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SHORT COMMUNICATION

Variation in haplotype frequencies of the TAS2R38 gene, associated with the perception of bitter taste.

Variación en las frecuencias de haplotipos del gen TAS2R38, asociadas con la percepción del sabor amargo

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ABSTRACT

Introduction: bitter taste perception is a genetic trait that influences food preferences and alcohol consumption behavior. This study investigates the variation in haplotype frequencies of the TAS2R38 gene, associated with sensitivity to bitter compounds, in 26 populations from diverse geographic regions. Three single nucleotide polymorphisms (SNPs) are analyzed: rs713598, rs1726866 and rs10246939, which determine haplotypes such as PAV and AVI.
Objectives: the objective is to analyze the variation in haplotype frequencies of the TAS2R38 gene, which is associated with bitter taste perception, in 26 populations.
Method: data from the 1000 Genomes Project were used, analyzing 5 008 genotyped chromosomes from 26 populations grouped into five macro-populations: African, American, East Asian, European and South Asian. Haplotype and diplotype frequencies were calculated, assessing Hardy-Weinberg equilibrium by Chi-square test ($p<0,05$) using R software.
Results: the results showed that the overall frequency of TAS2R38 diplotypes is 32 % for PAV/PAV, 44 % for PAV/AVI and 24 % for AVI/AVI. African populations presented a high frequency of PAV/AVI (46,4 %), while European populations showed a higher prevalence of AVI/AVI (31,5 %). Significant deviations in observed versus expected frequencies were identified.
Conclusions: the variation in haplotype frequencies of the TAS2R38 gene reflects evolutionary adaptation to different dietary environments. These findings suggest that bitter taste genetics may influence food preferences and consumption behavior.

Keywords: Haplotypes; T2R38 Taste Receptor; Human; Taste Perception; Genetic Variation.

RESUMEN

Introducción: la percepción del sabor amargo es un rasgo genético que influye en las preferencias alimentarias y el comportamiento de consumo de alcohol. Este estudio investiga la variación en las frecuencias de haplotipos del gen TAS2R38, asociado con la sensibilidad a compuestos amargos, en 26 poblaciones de diversas regiones geográficas. Se analizan tres polimorfismos de nucleótido simple (SNPs): rs713598, rs1726866 y rs10246939, que determinan haplotipos como PAV y AVI.
Objetivos: el objetivo es analizar la variación en las frecuencias de haplotipos del gen TAS2R38, que está

asociado con la percepción del sabor amargo, en 26 poblaciones.
Método: se utilizaron datos del Proyecto 1000 Genomas, analizando 5,008 cromosomas genotipados de 26 poblaciones agrupadas en cinco macro-poblaciones: africana, americana, este asiática, europea y sudasiática. Se calcularon frecuencias de haplotipos y diplotipos, evaluando el equilibrio de Hardy-Weinberg mediante la prueba Chi-cuadrado ($p<0,05$) utilizando R software.
Resultados: los resultados mostraron que la frecuencia global de los diplotipos TAS2R38 es del 32 % para PAV/PAV, 44 % para PAV/AVI y 24 % para AVI/AVI. Las poblaciones africanas presentaron una alta frecuencia de PAV/AVI (46,4 %), mientras que las europeas mostraron una mayor prevalencia de AVI/AVI (31,5 %). Se identificaron desviaciones significativas en las frecuencias observadas frente a las esperadas.
Conclusiones: la variación en las frecuencias de haplotipos del gen TAS2R38 refleja la adaptación evolutiva a diferentes entornos dietéticos. Estos hallazgos sugieren que la genética del sabor amargo puede influir en las preferencias alimentarias y el comportamiento de consumo.

Palabras clave: Haplotipos; Receptor del Gusto TAS2R38; Humano; Percepción del Gusto; Variación Genética.

INTRODUCTION

The perception of bitter taste plays a role in the interaction between individuals and their environment, as it provides information about food and helps detect potential dietary hazards.[1] Bitter taste receptors (TAS2Rs) are a subfamily of G-protein-coupled receptors expressed not only in the oral cavity but also in various extraoral tissues and in different diseases. These receptors are involved in various biological processes and have shown anticancer effects in several types of cancer.[2,3] Genetic variation in TAS2Rs, such as TAS2R38, influences bitter taste perception and can affect food preferences and alcohol consumption.[4,5] The ability to detect bitter compounds is partially genetically determined, which can influence food perception, preferences, and consumption.[6]

There are three single nucleotide polymorphisms (SNPs) associated with bitter taste perception in the TAS2R38 gene that have been extensively studied: rs713598, rs1726866, and rs10246939. These SNPs form haplotypes such as PAV (proline-alanine-valine) and AVI (alanine-valine-isoleucine), which determine an individual's sensitivity to bitter compounds like phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP).[7] Although there are eight possible amino acid combinations, only six haplotypes have been identified in relation to taste sensitivity: PAV and AVI are the most common, AAI and AAV are rare, PAI and PVI are extremely rare, and AVV and PVV have been found only in individuals with pathologies.[8] The SNP rs713598 has the greatest effect on bitter taste signal transduction, followed by rs1726866 and rs10246939.[9]

Individuals homozygous for the PAV haplotype are more sensitive to bitter compounds, while those homozygous for AVI are insensitive.[7] Additionally, these SNPs are associated with alcohol consumption behavior, where individuals with the AVI haplotype tend to consume more alcohol and more frequently than those with the PAV haplotype.[10] These genetic variations can also influence food preferences and dietary behavior, reflecting a complex interaction between taste genetics and eating behavior.[11]

The objective of this study is to analyze the worldwide variation in haplotype frequencies of the TAS2R38 gene, in a sample comprising 26 populations and 5 macro populations, in order to contribute with new evidence on the regional differentiation of bitter taste.

METHOD

Data from the 1000 Genomes Project, which provides a comprehensive and detailed genomic database of various human populations worldwide, was utilized. This study analyzed 26 populations from different geographical regions, grouped into five macro-populations: African, American, East Asian, European, and South Asian. Each population includes a representative set of individuals, with a total of 5,008 genotyped chromosomes.

Three single nucleotide polymorphisms (SNPs) associated with bitter taste perception were analyzed: rs713598, rs1726866, and rs10246939. These SNPs form haplotypes that determine sensitivity to bitter compounds such as phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). The most common haplotypes identified were PAV (proline-alanine-valine) and AVI (alanine-valine-isoleucine), along with other rare haplotypes like AAI, AAV, PVI, PAI, AVV, and PVV.

Haplotype frequencies were calculated from phased genotype data using standard methods in R. For each population, the frequencies of the PAV and AVI haplotypes, as well as the rare haplotypes, were determined. Diplotype frequencies were calculated by combining the haplotypes of each individual. The most common diplotypes (PAV/PAV, AVI/AVI, and PAV/AVI) were analyzed in detail.

The Hardy-Weinberg (HW) equilibrium for the diplotypes of the TAS2R38 gene was evaluated both globally

and within each macro-population. Allele frequencies were calculated and used to determine the expected diplotype frequencies under HW equilibrium. Observed and expected frequencies were compared using the Chi-squared test, with a p-value < 0,05 considered statistically significant.

Statistical analyses were conducted using R software (version 4.1.0). Bar charts and pie charts were generated to visualize differences in frequencies between populations and macro-populations. Additionally, a global map of the frequencies of the three main diplotypes in the 26 populations was created using geospatial visualization tools in R, specifically the "rworldmap" package.

RESULTS

Table 1 shows the haplotype frequencies obtained in this study, as well as those reported in Boxer & Garneau.[1]

Table 1. Haplotype frequencies obtained in this study

Haplotype (DNA)	Haplotype (aa)	Count	Frequency (%)	Count	Frequency (%)
CCG	PAV	2523	50,4	978	42,3
GTA	AVI	2124	42,4	1227	53,1
GCA	AAI	272	5,4	28	1,2
GCG	AAV	80	1,6	59	2,5
CTA	PVI	3	0,1	2	0,1
CCA	PAI	2	0	18	0,8
GTG	AVV	4	0,1	0	0
CTG	PVV	0	0	0	0

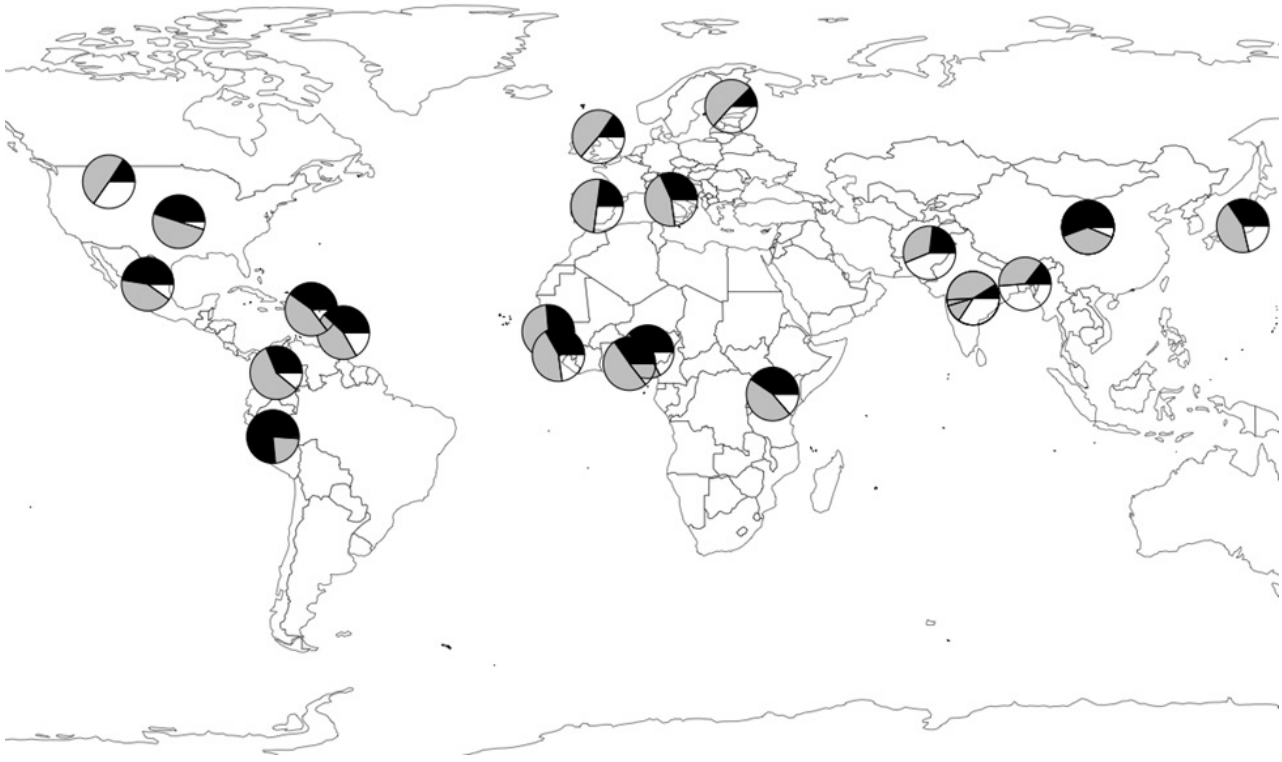

Figure 1. Global map of diplotype frequencies obtained in this study

The Chi-squared test comparing global distribution of haplotypes with the reported by Boxer and Garneau[1] was 985,5 (P= 0), indicating a highly significant difference between both data sets. The analysis of the TAS2R38 haplotypes revealed several significant deviations between the observed and expected frequencies. Notable excesses were observed for the AAI haplotype (4,62) and the PAV haplotype (2,63) in the current study, while significant deficits were noted for the AVI haplotype (-3,56) and the PAI haplotype (-3,17). In comparison to Boxer and Garneau[1], the observed excesses included the AVI haplotype (5,22) and the PAI haplotype (4,65), whereas deficits were prominent for the AAI haplotype (-6,85) and the PAV haplotype (-3,83). These deviations

highlight the significant differences in the distribution of haplotype frequencies, suggesting potential sampling bias or different population genetic structure between both samples.

Applying the Hardy-Weinberg (HW) test globally, a pchi2 of 2,4 x 10-7 was obtained, indicating that the frequencies of TAS2R38 diplotypes are not in Hardy-Weinberg equilibrium globally. At the level of the five macro-populations, only the South Asian macro-population was out of equilibrium (p = 0,036). Finally, at the level of the 26 individual populations, only the Punjabi from Lahore, Pakistan population was out of equilibrium (p = 0,03). These results suggest that although genotypic frequencies are in equilibrium globally and in most macro-populations and individual populations, there are significant exceptions in South Asia.

Globally, the frequencies of TAS2R38 gene diplotypes are as follows: PAV/PAV at 32 %, PAV/AVI at 44 %, and AVI/AVI at 24 %. This suggests that, worldwide, most of the population has an intermediate perception of bitter compounds, followed by a high perception, and to a lesser extent, a low perception.

Significant differences are observed when comparing between macro-populations. African populations (AFR) have a high frequency of PAV/AVI (46,4 %) and PAV/PAV (35,6 %), with a low frequency of AVI/AVI (18 %). In America (AMR) and East Asia (EAS), there is a high prevalence of PAV/PAV (49 % and 47,3 %, respectively) and a low frequency of AVI/AVI (9,2 % and 11,8 %, respectively). In contrast, Europe (EUR) and South Asia (SAS) show different patterns: Europe has a high frequency of AVI/AVI (31,5 %), while South Asia has an even higher frequency (39 %). Figure 1 shows a global map of the diplotype frequencies obtained in this study.

DISCUSSION

The results of this study shown considerable variation in the frequencies of TAS2R38 gene diplotypes among different macro-populations and individual populations. Globally, it is observed that most of the population has an intermediate perception of bitter compounds (PAV/AVI 44 %), followed by a high perception (PAV/PAV 32 %) and a lower proportion of low perception (AVI/AVI 24 %).[12] These findings are consistent with the idea that bitter taste perception is a genetically diverse trait, likely influenced by local adaptations.[13]

African populations have a high frequency of PAV/AVI (46,4 %) and PAV/PAV (35,6 %), while the frequencies of AVI/AVI are relatively low (18 %). This suggests that in Africa, the ability to perceive bitter compounds is prevalent, which could be related to diet and exposure to plant toxins.[2] In contrast, European and South Asian populations show a higher prevalence of AVI/AVI (31,5 % and 39 %, respectively), indicating a lower perception of bitter tastes. This pattern may reflect differences in dietary history and natural selection in these regions.[13]

A particularly interesting case is the Peruvian population, which stands out for its high frequency of bitter taste perception diplotypes. In this population, only 1 % has the AVI/AVI diplotype, indicating an almost total prevalence of bitter taste perception (PAV/PAV and PAV/AVI). This exception suggests a specific dietary adaptation in the Andean region, or well the result of genetic drift. Both hypothesis can be tested in further studies analyzing genomic signatures, around TAS2R38, in that population.

Notable exceptions to Hardy-Weinberg equilibrium at the global level and in the South Asian population suggest that additional factors influence the distribution of diplotypes in these regions. The deviation from equilibrium in the Punjabi from Lahore, Pakistan population could indicate an effect of genetic drift or sampling error. These findings underscore the importance of considering genetic variability and evolutionary factors when studying taste perception and its implications for health and dietary behavior.[7]

CONCLUSIONS

The variation in the frequencies of TAS2R38 gene diplotypes between and within macro-populations reflects the genetic diversity and evolutionary adaptation of human populations to their dietary environments. The ability to detect bitter compounds, partially determined by genetics, has significant implications for food preferences, alcohol consumption, and overall health. These results provide a basis for future research on the interaction between taste genetics, micro evolution, and dietary behavior in diverse populations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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