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RESEARCH ARTICLE

TAS2R38 bitter taste perception in the Koṅkaṇī Sārasvata Brahmin population

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Abstract

Background The *TAS2R38* gene carries markers for phenylthiocarbamide (PTC) sensitivity. Various studies have investigated the genotype–phenotype association pattern for bitter tasting ability and other factors in different populations. However, a paucity of such information for endogamous Indian populations is the reason behind this study.

Objective To study the association of phenylthiocarbamide (PTC) sensitivity with *TAS2R38* gene variations in Koṅkaṇī Sārasvata Brahmin population.

Methods We studied the association of the alleles rs714598, rs1726866, rs10246939 with PTC sensitivity and other factors in the Koṅkaṇī Sārasvata Brahmin population. DNA was extracted from 114 individuals belonging to the Koṅkaṇī Sārasvata Brahmin community. The *TAS2R38* gene was sequenced to find the genotype distribution pattern. The association between genotype and phenotype was checked using the Chi-Square test and multifactorial logistical regression.

Results We observed a 58.8% frequency of the AVI haplotype, which is the most prevalent in European populations. A higher number of non-taster haplotypes and diplotypes were observed in Koṅkaṇī Sārasvata Brahmins, with the allele rs10246939 showing a significant association with PTC bitter taste sensitivity in both allelic ($p = 8.6 \times 10^{-4}$; Allele-*G*, OR = 3.57 [95% CI = 1.66–7.69]) and genotype-based ($p = 6.9 \times 10^{-4}$; genotype-*AG*, OR = 3.11 [95% CI = 0.73–13.20]; genotype-*GG*, OR = 40 [95% CI = 3.58–447.03]) tests.

Conclusion Our results are in line with earlier studies, which report an association between PTC sensitivity and the *TAS2R38* gene in different populations. In the global context, Koṅkaṇī Sārasvata Brahmins, who are mostly distributed along the southwestern coast of India, show a PTC sensitivity pattern slightly similar to that of West Eurasian populations. Our findings suggest ancestry specific selection in *TAS2R38* gene variations for taste sensitivity at global level.

Keywords *TAS2R38* gene · Bitter tasters · PTC · Genotype phenotype association · Koṅkaṇī Sārasvata Brahmin

Abbreviations

PTC	Phenylthiocarbamide
PROP	6-N-propylthiouracil
SNP	Single nucleotide polymorphism
P	Proline
A	Alanine
V	Valine
I	Isoleucine
BMI	Body mass index
GSB	Gauḍa Sārasvata Brahmins
CSB	Citrapur Sārasvata Brahmins
RSB	Rājāpur Sārasvata Brahmins
NKS	Non Koṅkaṇī Sārasvata

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Introduction

Variation in the *TAS2R38* gene associated with the sensitivity towards phenylthiocarbamide (PTC) was first reported in 2003 (Kim et al. 2003). Thereafter, single nucleotide polymorphisms (rs714598, rs1726866, rs10246939) in three amino acid positions at 49, 262 and 296, coding for

Proline or Alanine, Alanine or Valine, and Valine or Isoleucine respectively, were discovered. The resulting haplotypes classified individuals into 'tasters' and 'non-tasters' based on their ability to sense the bitter tasting PTC compound (Kim and Drayna 2005; Risso et al. 2016b). The most common taster haplotype is PAV, whilst the most common non-taster haplotype is AVI. In addition, many rare haplotypes are found in various populations around the globe. Since the discovery of this genotype–phenotype association, numerous studies have been conducted to understand the physiological, dietary and disease-specific associations of the *TAS2R38* gene. Bitter taste perception is known to play a protective role against the ingestion of plant based toxic substances (Diószegi et al. 2019). Along with haplotypes, diplotype combinations are also found to be associated with PTC sensitivity (Kim et al. 2003).

In the global perspective, PAV tasters amongst Asians and Americans range in frequency between from ~ 64% to 68%, whereas amongst Europeans and Africans the frequency ranges between from ~ 45% to 50%. Non-taster AVI frequency peaks in Europeans (viz. ~ 49%), whilst in other populations the frequency varies between ~ 26% and 35% (Risso et al. 2016b). Other haplotypes are found in compartively low frequencies, with AAI peaking in Africans (viz. ~ 13%). Earlier studies have suggested two hypotheses for the predominance of both the PAV and AVI haplotypes, i.e. balancing natural selection (Fisher et al. 1939; Wooding et al. 2004; Campbell et al. 2012) and ancient balancing selection followed by recent demographic bottleneck events (Risso et al. 2016b). Such a bimodal distribution is observed in PTC diplotypes as well. The AVI/AVI (non-taster), PAV/PAV (taster) and PAV/AVI or PAV/* heterozygote (taster) are the common compositions. Wooding et al. (2004) have proposed a fitness advantage of heterozygotes over homozygotes, linking this enhanced selective fitness with their higher global frequency (Wooding et al. 2004).

In the last two decades, since the discovery of *TAS2R38* variation being associated with PTC sensitivity, very few studies have been conducted to explore the footprints of this gene in Indian populations. In an Asian Indian cohort (Pemberton et al. 2008), the frequency of AVI was found to be double the frequency of PAV. In the same study, more than half of the individuals were heterozygote tasters (AVI/PAV). Homozygote non-tasters (AVI/AVI) were almost four times more frequent than the homozygote tasters (PAV/PAV). Similar findings were reported in an Indian cohort (Deshaware and Singhal 2017; Gupta et al. 2018) as well as a tribal population on the west coast of India (Vinuthalakshmi et al. 2019). Overall, tasters are relatively less frequent in Indians (Pemberton et al. 2008) compared to the global populations (Wooding et al. 2004; Kim and Drayna 2005).

In the Indian context, PTC sensitivity is found to be associated with alcohol dependence and tobacco chewing (Vinuthalakshmi et al. 2019). Its association with body mass index (BMI) is disputed, as we find both significant (Gupta et al. 2018) and insignificant (Deshaware and Singhal 2017) results. Globally, association studies have turned up similar contradictions for alcohol dependency (Duffy et al. 2004; Wang et al. 2007). Smoking status is reported to be associated with *TAS2R38* in Hàn Chinese (Qi et al. 2022) and North Americans of European ancestry, but not in North Americans of African ancestry (Risso et al. 2016a). Body mass index is associated with non-tasters in Italian females (Tepper et al. 2008) and inversely associated in a Spanish cohort (Coltell et al. 2019). Disease-specific association has also been reported for *TAS2R38*, including cancer (Sacerdote et al. 2007; Carrai et al. 2011; Choi et al. 2016) and nonpolypoid chronic rhinosinusitis (Adappa et al. 2016). Contradictions have also been reported (Timpson et al. 2005; Gallo et al. 2016; Lambert et al. 2019). An association has also been observed with longevity (Melis et al. 2019) and food preferences.

In this study, we try to understand the status of PTC sensitivity in Koṅkaṇī Sārasvata Brahmins and their subgroups. We also explore the association of PTC sensitivity with factors such as sex, blood group, alcohol consumption, diabetes, lactase persistence, BMI, Rh factor, etc. The Koṅkaṇī Sārasvata Brahmins constitute a group of Sārasvata Brahmins settled along the Koṅkaṇ Malabar coast of India. Koṅkaṇī Sārasvata Brahmins are a migrant population, who trace their origin to the archaeologically attested Sarasvatī river in the northwest of the subcontinent. Koṅkaṇī Sārasvata Brahmins mainly include the following genealogically based self-identifying subgroups or moeities: Gauḍa Sārasvata Brahmins (GSB), Citrapur Sārasvata Brahmins (CSB) and Rājāpur Sārasvata Brahmins (RSB). Koṅkaṇī Sārasvata Brahmins are an endogamous caste population, who speak the Koṅkaṇī language and represent a major section of the Indian Brahmin community.

Materials and methods

Sample details

We collected blood samples and phenotype data (PTC tasting ability) from 114 Sārasvata Brahmin subjects, including 15 non-Koṅkaṇī Sārasvata Brahmins (NKS) for this analysis. During sample collection, details about sex, blood group, alcohol consumption, diabetes, lactase persistence, BMI, Rh factor etc. were documented. PTC tasting ability was checked by placing a drop of PTC solution on the tip of the tongue of the participants. Bitter tasters and non-tasters were determined. Participants were asked to spit out the saliva soon after the test. Samples of 5–10 ml of blood samples were collected in EDTA vacutainers. Samples were collected

only after approval had been received from the Institutional Human Ethics Committee of Mangalore University (MU-IHEC-2020–3). Participants were informed about the study, and data were collected from individuals after obtaining their written consent. The present study is conducted in accordance with the Declaration of Helsinki.

DNA extraction and genotyping

DNA was extracted using the Phenol–Chloroform method. The *TAS2R38* gene was amplified (Forward primer 5′-TAG GCAAAGAGCTGGATGCT-3′ and Reverse primer 5-ATT GGAAGGCTTTGTGAGGA-3) using Applied Biosystems™ Veriti™ 96-Well Thermal Cycler with the following PCR conditions: 95 ℃ for 5 min followed by 40 cycles of 95 ℃ for 30 s, 57 ℃ for 30 s and 72 ℃ for 60 s, and 72 ℃ for 7 min. PCR products were sequenced using Sanger sequencing method. The variants that determine the PTC phenotypes (rs713598, rs1726866 and rs10246939) were scored, and the corresponding genotypes were tabulated.

Statistical analysis

The Chi-Square test, Fisher's Exact test and Odd Ratio test were performed to assess the relationship between the variables. Phenotype data were converted to frequency distribution. Odd Ratio analysis was conducted in order to check for the likelihood of finding PTC sensitivity in individuals based on factors such as sex, blood group, alcohol consumption, diabetes, lactase persistence, BMI, Rh factor, etc. The allele frequencies for rs713598, rs1726866 and rs10246939 were derived from the genotype for the population as a whole and the constituent subgroups. The SNP allele frequency was calculated by counting the alleles manually. The haplotype and diplotype frequency distribution was tabulated. The association between PTC sensitive genotypes and the various factors was measured using Chi-Square test and Fisher's Exact test. The p value was used for interpretation. Any p value < 0.05 was considered significant. Only the two alleles coding for Proline, Alanine, Valine and Isoleucine were considered for analysis. Since other environmental factors such as age can exert an effect on the sensitivity of tasting ability, a correction was performed using multifactorial logistical regression (MLR). The mathematical formula of the MLR is as follows:

$$y = \frac{e^{m1x1+m2x2+..+c}}{1 + e^{m1x1+m2x2+..+c}}$$

Here, y is taste, c is the error, x_i represents the different co-factors (allele or genotype of rs10246939, sex, age, diet, body mass index of the individual, lactase persistence, blood group, diabetic, alcoholism, smoking habit and tobacco use) and m_i represents the co-factors-associated regression coefficient. To perform this analysis, we used the function lm() in R (version 4.2.0) in order to fit the data into a linear model. All the genetic association analysis was performed using basic package of R (version 4.2.0).

Results

PTC sensitivity phenotype distribution in Koṅkaṇī Sārasvata Brahmins

In Koṅkaṇī Sārasvata Brahmins, the frequency of tasters was found to be 57%, and of non-tasters to be 43% (Table 1). The likelihood of finding tasters is higher in females (0.655; OR=1.61) as compared to males (0.541; OR=0.062). The Odds Ratio test showed a higher probability of tasters amongst non-drinkers (0.578; OR=0.16). Interestingly, the incidence of diabetes was found to be higher amongst tasters (0.625; OR=1.38). A frequency of 60% of lactose-tolerant individuals were found to be tasters (OR=1.33). We also found a higher number of tasters amongst individuals who follow a non-vegetarian diet (0.650; OR=2.19). Individuals with A and AB blood groups, and Rh+ showed a higher frequency of the taster phenotype. Interestingly, obese individuals did not show any significant correlation with taste sensitivity when compared with healthy and overweight individuals.
In the context of subgroups, non-taster frequency was lower in the Citrapur moiety (0.433) and the non-Koṅkaṇī Sārasvata Brahmins (0.400), whilst the Gauḍa (0.672) and the Rājāpur moeities (0.636) had a higher number of tasters. The Odds Ratio test showed that the likelihood of finding tasters amongst the Gauḍa Sārasvata Brahmins and Rājāpur Sārasvata Brahmins was higher when compared with the Citrapur Sārasvata Brahmins and the non-Koṅkaṇī Sārasvata Brahmins.

PTC sensitivity genotypical distribution in Koṅkaṇī Sārasvata Brahmins

The *TAS2R38* taste receptor gene has a single exon comprising 1143 base pairs which encode seven transmembrane G protein-coupled receptor that binds to thiourea group present in synthetic compounds such as PTC and PROP (Fig. 1). We assessed the genotype profile for three major SNPs this gene in Koṅkaṇī Sārasvata Brahmins and their subgroups.

Table 1 The PTC phenotype distribution in Koṅkaṇī Sārasvata Brahmins based on factors such as sex, blood group, alcohol consumption, diabetes, lactase persistence, BMI and Rh factor

Category	Total (n)	Taster	Frequency	Non Taster	Frequency	Odds Ratio with 95% C.I.		
Overall	114	65	0.570	49	0.430			
CSB	30	13	0.433	17	0.567	vs. GSB 0.37 [0.14, 0.93]	vs. RSB 0.44 [0.09, 1.87]	**vs. NKS 1.15 [0.31, 4.27]**
GSB	58	39	0.672	19	0.328	**vs. CSB 2.68 [1.06, 6.72]**	**vs. RSB 1.17 [0.27, 4.55]**	**vs. NKS 3.08 [0.93, 10.40]**
RSB	11	7	0.636	4	0.364	**vs. CSB 2.29 [0.53, 10.46]**	vs. GSB 0.85 [0.21, 3.69]	**vs. NKS 2.63 [0.49, 14.11]**
NKS	15	6	0.400	9	0.600	vs. CSB 0.87 [0.23, 3.14]	vs. GSB 0.32 [0.09, 1.07]	vs. RSB 0.38 [0.07, 2.00]
Sex								
Males (M)	85	46	0.541	39	0.459	vs. F 0.62 [0.25, 1.49]		
Females (F)	29	19	0.655	10	0.345	**vs. M 1.61 [0.66, 3.99]**		
Alcohol consumption								
Drinker (Dr)	24	13	0.542	11	0.458	vs. NDr 0.86 [0.34, 2.18]		
Non-drinker (NDr)	90	52	0.578	38	0.422	**vs. Dr 1.16 [0.45, 2.89]**		
Diabetes								
Diabetic (Dia)	40	25	0.625	15	0.375	**vs. NDia 1.38 [0.62, 3.07]**		
Non-diabetic (NDia)	73	40	0.548	33	0.452	vs. Dia 0.73 [0.32, 1.60]		
Lactase persistence								
Lactose-intolerant (LI)	17	9	0.529	8	0.471	vs. LT 0.75 [0.25, 2.21]		
Lactose-tolerant (LT)	85	51	0.600	34	0.400	**vs. LI 1.33 [0.45, 3.88]**		
Diet								
Non-Vegetarian (NV)	60	39	0.650	21	0.350	**vs. V 2.19 [1.00, 4.80]**		
Vegetarian (V)	48	22	0.458	26	0.542	vs. NV 0.46 [0.20, 0.99]		
Blood group								
A	22	15	0.682	7	0.318	**vs. B 2.86 [0.79, 10.27]**	vs. AB 0.61 [0.07, 3.72]	**vs. O 1.75 [0.60, 5.28]**
B	21	9	0.429	12	0.571	vs. A 0.35 [0.09, 1.25]	vs. AB 0.21 [0.02, 1.29]	vs. O 0.61 [0.21, 1.74]
AB	9	7	0.778	2	0.222	**vs. A 1.63 [0.26, 13.83]**	**vs. B 4.67 [0.77, 37.59]**	**vs. O 2.85 [0.55, 21.41]**
O	49	27	0.551	22	0.449	vs. A 0.57 [0.18, 1.65]	**vs. B 1.64 [0.57, 4.71]**	vs. AB 0.35 [0.04, 1.78]
Rh factor								
Rh +	90	54	0.600	36	0.400	**vs. Rh-ve 2.63 [0.70, 10.79]**		
Rh-	11	4	0.364	7	0.636	vs. Rh + ve 0.38 [0.09, 1.4]		
BMI								
Healthy (H)	10	6	0.600	4	0.400	vs. OW 0.99 [0.24, 4.35]	**vs. Ob 1.38 [0.33, 6.15]**	
Overweight (OW)	58	35	0.603	23	0.397	vs. H 1.01 [0.22, 4.11]	**vs. Ob 1.39 [0.63, 3.07]**	
Obese (Ob)	46	24	0.522	22	0.478	vs. H 0.73 [0.16, 3.02]	vs. OW 0.72 [0.32, 1.58]	

OR > 1.0 are in Bold

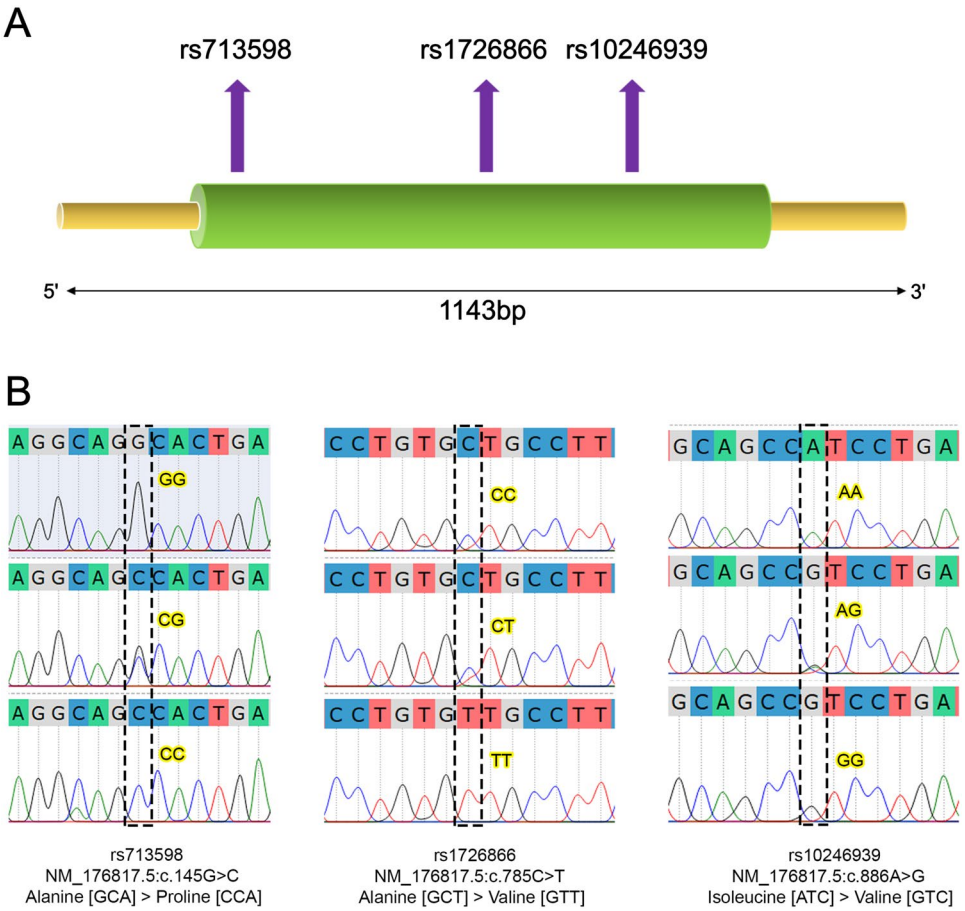

Fig. 1 Genetic variations in *TAS2R38* gene tested for association with PTC sensitivity. Panel A shows physical location of variants in the gene and panel B shows representative electropherograms for all three variants

Homozygous individuals were observed at a higher frequency for the alleles rs713598 (GG) and rs1726866 (TT), whilst the alleles 10246939 showed a higher frequency of heterozygotes (AG) (Table 2). The allelic distribution pattern showed ancestral alleles at higher frequencies. The minor allele frequency for the alleles rs713598, rs1726866 and rs10246939 in Koṅkaṇī Sārasvata Brahmins is 0.21, 0.44 and 0.45 respectively. The average minor allele frequency is 0.366.

We observed a higher number of homozygotes GG and TT, and heterozygotes AG in all the subgroups (Table 3). However, the minor allele frequency differed in each of the subgroups. For rs713598, the minor allele C was found at positions 0.207, 0.203 and 0.400 in the Citrapur, Gauḍa and Rājāpur subgroups respectively, whereas the minor allele C was absent in the non-Koṅkaṇī moiety. The minor allele C at rs1726866 was predominant in the Rājāpur moiety (0.864), and found to be lowest in the non-Koṅkaṇī moiety (0.286). Similarly, the occurrence of the minor allele G at rs10246939 was the highest in the Rājāpur subgroup (0.600) and the lowest in the non-Koṅkaṇī subgroup (0.375). Interestingly, the minor allele frequency amongst the Rājāpur Sārasvata Brahmins for rs1726866 and rs10246939 (including the Citrapur moiety) was higher than the ancestral allele frequency.

Table 2 Genotypic counts and allelic frequency distribution in Koṅkaṇī Sārasvata Brahmins

	rs713598		rs1726866		rs10246939	
Genotype count	GG	105	TT	50	AA	24
	CG	27	CT	19	AG	55
	CC	18	CC	37	GG	14
Allele frequency	G	0.79	T	0.56	A	0.55
	C	*0.21*	*C*	*0.44*	*G*	*0.45*

Minor allele frequency is given in italics

Table 3 Genotypic counts and allelic frequency in Koṅkaṇī Sārasvata Brahmins

	Genotype			Allele frequency	
rs713598					
	GG	CG	CC	G	C
CSB	22	2	5	0.793	*0.207*
GSB	67	19	10	0.797	*0.203*
RSB	6	6	3	0.600	*0.400*
NKS	10	0	0	1.000	*0.000*
rs1726866					
	TT	CT	CC	T	C
CSB	16	5	7	0.661	*0.339*
GSB	28	13	19	0.575	*0.425*
RSB	1	1	9	0.136	*0.864*
NKS	5	0	2	0.714	*0.286*
rs10246939					
	AA	AG	GG	A	G
CSB	8	15	14	0.419	*0.581*
GSB	12	30	7	0.551	*0.449*
RSB	2	4	4	0.400	*0.600*
NKS	2	6	0	0.625	*0.375*

Minor allele frequency is given in italics

Table 4 Haplotype distribution

Haplotype	Overall %
AAI	2.4
AAV	2.4
AVI	58.8
AVV	11.8
PAI	5.9
PAV	8.2
PVI	3.5
PVV	7.1

Haplotype distribution in Koṅkaṇī Sārasvata Brahmins

The AVI haplotype is predominantly found in the Koṅkaṇī Sārasvata Brahmin population (58.8%) followed by the AVV haplotype (11.8%). The PAV haplotype commonly found in tasters is present at a frequency of 8.2% (Table 4).

Based on PTC sensitivity, the non-taster AVI haplotype frequency is 80% in Koṅkaṇī Sārasvata Brahmins (Fig. 2). The frequency of the AVI haplotype in tasters is 40%. The frequency of the PAV haplotype in tasters is 13.3%, whereas in non-tasters the frequency of the PAV haplotype is 2.5%. Other haplotypes such as AVV, PAI, PVV, AAI, AAV and PVI are observed in tasters and non-tasters at lower frequencies, ranging from 2 to 18%.

Diplotype distribution in Koṅkaṇī Sārasvata Brahmins

The most common diplotype found in Koṅkaṇī Sārasvata Brahmins is AVI/AVV (25%) followed by AVI/AVI (22.6%) (Table 5). Taster homozygote PAV/PAV is found at 8.3%. Other diplotype combinations found in this population are listed in Table 5. Most of the tasters are determined by PAV/PAV (22.7%), PAV/AAV (13.6%), PAI/PAV (13.6%), AAI/AAV (13.6%) and AAI/AVV (13.6%). Non-tasters carry AVI/AVI (34.5%) and AVI/AVV (44.8%) diplotypes and traces of other combinations (Fig. 3).

Association between PTC sensitivity genotype and traits

Association analyses were performed using Chi-Square test and Fisher's exact test. Table 6 summarises the results

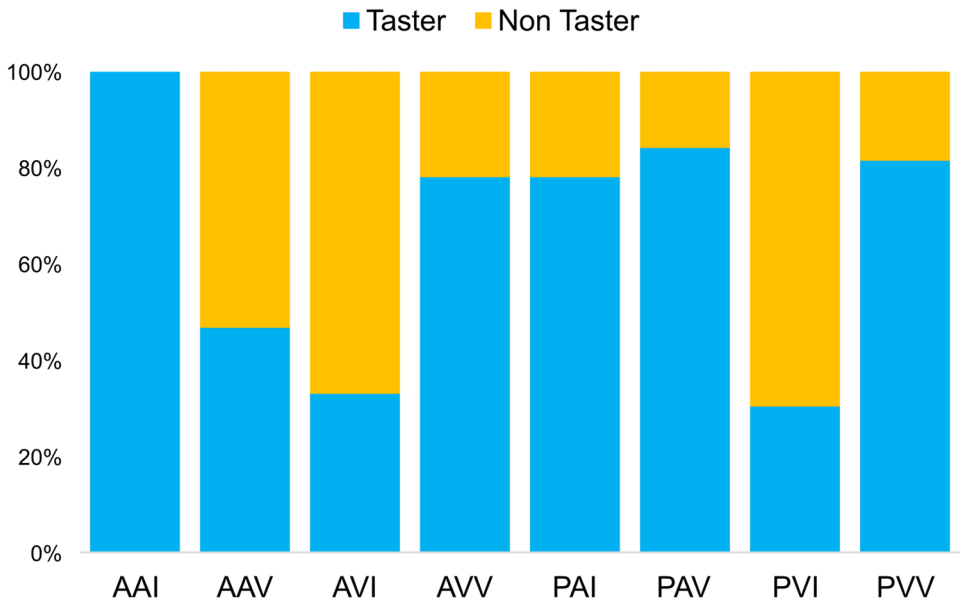

Fig. 2 Haplotype distribution based on PTC sensitivity

Table 5 Diplotype distribution

Diplotype	Genotype			Percentage (%)
AAI/AAI	GG	CC	GG	1.2
AAI/AAV	GG	CC	AG	7.1
AAI/AVV	GG	CT	AG	11.9
AAV/AAV	GG	CC	AA	1.2
AVI/AVI	GG	TT	AA	22.6
AVI/AVV	GG	TT	AG	25.0
PAI/AAV	CG	CC	AG	3.6
PAI/AVV	CG	CT	AG	4.8
PAI/PAI	CC	CC	AA	2.4
PAI/PAV	CC	CC	AG	6.0
PAV/AAV	CG	CC	CC	4.8
PAV/PAV	CC	CC	GG	8.3
PVV/AVV	CG	TT	GG	1.2

for the association of factors such as PTC sensitivity, sex, blood group, alcohol consumption, diabetes, lactase persistence, BMI etc. with the taster and non-taster genotype.

PTC sensitivity is significantly associated with the haplotypes (Fisher's $p < 0.01$) and diplotypes (χ^2 $p < 0.001$) found in Koṅkaṇī Sārasvata Brahmins. We report a significant association between PTC sensitivity diplotype and lactase persistence ($p < 0.05$). The diplotype AVI/AVV (27.3%) represents the common diplotype found in lactose-intolerant individuals, whilst AVI/AVV (23.9%) and AVI/AVI (23.9%) are commonly found in lactose-tolerant individuals (Fig. 3).

A trend towards association ($p < 0.1$) is observed with sex and blood group in Koṅkaṇī Sārasvata Brahmins. The factors of BMI, dietary preferences, alcohol consumption and the occurrence of diabetes in the population was not found to be associated with PTC sensitivity genotype (Table 6).

Association between PTC genotype and phenotype

Mutations deviating from the Hardy Weinberg equilibrium often show association with the phenotype. However, this association is biased and originates due to the bad quality of the dataset, the non-random selection of samples, natural selection etc. Therefore, it is common practice to exclude those mutations not present in the Hardy Weinberg equilibrium. We observed a departure from the Hardy Weinberg equilibrium in the case of the genotypes rs713598 (p value $= 1 \times 10^{-5}$) and rs1726866 (p value $< 1 \times 10^{-27}$ or ~ 0). The rs10246939 genotypes did not show significant deviation (p value = 0.71) (Table 7).

Homozygous genotypes at rs713598 are known to be associated with differential bitter taste sensitivity (Kim et al. 2003; Genick et al. 2011). The GG homozygote (otherwise termed AA for Alanine at 49th position) is linked with PTC/PROP tasting ability, whilst the CC genotype (otherwise termed PP for Proline) is associated with a lack of tasting ability. In order to understand the association of these genotypes with PTC phenotypes, Chi-Square test was performed (Table 8).

A strong association between genotypes and PTC phenotypes was observed in the Koṅkaṇī Sārasvata Brahmins population. Although the marker rs713598 is known to be associated with bitter taste perception, we cannot confirm it as rs713598 did not pass Hardy Weinberg equilibrium test. Therefore, a significant association for rs713598 and rs1736866 might reflect an artefact or a bias. To replicate the genetic association of rs713598 and rs1736866, a large

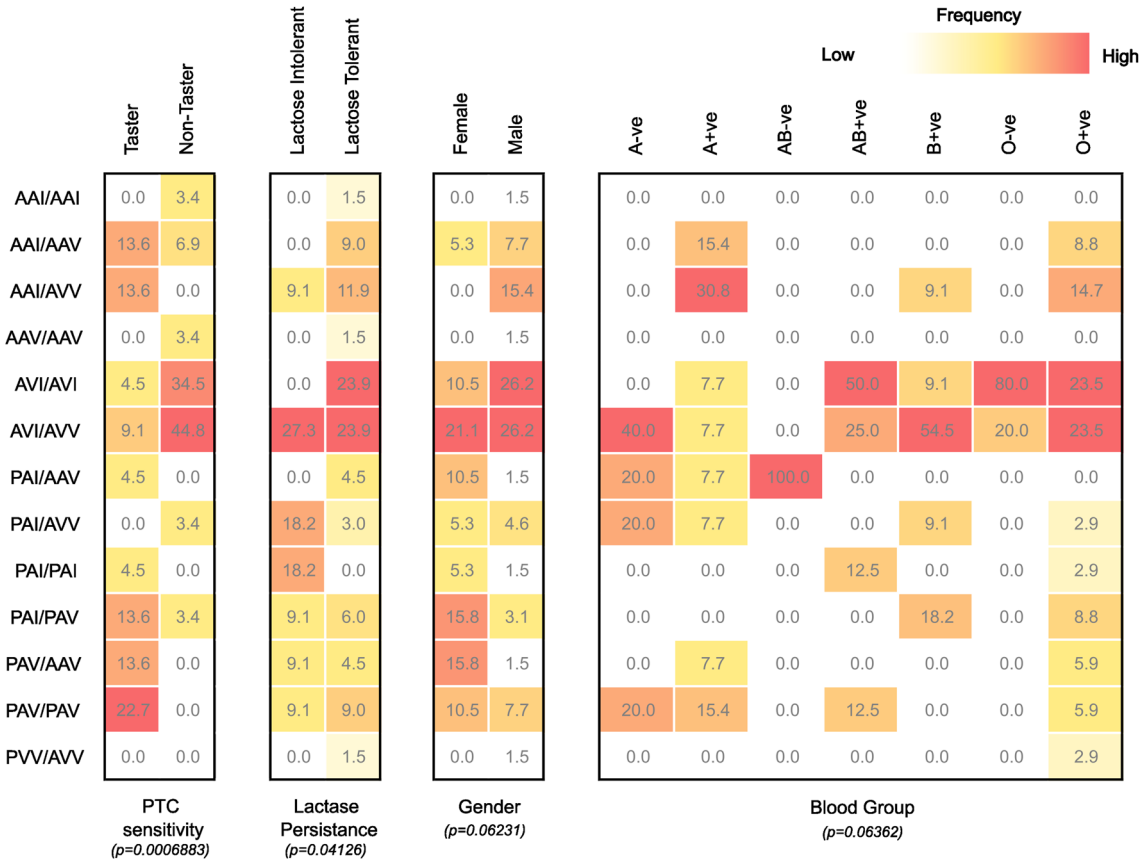

Fig. 3 Diplotype frequency distribution based on PTC sensitivity and other factors

Table 6 *TAS2R38* association profile in Koṅkaṇī Sārasvata Brahmins

Phenotype	Haplotype (p value)	Diplotype (p value)
PTC	**0.01361 (4.835×10^{-3})****	**0.0006883** (9.501×10^{-6})**
Sex	0.5856	**0.06231***
Diet	0.6356	0.5687
Lactase persistence	0.4972	**0.04126****
BMI	0.3423	0.771
Blood Group	0.8405	**0.06362***
Diabetes	0.9493	0.2600
Alcohol Consumption	0.2957	0.2597

Chi-Square test p values are shown

Fisher's Exact Test p value in shown in parenthesis; Significant p values are in bold; *p < 0.1 **p < 0.05

number of samples is required. The marker rs10246939 was found to be in association with the phenotype in both allelic and the genotype-based association analyses. The age, sex, alcoholism, tobacco use and other co-factors can affect the sensitivity to tasting the bitterness of the compound. Hence, a multifactorial logistic regression analysis was performed, and the p value was corrected for these factors. The marker rs10246939 was found in association with phenotype even after correction of the p value with these co-factors (Table 9).

This outcome suggests that rs10246939 is indeed a genetic factor for tasting, and is therefore truly associated with the phenotype. The likelihood of being a non-taster is ~ 3.5 higher in those Koṅkaṇī Sārasvata Brahmin individuals who have allele rs10246939-G as compared to those who have allele rs10246939-A. Similarily, individuals who have

Table 7 Hardy Weinberg equilibrium test

rsIDs	Genotype	Count	Observed	Expected	p value (Chisq. test)
rs713598	CC	11	0.13	0.04	$\mathbf{1\times10^{-5}}$**
	CG	13	0.15	0.33	
	GG	60	0.71	0.63	
rs1726866	TT	24	0.42	0.22	~0
	TC	5	0.09	0.50	
	CC	28	0.49	0.29	
rs10246939	AA	15	0.26	0.29	7.1×10^{-1}
	AG	32	0.55	0.50	
	GG	11	0.19	0.22	

Chi-Square test p values are shown

Significant p values are in bold; **p < 0.01

Table 8 Genotype-based association analysis for PTC phenotypes

rsIDs	Genotype	Non taster	Taster	p value (Chisq. test)
rs713598	CC	01	10	$\mathbf{3.051\times10^{-5}}$ **
	CG	01	12	
	GG	38	22	
rs1726866	TT	25	03	$\mathbf{1.356\times10^{-6}}$ **
	TC	01	04	
	CC	05	19	
rs10246939	AA	12	03	$\mathbf{1.466\times10^{-3}}$ **
	AG	18	14	
	GG	01	10	

Chi-Square test p values are shown

Significant p values are in bold; **p < 0.01

the allele rs10246939-GG or the rs10246939-AG genotype in the TASR38 gene, have 40 and 3.11 times higher chances respectively of being a non-taster as compared to those who have the rs10246939-AA genotype (Table 9).

Haplotypes resulting from amino acid combinations are known to be associated with PTC phenotypes. The most commonly found haplotypes are PAV and AVI for tasters and non-tasters respectively. We observe a significant association between haplotypes and PTC phenotypes in Koṅkaṇī Sārasvata Brahmin population also (p value = 6.9×10^{-3}) (Table 10). This observation was replicated with multifactorial regression analysis using the allele or genotype of rs10246939, sex, age, diet, body mass index of the individual, lactase persistence, blood group, diabetic, alcoholism, smoking habit and tobacco use as co-factors. Our findings are in line with earlier studies which reported a similar association pattern in other populations (Kim et al. 2003; Pemberton et al. 2008; Risso et al. 2016b).

Discussion

To date, this is the second study on a southwest Indian population reporting PTC sensitivity genotypes and associations. An earlier study on the Koragas, a tribal population of the Koṅkaṇ Malabar coast (Vinuthalakshmi et al. 2019) reported an association of PTC sensitivity with alcohol consumption and tobacco chewing. Similar observations were made in earlier studies (DiCarlo and Powers 1998; Duffy et al. 2004; Wang et al. 2007). We did not find any such association with alcohol consumption. Lack of any association between PTC sensitivity and alcoholism has been reported earlier as well (Fischer et al. 2014; Choi et al. 2016). Also, our results correspond to an earlier study on an Indian cohort which did not report any association with BMI or food preferences (Ooi et al. 2010; Choi et al. 2016; Deshaware and Singhal 2017). Contradictions to our findings are reported in study (Gupta et al. 2018). Besides a strong association of PTC sensitivity with taster and non-taster genotypes (p < 0.001), we show an association between PTC diplotypes and the lactase persistence trait (p < 0.05). The LCT gene associated with lactose intolerance and the *TAS2R38* gene have been studied together earlier for their involvement in food intake and a possible BMI association (Sacerdote et al. 2007). The rs1446585 loci in the LCT gene and non-taster diplotypes

Table 9 Genetic association test for rs10246939

rsIDs	Genotype/ Allele	Taster	Non-taster	p value (logistical regression)	Corrected p value (logistical regression)	Odd ratio (95% CI)
rs10246939	AA	3	12	$\mathbf{6.9\times10^{-4}}$**	$\mathbf{1.4\times10^{-3}}$**	–
	AG	14	18			3.11 (0.73–13.20)
	GG	10	1			40 (3.58–447.03)
	A	20	42	$\mathbf{8.6\times10^{-4}}$**	$\mathbf{1\times10^{-2}}$	–
	G	34	20			3.57 (1.66–7.69)

Both uncorrected and corrected p values are shown in the table for the genotype and allelic association analysis

Logistical regression p values are shown

Significant p values are in bold; **p < 0.01

Table 10 Haplotype-based association analysis. Both uncorrected and corrected p value of logistical regression analysis is shown in the table

Haplotype	Taster	Non-taster	p value (logistical regression)	Corrected p value (logistical regression)
AAI	2	0	**0.006897****	**0.0002081****
AAV	1	1		
AVI	18	32		
AVV	8	2		
PAI	4	1		
PAV	6	1		
PVI	1	2		
PVV	5	1		

Logistical regression p values are shown

Significant p values are in bold; **$p < 0.01$

have been shown to be associated with colorectal cancer (Carrai et al. 2011). Both these genes are involved in BMI-related phenotypes (Corella et al. 2011; Almon et al. 2012; Ortega et al. 2016; Choi 2019; Coltell et al. 2019; Robino et al. 2021). Therefore, our results can potentially be substantiated with a larger cohort and assessed for the genotype of this trait. The PROP sensitivity differences between males and females have been reported before (Bartoshuk et al. 1994; Drewnowski et al. 2001; Fischer et al. 2014). We report a trend towards association of the PTC sensitivity diplotype with sex. There are not enough data to conclude that PTC sensitivity is associated with blood groups. A few studies have correlated blood group (Malini et al. 2010) and specifically blood group B (Leite et al. 2018) with the PROP phenotype. Here, we report a trend towards association between blood groups and the PTC sensitivity diplotype.

Although a strong association was observed between the *TAS2R38* genotypes rs713598, rs1726866 and rs10246939, and tasters/non-taster phenotypes, the association profile for the rs713598 and rs1726866 genotypes needs to be studied in a larger cohort, as these markers deviated from the Hardy Weinberg equilibrium in the current study. A notable finding of our study is the significant association of rs10246939 and PTC sensitivity.

The frequencies of taster (57%) and non-taster (43%) phenotypes found in the study population are similar to those found in the earlier studies, which show a higher number of tasters as compared to non-tasters (Fareed et al. 2012; Gupta et al. 2018). However, the genotype frequency showed a higher number of non-taster haplotypes and diplotypes. Such an observation is made in earlier studies as well (Ghosh 1973; Hakim et al. 1973; Deshaware and Singhal 2017; Vinuthalakshmi et al. 2019). The frequencies of taster haplotypes (PAV) and homozygote diplotypes (PAV/PAV) in Koṅkaṇī Sārasvata Brahmins are 8.2% and 8.3% respectively. These frequencies are lower than the global average, which is ~ 50% (Risso et al. 2016b). Only 22.7% of the tasters had PAV/PAV, and only 13.3% carried PAV. We observed a 58.8% prevalence of the AVI haplotype, which is most prevalent in European populations (Risso et al. 2016b). Interestingly, this non-taster haplotype peaked at 40% in the PTC tasters in our study population. Such contradictions are available in the literature (Kim et al. 2003; Bufe et al. 2005). We observe a higher frequency of single and double copies of AVV in Koṅkaṇī Sārasvata Brahmins. In tasters, the AVV haplotype is found at a frequency of 17.8%, and in non-tasters the AVV haplotype is found as a heterozygous diplotype (3.4%–44.8%). The AVI/AVV combination is also prevalent in lactose intolerant individuals (27.3%). The AVI and AVV haplotypes and diplotypes are reported to be tasters, and the PAV and PAI haplotypes are reportedly non-tasters (Bufe et al. 2005). We observed a significant association between haplotypes and PTC sensitivity phenotype in Koṅkaṇī Sārasvata Brahmins. In our previous study, we identified the same correlation, i.e. the AVI/AVI haplotype in association with non-tasters, whilst the PAV/PAV haplotype was associated with tasters in the Koraga population (Vinuthalakshmi et al. 2019).

The minor allele frequency observed for rs713598, rs1726866 and rs10246939 in this population is comparable with the global datasets (Fig. 4). The present generation of Koṅkaṇī Sārasvata Brahmins believe that their ancestors have migrated from the northern part of India. Genetic studies have supported this claim by finding Ancestral North Indian components in this population (Mascarenhas et al. 2015; Kumar et al. 2021). Moreover, Sārasvata Brahmins are found all over India with higher presence in the North West region. It is therefore a plausible hypothesis that Koṅkaṇī Sārasvata Brahmins who are presently found along the south west coast have migrated from the north. Earlier studies including ancient DNA studies have emphasised on Bronze age admixture of the Steppe pastoralists with the north-western groups giving rise to Ancestral North Indians (Narasimhan et al. 2019; van Driem 2021). Coincidentally, the Sarasvatī River, which is often mentioned in the local folklore of the Koṅkaṇī Sārasvata Brahmins, is also believed to have dried up at the same time depth. Although the present study does not establish such a complex demographic event

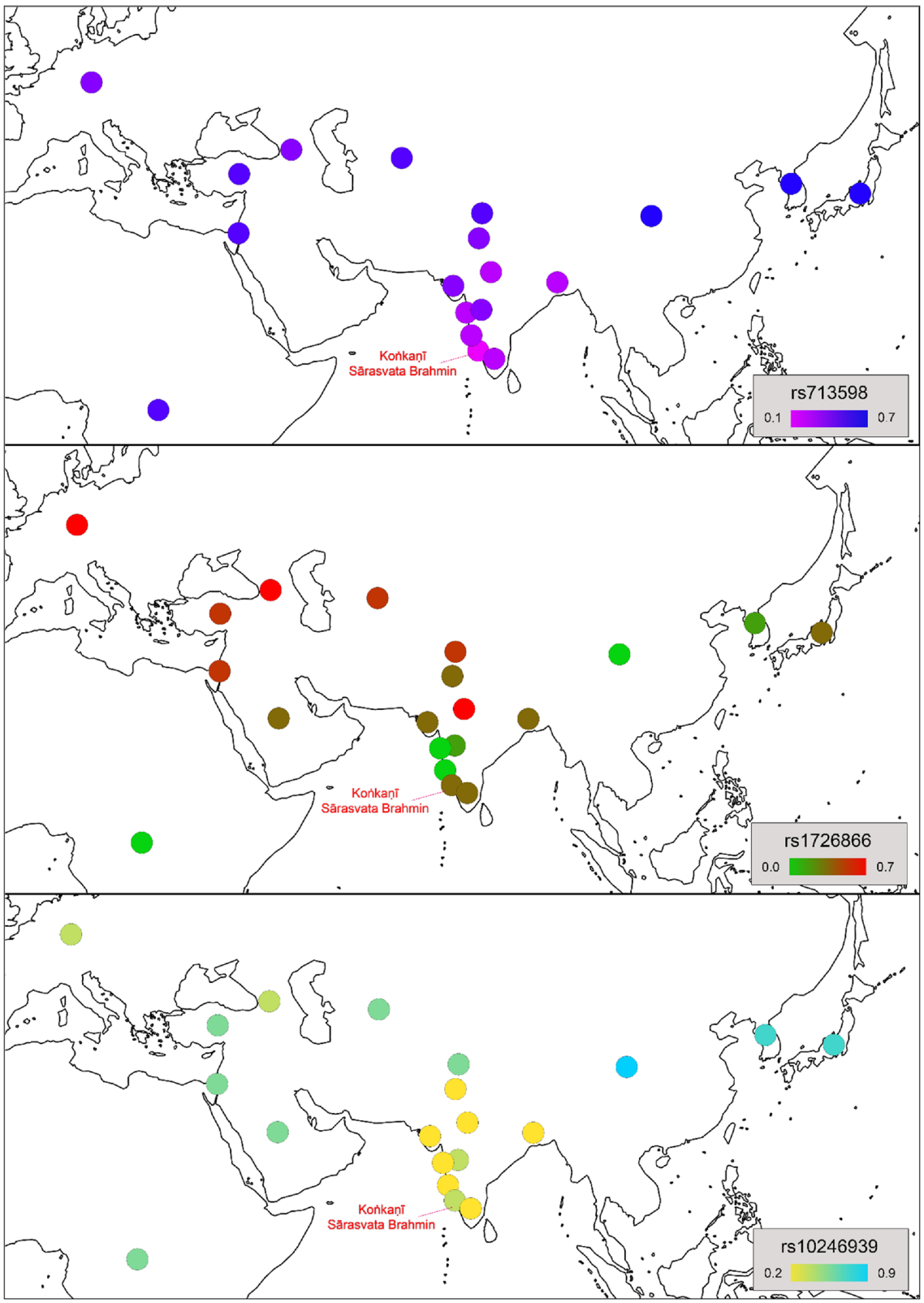

Fig. 4 Global distribution of rs713598, rs1726866 and rs10246939 minor allele frequency

using SNP allele frequency variation, earlier studies have suggested ancestry specific selection for lactase persistence in specific ancestries (Gallego Romero et al. 2012; Ranciaro et al. 2014; Liebert et al. 2017). In our study, both allelic and haplotypic variations observed in *TAS2R38* genotype of Koṅkaṇī Sārasvata Brahmins and other populations suggest ancestry specific selection in four broad clusters (Fig. 4) namely African, West Eurasian, Indian and East Asian. The alternate allele frequency for rs713598 (0.21), rs1726866 (0.44) rs10246939 (0.45) in Koṅkaṇī Sārasvata Brahmins is slightly less than the global average (0.422, 0.528 and 0.464 respectively) (Sayers et al. 2022). Overall there appears to be a similarity in the allele frequencies between the study population and South Asian and West Eurasian datasets. When compared with the African, East Asian and West Eurasian datasets, the rs10246939 minor allele frequency in Koṅkaṇī Sārasvata Brahmins appeared more similar to that of West Eurasians. Although there exists a pattern in distribution, it does not provide enough support for the correlation of *TAS2R38* gene variation with micro-level demographic events, as we also observe a similar distribution pattern in South Asian populations with different ancestries. Nevertheless, these aspects can be explored further by genotyping larger cohorts of migrant populations in order to discern the genetic footprint of ancient migratory events on PTC sensitivity.

Conclusion

The *TAS2R38* is a bitter taste receptor gene, the association of which with PTC and PROP tasting ability has been considered to represent a classic example of a genotype–phenotype correlation. Researchers have been investigating the association of *TAS2R38* gene variations with other factors including alcoholism, BMI and cancers. The worldwide distribution of *TAS2R38* haplotypes shows a pattern suggesting that demographic events may have shaped the bitter tasting ability in populations. Therefore, these gene variations could be considered to represent potential markers for migration and adaptation. The Koṅkaṇī Sārasvata Brahmin population, with a purported known migratory history, affords an ideal population to study the genetic repercussions of migration. Their movement from the north to the south is often linked with the time depth of the demise of the Indus Valley Civilisation. Recent genetic studies have accumulated evidence in support of this hypothesis. The evidence that we present does not yet corroborate the conventional consensus, but also yields no contradictory evidence. The present study uses the pattern of bitter taste sensitivity haplotype distribution in Koṅkaṇī Sārasvata Brahmins to suggest that this population indeed shows similarity towards the West Eurasian populations, with their higher frequency of the non-taster AVI haplotype. We further establish the association of the genotype rs10246939 with PTC bitter taste sensitivity in an Indian population. Signals of *TAS2R38* diplotype association with lactase persistence, sex and blood group in this population provide a basis for conducting large cohort studies in the future.

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Author contributions JJS conceived the study, collected the samples, performed the experiments and statistical analyses, and wrote the first draft. SN contributed to the statistical analysis and manuscript drafting. GvD reviewed, revised and redacted the entire manuscript draft. MSM verified the experimental design and contributed to the final draft. All authors read and approved the final manuscript.

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Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author upon request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate The usage of human blood samples and data for this study have been approved by Institutional Human Ethics Committee, Mangalore University (MU-IHEC-2020-3). Informed consent was obtained from all participants included in the study.

Consent for publication Not applicable.

References

Adappa ND, Farquhar D, Palmer JN et al (2016) TAS2R38 genotype predicts surgical outcome in nonpolypoid chronic rhinosinusitis. Int Forum Allergy Rhinol 6:25–33. https://doi.org/10.1002/alr.21666

Almon R, Álvarez-León EE, Serra-Majem L (2012) Association of the European lactase persistence variant (LCT-13910 C>T polymorphism) with obesity in the Canary Islands. PLoS One 7:e43978

Bartoshuk LM, Duffy VB, Miller IJ (1994) PTC/PROP tasting: anatomy, psychophysics, and sex effects. Physiol Behav 56:1165–1171. https://doi.org/10.1016/0031-9384(94)90361-1

Bufe B, Breslin PAS, Kuhn C et al (2005) The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. Curr Biol 15:322–327. https://doi.org/10.1016/j.cub.2005.01.047

Campbell MC, Ranciaro A, Froment A et al (2012) Evolution of functionally diverse alleles associated with PTC bitter taste sensitivity in Africa. Mol Biol Evol 29:1141–1153. https://doi.org/10.1093/molbev/msr293

Carrai M, Steinke V, Vodicka P et al (2011) Association between TAS2R38 gene polymorphisms and colorectal cancer risk: a case-control study in two independent populations of caucasian origin. PLoS One 6:e20464

Choi J-H (2019) Variation in the TAS2R38 bitterness receptor gene was associated with food consumption and obesity risk in Koreans. Nutrients 11:1973

Choi J-H, Lee J, Choi IJ et al (2016) Genetic variation in the TAS2R38 bitter taste receptor and gastric cancer risk in Koreans. Sci Rep 6:26904. https://doi.org/10.1038/srep26904

Coltell O, Sorlí JV, Asensio EM et al (2019) Association between taste perception and adiposity in overweight or obese older subjects with metabolic syndrome and identification of novel taste-related genes. Am J Clin Nutr 109:1709–1723. https://doi.org/10.1093/ajcn/nqz038

Corella D, Arregui M, Coltell O et al (2011) Association of the LCT-13910C>T polymorphism with obesity and its modulation by dairy products in a Mediterranean population. Obesity 19:1707–1714. https://doi.org/10.1038/oby.2010.320

Deshaware S, Singhal R (2017) Genetic variation in bitter taste receptor gene TAS2R38, PROP taster status and their association with body mass index and food preferences in Indian population. Gene 627:363–368. https://doi.org/10.1016/j.gene.2017.06.047

DiCarlo ST, Powers AS (1998) Propylthiouracil tasting as a possible genetic association marker for two types of alcoholism 11based on a dissertation submitted by S. T. D. to the faculty of St. John's University in partial fulfillment of the requirements for the PhD in psychology. Physiol Behav 64:147–152. https://doi.org/10.1016/S0031-9384(98)00043-2

Diószegi J, Llanaj E, Ádány R (2019) Genetic background of taste perception, taste preferences, and its nutritional implications: a systematic review. Front Genet. https://doi.org/10.3389/fgene.2019.01272

Drewnowski A, Kristal A, Cohen J (2001) Genetic taste responses to 6-n-Propylthiouracil among adults: a screening tool for epidemiological studies. Chem Senses 26:483–489. https://doi.org/10.1093/chemse/26.5.483

Duffy VB, Davidson AC, Kidd JR et al (2004) Bitter receptor gene (TAS2R38), 6-n-Propylthiouracil (PROP) bitterness and alcohol intake. Alcohol Clin Exp Res 28:1629–1637. https://doi.org/10.1097/01.ALC.0000145789.55183.D4

Fareed M, Shah A, Hussain R, Afzal M (2012) Genetic study of phenylthiocarbamide (PTC) taste perception among six human populations of Jammu and Kashmir (India). Egypt J Med Hum Genet 13:161–166. https://doi.org/10.1016/j.ejmhg.2012.01.003

Fischer ME, Cruickshanks KJ, Pankow JS et al (2014) The associations between 6-***n***-Propylthiouracil (PROP) intensity and taste intensities differ by ***TAS2R38*** haplotype. Lifestyle Genomics 7:143–152. https://doi.org/10.1159/000371552

Fisher RA, Ford EB, Huxley J (1939) Taste-testing the Anthropoid Apes. Nature 144:750. https://doi.org/10.1038/144750a0

Gallego Romero I, Basu Mallick C, Liebert A et al (2012) Herders of Indian and European cattle share their predominant allele for lactase persistence. Mol Biol Evol 29:249–260. https://doi.org/10.1093/molbev/msr190

Gallo S, Grossi S, Montrasio G et al (2016) TAS2R38 taste receptor gene and chronic rhinosinusitis: new data from an Italian population. BMC Med Genet 17:54. https://doi.org/10.1186/s12881-016-0321-3

Genick UK, Kutalik Z, Ledda M et al (2011) Sensitivity of genome-wide-association signals to phenotyping strategy: the PROP-TAS2R38 taste association as a benchmark. PLoS One 6:e27745

Ghosh AK (1973) ABO blood groups and PTC taste sensitivity among the Kota of Nilgiri Hills. Hum Hered 23:78–82. https://doi.org/10.1159/000152557

Gupta V, Kumar A, Sharma L et al (2018) Association of TAS2R38 polymorphism with measures of adiposity in Indian population. Meta Gene 18:68–72. https://doi.org/10.1016/j.mgene.2018.08.001

Hakim SMA, Baxi AJ, Balakrishnan V et al (1973) Blood groups, secretor status and ability to taste phenylthiocarbamide in some Muslim groups. Hum Hered 23:72–77. https://doi.org/10.1159/000152556

Kim UK, Drayna D (2005) Genetics of individual differences in bitter taste perception: lessons from the PTC gene. Clin Genet 67:275–280. https://doi.org/10.1111/j.1399-0004.2004.00361.x

Kim U, Jorgenson E, Coon H et al (2003) Positional Cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. Science 299:1221–1225. https://doi.org/10.1126/science.1080190

Kumar L, Farias K, Prakash S et al (2021) Dissecting the genetic history of the Roman Catholic populations of West Coast India. Hum Genet. https://doi.org/10.1007/s00439-021-02346-4

Lambert JD, VanDusen SR, Cockroft JE et al (2019) Bitter taste sensitivity, food intake, and risk of malignant cancer in the UK Women's Cohort Study. Eur J Nutr 58:2111–2121. https://doi.org/10.1007/s00394-018-1772-4

Leite ICR, dos Santos Júnior JC, de Sousa CCS et al (2018) Recognition of phenylthiocarbamide (PTC) in taste test is related to blood group B phenotype, females, and risk of developing food allergy: a cross-sectional Brazilian-based study. Nutr Res 52:22–38. https://doi.org/10.1016/j.nutres.2017.12.013

Liebert A, López S, Jones BL et al (2017) World-wide distributions of lactase persistence alleles and the complex effects of recombination and selection. Hum Genet 136:1445–1453. https://doi.org/10.1007/s00439-017-1847-y

Malini SS, Kavitha P, Vineeth VS et al (2010) Expression of genetic traits among PTC tasters and non tasters in Mysore population, South India. Cafe Tech Soc 1:216

Mascarenhas DD, Raina A, Aston CE, Sanghera DK (2015) Genetic and cultural reconstruction of the migration of an ancient lineage. Biomed Res Int. https://doi.org/10.1155/2015/651415

Melis M, Errigo A, Crnjar R et al (2019) TAS2R38 bitter taste receptor and attainment of exceptional longevity. Sci Rep 9:18047. https://doi.org/10.1038/s41598-019-54604-1

Narasimhan VM, Patterson N, Moorjani P et al (2019) The formation of human populations in South and Central Asia. Science 365:eaat7487. https://doi.org/10.1126/science.aat7487

Ooi S-X, Lee P-L, Law H-Y, Say Y-H (2010) Bitter Receptor Gene (TAS2R38) P49A genotypes and their associations with aversion to vegetables and sweet/fat foods in Malaysian subjects. Asia Pac J Clin Nutr 19:491–498

Ortega FJ, Agüera Z, Sabater M et al (2016) Genetic variations of the bitter taste receptor TAS2R38 are associated with obesity and impact on single immune traits. Mol Nutr Food Res 60:1673–1683. https://doi.org/10.1002/mnfr.201500804

Pemberton TJ, Mehta NU, Witonsky D et al (2008) Prevalence of common disease-associated variants in Asian Indians. BMC Genet 9:13. https://doi.org/10.1186/1471-2156-9-13

Qi F-Y, Zhu Z-H, Li M et al (2022) Genetic variations in the bitter taste receptor gene TAS2R38 are related to cigarette smoking behavior in Han Chinese smokers. Genes Genomics 44:1363–1374. https://doi.org/10.1007/s13258-022-01311-3

Ranciaro A, Campbell MC, Hirbo JB et al (2014) Genetic origins of lactase persistence and the spread of pastoralism in Africa. Am J Hum Genet 94:496–510. https://doi.org/10.1016/j.ajhg.2014.02.009

Risso DS, Kozlitina J, Sainz E et al (2016a) Genetic variation in the TAS2R38 bitter taste receptor and smoking behaviors. PLoS One 11:e0164157

Risso DS, Mezzavilla M, Pagani L et al (2016b) Global diversity in the TAS2R38 bitter taste receptor: revisiting a classic evolutionary PROPosal. Sci Rep 6:25506. https://doi.org/10.1038/srep25506

Robino A, Rosso N, Guerra M et al (2021) Taste perception and expression in stomach of bitter taste receptor tas2r38 in obese and lean subjects. Appetite 166:105595. https://doi.org/10.1016/j.appet.2021.105595

Sacerdote C, Guarrera S, Smith GD et al (2007) Lactase persistence and bitter taste response: instrumental variables and mendelian randomization in epidemiologic studies of dietary factors and cancer risk. Am J Epidemiol 166:576–581. https://doi.org/10.1093/aje/kwm113

Sayers EW, Bolton EE, Brister JR et al (2022) Database resources of the national center for biotechnology information. Nucleic Acids Res 50:D20–D26. https://doi.org/10.1093/nar/gkab1112

Tepper BJ, Koelliker Y, Zhao L et al (2008) Variation in the bitter-taste receptor gene TAS2R38, and adiposity in a genetically isolated population in Southern Italy. Obesity 16:2289–2295. https://doi.org/10.1038/oby.2008.357

Timpson NJ, Christensen M, Lawlor DA et al (2005) TAS2R38 (phenylthiocarbamide) haplotypes, coronary heart disease traits, and eating behavior in the British women's heart and health study. Am J Clin Nutr 81:1005–1011. https://doi.org/10.1093/ajcn/81.5.1005

van Driem GL (2021) Ethnolinguistic prehistory: the peopling of the world from the perspective of language, genes and material culture. Brill, Leiden, The Netherlands

Vinuthalakshmi K, Sheik N, Mustak MS (2019) TAS2R38 gene polymorphism and its association with taste perception, alcoholism and tobacco chewing among the Koraga -a primitive tribal population of Southwest coast of India. Meta Gene 20:100549. https://doi.org/10.1016/j.mgene.2019.100549

Wang JC, Hinrichs AL, Bertelsen S et al (2007) Functional variants in TAS2R38 and TAS2R16 influence alcohol consumption in high-risk families of African-American origin. Alcohol Clin Exp Res 31:209–215. https://doi.org/10.1111/j.1530-0277.2006.00297.x

Wooding S, Kim U, Bamshad MJ et al (2004) Natural selection and molecular evolution in PTC, a bitter-taste receptor gene. Am J Hum Genet 74:637–646. https://doi.org/10.1086/383092