Eurasian Journal of Anthropology Euras J Anthropol 6(1):15−23, 2015

Genetic variation in taste sensitivity to phenylthiocarbamide in six populations of Manipur, India

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Received May 1, 2015
Accepted November 18, 2015

Abstract

Ability to taste Phenylthiocarbamide (PTC) a bitter compound is of genetic, epidemiologic, and evolutionary interest because the ability to taste PTC is correlated with the ability to taste other bitter substances, many of which are toxic. Our study was taken to determine PTC taste sensitivity among Manipuri Muslim males and females and discussed it with reference to variability and disease. Unrelated individuals of both sexes belonging to six populations were randomly selected and screened using serial dilution method of Harris and Kalmus (1949). The study was conducted with six populations viz. Sheikh, Syed, Pathan and Mughal, Meitei (Hindu) and Naga. Naga population shows the highest taster frequency in both males and females (males 90.59% and females 92.35%). While the least taster frequency were observed in Pathan population (males65.38% and females 62.86%). Females shows higher PTC tasting ability (χ^2=62.028, df=5, P=*0.00). The findings are discussed with reference to variability and disease. The frequency of PTC tasters is greater than non-tasters and the females have lower non-taster phenotypes as compared to males. Such type of study will provide background information about genetic structure of population studied and serves as useful interaction of genetics, food preferences and dietary patterns.*

Keywords: *Phenylthiocarbamide, Manipur, gene frequency, population, India*

Introduction

Study of genetic variability between population have been under taken by several investigators and important information concerning mutation, selection, random genetic drift, inbreeding, protein polymorphism and association between genetic markers and diseases in different regions of the world have been obtained (Cavalli-Sforza, 1973, 1998; Penrose, 1975). The ability or inability to taste the compound phenylthiocarbamide (PTC), which was synthesized by Fox, 1931 is a classic inherited trait in humans and has been the subject of genetic and anthropological studies for over 70 years for studying human variability (Kim and Drayna, 2004). The compound 6-*n*-Propylthiouracil (PROP) and phenylthiocarbamide (PTC) are members of a class of compounds known as "thioureas." These compounds carry the chemical group N-

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ISSN: 2166-7411

C5S, which is responsible for their characteristic bitter taste (Bartoshuk et al., 1994; Drewnowski and Rock, 1995). The studies on sensitivity of the bitter-tasting antithyroid compound phenylthiocarbamide (PTC) have demonstrated it to be an inherited trait determined by a dominant allele (Reddy and Rao, 1989; Kim et al., 2003). This gene, now designated as T2R38 or PTC, is a member of bitter taste receptor gene family in humans (Adler et al., 2000). It consists of a single coding exon 1002 bp long, encoding a 333 amino acid, 7-transmembrane domain G-protein-coupled receptor (Kim et al., 2003).

This phenotype is of genetic, epidemiologic, and evolutionary interest because the ability to taste PTC is correlated with the ability to taste other bitter substances (Wooding, 2004). Although PTC itself has not been found in nature, the ability to taste PTC is correlated strongly with the ability to taste other naturally occurring bitter substances, many of which are toxic (Harris and Kalmus, 1949; Tepper, 1998). Furthermore, variation in PTC taste sensitivity has been correlated with dietary preferences that may have significant health effects (Bartoshuk et al., 1994). For example, isothiocyanates and goitrin are bitter PTC-related compounds caused by hydrolysis of glucosinolates naturally present in raw cabbage (Fenwick et al., 1983). The PTC presents a unique opportunity in the field of bitter taste transduction. It has been hypothesized that this phenotype is a marker for individual differences in taste perception that influence food preferences and dietary behaviour with subsequent links to body weight and chronic disease risk. The PTC non-taster status may be an endophenotypic marker of an inherited neuronal abnormality that conveys risk for the development of schizophrenia (Moberg et al., 2005).

The thiocarbamides are known to be active goitrogenic substances, being inhibitors of thyroid function, and some of these are naturally present in the edible plants of the Brassica genus including cabbage, cauliflower, kale, brussel sprouts, turnips, etc. The ability to taste these substances has been suggested as a possible balanced polymorphism related to the metabolic differences of thyroid activity (Tepper, 1998). Apart from goiter, several other diseases (diabetes, tuberculosis, mongolism, mucoviscidosis, duodenal and gastric ulcers) have been reported to be associated with the ability to taste PTC (Saldanha, 1956; Manlapas, 1965). A high incidence of non-tasters has been reported in patients with nodular goiter, congenital athyreotic cretinism and dental caries (Facchini et al., 1990; Sheppard and Gartler, 1960). Higher frequency of non-tasters is reported in epileptic twins (Sharma K, 2005). Higher frequency of non-tasters suffers with epilepsy (Pal et al., 2004).

Today, it has been established that the ability to taste P.T.C. exhibits a strong dimorphism in human populations other factors like sex, age, the presence or absence of the saliva of the subject and also the strength of the test solution. These factors invariably modify the phenotypic expression and their genetic relationships to tasting and non-tasting alleles are not yet determined (Pal et al., 2004). The purpose of the study is determine PTC taste sensitivity among Manipuri Muslim males and females and discussed it with reference to variability and disease.

Material and methods

Populations

Manipur is a small hilly state, situated in the north eastern extreme corner of India that connects the Indian subcontinent to East Asia and South East Asia as a unique narrow passageway (Cordaux et al., 2004). Manipur is situated between 23.83^0 north latitude to 25.68^0 north latitude and 93.03^0 east longitude to 94.78^0 east longitude. It is bound by China in the North, Bangladesh in the South West, Bhutan in the North

West and Burma in the East and also isolated from the rest of India, both geographically and economically (Cordaux et al., 2004). The survey was conducted in the given districts of Manipur i.e. Imphal East, Imphal West, Thoubal, Ukhrul and Senapati taking various populations viz. Manipur Muslims belonging to biradari Sheikh, Syed, Pathan and Mughal, Meitei (Hindu) and Naga.

Manipuri Muslims comprises 8.32% of the total population according to the 2001 census and are mostly migrants who started coming to the state in the middle of the 16th century and they belong to Sheikh, Syed, Pathan or Mughal castes (Sharma and Badaruddin, 1991; Shah and Afzal, 2013, 2015). Meitei are presumably formed by the admixture of Koomal, Looang, Moirang and Meitei, all of whom came in different periods of time from different directions and now represent the clans of the community (Hodson, 1975). While the Naga are the indigenous tribal population of Manipur, they belong to the Naga-Kuki-Chin group of the Tibeto-Burman linguistic family and are believed to have migrated to Manipur probably between 300 and 400 years ago from Burma (Saha and Tay, 1990). The total sample size taken in present study is 1289 (Sheikh: 434, Pathan: 270, Syed: 163, Moghul: 80, Meitei: 146, and Naga: 196).

Methodology

Serial dilution method of Harris and Kalmus (1949) was employed to determine the taste threshold of individuals to PTC.

Genetic data analysis

The genotype and allele frequencies were calculated according to Hardy-Weinberg law. The level of heterozygosity was calculated using the formula,

$$\text{Hetrozygosity} = 1-\sum H_o$$

where H_o is the homozygosity of the allele,

$$H_o=\sum Pi^2$$

Chi-square test: It is used for the measurement of the size of the discrepancy between the observed and expected values at particular degrees of freedom.

$$\chi^2= \sum\frac{(\text{Observed-Expected})^2}{\text{Expected}}$$

Results

Phenotypic frequency

Table 1 shows the number and percentage of phenylthiocarbamide tasters and non-tasters in six different populations of Manipur. In all the populations studied, the numbers of tasters are considerably higher than non-tasters and are statistically significant (χ^2=54.283, df=5, *P*=0.00). The Naga population shows the highest taster frequency in both males and females (males 90.59% and females 92.35%), while the least taster frequency were observed in Pathan population (males65.38% and females 62.86%). Among Muslims Moghul shows highest PTC tasting ability (males75.47% and females 77.78%). Females show higher PTC tasting ability (χ^2=62.028, df=5, *P*=0.00) in comparison to males (χ^2=46.988, df=5, *P*=0.00) and the difference is statistically significant.

Table 1: Phenotypic frequency of PTC tasting ability in different populations of Manipur

Populations	n	Males		Females		Combined	
		Taster	Non taster	Taster	Non taster	Taster	Non taster
Sheikh	434	168 (71.19)	68 (28.81)	150 (75.76)	48 (24.24)	318 (73.27)	116 (26.73)
Pathan	270	85 (65.38)	45 (34.62)	88 (62.86)	52 (37.14)	173 (64.07)	97 (35.93)
Syed	163	30 (71.43)	12 (28.57)	90 (74.38)	31 (25.62)	120 (73.62)	43 (26.38)
Moghul	80	40 (75.47)	13 (24.53)	21 (77.78)	6 (22.22)	61 (76.25)	19 (23.75)
Meitei	146	50 (80.65)	12 (19.35)	70 (83.33)	14 (16.67)	120 (82.19)	26 (17.81)
Naga	196	77 (90.59)	8 (9.41)	104 (93.69)	7 (6.31)	181 (92.35)	15 (7.65)
Combined	1289	450 (74.01)	158 (25.99)	523 (76.8)	158 (23.20)	973 (75.48)	316 (24.52)

The value in parentheses represents the percentage. The chi-square (χ^2) values for phenotypic frequency in male (χ^2=46.988, df=5, *P*=0.00), Female (χ^2=62.028, df=5, *P*=0.00) and combined are (χ^2=54.283, df=5, *P*=0.00) are statistically significant.

Allele frequency

Table 2 shows allele frequency of PTC tasting ability in six different populations of Manipur and it is statistically significant (χ^2=24.603, df=5, *P*=0.00). Allelic frequency of *T* was found to be highest in Naga (0.513) while the least was observed in Pathan population (0.401). The Naga population again shows highest allelic frequency of *T* in both males and females (males 0.693 and females 0.723). Among Muslim highest allelic frequency of *t* was observed in Pathan (*t*=0.599) and least in Moghul population (0.487). Females (χ^2=28.93, df=5, *P*=0.00) show higher allelic frequency of *T*in comparison to males (χ^2=19.86, df=5, *P*=0.00) and the difference is statistically significant. The chi-square value for allelic variation differences between tasters and non-tasters differ in each population is 0.236 (df=5, *P*=0.01) (Table 3).

Table 2: Allele frequency of PTC tasting ability in different populations of Manipur

Populations	Males		Females		Combined	
	T	*t*	*T*	*t*	*T*	*t*
Pathan	0.412	0.588	0.391	0.609	0.401	0.599
Syed	0.465	0.535	0.494	0.506	0.486	0.514
Moghul	0.505	0.495	0.529	0.471	0.513	0.487
Meitei	0.56	0.44	0.592	0.408	0.578	0.422
Naga	0.693	0.307	0.749	0.251	0.723	0.277

The chi-square (χ^2) values for allele frequency in male (χ^2=19.86, df=5, *P*=0.0133), Female (χ^2=28.93, df=5, *P*=0.00002) and combined are (χ^2=24.603, df=5, *P*=0.00017) are statistically significant.

PTC threshold

The threshold values for PTC among six populations studied lies in the range of 8.28-9.75. In males threshold lies in the range of 8.425–9.47 while among females PTC threshold range is 8.33-10.51. Pathan population shows highest PTC threshold (males 9.47, females 10.01), while the least threshold is shown by Moghul (males 8.425, females 8.33) (Fig. 1).

Table 3: The chi-square (χ^2) values for allele frequency in different populations of Manipur

Populations	Tasters	Non- tasters
Sheikh	0.004	0.005
Pathan	0.032	0.036
Syed	0.004	0.004
Moghul	0.001	0.001
Meitei	0.004	0.005
Naga	0.061	0.079

Chi-square (χ^2) values for allele frequency between tasters and non-tasters differ in each population (χ^2=0.236, df=5, *P*=0.999).

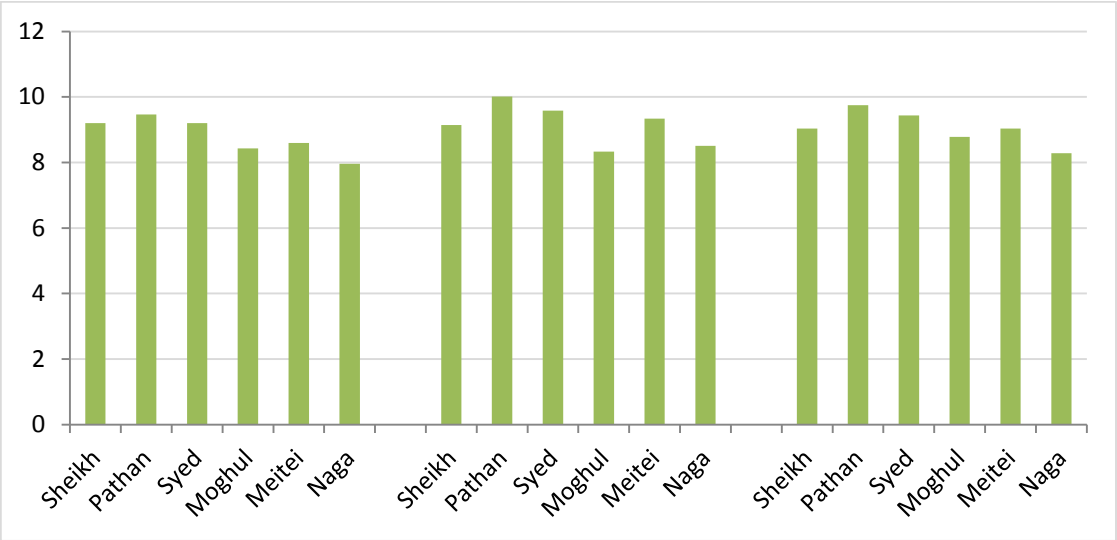

Figure 1: Threshold values of PTC tasting ability in different populations of Manipur.

Discussion

Tasting ability is also likely to be influenced by many other sensory and proprioceptive pathways, and the probable result is that no single genetic marker has a great effect. In particular, other pathways are likely to include olfactory contributions to food preference, although digestive and cognitive factors may complicate the overall system and modify the ability to perceive bitter taste (Timson et al., 2005). Bitter taste receptors are encoded by 25-30 TAS2R genes, located on chromosomes 12p13, 7q34, and 5p15 (Grimm and Steinle, 2011). The ligand specificity of TAS2Rs appears to be quite broad, consistent with their roles in detecting thousands of bitter-tasting compounds (Sausenthaler, 2009). One of these, TAS2R38 has been extensively characterized in vitro, in vivo, and in human populations, and is responsive to the bitter stimuli phenylthiocarbamide, propylthiouracil (PROP), and to thiocyanates – bitter compounds found in brassica vegetables such as Brussels sprouts and broccoli. Single nucleotide polymorphisms (SNP) located within a linkage disequilibrium block of these genes account for the association of taste, food preference and increase in weight (Sausenthaler, 2009).

The incidence of taste blindness to PTC/PROP varies around the world, from ~3% in western Africa to ~40% in India. Approximately 30% of the adult Caucasian population of North America are taste blind to PTC/PROP (i.e., are non-tasters) and 70% are tasters (Fenwick, 1983). The ability to taste PTC/PROP is present in young children and declines slowly with age (Whissell-Buechy, 1990). The frequency of allele *T* among Indian populations is 0.457 (varies from 0.108 among Munda of

Ranchi-Bihar to 0.912 in scheduled caste of Andhra Pradesh) which is little low as compared to Europeans but similar to that of Southwest Asian populations (Pal et al., 2004). In the present study the frequency of allele *T* varies from 0.412 to 0.693. Naga population shows the highest frequency of allele *T* and the least is shown by Pathan population. Naga (0.693) and Meitei (0.56) population shows higher allele frequency of *T* in comparison to other four Muslim populations. It has been reported that among the states of Nagaland, Tripura, Meghalaya, Sikkim and Darjeeling district of West Bengal, the populations with Mongoloid affinities, the frequencies of *T* allele are quite high (0.702, 0.597, 0.580, 0.694 and about 0.600, respectively) (Pal et al., 2004). This similarity is because Meiteis and Nagas belong to the Mongoloid origin or are at least more or less genetically influenced by it, while Muslims on the other hand are of Caucasoid origin shows lower *T* allele frequency.

The females show higher frequency of PTC tasting ability in all the populations studied with the exception of Pathan Population where males (65.38%) show higher percentage of tasters in comparison to females (62.86%). The overall taster frequency for female is 76.8% while that for males is 74.01%. The trait is reported to be more common among women than among men, and there is limited evidence that reproductive hormones may a role in its phenotypic expression (Whissell-Buechy and Wills, 1989). For example, one study found that girls who were PTC/PROP tasters matured ~3.8 earlier than girls who were non-tasters (Whissell-Buechy and Wills, 1989). The PTC taste thresholds also vary among six populations. Muslims with different castes also show differences in the distribution of these taste thresholds. The reason for these heterogeneities might be because of different ancestors of these castes, who started settling in different parts of the Manipur valley during different periods. In the present study, overall males were found to taste PTC at lower thresholds than females. The PTC heterozygous (*Tt*) genotypes were found to be more common as compared to dominant (*TT*) and recessive (*tt*) homozygous genotypes. Differences in heterozygosity, dominant and recessive homozygosity between populations was observed to be very minor. Heterozygosity increases the sensitivity to PTC as reported by Mennella et al., i.e., more heterozygous children perceived bitterness at the lower concentrations than did adults with the same genotype, with adolescents intermediate between adults and children (Mennella et al., 2010).

Virtually, all human populations studied to date display bimodality in sensitivity to PTC, such that approximately 75% of individuals worldwide perceive this compound as intensely bitter, while to others, this compound is relatively tasteless. This difference has motivated the use of PTC in many studies of taste perception in humans and over the past 70 years, these studies have provided many insights in human psychophysics and physiology (Kim and Drayna, 2004). On a larger scale, the PTC gene may be illustrative of ancient genetic variation that has been proposed to underlie common disease in modern populations (Mourao and Salzano, 1978). The PTC non-taster allele is common, both because it is very old and because it appears to confer selective advantage, at least in the heterozygote state (Fareed et al., 2012). Several studies showed that people who can taste PTC (taster) are more sensitive to salt, sweet foods, sharp tasting foods, spicy foods, and alcohol. Anatomical studies reported that tasters actually have more taste buds than non-tasters (Saraswathi et al., 2011). Tasters are also better in discriminating between high and low fat foods, such as various types of salad etc. (Volkers, 2003). Reported that non tasters like high fat diet more, than low fat diet, whereas tasters show the lack of preference for food (Keller et al., 2002). The taste of sucrose is more intensively sweet to tasters than to non-tasters. Increased frequency of non-taster allele is evident in children with

overweight/obese condition resulting in lack of preference for taste sensitivity in non-tasters (Bartoshuk et al., 2005). As phenotypic variation in PTC sensitivity is genetic in origin, this may represent a surrogate risk factor for the development of childhood obesity (Saraswathi et al., 2011). Many observations have suggested that lipid pathways involved in the etiology of congenital heart defects may be affected by tasting ability (Ueda et al., 2001). A preference for sweet and high-fat food was observed to decrease with increasing perception of bitter taste and further research highlighted relations between bitter compound–tasting ability and body mass index (BMI: kg/m^2), adiposity levels, and risk factors for cardiovascular disease (Duffy et al., 2004).

The PTC tastes blindness, though a classical trait is an important genetic marker which helps in understanding genetic variability. Like in the present study, all the six population shows variation in ability to taste PTC. Even Muslims with different caste have exhibited variation showing different ancestors of these castes, who started settling in different parts of Manipur valley during different periods. Meiteis and Nagas belong to the Mongoloid origin or are at least more or less genetically influenced by it, and can also been seen as they show higher tasting ability. Various studies have reported that Mongoloid populations of East Asia and Southeast Asia have the frequency of allele *T* as very high (about 0.70, ranges from 0.55 to 0.95). The frequency among Tibetans varies from 0.62 to 0.67 (Bhasin, 2006). There is no treatment for taste-blindness, nor is it usually the cause of any significant disability. As taste blindness study have been reported to help in understanding genetic variation in taste perception and food acceptance, the availability of genetic markers for tasting ability may offer insight into individual's risk of predisposition to child-hood obesity or obese traits (Saraswathiet al., 2011). Awareness of taste blindness trait in the population could also help in minimising the development of certain disease like cardiovascular disease, diabetes, etc.

Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

Thanks are due to the Department of Science and Technology (DST), New Delhi, for awarding INSPIRE Fellowship to the first author Ahsana Shah (No. IF10378) and to the Chairman, Department of Zoology, A.M.U., Aligarh (U.P), India, for laboratory facilities. I am also thankful to all the headmasters, teachers, students of various schools and also the individuals who participated as subjects in this study.

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