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Research Article

TAS2R38 gene in relation to *Helicobacter pylori* infection and blood groups in different age groups

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Abstract

Of the factors predisposing to gastric cancer is *Helicobacter pylori* infection affecting more than 50% of the general population. Genetic variation is an established player in certain diseases susceptibility. *TAS2R38* gene polymorphisms have been found to influence bitter taste ability to chemicals with malicious characteristics and consequently affect metabolism and disease development. This study aimed to investigate the correlation between *TAS2R38* gene polymorphisms and *H. pylori* seropositivity. The study involved 105 apparently healthy individuals. They were grouped into four groups according to their age and gender; young male, young female, middle-aged male and middle-aged female. All groups were tested for *H. pylori* serum antibody using screening rapid test. Participants were also tested for tasting PTC for *TAS2R38* gene detection by using Bartovation PTC test paper and grouped accordingly into: homozygote (highly bitter taste), heterozygote (slight to moderate bitter taste), or negative gene carrier (no taste at all). ABO and Rhesus- blood grouping was determined by standard serological analysis. Of the 105 patients, 22.85% were tested homozygotes for *TAS2R38* gene, 40.95% were heterozygotes and 36.19% were nontasters, no significant difference ($p > 0.9$). *H. pylori* seropositivity was encountered in 16.19% of the whole participants, 11.5% of the male participants and 20.75% of the female participants ($p > 0.9$). No significant difference in seropositivity was monitored among the four age groups ($p > 0.3$) and the ABO/Rh blood groups ($p > 0.9$). A lack of significant correlation (r = 0.046) between *H. pylori* antibody test positivity and tasting PTC (*TAS2R38* gene) was reported. Similarly, no association was found between PTC tasting and participants' ABO blood grouping, age or gender (r = 0.086, 0.083 and 0.029, respectively). Yet, weak negative (reverse) relationship (r = -0.29, *p*-value = 0.002) was gained between PTC and Rh grouping. No correlation was revealed between *TAS2R38* polymorphism and the studied variable; age, gender and blood group indicating the absence of an apparent role of the gene in vulnerability to *H. pylori* infection. Further studies involving a larger sample size is required to confirm the obtained result.

Keywords

Helicobacter pylori, *TAS2R38* gene, bitter taste, gastric ulcer

Introduction

Helicobacter pylori (*H. pylori*) infection has been reported to infect more than 50% of the global population (Danesh 1999). It has significantly been considered as a main predisposing factor for the development of gastric carcinoma (Hamilton and Aaltonen 2000; Tsuji et al. 2006) with 2-6 fold increase in risk (Eslick et al. 1999).

Eradication of *H. pylori* diminishes the chance for developing gastric malignancy especially in people with

high risk (Fukase et al. 2008). Gastric ulceration and tissue destruction owed to *H. pylori* infection varies from patient to patient, this might be attributed to the presence of certain genetic factors that might influence the ultimate consequence of *H. pylori* invasiveness (Hishida et al. 2010). Gastrointestinal chemosensing system functions to identify malicious compounds and induce process to eliminate or counteract them. By doing so, the alimentary tract promotes survival in the presence of these internal or external incentives. Hence, the molecular sensing of the GI system can act as an additional gate-keeper sideway with the taste perception in the oral cavity (Sternini et al. 2008; Carrai et al. 2011). Bitterness is a well-thought critical taste category that can influence food consumption and collections of bitter chemotoxins such as phytochemicals (Ames et al. 1990; Sandell et al. 2014). Therefore, oral and gastric perception of bitter taste, mediated via receptors of type 2 bitter-taste (*T2R*s and *TAS2R*s), may play as a potential warner for disease etiology. The highly polymorphic human *TAS2R* genes are located on chromosomes 5, 7 and 12 with the diplotype of *TAS2R38* has been well described (Kim et al. 2005). *TAS2R38* gene encodes a receptor that initiates the potential ability to palate the bitterness of phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). Globally, two forms of this gene has been reported; the PAV (Proline, Alanine, Valine, "PTC taster") and AVI (Alanine, Valine, Isoleucine, "PTC non-taster") haplotypes (Kim et al. 2003).

Studies have shown that the AVI haplotype differs in its molecular and phenotypic properties in comparison with the PAV haplotype characteristics. Consequently, it has been supposed that structural changes in *TAS2R38* caused by the genetic variations are pivotal elements in sensitivity to bitter taste of molecules harboring harmful characteristics (Bufe et al. 2005) and therefore, might influence metabolism and predisposition to disease. Researchers have recently focused their work on the association of *TAS2R38* genetic variation and GI anomalies. They have come up with the finding that the AVI haplotype or AVI homo-diplotype is linked with an increased risk of gastric and colorectal cancer (Carrai et al. 2011; Choi et al. 2017). Moreover, taste receptors have been suggested to be involved in defense against pathogenic bacteria, particularly Gram negative (Lee et al. 2012).

However, the association between *TAS2R38* genetic variation and *H. pylori* gastric infection, with the latter's correlation with GI cancer, is still questionable. Besides, studies have demonstrated a correlation between ABO- and Rhesus-blood grouping, age, and gender of peptic ulcer patients with seropositivity for infection with *H. pylori* (17-Kanbay et al. 2005; Jaff 2011).

Therefore, this study aimed to evaluate the potential correlation between variants of *TAS2R38* and seropositivity for *H. pylori*, ABO/Rhesus blood grouping, age and gender of the participants.

Materials and methods

Subjects and study strategy

A total of 105 apparently healthy persons composed of Mosul university/Iraq students and staff voluntarily participated in this study. They were divided into four groups according to age and gender; young male, young female, middle-aged male and middle-aged female (Lu et al. 2015). All groups were tested for *H. pylori* serum antibody using screening rapid test (Plasmatec) according to the manufacturer's instruction. Briefly, two drops of blood were drawn from each participant thumb into the specific sample well on a rapid test strip. Quickly two drops of the provided buffer were added and result was read after 5 minutes. Study contributors were also tested for tasting PTC for *TAS2R38* gene detection by using Bartovation PTC test paper. Briefly, PTC paper was placed on the participant's tongue and was asked for the resultant taste. This test is scaled for detection of: homozygote (highly bitter taste), heterozygote (slight to moderate bitter taste), or negative gene carrier (no taste at all). ABO and Rhesus-blood grouping was determined by standard serological analysis (Sajan et al. 2021).

Statistical analysis

The data was recorded and analysed by Excel Microsoft program and statistically analysed by Graphpad InStat 3. Samples age was expressed as mean ± standard deviation. Kruskal-Wallis Test (Nonparametric ANOVA) and Chi-square test were used for evaluating statistical difference among different subgroups. Spearman's nonparametric correlation was employed for estimating correlation coefficient and p-value between PTC tasting and the different variables studied. A p-value < 0.05 was considered significant.

Result

Sample features

The average age of the 105 subjects (males and females) involved in the study was 31.83 ± 10.72 year (mean ± standard deviation). Accordingly they were grouped into four groups; young male aged between 19–25 year (n=26), young female aged between 19–26 (n=28), middle-aged male aged between 30–50 year (n=26) and middle-aged female aged between 34–50 (n=26). Among all participants, 24 were found homozygous for *TAS2R38* gene (22.85%), 43 were heterozygous (40.95%) and 38 were negative gene carriers (36.19%). The most prevalent was blood group O (41.9%) followed by group A (35.2%), group B (15.2%) and finally group AB (7.6%). The majority of the participants (89.5%) were tested Rh positive.

Distribution of *H. pylori* positivity among the study groups

Of the 105 subjects enrolled in the study, only 17 (16.19%) were tested positive for *H. pylori* antibodies by the rapid test. Among the 24 subjects tested as homozygote for *TAS2R38* gene, four were found positive for *H. pylori* (16.6%). Eight out of the 43 heterozygotes (18.6%) were tested positive for *H. pylori* and 5 out of the 38 negative gene carriers (13.15%) were shown harboring the pathogen's antibodies. None of the Rh negative individuals was reported as *H. pylori* positive while 17 out of the 94 Rh positives (18.08%) were shown positive for *H. pylori* as well. Considering ABO blood grouping, the dominant blood group O also had the highest percentage of *H. pylori* positivity (8/44, 18.18%). Following was group A with 6 individuals out of 37 (16.2%) were positive for *H. pylori*. Three out of the 16 blood group B were positive for *H. pylori* while no one of the 8 subjects of blood group AB was positive for *H. pylori*. Distribution of *H. pylori* according to participants' genders showed that a higher percentage (20.75%) of positivity was reported for female gender compared to 11.5% in male contributors. Young participants of both genders had a higher percentage of *H. pylori* positive rate (18.5%) than middle-aged ones (13.72%).

Table 1. Descriptive data of the study groups.

	Total (N=105)	*p*-value	*H. pylori* positivity in each subgroup	*p*-value
	n (%)		n (%)	
TAS2R38				
Homozygote	24 (22.85%)		4 (16.60%)	
Heterozygote	43 (40.95%)	> 0.9	8 (18.60%)	> 0.85
Non-taster	38 (36.19%)		5 (13.15%)	
Gender				
Male	52 (49.5%)		6 (11.50%)	0.3
Female	53 (50.47%)		11 (20.75%)	(Chi-square)
Age group				
Young male	26 (24.76%)		3 (11.5%)	
Young female	28 (26.67%)		7 (25%)	> 0.39
Middle aged male	26 (24.76%)		3 (11.5%)	
Middle aged female	25 (23.80%)		4 (16%)	
ABO Blood group				
O	44 (41.9%)		8 (18.18%)	
A	37 (35.2%)	> 0.9	6 (16.21%)	> 0.9
B	16 (15.2%)		3 (18.75%)	
AB	8 (7.6%)		0	
Rh				
Rh+	94 (89.50%)		17 (18.08%)	0.26
Rh-	11 (10.47%)		0	(Chi-square)

p-value is calculated using Kruskal-Wallis Test (Nonparametric ANOVA) and Chi square test

Correlation of *TAS2R38* variants with study variables

Using non-parametric Spearman's correlation (Table 2), result demonstrated a lack of significant correlation (r = 0.046) between *H. pylori* rapid antibody test positivity and tasting PTC. Similarly, no correlation was encountered between PTC tasting (*TAS2R38* gene) and participants' ABO blood grouping, their age or gender (r = 0.086, 0.083 and 0.029, respectively). However, weak negative (inverse) correlation (r = -0.29, *p*-value = 0.002) was obtained between PTC and Rh grouping.

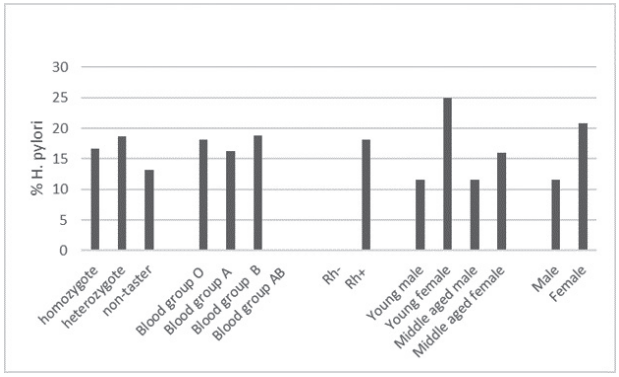

Figure 1. Percentage of *H. pylori* positivity to the total number of each subgroup.

Table 2. Correlation of *TAS2R38* with different measured variables.

Variables	Spearman *r*	95% CI	two-tailed *p*-value
H. pylori	0.046	-0.15 to 0.24	0.64
Rh	-0.29	-0.46 to -0.10	0.0020*
ABO Blood group	0.086	-0.11 to 0.27	0.37
Age	0.083	-0.11 to 0.27	0.39
Gender	0.029	-0.16 to 0.22	0.76

r, correlation coefficient; *, significant *p*-value using Spearman's non-parametric correlation; CI, confidence interval

Discussion

Infection caused by colonization of *H. pylori* at younger age is one of the leading cause of elderly gastric cancer due to the induced inflammation. This correlation can be elucidated from evolutionary viewpoint. The polymorphic *TAS2R38* gene has been found associated with a variety of people behaviors impacting their health status such as cigarette smoking behavior, alcohol consumption (Duffy et al. 2004; Ramos-Lopez et al 2015; Baker et al. 2018) and susceptibility to different cancers and bacterial infections particularly those of negative reaction to Gram stain (Gallo et al. 2013; Cantone et al. 2018). Non-taster (AVI/AVI), super-taster (PAV/PAV) and other intermediate combinations associated with intermediate phenotypes explains the different individual's acuity to the bitterness of the different bitter molecules.

In view of the premise that the AVI is apparently non-functioning and thereby confers a potential health weakness to the AVI/AVI people in regard to protection against infections and in safeguarding against the consumption of bitter-toxic materials, a remarkable question has been ascended of why this population has a comparatively international high frequency (Risso et al. 2016). The balancing selection that prefers the intermediate tasing heterozy-

gous phenotype could be a conceivable justification of this global trend (Kim et al. 2005). Similarly, more than 40% of the tested samples in the current study were heterozygous showing the highest percentage in comparison to the homozygotes (22.85%) and the non-tasters (36.19%). The lack of statistical significance among the three groups of PTC taster ($p > 0.9$) might be due to the small sample size encountered in the current evaluation.

Having the super-taster PAV/PAV genotype hypothesized to play a protective role against Gram negative infection, recent studies have confirmed this claim and showed a significant rareness of PAV/PAV genotypes in patients with chronic rhinosinusitis (one out of 28 chronic rhinosinusitis patients was detected as a super-taster) (Adappa et al. 2013). Another study also demonstrated a higher rate of AVI/AVI genotype among chronic rhinosinusitis patients when equated to the health control individuals of the same area (Cantone et al. 2018). Studies have justified this higher rate of Gram negative infections in people with nonfunctional *T2R38* allele to the blunted NO in response to the bacterial infection (Adappa et al. 2014).

Moreover, expression of *TAS2R38* receptors has been shown to stimulate the innate immune defensive response to quorum sensing bacterial molecules (Cantone et al. 2018). However, in our study we found that the number of *H. pylori* seropositive persons among the homozygotes is 4/24 (16.6%) complying no statistical difference to the heterozygotes and non-tasters (18.6 and 13.15%, respectively). This result might be due to genetic variation of the studied individuals compared to other population or due to the fairly small sample size tested. It also worth mentioning that the number of conducted studies is not large enough to draw a conclusive remark and that these studies involved individuals of Caucasian descent (Gallo et al. 2016; Cantone et al. 2018). Similar to our finding, Choi and Kim (2019) meta analyzed the published articles related to the association between *TAS2R38* and GI neoplasm and concluded that *TAS2R38* diplotype negligibly influenced the risk of GI neoplasm (Choi and Kim 2019). The authors also recommended larger, well-designed investigations to truly evaluate *TAS2R38* polymorphisms contribution in cancer and infection susceptibility.

On the other hand, ABO blood groupings have been reported to correlate with *H. pylori* infection. A number of studies demonstrate a significant link between blood group O and infection with *H. pylori* (Henriksson et al. 1993; Alkout et al. 1997; Hein et al. 1997; Lin et al. 1998; Kanbay et al. 2005). This higher tendency is likely to be due to the higher incidence of secretor status in blood group O subjects and to the expression of H antigen in the mucosal membrane of gastric tissue which acts as a receptor for *H. pylori* attachment and colonization (Alkout et al. 2000; Jaff 2010b). Blood group B and AB were found the least groups prone to *H. pylori* (Kanbay et al. 2005). However, and comparable with our finding, other studies were unable to prove this correlation (Loffeld and Stobberingh 1991; Dickey et al. 1993; Niv et al. 1996).

Considering Rh status, in the present study more than 89% were Rh+ and around 11% were Rh- which is in agreement with the normal distribution in some other provinces in Iraq (Jaff 2010a; Haider and Al-Maliki 2015). No significant difference is reported between *H. pylori* positivity and Rh status, this finding comes in accordance with other studies (Jaff 2011; Petrović et al. 2011). Moreover, a weak downhill but significant correlation was documented between Rh and *TAS2R38* status, though such result should require further investigation to confirm it considering the small sample size encountered in this study. Keller and his colleagues (2010) failed to establish a significant difference between taster and non-taster and participants' gender (Keller et al. 2010), however, they proposed from their study that sex, *TAS2R38* and thiourea phenotype interrelate to influence risk of developing obesity in children. Similarly, we could not find any correlation between *TAS2R38* and gender of the study subjects.

Conclusion

In spite of the significant investigational labors that have been paid previously, the pathophysiology of certain diseases are still unclear. For instance, we still have no logic answer for the reason why certain patients show higher likelihood to develop certain diseases or infections and why certain individuals demonstrate a better responsiveness to therapy while others demonstrate either weak, if at all, response to therapy or exacerbation of the disease course. Genetic plays a substantial role in individual's susceptibility to certain diseases and in response to therapy. Therefore, we tried here to find, if there any, a link between genetic predisposing factor; *TAS2R38*; and susceptibility to *H. pylori* as the main agent of gastric ulcer in individuals with different age, blood group and gender. It seems from the statistical difference and correlation, no difference between the study groups in terms of *TAS2R38* polymorphism, *H. pylori* seropositivity and seronegativity in the different age groups was encountered. Moreover, no correlation was revealed between *TAS2R38* polymorphism and the studied variable; age, gender and blood group indicating the absence of an evident role of the gene in susceptibility to *H. pylori*. These findings could be due to genetic variation among different population or and/or to the sample size. Further investigations including a larger population size and more specific detection techniques would be beneficial to prove the results.

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