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THE PREVALENCE OF TAS2R38 GENE PHENOTYPES AMONG THE PATIENTS WITH SOME ENDOCRINE SYSTEM DISORDERS

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Abstract

PTC (phenylthiocarbamide) is one of the focuses of interest from the medical point of view since a number of associations of the taster/nontaster status of PTC sensitivity with various human diseases have been found. It is estimated that ability of sense of PTC bitterness coded by a single gene TAS2R38. The threshold at which people can taste phenylthiocarbamide (PTC) is bimodal, and some people are tasters while, others are nontasters. In recent years, it is actively conducted the studies of genetic markers in various endocrine disorders. Endocrine diseases, particularly thyroid gland prevalence statistics in Georgia is very high. The goal of our research was to study the phenotype of PTC sensitivity among the patients with some endocrine system disorders in the population of Ajara region of Georgia, particularly diabetes type II and different type of goiter (nodular, diffuse etc.) to reveal any correlation between them. A total of 319 individuals including 136 patients with endocrine system and 183 randomly chosen healthy individuals participated in this study. Obtained results shows, that there is an increased incidence of diffuse toxic goiter in individuals with recessive phenotype of TAS2R38 gene and who are unable to taste PTC bitterness. While, PTC sensibility phenotype inclined to develop nodular goiter. Thus PTC- Sensibility phenotype may be considered one of the genetic markers in the forms of Goiter.

Keywords: TAS2R38 gene, PTC sensitivity, taster, nontaster, nodular goiter, diffuse goiter

1. Introduction

The ability of feeling the PTC (phenylthiocarbamide) bitterness represents one of the well-known and convenient genetic marker with regards to the phenotype or genetic structure of human populations and various biomedical studies [1,2,3] . Synthetic compound of phenylthiocarbamide cause the stimulation of bitterness receptors and feeling of bit taste, while in others do not . Accordingly, there are two phenotypes of PTC sensibility: PTC-taster (sensitive) and PTC-nontaster (insensitive). It should be mention, that phenotype of PTC sensibility is variable in different ethnic groups or populations [4,5,6,7]. The prevalence of taste blindness or an inability to taste bitter chemicals ranges from 3% in West Africa to 6–23% in China, 40% in India, and 50% in Australian Aborigens [8].

Mainly, it is estimated that ability of sense of PTC bitterness coded by a single gene TAS2R38 [9]. Geneticists offered different types of inheritance for the PTC sensitivity, including both single-locus and double-locus models [10]. Most family studies indicated the monogenic nature of the sensitivity to PTC. It was considered that the ability to sense the compound was controlled by a dominant allele of the autosomal gene, and the inability by a recessive allele [11].

The gene contains long exon (1002bp). Sensibility of bitterness is due to presence of three basic single-nucleotide polimorphism (SNPs) that encode three different amino acids (C145G/P49A, C785T/A262V and A886G/I296V) [12,13]. Those three polymorphic variations give 8 combinations (haplotypes), but among them the most frequent are two- PAV (taster) და AVI (nontater) haplotypes. AVI/AVI homozygotes mainly are nontasters of bitterness; PAV/PAV homozygotes are tasters, while AVI/PAV heterozygotes have the moderate sensitivity to bitterness. According to some researchers, the variability of PTC sensibility except of SNPs depends on other genetic and environmental factors [9].

The threshold at which people can taste PTC is bimodal, and some people are tasters and others are nontasters. Family and twin studies suggest that this trait is inherited as a Mendelian autosomal recessive, with two alleles typically represented as T – "tasting" allele and t – "nontasting: allele. Estimated that the majority of the world's population (approximately 70%) belongs to the PTC sensitive phenotype, and the rest 30% - to insensitive one [2]. It is interesting to know that according to these markers, different populations are characterized with different phenotype structure.

PTC is one of the focuses of interest from the medical point of view since a number of associations of the taster/nontaster status with various human diseases have been found. According to PTC sensitivity there was possible to reveal predisposition of some inherited or multifactorial diseases [14,15,16]. Moreover, it has been found that smokers and frequent drinkers were more prevalent among nontasters than tasters [17, 18].

Recently, the researches has proved that the carriers of PTC taster phenotype and the correspondent recessive allele of the gene are more inclined to the pathologies of thyroid glands (68%) than the PTC nontaster phenotype (32%), and, moreover, the detection of polymorphism of TAS2R38 gene at an early stage is the risk groups measuring factor, which, in turn will facilitate an implementation of preventive measures [13].

Prevalence of endocrine diseases, particularly thyroid gland pathologies in Georgia is very high. At the same time it is a fact that, the ability of PTC bitterness sensitivity represents one of the ethno-specific genetic markers, the phenotype of the gene is specific for each particular population among them for Georgians as well.

Thus, the goal of our research was to study of PTC - bitterness sensitivity phenotype among the patients with some endocrine system disorders, namely diabetes type II and different type of goiter (nodular, diffuse etc.) in the population of Ajara region of Georgia to reveal any correlation between them.

2. Materials and methods:

According to phenylthiocarbamide (PTC) sensitiveness the study to reveal different phenotype groups was done on the patients with various pathologies of thyroid gland (nodular goiter, diffuse goiter etc.) The main target group was the patients being registered Batumi endocrinology center (Ajara, Georgia).

319 patients were studied in total, where 136 patients (14 males and 122 females with different ages) were with endocrine system pathologies and 183 randomly chosen healthy individuals (115 Females and 68 males) from Batumi Shota Rustaveli State university students and personal without any thyroid gland pathologies as a control group. The research was made under the protection of the ethic principles of Helsinki Declaration *(World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects)*. Every participant of the experiment confirmed their consents in written form.

The research was based on Harris and Kalmus method [19]; we have used standard taster strips which contained 3,4 mg/kg PTC compounds. The participants fixed the taste sensitivity data of the tester in written form. According to the bitterness sensitivity with the data obtained via PTC testing, the participants of the experiment were divided into two groups: PTC sensitive "tastes" and PTC insensitive "nontasters" phenotypes.

The obtained results were mathematically processed applying the statistical method. We calculated the concentration of PTC gene allelic frequency of its propagation applying Hardy-Weinberg equation - $\mathbf{q^2+2q(1-q)+(1-q)}$, which reflects the distribution of genotypes in panmictic population. The authenticity of the obtained results was confirmed with the formula: $\mathbf{M=\pm\sqrt{p(100-p)/n}}$ Where, P denotes the percentage data, n – the number of the researched people.

3. Results and Discussions:

According to the experimental data majority of the patients has been diagnosed with different form of goiter (nodular and/or diffusive goiter, mainly toxic) and only few (16%) were with diabetes type II. Age of the individuals in the research groups and in the controls were ranged from 16 to 80 years old.
According to the experiment, revealed that part of individuals were tasting phenylthiocarbamide taste universal margin dose 3,4 mg/kg as a very bit taste, while other part of individuals were feeling moderate or little bit more bitterness, and rest part of patients has not been feeling PTC bitterness at all. PTC-insensible individuals have been feeling of only paper taste or none of the taste.
Obtained results has shown, that from the patients portion (136 individuals in total) with both of endocrine disorders (goiter and diabetes mellitus type II) 89 individuals were with PTC-taster phenotype, while 47 were PTC-nontaster. Accordingly, the percentage of PTC-taster phenotype carrier individuals amounted 65%±4.0 from whole research group, and individuals with PTC-nontaster phenotype amounted only 35%±4.0. As for the control group (183 individuals in total) 125 individuals were PTC-taster and only 58 PTC-nontaster. Accordingly, percentage of PTC-taster controls was 68% ±3.4 and the PTC-nontaster controls were 32%±3.4 (diagram 1).

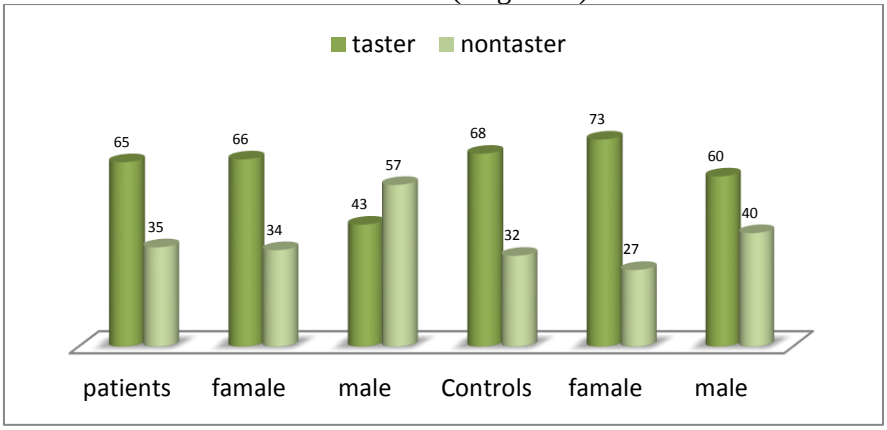

Diagram 1. The distribution frequency (%) of PTC sensitivity among the patients with endocrine system and control group in females and males

As we can see, the study revealed PTC-taster phenotype in the majority of patients with endocrine disorders (65%±4.0) as in control group (68%±3.4). The phenotype structure of PTC-sensitivity in endocrine system pathologies were analyzed according sex as well, to find out any correlation. In patients, PTC-taster females equaled to 66%±4,3 and PTC-nontasters 34% ±4,3; As for male

individuals, actually they were presented less in amount of the patients with endocrine disorders (14 males), where fixed 43% PTC-taster and 57% PTC-nontaster (diagram 1). The data was almost similar in control group number of females in the control group was 115 individuals from where 73%±4,1 of them appeared PTC-taster and 27% ±4,1 - PTC-nontaster. Apparently, the data shows that there is no any correlation between PTC-sensitivity and endocrine system pathologies. According to the obtained results, the distribution of PTC sensitive/taster phenotypes in patients with endocrine system disorders is almost similar to the Georgian population of control group. Accordingly any type of correlation with PTC-sensibility was not revealed in this research group.

The frequency of genotype has shown the following picture: patients – dominant homozygote TT – 0,16, heterozygote Tt – 0,49 and tt 0,35. In Controls TT – 0,27, Tt – 0,5 and tt – 0,23 (diagram 2).

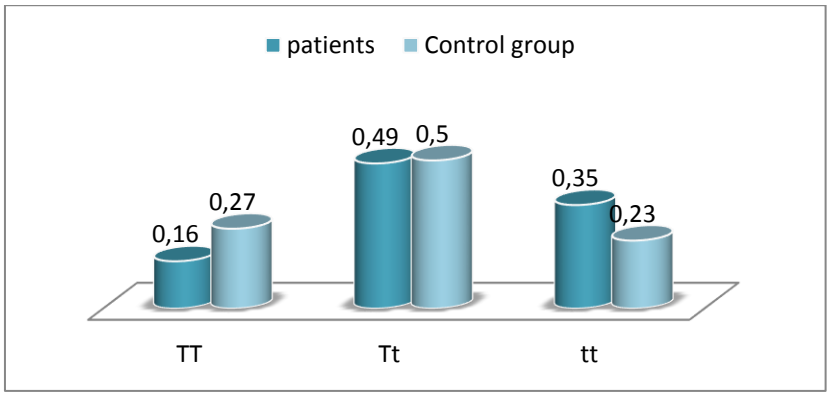

Diagram 2.The distribution frequency of PTC sensitivity genotype in patients and control group

The research of bitterness sensitive genotype frequency in female patients has shown following ratio: TT – 0.18, Tt – 0,48 and tt – 0.34. In male patients the picture was like that TT-0,06, Tt-0,38 and tt-0,56. In the control group males with PTC-taster phenotype equals to 60% of control group while PTC-nontaster is 40%. The genotype frequency in the given population is as follows: TT -0,13; Tt-0,47; tt-0,4.

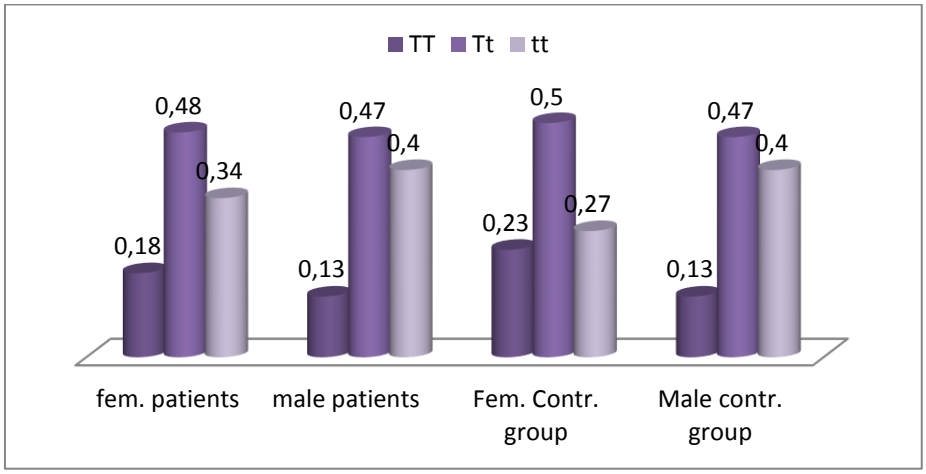

Diagram 3. The distribution frequency of PTC sensitivity genotype in control group and in patients according sex.

According to the obtained results, male patients are much more likely to have PTC-nontaster phenotype, which is proved with 40% in the control group and 57% in the patients with endocrine system disorders. However, due to the small number of male patients, it is difficult to prove that men tasters are more likely to have a tendency to develop endocrine system pathologies regardless there was some sign of inclination.

We tried to clear if there was any inclination according to concrete pathology not like as generalize. there was allocated following group of patients where 60% ±4,2 of patients have been diagnosed with nodular goiter, 16% ±3,1 of patients with diffuse goiter (mainly toxic form), 13%±2.8 of patients have been diagnosed with unidentified etiology and the rest 11%±2.6 with hyperthyroidism, hypothyroidism and an euthyroid. Among them our attention turned out nodular and diffuse goiter.
In the group of patients with nodular goiter the PTC-tasters were 62% ±4,2 of patients and 38%±4,2 PTC-nontesters, respectively. While in the patients with diffusive (toxic) form of goiter the PTC-tasters were pretty low - 36% ±4,2, while most of the patients 64%±4,2 was not able to sense PTC taste (diagram 4). Thus, we can conclude that PTC-taster phenotype is inclined to develop nodular goiter, while diffuse goiter is more likely associated with PTC-nontaster phenotype. This relationship between PTC and thyroid gland activity led by Harris, Kalmus, and Trotter to test the taste response to PTC of groups of patients with thyroid disease. Their data suggested that nontasters of PTC were slightly more susceptible to the development of adenomatous goiter than controls [19]. It had been revealed the high correlation with adenomatous goiter non-tasters in brazil [20]. However, our data contradicts results of the research conducted in endemic area of Brazil, where risk for first-stage diffuse goiter is little affected by taster status but that goiter in a nontaster is more likely to evolve into the nodular form [21].

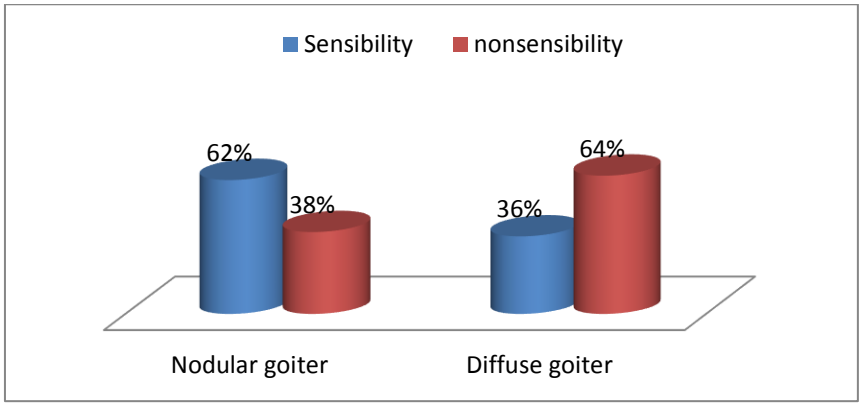

Diagram 4.The distribution frequency of PTC sensitivity phenotype in patients with different form of goiter

The distribution of genotypes in patients with nodular goiter prove the phenotype results as well which is presented on diagram 5(diagram 5).

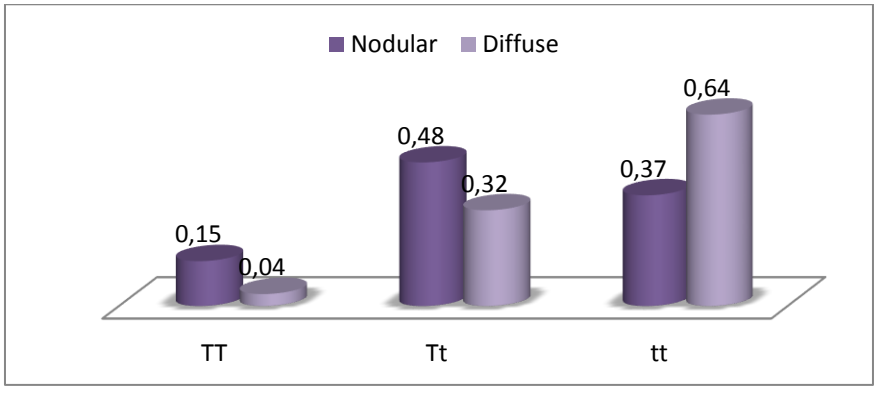

Diagram 5. The distribution frequency of PTC sensitivity genotypes in the patients in nodular and diffuse goiter.

4. Conclusions:

Based on to the results obtained, the analysis of the endocrine system pathologies shows that the phenotypic structure of the PTC sensitivity is slightly different from the general structure of the population, but the explicit correlation between the PTC sensation and the endocrine system different pathologies is not clear. At the same time, the PTC phenotypic structure is radically modified in patients with both of - nodular and diffuse (toxic) forms of goiter. The correlation of nontaster phenotype of PTC gene is quite clear with diffuse goiter (64%±4,2). While, PTC sensibility phenotype inclined to develop nodular goiter. The biochemical base of this pathology may be is an activation of strumogenic/thyreostatic factors supposedly, that leads depression of synthesis and secretion of thyroid hormones and ultimately violates the normal homeostasis of organism. Thus, recessive homozygote (tt) of the gene can be considered as one of the inclined genetic factors for diffuse goiter among various genetic markers associated with the multifactorial diseases, among them TAS2R38 gene recessive may considered as only one of those factors for diffuse (toxic) goiter. As for the results of diabetes melituss type II have not revealed any significant correlation with PTC sensitivity.

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