neuropeptides, such as leptin, GLP-1 and NPY, important modulators at both peripheral and central level (Feeney 2011; Loper 2015).

Neuromedin U (NMU) is a neuropeptide with a highly conserved genetic structure, thought to have several important functions. Transgenic mouse models and experimental studies showed its main involvement in the regulation of body weight, through its effect on appetite, feeding and energy balance (Martinez 2015). Recently, an increased preference for obesogenic food was observed in rats knockdown for NMU Receptor 2 (NMUR2), the NMU receptor mainly expressed in the central nervous system (Benzon 2014). Although the effects of NMU are well understood in animal models, little is known about its role in humans besides a suggested role in adiposity

regulation from epidemiological evidence. A rare NMU variant was in fact associated with overweight and obesity (Hainerová 2006). In addition, our group observed an association between NMU genetic polymorphisms and adiposity indices in a European children population (Gianfagna 2017). While a link between NMU and adiposity regulation was identified, no data have been produced to link this neuropeptide to adiposity intermediate phenotypes. To this respect, NMU could cooperate in modifying taste perception and selective appetite.

In this study, we aimed at evaluating the potential association of NMU with food preferences and taste perception, by investigating NMU genetic variants in a European children population recruited for the IDEFICS Study (Ahrens 2011).

MATERIALS AND METHODS

Study population

IDEFICS (Identification and prevention of dietary - and lifestyle - induced health effects in children and infants) is a large European multi-center study aimed at investigating risk factors associated with childhood obesity (Ahrens 2011). A cohort of 16,229 children aged 2.0–9.9 years was recruited in a population-based survey between September 2007 and May 2008 (T0), in eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden).

For taste threshold and food preference test, from the subgroup of participating primary schoolchildren aged 6–9 or 7–9 years (depending on age of school enrolment), a subsample of 1839 (20.8%) children were randomly selected (Lanfer 2012). For genetic analyses, a subgroup of 4,678 (28.8%) samples was randomly selected from the total study population of European descent

children, stratifying by age, sex and country (about 600 subjects from each country) (Gianfagna 2013; Cugino 2013). Finally, 578 children, 6–9-year-old with *NMU* genotype and food preference and taste threshold test available were selected for the present analysis.

Ethical approval was obtained by the ethical committees of each center engaged in the fieldwork: Ethics Committee, University Hospital, Gent, Belgium; Cyprus National Bioethics Committee, Strovolos, Cyprus; Tallinn Medical Research Ethics Committee, Tallinn, Estonia; Ethics Committee, University of Bremen, Bremen, Germany; Egészségügyi Tudományos Tanács, Pécs, Hungary; Comitato Etico, ASL Avellino, Avellino, Italy; Comité Ético de Investigación, Clínica de Aragón (CEICA), Zaragoza, Spain; Regional Ethics Committee, University of Gothenburg, Gothenburg, Sweden. Both children and their parents gave oral (children) and written (parents) informed consent.

Data collection

Food preference test. The preference test was organized as paired and forced choice on a board as previously described (Lanfer 2012, Knof 2011). Briefly, participating children had their last meal 1 h before to ensure that they were neither hungry nor sated. The test was conducted using five preference tests for five tastes. To evaluate sweet preference apple, juice was administered in small cups with a volume of 30 ml at 18±2 °C and with different addition of sucrose (0.53-3.11%). For the evaluation of flavour preferences, 0.05% apple flavour (nature identical, Sensient Flavors, Bremen, Germany) was added to the basic recipe. The children had to rinse their mouths with water between each pair sequence of the test. To assess the preference for salty, fatty and umami tastes, crackers were selected as food sample. The crackers were covered with 0.5% aqueous solution of sodium hydroxide (soda lye, Carl Roth Chemicals, Karlsruhe, Germany) to make them tastier to the children. The basic recipe of cracker included water, flour (wheat), fat (8%) and salt. The same type of crackers was modified with an increased 8% of fat to assess high-fat preference, an increased 1% of salt for salty taste and monosodium glutamate (1%) for umami crackers. In each sequence, the

children had to choose their preferred food sample between the basic recipe and a modified one. The order of assessment for the food choice was fat, salt and umami. The test procedure was subject to pre-testing before the beginning of the study (Suling 2011) and yielded reliable results in a reproducibility study (Knof 2011).

Taste detection threshold test. As a measure of taste sensitivity, detection threshold is the lowest value of a tastant that must be exceeded to have any effect on the observer. The procedure to evaluate the taste threshold was described in detail in Knof et al. (2011). In brief, a paired comparison test with five different watery solutions at different concentrations of tastants was served to the children in small cups of 20 ml. The concentration ranges of the tastants were sucrose (8.8-46.7 mmol/l), sodium chloride (3.4-27.4 mmol/l), caffeine (0.26-1.3 mmol/l) and monosodium glutamate (MSG) (0.6-9.5 mmol/l). The paired test was prepared as a board game and the children had to compare each test solution at increasing concentrations of tastants with a cup containing pure water, to find the cups that would taste differently from the previous one. Taste detection at lower tastant concentration (lower detection threshold value) indicates increased sensitivity for a specific tastant. Between the taste modalities, the children had to neutralize their taste with distilled water.

Anthropometric data. Height was measured using a standard clinical Seca 225 stadiometer (Seca, Hamburg, Germany) to the nearest 0.1 cm, and weight was measured using a scale (BC 420 SMA; Tanita, Amsterdam, The Netherlands) to the nearest 0.1 kg, on children wearing underwear clothes and without shoes. BMI was calculated as weight(kg)/height(m)^2. Waist and hip circumference was measured with an inelastic tape (Seca 200, precision 0.1 cm, range 0–150 cm). Age- and sex-specific BMI and waist circumference *z*-scores and BMI categories were calculated according to the criteria of the International Obesity Task Force (IOTF) (Cole 2012). Leg-to-leg impedance was measured with the Tanita scale and fat-free mass was calculated using the formula of Tyrrell *et al* (2001). Skinfold thicknesses (tricipital and subscapular) were measured with a Holtain caliper (Holtain, Holtain Ltd, Pembrokeshire, UK, range 0±40 mm), taking measures twice on the right hand body side and using the mean of the two measures for the analyses. All

measurements were collected by standardized protocols across centers, checking intra- and inter-observer reliability (Stomfai 2011).

Genotyping. DNA extraction was carried out from saliva samples (Oragene DNA Self-Collection Kit, OG-300/OG-250; DNA Genotek Inc., Kanata, Ontario, Canada) (Koni 2011). Among the three main blocks of the *NMU* gene (chr4, 55595229–55636698, GRCh38.p7 assembly), three tag SNPs (rs6827359, rs12500837, rs9999653; intronic regions) were selected from the Caucasian HapMap Project data using the Tagger Pairwise method of Haploview software (version 4.1; Broad Institute, Cambridge, MA, USA) (Barrett 2005). Tag SNP selection criteria were described in Gianfagna et al (2017). The SNPs were genotyped by a multiplexed end-point assay. The allelic discrimination was performed by 7500 Fast Real-Time System (Applied Biosystems). The genotyping success rate was on average 97.6% and a randomly selected sample (5%) was newly genotyped for all SNPs with 100% concordance.

Statistical analysis

The analyses were conducted with SAS (v9.3, SAS Institute Inc., Cary, NC) and R (v3.2.1; https://www.R-project.org/) software. Distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and log-transformed variables were used where appropriate. Hardy-Weinberg equilibrium (HWE) was assessed with the chi-square test. The best genetic model was checked for each genotype–phenotype association, testing dominance deviation from additivity and considering the additive model as default (Hoffman 2004). The Haplo.stats package of R software was used to estimate the haplotype frequencies and to verify the associations between haplotype and phenotype (haplo.glm function, the most prevalent haplotype as reference). Haplotypes with frequencies lower than 1% were excluded. Multiple regression analyses were performed using age, sex and countries as covariates, to evaluate the association between genotypes and food preferences (basic food or modified food with salty, fatty, umami, sweet and flavor tastes) or taste thresholds (sweet, salty, umami, bitter). The Benjamini-Hochberg false discovery rate (FDR) (Benjamini

1995) was used to adjust the results for multiple comparisons, using PROC MULTTEST in SAS. A FDR-adjusted *p* value (*p*FDR) <0.05 was considered as statistically significant.

RESULTS

Population characteristics

Characteristics of the study population are shown in Table 1. Children with at least one SNP successfully genotyped in NMU gene and eating behavior data available were 578 (mean age 7.5±0.8 SD, boys 53.6%). The lowest taste threshold value was found for sweet taste, taking into account mean thresholds and concentration ranges of test solutions (sucrose, 19.9 mmol/l; range 8.8-46.7). In food preference tests, the most appreciated food were salt-added crackers (63.7% of children preferred them to the basic recipe crackers), while sodium glutamate-added crackers (umami taste) were the less appreciated (33.4%). Genotype frequencies are reported in Table 2a. No statistically significant differences were found between genotype frequencies of children randomly selected to be included or excluded from this analysis subjects (data not shown). All genotypes were in Hardy-Weinberg equilibrium and the minor allele frequencies (MAF) were similar to values reported in the HapMap database for Caucasians. Six haplotypes were inferred (Table 2b; wild-type haplotype 43.9%).

Associations with food preferences and taste thresholds

Deviation from additivity test showed codominance as the best genetic model for all phenotype-SNP and phenotype-haplotype associations, except for umami food preference for the reference haplotype TTC (H7), that showed a dominant model.

The analysis of the association between NMU genetic variants and food preferences are shown in Table 3. Children carrying mutant allele in ~~Two~~ two out of the three *NMU* SNPs studied were more likely to prefer ~~associated with preference for~~ food containing sodium glutamate (umami taste) with respect to the same food prepared with a basic recipe (~~;~~ rs6827359, odds ratio - OR=1.61, 95% confidence interval - 95%CI:1.20-2.17; rs9999653, OR=1.59, 95%CI:1.18-2.13; Table 3). The haplotype analysis confirmed the association between genetic variants and preference for ~~with~~ umami ~~preference~~food. Subjects carrying the CTT haplotype showed an OR of 1.70 (95%CI:1.16-2.50) for the umami preference, while CCT haplotype showed an OR of 1.63 (95%CI:1.11-2.40), as compared to the most frequent TTC haplotype. The reference haplotype showed a reduced odd for umami preference when compared to all other haplotypes (OR=0.42; 95%CI:0.27-0.66). The association between umami food preference and the two SNPs as well as the TTC haplotype remained statistically significant after FDR correction. The same analysis considering each single genotype or haplotype versus the correspondent wild-type (Table 3, last rows) showed even higher association values. Homozygotes for mutant allele of rs6827359 (OR=2.57; 95%CI:1.43-4.61) and of rs9999653 (OR=2.31; 95%CI:1.29-4.15) versus the opposite homozygotes showed FDR-significant association with umami food preference. Similarly, homozygotes for CTT (OR=4.78; 95%CI:1.86-12.30), as well as carriers of TTC (OR=0.43; 95%CI:0.26-0.68) haplotype showed FDR-significant association with umami food preference when compared with subjects without that specific haplotype. No significant associations were found between *NMU* genotypes or haplotypes and the other food preferences (Suppl. Table 1).

The analysis of the association between *NMU* genetic variants and taste thresholds showed no significant results (Table 4, codominant model, and Suppl. Table 2, genotype or haplotype contrasts).

Association between umami preference and adiposity indices

Preference for umami food was associated with lower levels of the main anthropometric measures (Table 5, Model 1), such as *z*-score BMI (-0.25, *p*=0.034) and fat mass (-0.93, p=0.012). The association between preference for umami food and overweight/obesity was not statistically significant (OR=0.70; 95%CI:0.42-1.17). An association was also found with skinfolds (sum of triceps and subscapular skinfold, -1.75, *p*=0.025) and arm circumference (-0.63, *p*=0.011). The association between umami and anthropometric measures did not change when NMU genetic variants were added as covariates in the regression model (Table 5, Model 2). The association between the NMU haplotypes and anthropometric measures, previously observed in the whole sample of subjects with genetic data available, was not significant in this smaller subsample of children with taste thresholds and food preference data.

DISCUSSION

In this study, conducted in a sub-sample of children from the large European IDEFICS cohort, we found variants (two SNPs and two haplotypes) of *NMU* gene associated with preference for food containing glutamate. Preference for umami food was inversely associated with several anthropometric parameters such as BMI, weight, waist and arm circumference, skinfolds and fat mass.

This is the first study in humans investigating the potential involvement of NMU in influencing food preferences and taste perception in humans, although some experimental studies suggested this potential role. A recent experimental study in rats revealed that NMUR2, one of the two NMU receptors, could induce preference for high-fat foods (Benzon 2014). The NMUR2 is located mainly in central nervous system and is highly expressed in the hypothalamous and in other regions receiving fibers from taste sensory ganglia (Stanska 2016; Li 2017). Our results on the association between NMU genetic variants and umami food preference support the role of NMU in

regulating feeding behavior (Jethwa 2005; Kowalski 2005), specifically in neuronal pathways of taste-like/dislike preferences for umami food. We found no association with other food preferences. In line with our negative findings, a recent experimental study in mice showed that a NMU analog has no effect on preference for a sweet drink (Kaisho 2017). Although several hormones and neuropeptides were suggested as modulators of peripheral gustatory system (Loper 2015), we found no association between *NMU* genetic variants and taste perception thresholds. The reason of this negative result could be a lack of expression of NMU receptors in oral cavity. In fact, we found no literature data on expression of NMUR1 and NMUR2 in oral cavity, although at least NMUR1 is abundantly present along the gastrointestinal tract (Li 2017; Hedrick 2000; Raddatz 2000). These findings confirm that the associations of NMU with food preference is mediated by central nervous and not peripheral gustatory system.

In our population, we found significant associations between umami preference and anthropometric parameters. Although some associations did not reach statistical significance, all were concordantly in the direction of a protective effect for umami preference. The strongest significant association was found for fat mass. Children with preference for umami food present a decreased fat mass of approximately 1 kg. The umami taste is the fifth taste identified (Ikeda 2002), induced principally by three molecules: monosodium glutamate (MSG), inosine-5'-monophosphate (IMP) and guanylo-5'-monophosphate (GMP). These substances enhance the savory of foods and cause sensation such as pleasure and satisfaction (De Araujo 2003; Kurihara 2015), as well as insulin release, salivary, gastric and pancreatic secretion, gastric emptying and distal colon peristalsis (Stanska 2016). These effects could result in the modulation of short-term intake and satiety by giving umami an important role in appetite control (Masic 2014). The variants found associated with an increased preference for umami food were the same identified associated with lower BMI values, in a larger sample of the same population (Gianfagna 2017), suggesting that an increase in food preferences for umami could be also associated with decreased BMI. Supporting this hypothesis, a study in rats showed an association between preference of monosodium glutamate

solution and reduction of obesity (Kondoh 2008). This may suggest a potential mediating effect of umami food preference in the association between *NMU* genetic variants and BMI. However, in the subgroup with food preference data available, the association between *NMU* variants and BMI was not significant as we previously reported in the whole sample with genetic data available (Gianfagna 2013) due to the smaller sample size. The regression coefficient was however similar.

The strength of this study is the availability of a children population, which represent a good model for genetic studies. In fact, since the environment has had less time to exert its effect, phenotypes have a larger genetic component than in adults. However, taste and food preferences are influenced by several non-genetic factors, such as social, community and environmental factors, operating at multiple levels throughout life (Beckerman 2017; Russell 2013), which were not considered in this analysis. Although a confounding effect should be excluded due to the genetic study design, we cannot exclude a modification of the genetic effect due to factors not considered in the analyses. A further limitation of this study is the sample size, which is underpowered for the mediation effect analysis of umami preferences.

In conclusion, variants in the *NMU* gene might play a role in determining umami food preferences. This mechanism could mediate part of the association between the same *NMU* genetic variants and BMI, previously observed, although further studies are necessary to confirm this hypothesis.

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Table 1. Anthropometric characteristics of N = 578 children with genotype and food preferences or taste threshold data available.

Variables	**N**	**Mean±SD, n (%)**
Age (years; mean±SD)	578	7.5 ±0.8
Males (n, %)	578	310 (53.6%)
Body Mass Index (mean±SD)	578	16.8 ±2.7
BMI *z*-score (mean±SD)	578	0.47 ±1.17
Weight (kg; mean±SD)	578	27.3 ±6.1
Waist circumference (cm; mean±SD)	578	57.0 ±7.0
Hip Circumference (cm; mean±SD)	577	67.1 ±6.7
Waist to hip (mean±SD)	577	0.85 ±0.05
Arm circumference (cm; mean±SD)	572	19.7 ±2.5
Skinfolds (sum of tricipital and subscapular, mm; mean±SD)	570	19.1 ±8.1
Fat mass (kg; mean±SD)	569	8.1 ±3.8
Overweight+obese	578	135 (23.4%)
Obese	578	49 (8.5%)
Children preferring each modified food versus basic recipe		
Fat (n,%)	460	258 (56.1%)
Salt (n,%)	466	297 (63.7%)
Umami (n,%)	461	154 (33.4%)
Sweet (n,%)	514	300 (58.4%)
Flavour (n,%)	518	304 (58.7%)
Taste detection thresholds		
Sweet (sucrose 8.8–46.7 mmol/l; mean±SD)	517	19.9 ±11.1
Salty (sodium chloride 3.4–27.4 mmol/l; mean±SD)	522	12.9 ±7.2
Bitter (caffeine 0.26–1.3 mmol/l; mean±SD)	521	0.88 ±0.49
Umami (MSG 0.6–9.5 mmol/l; mean±SD)	516	4.2 ±3.1

Table 2a. Allele frequencies and Hardy-Weinberg equilibrium of the Neuromedin U (NMU) single nucleotide polymorphisms (SNPs; n = 578 with at least one SNP successfully genotyped).

SNP	Major:minor allele	N	Homozygous (major allele)	Heterozygous	Homozygous (minor allele)	HWE* (*p*)	MAF* (%)	CEU (%)
rs6827359	T*:C	576	161 (27.9%)	268 (46.5%)	147(25.5%)	0.11	49	40
rs12500837	T*:C	577	323 (56.0%)	216(37.4%)	38 (6.6%)	0.91	24	21
rs9999653	C:T*	574	132 (23.0%)	264 (46.0%)	178(31.4%)	0.42	54	49

*Hardy-Weinberg Equilibrium (HWE) and Minor Allele Frequency (MAF) were checked on the whole sample of 4649 subjects genotyped; rs9999653T allele is considered the minor allele based on population frequencies; CEU=Utah Residents (Caucasians) with Northern and Western European Ancestry

Table 2b. Haplotype frequencies (n = 578 with at least one SNP successfully genotyped).

rs6827359	rs12500837	rs9999653	Freq (%)
T	T	C	43.2%
T	T	T	7.9%
C	C	C	2.7%
C	C	T	22.6%
C	T	T	23.6%

Table 3. Odds ratios (OR) for preferring specific modified food to basic recipe, in children carrying genetic variants versus wild-type (codominant model, OR per minor allele).

Food preferences	Genotypes OR (95%CI)			Haplotypes OR (95%CI)			
	rs6827359 (C)	**rs12500837 (C)**	**rs9999653 (T)**	**H2 (CCT)**	**H4 (CTT)**	**H8 (TTT)**	**H7 (TTC)°**
Fat	1.04 (0.79-1.36)	0.91 (0.67-1.25)	1.07 (0.82-1.40)	0.98 (0.70-1.38)	1.10 (0.77-1.56)	0.94 (0.57-1.57)	1.00 (0.76-1.31)
Salt	1.07 (0.81-1.40)	0.98 (0.71-1.35)	1.11 (0.84-1.46)	1.06 (0.74-1.51)	1.15 (0.81-1.64)	1.04 (0.62-1.73)	0.93 (0.71-1.22)
Sweet	1.11 (0.87-1.42)	0.95 (0.71-1.26)	1.16 (0.91-1.49)	1.04 (0.75-1.44)	1.24 (0.90-1.70)	1.21 (0.77-1.89)	0.88 (0.68-1.13)
Flavour	0.93 (0.73-1.20)	0.90 (0.67-1.20)	0.89 (0.69-1.15)	0.85 (0.61-1.18)	0.98 (0.70-1.36)	0.94 (0.59-1.51)	1.08 (0.83-1.41)
Umami	**1.61 (1.20-2.17)***	1.34 (0.96-1.87)	**1.59 (1.18-2.13)***	**1.63 (1.11-2.40)**	**1.70 (1.16-2.50)**	1.38 (0.78-2.42)	**0.42 (0.27-0.66)*§**
W/M vsW/W†	*1.17 (0.69-1.97)*	*1.26 (0.80-1.96)*	*0.94 (0.54-1.64)*	*1.56 (0.96-2.53)*	*1.29 (0.78-2.11)*	*1.50 (0.76-2.95)*	***0.42 (0.26-0.68)****
M/M vsW/W†	***2.57 (1.43-4.61)****	*1.98 (0.87-4.50)*	***2.31 (1.29-4.15)****	***2.92 (1.17-7.33)***	***4.78 (1.86-12.30)****	*1.00 (0.18-5.70)*	***0.43 (0.24-0.78)***

Bold: nominally significant associations; *significant also after FDR correction, including rare haplotypes (not shown); § results for dominant model °all other haplotypes as reference; †Genotype or haplotype contrasts: for genotype analysis, heterozygotes or homozygotes for variant alleles (M) vs homozygotes for wild-type allele (W, ref); for haplotype analysis, subjects with 1 (w/M) or two (M/M) copies of a specific haplotypes versus subjects with the most frequent haplotype (TTC). Analyses adjusted for age, sex, country

Table 4. Differences in detection thresholds for specific tastes, in children carrying genetic variants versus wild-type (codominant model, threshold change per minor allele).

Taste thresholds	Genotypes (beta±SE, *p*)			Haplotypes (beta±SE, *p*)			
	rs6827359 (C)	**rs12500837 (C)**	**rs9999653 (T)**	**H2 (CCT)**	**H4 (CTT)**	**H8 (TTT)**	**H7 (TTC)°**
Sweet	-0.34±0.65 (0.60)	-0.03±0.75 (0.97)	-0.90±0.64 (0.16)	-0.59±0.83 (0.48)	-0.79±0.84 (0.35)	-1.57±1.31 (0.23)	0.74±0.65 (0.26)
Salty	0.37±0.42 (0.38)	0.59±0.49(0.23)	-0.18±0.42 (0.66)	0.35±0.54 (0.52)	-0.15±0.55 (0.78)	-1.57±0.84 (0.06)	0.07±0.42 (0.87)
Bitter	-0.02±0.03 (0.51)	0.02±0.03 (0.63)	-0.02±0.02 (0.52)	-0.004±0.04 (0.92)	-0.03±0.037 (0.44)	0.06±0.06 (0.33)	0.001±0.03 (0.97)
Umami	-0.08±0.18 (0.66)	0.12±0.22 (0.59)	-0.14±0.19 (0.46)	0.002±0.24 (0.99)	-0.24±0.24 (0.32)	-0.08±0.38 (0.83)	0.10±0.19 (0.61)

°All other haplotypes as reference. Analysis adjusted for age, sex and country. Lower detection threshold values indicate higher sensitivity for a specific tastant.

Table 5. Associations between anthropometric variables and umami or NMU variants in the IDEFICS children population.

	N	Model 1	Model 2			
Anthropometric	**N**	**Umami preferences**	**Umami preferences**	**H2/H2**	**H4/H4**	**H8/H8**
BMI *z*-score (beta±SE, *p*)	456	**-0.25±0.12 (0.034)*°**	**-0.23±0.12 (0.043)°**	-0.12±0.26 (0.64)	-0.15±0.23 (0.52)	0.22±0.60 (0.71)
Waist *z*-score (beta±SE, *p*)	456	-0.16±0.19 (0.42)	-0.12±0.19 (0.53)	-0.11±0.28 (0.69)	0.29±0.29 (0.32)	0.03±0.82 (0.97)
Arm circumference (beta±SE, *p*)	450	**-0.63±0.25 (0.011)***	**-0.58±0.23 (0.011)***	-0.26±0.52 (0.61)	-0.41±0.44 (0.36)	0.61±1.34 (0.65)
Skinfolds§ (beta±SE, *p*)	450	**-1.75±0.78 (0.025)***	**-1.71±0.68 (0.012)***	-0.53±1.49 (0.72)	0.05±1.45 (0.98)	-2.18±1.92 (0.26)
Fat mass (beta±SE, *p*)	453	**-0.93±0.37 (0.012)***	**-0.85±0.34 (0.012)***	-0.21±0.77 (0.78)	-0.74±0.61 (0.23)	0.98±2.08 (0.64)
Overweight/obesity (OR, 95%CI)	456	0.70 (0.42-1.17)	0.72 (0.44-1.19)	1.09 (0.40-2.98)	0.80 (0.29-2.16)	0.96 (0.09-10.66)

Model 1: age, sex and country; model 2: all in model 1 plus haplotypes. Bold: nominally significant associations; *significant also after FDR correction; § sum of tricipital and subscapular skinfolds; ° This is equal to -6.1±3.0 (beta±SE) BMI percentiles of the European population distribution (extended definition, Cole et al. 2012) Analysis adjusted for age, sex, country

Supplementary Table 1. Associations between Neuromedin U genotypes and food preferences in the IDEFICS children population.

Food preferences	Genotype or haplotype contrast†	Genotypes OR (95%CI)			Haplotypes OR (95%CI)			
		rs6827359 (C)	rs12500837 (C)	rs9999653 (T)	H2 (CCT)	H4 (CTT)	H8 (TTT)	H7 (TTC)°
Fat	W/M vsW/W	1.06 (0.67-1.68)	0.83 (0.55-1.25)	0.84 (0.55-1.25)	0.91 (0.59-1.40)	1.04 (0.67-1.61)	0.81 (0.44-1.49)	0.88 (0.57-1.36)
	M/M vsW/W	1.07 (0.63-1.84)	0.98 (0.44-2.19)	1.13 (0.66-1.92)	1.15 (0.50-2.67)	1.35 (0.52-3.49)	1.84 (0.34-9.97)	1.03 (0.59-1.79)
Salt	W/M vsW/W	1.21 (0.76-1.93)	1.05 (0.69-1.60)	1.22 (0.74-2.02)	1.14 (0.73-1.80)	1.23 (0.78-1.94)	0.87 (0.49-1.56)	0.97 (0.62-1.54)
	M/M vsW/W	1.12 (0.65-1.94)	0.85 (0.39-1.88)	1.24 (0.72-2.13)	0.96 (0.40-2.30)	1.15 (0.50-2.65)	2.99 (0.28-32.52)	0.85 (0.49-1.47)
Sweet	W/M vsW/W	1.06 (0.69-1.63)	1.00 (0.68-1.46)	1.11 (0.70-1.77)	1.03 (0.69-1.54)	1.21 (0.81-1.82)	1.13 (0.66-1.95)	0.84 (0.56-1.25)
	M/M vsW/W	1.24 (0.75-2.04)	0.82 (0.40-1.68)	1.34 (0.81-2.20)	1.11 (0.48-2.57)	1.59 (0.71-3.56)	1.87 (0.47-7.41)	0.79 (0.47-1.32)
Flavour	W/M vsW/W	1.26 (0.82-1.96)	0.87 (0.59-1.29)	1.20 (0.74-1.93)	0.77 (0.51-1.16)	0.93 (0.61-1.42)	0.94 (0.56-1.59)	1.42 (0.94-2.13)
	M/M vsW/W	0.86 (0.52-1.42)	0.84 (0.41-1.75)	0.83 (0.50-1.37)	0.89 (0.38-2.08)	1.07 (0.47-2.41)	0.88 (0.16-4.80)	1.08 (0.64-1.84)
Umami	W/M vsW/W	1.17 (0.69-1.97)	1.26 (0.80-1.96)	0.94 (0.54-1.64)	1.56 (0.96-2.53)	1.29 (0.78-2.11)	1.50 (0.76-2.95)	**0.42 (0.26-0.68)***
	M/M vsW/W	**2.57 (1.43-4.61)***	1.98 (0.87-4.50)	**2.31 (1.29-4.15)***	**2.92 (1.17-7.33)**	**4.78 (1.86-12.30)***	1.00 (0.18-5.70)	**0.43 (0.24-0.78)**

Bold: nominally significant associations; *significant also after FDR correction, including rare haplotypes (not shown); °all other haplotypes as reference; † for genotype analysis, heterozygotes or homozygotes for variant alleles (M) vs homozygotes for wild-type allele (W, ref); for haplotype analysis, subjects with 1 (w/M) or two (M/M) copies of a specific haplotypes versus subjects with the most frequent haplotype (TTC). Analyses adjusted for age, sex, country.

Supplementary Table 2. Associations between Neuromedin U genotypes and taste thresholds in the IDEFICS children population.

Taste	Genotype or haplotype contrast†	Genotypes (beta±SE, *p*)			Haplotypes (beta±SE, *p*)			
		rs6827359 (C)	rs12500837 (C)	rs9999653 (T)	H2 (CCT)	H4 (CTT)	H8 (TTT)	H7 (TTC)°
Sweet	W/M vsW/W	-0.35±1.11 (0.75)	-0.08±0.99 (0.93)	-1.43±1.17 (0.22)	-1.01±1.05 (0.34)	-0.83±1.02 (0.41)	-1.79±1.32 (0.18)	0.69±0.99 (0.49)
	M/M vsW/W	-0.68±1.30 (0.60)	0.03±1.87 (0.99)	-1.83±1.29 (0.16)	-0.28±2.09 (0.89)	-1.46±2.06 (0.48)	-1.97±1.99 (0.32)	1.48±1.33 (0.26)
Salt	W/M vsW/W	1.12±0.72 (0.12)	1.24±0.64 (0.054)	0.24±0.77 (0.75)	0.68±0.69 (0.32)	-0.10±0.70 (0.88)	-1.51±0.82 (0.07)	0.70±0.67 (0.29)
	M/M vsW/W	0.67±0.84 (0.43)	0.04±1.22 (0.97)	-0.34±0.84 (0.69)	0.00±1.24 (1.00)	-0.41±1.30 (0.75)	-3.25±1.68 (0.053)	0.02±0.86 (0.98)
Bitter	W/M vsW/W	-0.01±0.05 (0.85)	0.03±0.04 (0.53)	-0.01±0.05 (0.84)	0.01±0.05 (0.80)	-0.02±0.05 (0.59)	0.01±0.06 (0.89)	-0.01±0.05 (0.90)
	M/M vsW/W	-0.04±0.06 (0.50)	0.01±0.08 (0.89)	-0.04±0.06 (0.53)	-0.03±0.09 (0.75)	-0.07±0.08 (0.37)	0.27±0.18 (0.13)	0.00±0.06 (0.95)
Umami	W/M vsW/W	-0.50±0.32 (0.12)	0.14±0.29 (0.61)	-0.43±0.34 (0.20)	0.01±0.31 (0.97)	-0.32±0.31 (0.30)	-0.09±0.46 (0.85)	-0.35±0.30 (0.25)
	M/M vsW/W	-0.13±0.38 (0.74)	0.19±0.54 (0.73)	-0.29±0.37 (0.43)	0.00±0.57 (0.99)	-0.34±0.49 (0.49)	-0.22±1.17 (0.85)	0.28±0.39 (0.47)

° All other haplotypes as reference; † for genotype analysis, heterozygotes or homozygotes for variant alleles (M) vs homozygotes for wild-type allele (W, ref); for haplotype analysis, subjects with 1 (w/M) or two (M/M) copies of a specific haplotypes versus subjects with the most frequent haplotype (TTC). Analyses adjusted for age, sex, country. Lower detection threshold values indicate higher sensitivity for a specific tastant.