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ARTICLE

Taste perception and lifestyle: insights from phenotype and genome data among Africans and Asians

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Abstract

Taste is essential for the interaction of animals with their food and has co-evolved with diet. Humans have peopled a large range of environments and present a wide range of diets, but little is known about the diversity and evolution of human taste perception. We measured taste recognition thresholds across populations differing in lifestyles (hunter gatherers and farmers from Central Africa, nomad herders, and farmers from Central Asia). We also generated genome-wide genotype data and performed association studies and selection scans in order to link the phenotypic variation in taste sensitivity with genetic variation. We found that hunter gatherers have lower overall sensitivity as well as lower sensitivity to quinine and fructose than their farming neighbors. In parallel, there is strong population divergence in genes associated with tongue morphogenesis and genes involved in the transduction pathway of taste signals in the African populations. We find signals of recent selection in bitter taste-receptor genes for all four populations. Enrichment analysis on association scans for the various tastes confirmed already documented associations and revealed novel GO terms that are good candidates for being involved in taste perception. Our framework permitted us to gain insight into the genetic basis of taste sensitivity variation across populations and lifestyles.

Introduction

Taste is a sense dedicated to the interaction between animals and their food. Humans and human populations present high variability in lifestyle and diets. Taste perception is influenced by diet [1], but little is known about the genetic basis of variation in taste perception in connection with lifestyle. Humans perceive five tastes: bitter, sweet, umami, salty, and sour. Tastes are mainly perceived on the tongue and mediated by the chemosensory gustatory system [2]. Taste sensations start by chemical compounds (tastants) binding to taste-receptor-cells (TRCs) assembled in taste buds located within gustatory papillae. TRCs are innervated by nerve fibers that transfer gustatory information to the brain.

There are well documented links between the five tastes and food properties. Many studies show on one hand a link between bitter taste, generating innate reluctance in newborns [3], and toxic substances from plants such as alkaloids [4]. On the other hand, sweet taste is innately perceived as pleasant [3] and correlates with food energy levels. Umami reveals the presence of several amino acids and nucleotides signaling high energy value in for instance

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meat and cheese [5]. Salty taste is indicative of the presence of minerals, important for terrestrial animals that lose minerals through sweating and excretion and need to regulate the mineral balance of the body [6]. Strong sourness is aversive and potentially reveals either unripe fruits or spoiled food, whereas mild sourness can be perceived as pleasant [6]. Taste is therefore providing useful information in order to avoid harmful food as well as distinguishing beneficial food fulfilling the organism's needs.

Anatomically modern humans have peopled almost all terrestrial environments and adopted various lifestyles. There is a high diversity of available resources at different places across the globe and humans have adapted to a wide range of diets. Adding to this, lifestyle also shapes the diet as, for instance, farmers tend to eat cereals and selected crops while herders consume more meat and dairy products and hunter gatherers have a high intake of meat and wild plants and fruits [7–9]. With diet variations during evolution, we expect that taste varies between populations and several studies have observed differences in perception of salty, sweet, and bitter compounds between populations with different lifestyles [10–12]. For instance, Inuits, exposed to harmful quantities of salt in drinking water, are more sensitive to salt than other groups [10, 13]. It has also been shown that populations living in savanna environments taste sweet at lower concentrations than populations living in forests. This observation has been interpreted as a consequence of savanna dwelling populations having less access to food rich in energy (e.g., fruits) in their environment [10, 13]. Moreover, East-African populations appear to be more sensitive to the bitterness of salicin (an anti-inflammatory compound found in, e.g., willow bark) than Central African populations [12].

The understanding of the molecular mechanism and genetic determinism of taste perception at various levels is steadily improved. First, taste receptors bind directly to tastants, this signal is then transduced in TRCs and released to neurons (for more details, see Supplementary materials). Several studies have identified alleles in taste receptors responsible for variation in taste perception among individuals for umami [14], salt [15], quinine [16, 17], caffeine, and other bitter compounds [17, 18]. Association studies have also been conducted in populations with different lifestyles and genetic ancestry [11, 17–19].

To summarize, taste perception plays an important role for dietary choice and the ability to detect tastes has a genetic basis [20]. However the phenotypic variation in taste perception is complex and environmental factors (especially diet) can impact this [1]. Taking this into account, to what extent allelic differences can explain the phenotypic variation observed across human populations is presently poorly understood.

In this study, we investigate potential local genetic adaptation to environments, bio-diversity and diet diversity among two pairs of neighboring human groups that are, past and present, associated with differing lifestyles. We measured taste sensitivity of individuals from all four populations. In Uzbekistan, Kazak speakers have lived as nomad herders in a steppe environment while Tajik speakers have lived as farmers in mountain and valley areas. In Cameroon, Baka pygmies have lived as hunter gatherers in the rain forest while their neighbors, the Nzimes, are farmers. We estimated taste recognition thresholds for sweet, bitter, umami, sour, and salty compounds [21], as well as a paper test for 6-n-propylthiouracil (PROP) bitterness detection [22]. Additionally, we genotyped all the sampled individuals for ~4 million SNPs.

We confirm that some receptor genes are involved in the variation in taste perception. We also find evidence for that taste perception has evolved differently in the two regions: genetic adaptation in the Central African comparison appear to involve genes more basal in the signaling pathway than adaptation in the Central Asian comparison.

Materials and methods

Sample collection

Nzime participants were recruited from the villages in the Mesok area and Baka participants from the "Le Bosquet" village both in the East Region of Cameroon. Tajik-speaking participants were recruited from Bukhara while Kazak-speaking participants were recruited from within a 100 km perimeter around Bukhara. In the following, we will refer to "Kazak-speakers" and "Tajik-speakers" as "Kazak" and "Tajik," respectively, in order to make the text more concise. All participants were adults and both sexes were represented. In Cameroon, the age was unknown, but varied from 18 to 50 years old, while in Uzbekistan, the participants' ages spanned from 18 to 63 years old. In total 42 Baka individuals, 36 Nzime individuals, 51 Kazak individuals, and 53 Tajik individuals participated.

DNA extraction and genotyping

DNA was sampled from the Cameroonian participants using Oragene® Saliva caps (2 mL). The DNA was extracted using the Oragene® kit for DNA extraction according to the manufacturer's instructions. The DNA extract was diluted in water to 50 ng/μL before genotyping. In total, 4 mL blood samples were obtained from the Uzbek participants. Red cells were lysed and centrifuged, leukocytes were lysed and centrifuged afterwards. Protein compounds were digested with Proteinase K and washed out using a phenol-

chloroform solution. DNA was diluted in water to 50 ng/μL before genotyping.

In total, 71 Cameroonian individuals (39 Baka individuals and 32 Nzime individuals) were genotyped using the Illumina® (San Diego, CA) Omni5M BeadChip (4,301,332 markers). Genotypes were called with GenomeStudio v2011.1. The average call rate of the 71 individuals was 96.56%. Using PLINK (v1.07) [23] we subsequently removed (1) SNPs with more than 15% missing data, (2) individuals with more than 5% missing SNPs, and finally (3) SNPs with more than 5% missing data in this specific order. The final dataset consists of 4,186,858 SNPs and 66 individuals (39 Baka individuals and 27 Nzime individuals).

In total, 91 Uzbek individuals (45 Kazakhs, 46 Tajiks) were genotyped using the Illumina® (San Diego, CA) Omni5M Exome BeadChip (4,511,703 markers). Genotypes were called with GenomeStudio v2011.1. The average call rate of the 96 individuals was 98.61%. Using PLINK (v1.07) [22], we subsequently removed (1) SNPs with more than 15% missing data, (2) individuals with more than 5% missing SNPs, and finally (3) SNPs with more than 5% missing data. The resulting dataset consists in 4,498,056 SNPs and 82 individuals (40 Tajik individuals and 42 Kazak individuals). We used hg19 as reference genome.

Datasets from Cameroon and Uzbekistan were phased separately using fastPHASE [24] using default parameters and labeling individuals according to their ethnic group with the "-u" flag.

Phenotype measurement

Taste perception can be measured in many ways each of them reflecting partially what people feel when eating [25]. In this article, we chose to measure taste recognition threshold of participants for sucrose, fructose, quinine, NaCl, monosodium glutamate (MSG) and citric acid using a simplified protocol version of the staircase method described by Cornsweet in 1962 [21] (see Simmen et al. in Macbeth and MacClancy [26]). The pure compounds were gradually diluted in 100 mL of water, the highest concentration being divided by two each time. We used filtered spring water in Cameroon and bottled water in Uzbekistan (the same brand was used during the whole experiment). Quinine chlorhydrate was diluted from 2×10^{-7} to 4×10^{-4} M (12 dilutions), sucrose (D+) and fructose (D−) from 1×10^{-3} to 0.9 M, MSG and NaCl from 4.4×10^{-4} to 0.9 M (12 dilutions). For citric acid, we used dilutions from 2×10^{-4} to 0.025 M (8 dilutions) in Cameroon and from 2×10^{-4} to 0.1 M (10 dilutions) in Uzbekistan to better cover the panel of sensitivities.

Previous to starting the test, participants were told that they would be trying water-based solution that could taste either like pure water, sweet, sour, bitter, or umami. Umami was further explained as a savory-glutamate-meaty-bouillon-"Chinese salt" (MSG commercialized in Uzbekistan and commonly called "Chinese salt") taste. Near guesses were considered as correct answer, e.g., honey for sweet solution, "Chloroquine" (malaria treatment) for bitter taste, "lemon" for citric acid etc. Informed translators would help in explaining the described taste by participants and local words for taste and food description were learnt and studied with linguists before fieldworks (see Supplementary Tables 1 and 2 for vocabulary details).

The participants were first asked to rinse their mouth with water and were then given 2 mL of a solution to try. They were then asked which taste they could identify (sweet, bitter, sour, salty, or umami (savory-glutamate-meaty-bouillon-"Chinese salt")) and were asked to describe their sensations and whether the taste is different from pure water. Before trying another solution, participants would rinse their mouth with pure water again. Participants were given increasing concentrations until they identified the correct taste for two consecutive concentrations. The recognition threshold was set as the lowest concentration for which a participant identified the correct taste. Compounds for which a participant failed recognizing the most concentrated were considered as missing data for this participant. All the phenotypes were normalized from 0 to 1 (see Supplementary materials for more details). Similarly to Ledda et al. [17] who developed an overall-sensitivity measure using a *Z*-score, we defined "Overall Sensitivity" (OS) as the average of all the scaled phenotypes measured in each participant.

We evaluated sensitivity to 6-*n*-propylthiouracil (PROP) with a paper test [22]. Each participant was given two 4 cm^2 filter paper disks to taste (Whatman-paper, grade 1). The first paper was plain without any additives and the second paper had been previously impregnated with a solution of PROP (50 mmol/l). The first paper functioned as a negative and for the second paper participants described their taste sensations according to three grades: nothing or weak taste (1, "non tasters"), medium bitter taste (2, "tasters") and extremely strong bitter taste (3, "super tasters").

Genome-wide association and meta-analysis

We scanned the genome for associations with the eight (sucrose, fructose, quinine, NaCl, MSG, citric acid, OS, and PROP) different taste perception phenotypes. We used a Genome-Wide Association Study (GWAS) strategy for six combinations: the four single-population association (SPA) (Bakas, Nzimes, Kazkas, Tajiks) and the two regions (RA) (Uzbekistan and Cameroon). Single-population GWAS were performed using PLINK [23] with a linear model (flags: --pheno --all-pheno --linear). For the combined Tajik

and Kazak data, and the Baka and Nzime data, we used a linear mixed model performed by GEMMA [27] that can account for population structure and relatedness among individuals. For the RAs, we first generated a relatedness matrix of the individuals (-gk 1) and then performed the associations using a univariate linear mixed model (-bfile -k -lmm 4 -n -o). To have well-calibrated p values, we relied on the genomic inflation factor estimated using the "estlambda" (default settings) function from the GenABEL R-package [28]. We corrected for multiple testing using Benjamini–Hochberg correction [29].

We performed a meta-analysis using Fisher's method to combine p values ("MADAM" R-package [30]) from the different GWAS to see if any signal would increase for taste perception assuming that the determinism is the same in the populations compared. Because the meta-analysis needs to be done on independent results, we performed two meta-analyses: one on the SPA GWAS p values and one on the RA GWAS p values.

Selection scans

We relied on F_{ST}, iHS, and XP-EHH to detect selection. F_{ST} was calculated using the R-package "hierfstat" [31] with SNPs with MAF < 0.05 removed (1,797,539 SNPs retained for the Cameroon study, 1,688,879 SNPs retained for the Uzbekistan study). We computed iHS and XP-EHH using selscan [32]. Default parameters were used. In total 1,399,856 SNPs were analyzed in Kazaks, 1,525,533 in Tajiks, 1,610,903 in Bakas and 1,704,087 in Nzimes. For XP-EHH 3,892,460 SNPs were analyzed in Cameroon and 3,916,014 in Uzbekistan.

Enrichment analysis

We used Gowinda [33] to perform unbiased gene-set enrichment of Gene-Ontology terms (GO terms) among "candidate SNPs" for the various statistics. A candidate SNP was (depending on the statistic) one of the following: SNPs with $p < 0.01$ from a GWAS or meta-analysis, SNPs with F_{ST} in the top 5% tail, SNPs with an |iHS| in the top 5% tail, or SNPs with XP-EHH in the top 5% tail (note that for each population comparison, we made two separate XP-EHH analyses so that positive values always corresponded to selection in a focal population). The GO term list was downloaded from the funcAssociate database [34], and we used the Human genome annotation from ENSEMBL build 37, release 75 [35].

We also performed a candidate-gene enrichment analysis, selecting candidate genes for taste associations from the list of the GO terms from funcAssociate database [34]. We kept GO terms explicitly involved in taste traits and all genes from these GO terms were considered as candidate genes. This resulted in a list of 13 GO terms, and a total of 51 genes (see Supplementary materials). A gene was considered "enriched" if the proportion of candidate SNPs (according to F_{ST}, iHS, or XP-EHH) among all the SNPs within the gene was significantly (based on Fisher's exact test) higher than expected compared to the genome-wide distribution of the proportion of candidate SNPs in genes.

Results

We measured taste recognition threshold phenotypes in four populations differing in lifestyle and genotyped participants for around 5 million variants. Phenotypes were assessed to cover all the tastes: sweet (fructose and sucrose), bitter (quinine), umami (MSG), salt (NaCl), and sour (citric acid). Based on the results from the single-taste tests, we defined for each participant the "OS" as the mean of all the scaled phenotypes. We investigated phenotype differences among populations, conducted GWAS and selection scans for genes and regions potentially involved in taste perception.

The results for the taste acuity tests of MSG followed the modified Harris–Kalmus test described by Simmen et al. in Macbeth and MacClancy [26].

We performed Kruskal–Wallis tests (7 tests in total) to determine if taste perception phenotypes differ among populations. For Quinine ($p = 0.00422$), Fructose ($p = 0.01102$), NaCl ($p = 0.03959$), and OS ($p = 0.02616$), taste perception phenotypes differed significantly among populations before correction for multiple testing. We then performed a Mann–Whitney test for pairs of populations in order to determine what populations significantly differ from each other. Within continents, Bakas and Nzimes significantly differ (before correction for multiple testing, 7 tests for each region) for Fructose ($p = 0.01$), Quinine ($p = 0.02$), and OS ($p = 0.001$) with a tendency of Baka being on average less sensitive than Nzimes for all three while Tajiks and Kazaks differ for Fructose ($p = 0.03$) for which Tajiks are on average more sensitive than Kazaks and NaCl ($p = 0.04$) with Kazaks being on average more sensitive than Tajiks (Fig. 1, see Supplementary materials for nonsignificant results ($p > 0.05$)).

The perception test of PROP is given as counts of participants grading the perceived taste as: 1 = "nothing or weak," 2 = "bitter," or 3 = "extremely bitter." The results for the PROP tasting tests are given in Table 1 and Supplementary Table 3. When we group "2" and "3" categories as "tasters" against "1" category as "nontasters," more than 50% of the Baka sample are nontasters, whereas in the other three populations, nontasters only represent around 25% of the sample (Table 1 or Supplementary Table 5). Although noteworthy, the difference is not significant ($\chi^2 = 5.2014$, df = 3, p value = 0.1576).

Using both phenotype and genotype data we conducted several GWAS. We conducted a GWAS within each

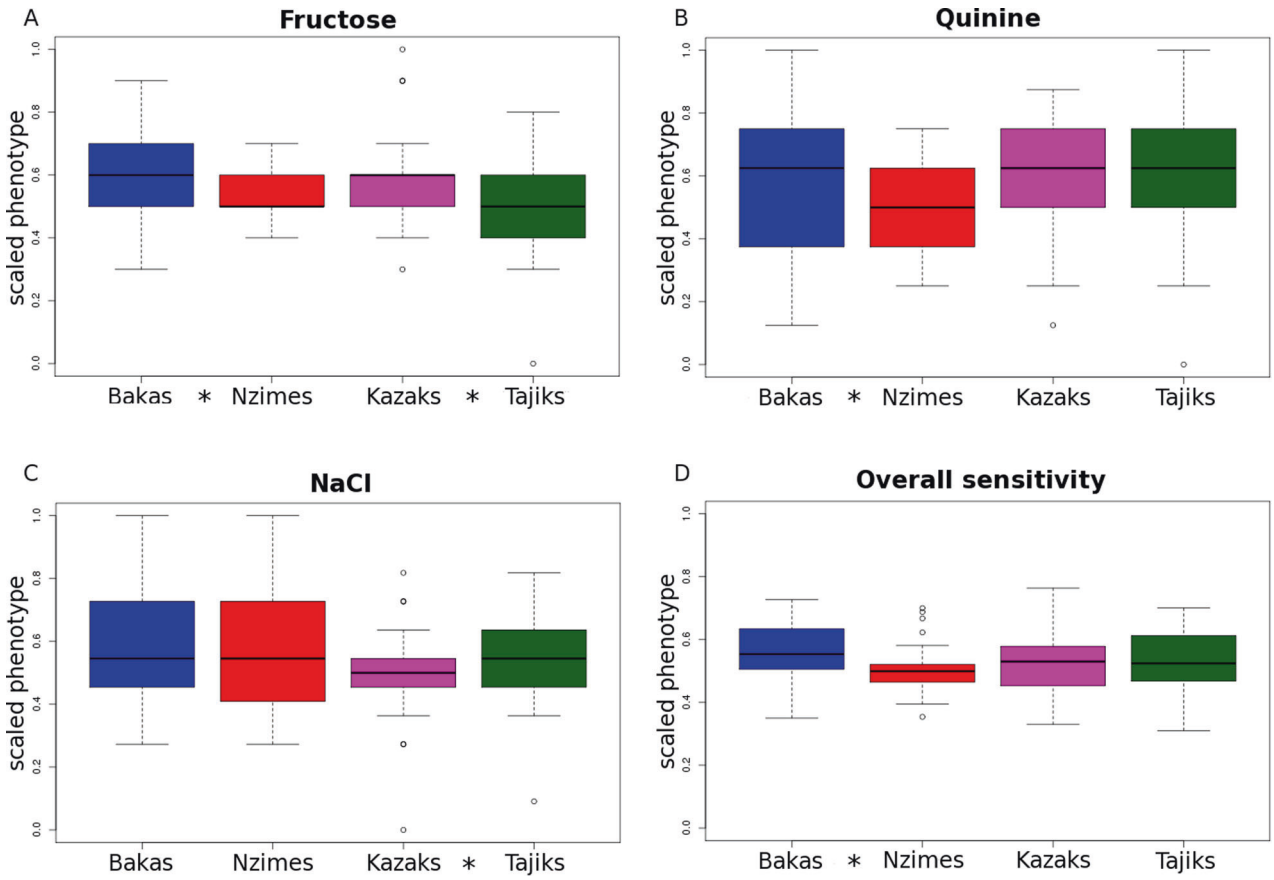

Fig. 1 Differences in taste perception among populations. Boxplot of scaled phenotypes for taste presenting difference between populations: Fructose, Quinine, NaCl and Overall sensitivity. Stars highlight significant difference at 0.05 level.

population (single-population association, SPA) (Supplementary Fig. 5), as well as a second GWAS of pairs of populations from the same region (region association (RA)) (Supplementary Fig. 6) in order to increase the sample size but avoiding false-positives due to structure (see "Material and methods"). We also performed meta-analyses to combine independent p values from each GWAS into a single p value to increase the power. This was done for both the SPAs and the RAs. We then used the results from the meta-analyses to perform enrichment analyses to identify Gene-Ontology terms (GO terms) that were enriched for variants potentially associated with the phenotypes (Supplementary Fig. 7).

Meta-analysis of associations

We ran Gowinda [33] to perform enrichment analyses of GO terms associated with "candidate variants"—SNPs with p value $< 10^{-3}$ in the GWAS meta-analyses (see "Material and methods")—for the different taste phenotype association studies. We found several GO terms enriched (FDR < 10%) for candidate variants according to the different phenotypes and these are listed in Supplementary Tables 6 and 7. For instance, the GO term "extracellular transport" is enriched among PROP tasting candidate variants (GO: 0006858, FDR = 4%). This GO term contains the following genes harboring at least one PROP tasting candidate variant: *DERL1*, *DYNLT1*, *IFIT1*, *TAP1*, and *TAP2*. Among quinine tasting candidate variants, we found two GO terms enriched: "sensory perception of taste" (GO: 0050909, FDR = 5.5%) and "olfactory receptor activity" (GO: 0004984, FDR = 5.5%). Among the 45 genes associated with the GO term "sensory perception of taste," 16 genes contain quinine tasting candidate variants of which 9 are TAS2R genes (bitter taste receptors), 5 from the chromosome 12 cluster previously shown to be associated with quinine perception [15] (see Supplementary materials). Among the 375 genes related to the "olfactory receptors activity" GO term, 35 contain quinine tasting candidate variants. Among these 35 genes, 9 are expressed in salivary and/or oral mucosa (see Supplementary Table 4). Among fructose tasting candidate variants, two developmental GO terms were enriched: "regulation of kidney development" (FDR = 8.5%, 24 genes with candidate variants, see Supplementary Table 4) and "rhombomere development" (FDR = 3%, 6 genes with candidate variants, see Supplementary materials). Three GO terms related to protein location to mitochondrion are

enriched for sucrose tasting candidate variants (GO: 0006626, GO: 0070585, and GO: 0072655, FDR of 3%, 5%, and 7%, respectively). "Norepinephrine metabolic process" (GO: 0042415, FDR = 4%) and "norepinephrine biosynthetic process" (GO: 0042421, FDR = 4%) were enriched among NaCl tasting candidate variants. No GO term was found to be enriched among sour tasting candidate variants. "Stereocilium" (GO: 0032420, FDR = 4%), a microvili-like organelle found mostly in hair cells of the ear and involved in hearing, was enriched among OS candidate variants. This GO term contains 24 genes of which 16 contain OS candidate variants (Supplementary Table 7).

PROP-bitterness perception

Gustatory PROP-detection is well described [20], and here we focus on alleles known to be responsible for variation in PROP perception among individuals (rs10246939, rs1726866, and rs713598 in *TAS2R38*). Our results reveal two things: in the meta-analysis, the SNPs rs10246939, rs1726866, and rs713598 are all significantly (p values $< 10^{-4}$) associated with PROP perception (Table 2, although these p values are not significant after adjusting for multiple testing). For the RAs, there is more evidence for an association (lower p values) with PROP tasting in Tajiks and Uzbeks from Central Asia than for Baka and Nzime from West Central Africa.

The three SNP-variants rs10246939, rs1726866, and rs713598 are all missense, we therefore give their haplotype counts (see Table 1) (using phased data, see "Material and methods") in the populations in terms of amino acids (Supplementary Table 8). The linkage disequilibrium between these three SNPs has been evaluated in each population separately. In Cameroon, the LD is 0.36 between rs172866 and the two other SNPs and 1 between rs10246939 and rs713598, in Uzbekistan, the LD is 0.88 between rs713598 and the two other SNPs and 1 between rs10246939 and rs1726866 (Supplementary Table 9). In terms of amino acids, the major haplotypes in the datasets are AVI and PAV. These haplotypes have previously been shown to explain 55–85% of the variance for PTC-perception in individuals with European ancestry [36] (PTC and PROP perception are closely related). We also find the haplotype AAI in the African populations (37% in Bakas, 18% in Nzimes) which was absent from the Uzbek populations. In addition, haplotype AAV, typically only found in African individuals [11], was not present in Kazak sample but at low frequency in the Tajik sample (4%, only heterozygous individuals).

When we compared the haplotypes of individuals and their phenotype for PROP tasting, PAV carriers were more likely to be super tasters for PROP than non-PAV carriers (χ^2 p value in Uzbekistan: 0.0006, χ^2 p value in Cameroon: 0.005). Haplotypes AAI and AAV appear to have an intermediate effect on sensitivity to PROP, although more data would be needed to test this.

Enrichment in selection signals

For each gene in our set of taste genes (identified using GO annotations, see "Material and methods" and Supplementary Table 1), we performed a Fisher's exact test to identify genes that contained significantly more SNPs in the top 5%

Table 1 Contingency table of haplotype frequencies and phenotypes.

	Uzbekistan				Cameroon			
	Haplotypes	Nontaster (NT)	Taster (T)	Super-taster (ST)	Haplotypes	Nontaster (NT)	Taster (T)	Super-taster (ST)
non-PAV carriers	AAI-AAI	–	–	–	AAI-AAI	1	0	1
	AAI-AVI	–	–	–	AAI-AVI	6	2	1
	AVI-AAV	1	1	0	AVI-AAV	–	–	–
	AVI-AVI	9	5	4	AVI-AVI	1	1	0
PAV carriers	AAI-PAV	–	–	–	AAI-PAV	5	4	15
	AAV-PAV	0	0	1	AAV-PAV	–	–	–
	AVI-PAV	3	4	25	AVI-PAV	2	5	5
	PAV-PAV	1	0	12	PAV-PAV	2	6	6

Table 2 p values for SNPs in TAS2R38 for associations with PROP tasting.

Gene	Chr	rs-ID	Position	Uzbekistan	Cameroon	Meta-analysis
TAS2R38	7	rs10246939	141672604	1.99×10^{-5}	0.023016	9.60×10^{-5}
TAS2R38	7	rs1726866	141672705	1.99×10^{-5}	0.012137	1.44×10^{-5}
TAS2R38	7	rs713598	141673345	4.96×10^{-6}	0.043146	5.23×10^{-5}

In the RA for Cameroon and Uzbekistan, the p values are corrected for genomic inflation (see "Methods"). Meta-analysis is from the SPA.

Table 3 Taste genes significantly (Fisher exact test) enriched for F_{ST} outliers.

Region	Gene	p value	Bonferroni corrected	Top F_{ST} value in gene
Uzbekistan	*GRM7*	1.61×10^{-6}	3×10^{-5}	0.19
Uzbekistan	*PKD2L1*	7.44×10^{-6}	1×10^{-4}	0.23
Uzbekistan	*TAS1R2*	7.54×10^{-5}	0.0014	0.11
Uzbekistan	*RTP4*	1.55×10^{-3}	0.0295	0.11
Uzbekistan	*SCNN1B*	5.18×10^{-3}	0.0983	0.12
Cameroon	*GNB1*	7.53×10^{-4}	0.019	0.23
Cameroon	*REEP2*	3.76×10^{-3}	0.094	0.2

The Bonferroni correction is performed over the total number of taste-involved genes containing at least one candidate variant.

tail (based on F_{ST}, |iHS| or XP-EHH) than expected based on the within genes genome average.

When testing for enrichment of candidate SNPs based F_{ST} (Table 3), two genes were identified in the comparison between Baka and Nzime. The gene *GNB1* codes for the beta subunit of a guanine nucleotide-binding proteins (G proteins), which integrates signals between receptors and effector proteins in the cell. The protein coded by this gene interacts with bitter and sweet/umami receptors and integrates taste signals in TRCs. *REEP2* encodes a member of the receptor expression enhancing protein family, its function with respect to taste is to enhance the function of sweet taste receptors by recruiting them to lipid-drafts on taste-cell membranes [37].

The genes *GRM7*, *PKD2L1*, *RTP4*, *SCNN1B*, and *TAS1R2* (Table 3) are the taste-implicated genes significantly enriched for extreme values of F_{ST} in the Tajik vs. Kazak comparison. The gene *SCNN1B* codes for the beta subunit of the receptor for salt perception, and *TAS1R2* codes for a subunit of the heterodimeric receptor for sweet taste [20]. The other genes in highly differentiated regions were linked to sour, umami, and bitter tasting. *PKD2L1* codes for a receptor for sour taste [38], *GRM7* codes for a glutamate receptor coupled with G proteins involved in conditioned taste aversion [39], and *RTP4* regulates bitter perception [40].

Testing for |iHS| outliers within the list of taste-implicated genes, several bitter taste receptors were identified in the four populations: TAS2R19 in Nzimes, TAS2R42 in Bakas, TAS2R13 in Tajiks, and TAS2R20 in Kazaks. Two candidate genes for salt perception were among the genes enriched for |iHS| outliers in Bakas (SCNN1G and SCNN1B). Apart from receptor genes and similar to F_{ST}, RTP4 is enriched for extreme values of |iHS| in Kazaks (Table 4a). Another nonreceptor but taste-implicated gene, ITPR3, is enriched for |iHS| outliers in Bakas (Table 4a). ITPR3 is the inositol triphosphate receptor 3 mediating the intracellular release of calcium ions, necessary in the depolarization of the taste-receptor cells at the synapse [41].

Finally, we find several TAS2R genes among taste-implicated genes significantly enriched for tail values of XP-EHH (TAS2R10, TAS2R13, and TAS2R14 in Kazaks; TAS2R3 and TAS2R4 in Nzimes; TAS2R7 and TAS2R39 in Bakas) (Table 4b). Other genes include GRM7 (a glutamate receptor involved in conditioned taste aversion) in Kazaks and SCNN1B (the beta subunit of the putative taste receptor for salt), FOS (a transcription factor involved in conditioned taste aversion [42]) and GNG13 (the gamma subunit of the G protein coupled with sweet [43], umami, and bitter taste receptors, integrating taste signals in the TRCs) all in Tajiks (Table 4b).

Detecting global patterns of selection events in Gene-Ontology enrichment

We performed enrichment analyses of Gene-Ontology terms among SNPs in the top 5% tail (based on F_{ST}, |iHS| or XP-EHH) using Gowinda [33]. Among SNPs in the top 5% tail of F_{ST} values, nine GO terms show an FDR lower than 10% in the Baka vs. Nzime comparison. Among these GO terms, there is "tongue morphogenesis" and "adrenergic receptor signaling pathway" (GO: 0043587 and GO: 0071875, respectively, both FDR of 8%) (Supplementary Tables 10 and 11). See also Fig. 2 for a comparison of the distribution of F_{ST} values at SNPs in genes associated to "tongue morphogenesis" and the genome-wide distribution of F_{ST} values at SNPs in genes for both Baka vs. Nzime and Tajik vs. Kazak comparisons, illustrating an excess of SNPs with high F_{ST} for this GO term in the comparison Baka vs. Nzime.

Among SNPs in the top 5% tail of |iHS| values, we identified 49 enriched GO terms in Bakas, 282 in Nzimes, 89 in Kazaks, and 108 in Tajiks (all with FDR < 10%, see also Supplementary Figs. 8–11). Although not directly linked with taste, we mention some GO terms of potential interest. In Tajiks, "olfactory receptor activity" (GO: 0004984, FDR = 0.1%) was significant, in Nzimes response to vitamin (GO: 0033273, FDR = 4%, GO: 0033280, FDR = 5%, GO: 0071305, FDR = 8%) and immune response to virus (GO: 0016032, FDR = 0.1%) were significant.

Finally, enrichment analyses among XP-EHH outliers were performed. For the comparison of African populations, these analyses revealed 88 enriched GO terms in the Bakas vs. Nzimes comparison, 25 in the Nzimes vs. Baka comparison. In both the Kazaks vs. Tajiks comparison and the Tajiks vs. Kazaks comparison there were 59 GO terms with FDR < 10%. Several of these GO terms were of interest. The GO term "detection of chemical stimulus involved in sensory perception of taste" (GO: 0050912, FDR = 4%) was enriched in the Kazaks vs. Tajiks comparison. The GO

Table 4 (a) Taste genes significantly (Fisher exact test) enriched for |iHS| outliers. (b) Taste genes significantly (Fisher exact test) enriched for XP-EHH outliers.

(a)

Population	Gene	*p* value	Bonferroni corrected	Top |iHS|
Tajik	*TAS2R13*	1.25×10^{-4}	1.15×10^{-3}	2.74
Kazak	*RTP4*	5.62×10^{-9}	5.06×10^{-8}	2.43
Kazak	*TAS2R20*	6.15×10^{-4}	5.53×10^{-3}	3.18
Nzime	*TAS2R19*	2.5×10^{-3}	0.032	3.55
Baka	*SCNN1G*	2.24×10^{-10}	3.14×10^{-9}	2.93
Baka	*ITPR3*	2.30×10^{-9}	3.22×10^{-8}	4.05
Baka	*SCNN1B*	5.00×10^{-4}	7.00×10^{-3}	2.7
Baka	*TAS2R42*	1.16×10^{-3}	0.016	2.21

(b)

Population	Gene	*p* value	Bonferroni corrected	Top XP-EHH
Tajik vs. Kazak	*FOS*	2.44×10^{-17}	1.95×10^{-16}	1.14
Tajik vs. Kazak	*GNG13*	4.88×10^{-15}	3.90×10^{-14}	2.40
Tajik vs. Kazak	*SCNN1B*	1.55×10^{-3}	0.012	2.24
Kazak vs. Tajik	*GRM7*	8.40×10^{-22}	1.01×10^{-20}	9.63
Kazak vs. Tajik	*TAS2R10*	1.53×10^{-21}	1.83×10^{-20}	2.90
Kazak vs. Tajik	*TAS2R13*	2.02×10^{-14}	2.42×10^{-13}	2.70
Kazak vs. Tajik	*TAS2R14*	2.01×10^{-3}	0.024	2.13
Nzime vs. Baka	*TAS2R3*	2.00×10^{-4}	1.93×10^{-3}	1.36
Nzime vs. Baka	*TAS2R4*	1.16×10^{-3}	0.012	1.98
Baka vs. Nzime	*TAS2R7*	1.60×10^{-9}	2.09×10^{-8}	1.65
Baka vs. Nzime	*TAS2R39*	3.12×10^{-7}	4.06×10^{-6}	4.37

The Bonferroni correction is performed over the total number of taste-involved genes containing at least one candidate variant.

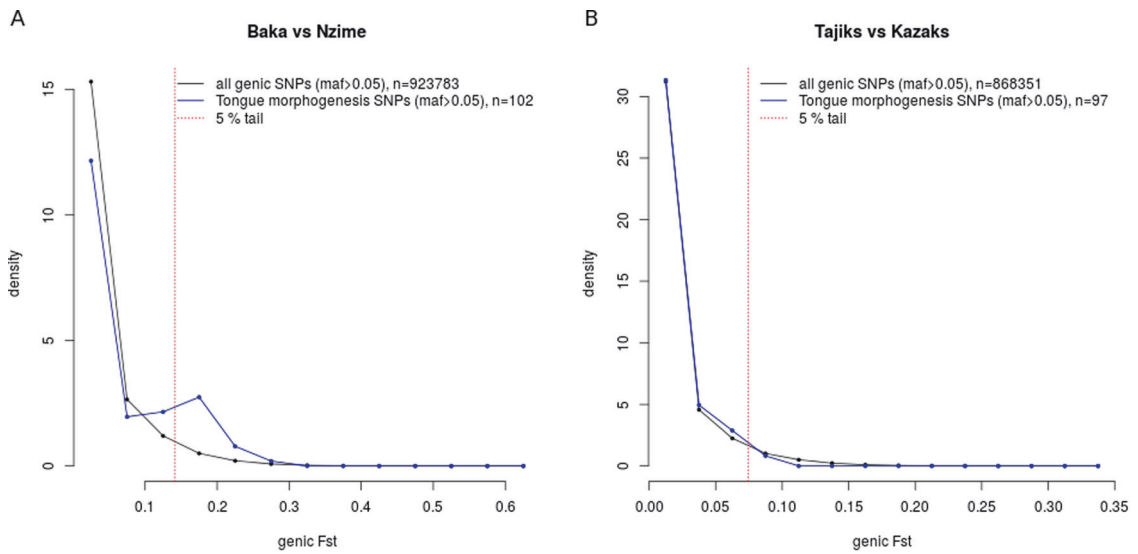

Fig. 2 F_{ST} values between populations. F_{ST} values at SNPs in genes associated to "tongue morphogenesis" (GO: 0043587) and the genome-wide distribution of F_{ST} values at SNPs in genes. **a** Bakas vs. Nzimes comparison, **b** Tajiks vs. Kazaks comparison.

terms "response to immobilization stress" (GO: 0035902, FDR = 6.6%), "interspecies interaction between organism" (GO: 0044419, FDR = 4%), and "viral process" (GO: 0016032, FDR = 7%) were also enriched in this comparison. In the Nzimes vs. Bakas comparison, two GO terms involved in response to fungus (GO: 0009620, FDR = 4% and GO: 0050832, FDR = 6%) were enriched. The GO term "interspecies interaction between organism" (GO: 0044419, FDR = 1%) was also enriched in this comparison. The GO term "olfactory receptor activity" was enriched in all four comparison (GO: 0004984) (see Supplementary Figs. 12–15).

Discussion

We have sampled taste phenotypes, using taste recognition thresholds, covering all major tastes in four populations differing in lifestyle. Combining this data with genotype data allowed us to conduct association and selection analyses. We used F_{ST}, iHS, and XP-EHH to conduct selection scans of which iHS and XP-EHH are more sensitive to recent adaptation [44]. Our study setup allowed us to investigate the genetic basis of taste perception variation. In light of our results, we discuss the evolution of taste perceptions in humans.

Two African groups

We found that, for OS, Bakas were less sensitive than Nzimes and that Nzimes were better (on average) at detecting fructose and quinine than Bakas. Being less sensitive overall could be related to previous suggestions that a hunter-gatherer lifestyle in a forest environment relies on a diet of a wide range of different plants in order to subsist without agriculture. One explanation is related to the idea that, in a population, PROP nontasters like most foods regardless of their adventurousness while PROP tasters have to be adventurous in order to like some foods [45]. In this study, we consider two different populations that supposedly evolved with different diets for which culture must have played a major role on food choice and therefore this hypothesis might apply to a smaller extent. Nevertheless, according to this idea, it could be that being less "picky" with food would have been advantageous in order to explore a large variety of foods. Forest environments have been suggested to be poor environments (in terms of food energy levels) to survive in without agriculture and people living there are constrained to use a large variety of different resources [46]. On the contrary, farmer groups like Nzimes, have been more specialized in their food consumption, and in this case, being sensitive to taste might help them to identify spoiled food. Since this difference affects all tastes, we suggest that it is related to genes at the basis of the taste perception pathway. Indeed, the F_{ST} enrichment analysis highlight genes that are located more at the base of the taste perception pathways like binding receptors (e.g., *REEP2*) or genes in the signal transduction pathway (e.g., *GNB1*). Furthermore, the GO term for tongue morphogenesis is enriched among F_{ST} outliers (Fig. 2). Tongue morphogenesis may be important for the ability to perceive tastes since it can impact the morphogenesis of taste buds themselves. It would therefore be interesting to measure taste bud density and other related morphological traits to better understand what is driving the difference in OS between Bakas and Nzimes.

An alternative explanation is related to the fact that farming communities are hosts for a multitude of infectious diseases that hunter-gathering communities typically are not immune to. The Bakas and Nzimes have been in close association probably for not more than a 1000 years [47] making it likely that the Bakas have recently (less than 50 generations at any rate) suffered from an increased infectious disease load. This is potentially relevant for this study because a gene close to the MHC region (chromosome 6: 29–33 Mb) is found to be enriched for extreme |iHS| values in Bakas. This gene –*ITPR3*– is located on chromosome 6 (33.5–33.6 Mb) and is responsible for the release of Calcium in taste cells and therefore involved in several tastes. Mouse lacking *ITPR3* have poor sensitivity to taste [41]. Thus that Bakas have a lower OS than Nzimes could be a side effect of selection on the MHC complex in the Bakas leading to an increased frequency of a less functional variant of *ITPR3*. *ITPR3* may also play a key role in exocrine secretion underlying energy metabolism and growth [48].

In Bakas, *TAS2R42* is enriched for |iHS| values in the 5% tail. This gene has been shown to be overexpressed in patients with phantogeusia (a spontaneous metallic, bitter, and salty taste in the mouth [49]). *TAS2R42* is considered as an orphan receptor since there is so far no known agonist for this receptor [17]. Bakas being less sensitive than Nzimes to quinine might be linked to selection on this orphan bitter taste receptor. It would be interesting to test more natural bitter compounds found in plants in the African rain forest to check whether *TAS2R42* is responsive to them. *TAS2R19*—previously shown as the bitter taste receptor most associated with quinine perception [16]—is enriched for |iHS| tail values in Nzime. This is consistent with the higher sensitivity to quinine in Nzimes than in Bakas. Importantly, quinine is a natural compound used to cure Malaria. Malaria is present in Central Africa and the ability to identify curing plants by being sensitive to quinine can be advantageous in populations living in this region. Moreover, genes enriched for 5% tail values of XP-EHH in both Bakas and Nzimes are all responsive to either Quinine, Chloroquine or both [17]. This suggest that although the Nzimes are better at detecting quinine, there has been convergent selection in Bakas and Nzimes on receptors sensitive to quinine—most likely for medical reasons related to Malaria.

The salt receptor subunits *SCNN1B* and *SCNN1G* are enriched for extreme values of |iHS| in Bakas although we did not detect any phenotypic difference with respect to salt. Likewise, we were not able to relate any genetic signal to the difference between Bakas and Nzimes in fructose sensitivity.

Our search for GO terms enriched among 5% tail values revealed that GO terms involved in immune response to virus (GO: 0016032, FDR = 0.1%) and fungi (GO:

0009620, FDR = 4% and GO: 0050832, FDR = 6%) are enriched in Nzimes among iHS outliers and XP-EHH outliers, respectively. This is interesting in light of the different lifestyles of Nzimes and Bakas as fungi rapidly develop on harvested plants when not properly stored. The GO term "interspecies interaction between organism" (GO: 0044419, FDR = 1%) is also enriched among XP-EHH outliers in Nzimes, suggesting that Nzimes also adapted to disease risks linked to animal husbandry (goats, chicken).

Two Central Asian groups

We did not detect any difference in OS in Central Asia but Kazaks were significantly better at detecting salt while Taijks were significantly better at detecting fructose. The difference in salt sensitivity is possibly related to the Kazaks having a diet with a higher concentration of salt as salt is often used as a conservative for meat and dairy products. However, we find that *SCNN1B* is enriched for XP-EHH tail values in the Tajiks vs. Kazaks comparison (as well as for F_{ST} tail values), and since *SCNN1B* codes for the beta subunit of the receptor for salt perception [15], this suggests that the change in ability to perceive salt is in fact selection for lower sensitivity in the agricultural based Tajiks.

The difference in fructose perception is genetically reflected in the gene *TAS1R2* (a gene that codes for a subunit of the heterodimeric receptor for sweet taste [15]) being enriched for F_{ST} tail values. Interestingly, Central Asia is the cradle of several fruit tree domestication events [7] which is likely to have changed the agriculturally based diet of the Tajiks more than the herder diet of the Kazaks.

In addition to *SCNN1B*, there were two genes with a significant enrichment for tail values of more than one statistic: *GRM7* and *RTP4*. *GRM7* codes for a glutamate receptor coupled with G proteins involved in conditioned taste aversions [39] and are enriched for XP-EHH and F_{ST} outliers in the Kazaks vs. Tajiks comparison. This suggests a recent selective sweep for a novel variant of *GRM7* in Kazaks. *RTP4* regulates bitter perception [40] and is enriched for tail values of |iHS| and F_{ST} which again suggest that the Kazaks and not the Tajiks have changed relative to the ancestral state with respect to bitter perception.

We also performed enrichment analyses of GO terms among SNPs that show evidence of recent, population specific, selection. Interestingly, Kazaks show an enrichment for the GO term "detection of chemical stimulus involved in sensory perception of taste" (GO: 0050912, FDR = 4%) among XP-EHH tail values. In light of their nomadic lifestyle, another interesting GO term enriched among XP-EHH tail values in Kazaks is "response to immobilization stress" (GO: 0035902, FDR = 6.6%) containing corticotropin and urotropin hormones and signalization genes involved (among others) in response to stress and effect of stress on appetite. Regarding the immune system, Kazaks also present enrichment for the GO terms "interspecies interaction between organism" (GO: 0044419, FDR = 4%) and "viral process" (GO: 0016032, FDR = 7%) among XP-EHH outliers (see Supplementary materials), suggesting that being nomad herders, Kazaks had to adapt to disease risks implied by living in close relationship to animals (horses, cattle, camel, etc.).

Notably, except for SCNN1B, it seems like more selective events with respect to taste have occurred on the Kazak branch than on the Tajik branch. This suggests that the Kazaks have changed their lifestyle more than the Tajiks—at least recently. Whether the Kazaks changed from a hunter-gatherer lifestyle or an agricultural lifestyle are however debated [9]. An alternative explanation is that it is easier to detect selective events on the Kazak branch than the Tajik branch due their different demographic histories.

Common to both regions

In both the Central Asian and the African population comparisons, we find that TAS2R genes are enriched for |iHS| and XP-EHH tail values but not for F_{ST} tail values, suggesting that bitter taste receptors have been affected by relatively recent selection events. Finally, observed as a target of selection in previous studies [50], we find that in all populations, olfactory receptors or detection of smell are enriched for either iHS or XP-EHH outliers (see Supplementary materials).

Bitter taste associations

Associations between variation at the SNPs rs10246939, rs1726866, and rs713598 in the *TAS2R38* gene and sensitivity to PROP have already been reported by Robino et al. [19]. We confirm these results as well as (at least in the Central Asian populations) the documented dominant effect of PAV haplotype on PROP sensitivity. The AAI haplotype has previously been reported by [12, 36] in African populations as giving intermediate sensitivity to PTC. Moreover, Campbell et al. [11, 12] showed that—on an AAI-haplotype background—additional SNPs in *TAS2R38* are linked with intermediate sensitivities to PTC in Bakas and Nzimes as well as in several other Cameroonese and East-African populations, suggesting a complex determinism for PTC/PROP perception in Africa.

Meyerhof et al. [51] performed an in vitro experiment testing the response of 25 TAS2R genes to 104 bitter compounds, including quinine. That study found nine genes that were responsive to quinine stimuli and among these genes, six are located in a cluster of taste receptors on chromosome 12 (12p13.2); a region shown to be associated with the ability to perceive quinine [16]. The candidate

SNPs in our quinine association study implicated nine TAS2R genes related to the GO term "sensory perception of taste" (GO: 0050909). Four of these (*TAS2R14*, *TAS2R43, TAS2R46* on chromosome 12 and *TAS2R4* on chromosome 7) were shown to be quinine receptors in the Meyerhof et al. [51] study. We also found that *TAS2R19* contained quinine tasting candidate variants. This gene was not included in the Meyerhof et al. [51] study but is part of the cluster on chromosome 12 and was indicated as a strong candidate for quinine perception in Reed et al. [16].

We also find quinine tasting candidate variants in *TAS2R1* on chromosome 5. *TAS2R1* (the only *TAS2R* gene on chromosome 5) did not respond to quinine in the Meyerhof study and it is not located inside any of the regions identified to be associated to quinine perception in the Reed et al. [16] study. Instead, *TAS2R1* responds to Yohimbine [51] which is a natural alkaloid found in the bark of an African tree (*Pausinystalia johimbe*) that is commonly used for medical purposes. Possibly, our dataset includes allelic variation at *TAS2R1* not present in the Meyerhof et al. [51] study that enables the ability to discern quinine.

There are also non-TAS2R genes within the GO term "sensory perception of taste" (GO: 0050909) that contain candidate SNPs from our quinine association study. Some of these have been shown to be associated with bitter taste perception in a more general sense. For instance, *GNAT3* (signal transduction coupled to TAS2Rs), *RTP4* (influence bitter receptor expression), *WNT10B* (development of taste papillae [52]), and *PLCB2* (active in taste-receptor cells signaling for bitter, umami and sweet taste [53]). *PKD2L1*, *SCNN1B*, and *SCNN1G* are also enriched in our analysis although these genes are not known to have a function for bitter tasting. Instead, these genes code for sour and salt receptors [20].

Conclusion

Lifestyles have shaped the genetic basis of taste perception. The rise of agriculture and other lifestyles have enforced adaptation to new environments and genetic changes in the signaling of taste perception. This study is the first to attempt to quantify differences in taste sensitivity associated with different lifestyles and map these phenotypic differences to genetic changes and variation. We find a generally good correspondence between selected genes and phenotypic differences. Our results also suggest that, perhaps not surprisingly, to fully understand the evolution of taste, it may be necessary to look beyond the category of genes directly associated with taste receptor and also consider traits such as nerve development and tongue structures. Measures of other phenotypes, such as the variation of papillae density on the tongue, would be valuable to better understand variation in taste perception among individuals and populations.

Data availability

Data are freely available for download after request at http://jakobssonlab.iob.uu.se/data/ and at EMBL-EBI web site: http://www.ebi.ac.uk/arrayexpress/arrays/A-MTAB-679 and http://www.ebi.ac.uk/arrayexpress/arrays/A-MTAB-678.

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Author contributions AES, MJ, EH, and MGB conceived and designed the study. AES, EH, TH, AN, and FS performed data sampling. AES and PS performed the analysis. AES, EH, MJ, MGB, and PS wrote the paper. All authors read and approved the final paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The research has been performed following authorization obtained from an agreement between the Immunogen Lab, the Academy of Sciences of Uzbekistan, and the Centre National de la Recherche Scientifique (CNRS) and Muséum National d'Histoire Naturelle (MNHN) in France. The research was approved by the Comite de protection des personnes—Ill de France 1, Paris, France, under the dossier numbers: DC-2009-1068 and 2010-avril-12276.

Informed consent For Cameroon, written and audio-recorded informed consent was obtained from all participants for the collected phenotypic and genetic data. The research has been performed according to an agreement between the IRD, the Cameroonese Ministry of Research, the Université Yaoundé 1, the Catholic university and the Douala University according to the French Cameroonese scientific collaboration agreement of 1984 ORSTOM. For Uzbekistan, participants gave written informed consent for the collected phenotypic and genetic data.

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