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Original Article

Genetically driven antioxidant capacity in a Caucasian Southeastern European population

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ABSTRACT

Previous studies have underlined the function of specific xenobiotic metabolizing phase–I or phase–II enzymes and endogenous antioxidant–related enzymes in the reduction and/or progression of oxidative stress and consequently the incidence of several diseases. In the present study, 10 polymorphic variants (rs4880, rs1799895, rs660339, rs1050450, rs1001179, rs28665122, rs1695, rs1138272, rs1051740 and rs2234922) were investigated in 1132 individuals of a Caucasian Southeastern European population. The frequency distribution of alleles and genotypes was compared to data of European (Northern, Central, Northwestern and Southwestern) and Global populations, extracted from the ensembl genome browser. The allele frequencies in the case of rs1051740 were similar to the frequencies noted in the global population. The majority of the present study allelic polymorphisms showed similar frequency distribution to those of the European or the Global populations ($0.88 \leq OR \leq 1.14$). The rs1051740 polymorphism demonstrated similar to the Global population frequencies ($OR = 1.09$). In conclusion, observed distributions of the polymorphisms studied in the Southeastern population demonstrate a positive impact (rs4880, rs1799895, rs660339, rs28665122) and a negative impact (rs1050450, rs1138272, rs109179, rs1695) against oxidative stress when compared to other population groups.

1. Introduction

Oxidative stress has been implicated in the formation of a variety of diseases, including cancer, neurodegenerative diseases, cardiovascular disease and diabetes (Baynes and Thorpe, 1999; Evans, 1993; Fischer and Maier, 2015; Hawk et al., 2016; Singal et al., 1998; Toyokuni, 1998). With regard to cancer and oxidative stress, several studies have focused on the contribution of specific xenobiotic metabolizing phase–I or phase–II enzymes (XREs) (Epoxide hydrolase, Glutathione S transferase) and endogenous antioxidant–related enzymes (AREs)(catalase, superoxide dismutase, glutathione peroxidase) (Conesa-Zamora et al., 2013; Geybels et al., 2015; Zhang et al., 2016). The presence of specific polymorphic variants of the aforementioned enzymes in certain human populations has been considered as a determining factor for the incidence of cancer. Polymorphisms in the coding region of genes encoding for XREs and AREs may affect enzymatic function (Nebert and Vasiliou, 2004; Saify et al., 2016).

The present study is focused on ten polymorphisms of 8 oxidative stress involved genes: rs4880 (SOD2), rs1799895 (SOD3), rs660339 (UCP2), rs1050450 (GPX1), rs1001179 (CAT), rs28665122 (SEPS1), rs1695 (GSTP1), rs1138272 (GSTP1), rs1051740 (EPHX1) and rs2234922 (EPHX1).

The SOD2 gene polymorphism rs4880 is located on chromosome 6 encoding isoform 2 of superoxide dismutase (Esih et al., 2017). The rs4880 polymorphism describes an amino acid alteration, resulting in lower MnSOD activity (Kim, 2010).

The SOD3 gene on chromosome 4 encodes the isoform 3 of superoxide dismutase (Kim, 2010). The rs1799895 decreases enzyme matrix binding, causing redistribution from the lungs to extracellular fluids (Mouradian et al., 2017).

A variation located on UCP2 gene, the rs660339, is associated with type 2 diabetes (T2D) and related complications (Zhou et al., 2016). The polymorphism is further associated with energy expenditure cost of excise (Astrup et al., 1999; Buemann et al., 2001; Wang et al., 2007).

The polymorphism rs1050450 of the gene encoding glutathione peroxidase (GPX1), results to substitution of proline with leucine and is reported to reduce enzyme activity (Bhatti et al., 2009; Hu and Diamond, 2003).

Catalase (CAT) detoxifies the O_2^- anions and H_2O_2, thus establishing the primary defence against reactive oxygen species ROS (Esih

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et al., 2017). The rs1001179 polymorphism of CAT gene, leads to alteration of the transcription factor binding site at the promoter region (Wenten et al., 2009). The presence of the mutant allele enhances gene transcription, although association with the enzyme activity remains unclear (Esih et al., 2017).

The polymorphism rs28665122 is located on SEPS1 gene, which encodes the selenoprotein P (Stoedter et al., 2010). This molecule is responsible for the retrotranslocation of misfolded proteins from the endoplasmic reticulum into the cytosol resulting in proteasomal degradation (Meusser et al., 2005; Todd et al., 2008). The rs28665122 affects the expression of selenoprotein P and enhances the production of inflammatory cytocines (Curran et al., 2005).

The GSTP1 gene encodes a glutathione S-transferase, a member of phase II enzymes (Yu et al., 2017). It is located on chromosome 11. The most reported polymorphisms are rs1695 and rs1138272. While rs1695 reduces the transferase activity, rs1138272 is associated with various disorders (Cornu et al., 2017; Stoehlmacher et al., 2002).

Polymorphisms rs1051740 and rs2234922 are associated with EPXH1 gene, on chromosome 1. Polymorphism rs1051740 decreases epoxide hydrolase activity and rs2234922 apparently enhances the activity by 25%, when compared to the wild-type expression of the protein (Zhang et al., 2015).

Aim of the present study is to investigate the frequency distribution of all above polymorphic variants in a Caucasian population of the Southeastern European region (Study population). Secondary scope is to compare the observed allelic and genotype frequency with published data of other populations from Northern, Central, Northwestern and Southwestern Europe (European population) as well as of Global population data.

2. Materials and methods

2.1. Sample collection

Genomic DNA of 1132 volunteers, 565 women and 567 men, was analyzed. No clinical information regarding their health status was provided and therefore the samples were considered to be part of a Caucasian Southeastern European general population. All volunteers provided written informed consent for the use of their data following their anonymization. No further demographic data were accessed to prevent volunteer re-identification. The study was approved by the Scientific Ethics committee of School of Pharmacy, National and Kapodistrian University of Athens.

2.2. Laboratory analysis

Epithelial cells were collected from the oral cavity of each volunteer using cotton buccal swabs. DNA was extracted using the Nycleospin DNA-extraction kit (Macherey-Nagel, Germany). Real-time Polymerase Chain Reaction (rtPCR) was used for DNA analysis, using LightSNiP kits (TIB MOLBIOL, Germany), according to the manufacturer's instructions. The examined genotypes were classified as homozygous for wild-type alleles, heterozygous and homozygous for mutant alleles of each studied polymorphism.

2.3. Statistical analysis

Contingency Tables 2 × 2 (1° of freedom, d.f.) were designed and odds ratio (OR), as well as their 95% confidence intervals (95% CI) were calculated. Statistical analysis was conducted at a significance level of 0.05. The P-value was calculated by Fisher's exact test. All polymorphisms were tested for Hardy-Weinberg equilibrium (HWE) using an open web-based software (Rodriguez et al., 2009). The population was assumed to be in HWE for a polymorphism if x^2 was less than the critical value of 3.84 (p = 0.05) for 2 × 2 table (1 d.f.) at a significance level a = 0.05.

Table 1
Allele and genotype frequency distribution of the 10 SNPs in Study, European and Global populations. Data for European and Global population derived from the ensembl genome browser (http://www.ensembl.org/index.html).

SNP	Population	% Allele		% Genotype		
SOD2		**C**	**T**	**C:C**	**C:T**	**T:T**
rs4880	Global	41.1	58.9	43.2	19.3	37.3
	European	46.6	53.4	46.6	47.9	29.4
	Study	49.0	51.0	22.4	53.3	24.3
SOD3		**C**	**G**	**C:C**	**C:G**	**G:G**
rs1799895	Global	97.6	2.4	95.4	4.5	0.2
	European	99.2	0.8	98.4	1.6	0.0
	Study	100.0	0.0	100.0	0.0	0.0
UCP2		**C**	**T**	**C:C**	**C:T**	**T:T**
rs660339	Global	58.4	41.6	33.6	49.5	16.9
	European	40.5	59.5	33.6	51.9	14.5
	Study	62.6	37.4	40.0	45.0	15.0
GPx1		**T**	**C**	**T:T**	**T:C**	**C:C**
rs1050450	Global	21.7	78.3	5.2	33	61.7
	European	33.6	66.4	10.1	46.9	42.9
	Study	30.0	70.0	8.8	47.3	43.9
CAT		**C**	**T**	**C:C**	**C:T**	**T:T**
rs1001179	Global	87.4	12.6	77.5	19.9	2.6
	European	76.5	23.5	58.3	33.6	5.2
	Study	76.3	23.7	57.3	37.5	5.1
SEPS1		**C**	**T**	**C:C**	**C:T**	**T:T**
rs28665122	Global	75.9	24.1	63.0	26.0	11.0
	European	86.6	13.4	75.0	24.0	1.0
	Study	87.6	12.4	77.0	22.0	1.0
GSTP1		**A**	**G**	**A:A**	**A:G**	**G:G**
rs1695	Global	64.7	35.3	43.4	42.7	13.9
	European	66.9	33.1	44.5	44.7	10.7
	Study	71.4	28.6	53.0	36.0	11.0
GSTP1		**C**	**T**	**C:C**	**C:T**	**T:T**
rs1138272	Global	96.6	3.4	93.4	6.5	0.1
	European	92.9	7.1	85.9	14.1	0.0
	Study	94.5	5.5	89.4	10.2	0.4
EPHX1		**T**	**C**	**T:T**	**T:C**	**C:C**
rs1051740	Global	78.5	21.5	49	11.7	39.3
	European	83.6	16.4	38.4	9.5	41.7
	Study	57.0	43.0	50.5	12.8	36.7
EPHX1		**A**	**G**	**A:A**	**A:G**	**G:G**
rs2234922	Global	78.5	21.5	62.6	31.7	5.7
	European	83.6	16.4	68.6	30	1.4
	Study	84.0	16.0	68.9	29.4	1.7

3. Results

The frequency of genetic distribution of polymorphic alleles in the study population is documented in Table 1.

Data collected for polymorphism rs4880 revealed that 22.4% of the Study population were homozygous wild-type (C:C), 53.3% heterozygous (C:T) and 24.3% homozygous for the mutant allele (T:T). The frequency of wild-type C alleles was 49% and that of the mutated T allele 51%. Polymorphism rs4880 was not in HWE in the population of the present study (x^2 = 4.89).

No volunteer of the Study population carried the mutant G allele of rs1799895 polymorphism, resulting in HWE disequilibrium for this very rare mutation.

Genomic analysis of rs660339 demonstrated that 40% of the examined population were homozygous wild-type (C:C), 45% heterozygous (C:T) and 15% were classified as homozygous mutant (T:T). According to these data, the C allele appeared in 62.6%, while the T allele exhibited a frequency of 37.4%. The polymorphism was in HWE (x^2 = 1.88).

Polymorphism rs1050450 was present at a frequency of 43.9% for the homozygous wild-type (C:C) carriers, whereas 47.3% of the participants were heterozygous (C:T) and 8.8% homozygous mutants out of 1132 participants. The frequency of the wild-type C alleles was 30%, while the mutant T demonstrated a frequency of 70%. This polymorphism was not in HWE (x^2 = 6.85).

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