Journal of the American Society of Hypertension 9(11) (2015) 902–906

Short Communication

Gender-specific protective effect of the −463G>A polymorphism of myeloperoxidase gene against the risk of essential hypertension in Russians

Olga Bushueva, MD, PhD*, Maria Solodilova, PhD, Vladimir Ivanov, MD, PhD, and Alexey Polonikov, MD, PhD

Department of Biology, Medical Genetics and Ecology, Kursk State Medical University, Kursk, Russian Federation

Manuscript received January 20, 2015 and accepted August 6, 2015

Abstract

The purpose of this study was to investigate whether a common polymorphism −463G>A (rs2333227) in the promoter of myeloperoxidase (MPO) gene, an oxidant enzyme producing hypohalogenic radicals, is associated with the risk of essential hypertension (EH) in Russian population. A total of 2044 unrelated subjects including 1256 EH patients and 788 normotensive controls were recruited for this study. Genotyping of the MPO gene polymorphism was done using TaqMan-based assay. A genotype −463GA was associated with decreased risk of EH (odds ratio = 0.82; 95% confidence interval: 0.68–1.00) at a borderline significance level ($P = .05$). The gender-stratified analysis showed that a carriage of the −463GA and −463AA genotypes is associated with decreased EH risk only in females (odds ratio = 0.74, 95% confidence interval: 0.56–0.96; $P = .02$). To the best of our knowledge, this is the first study reporting a negative association between the −463G>A polymorphism of the MPO gene and EH risk. Molecular mechanisms by which MPO gene is involved in the pathogenesis of EH are discussed. J Am Soc Hypertens 2015;9(11):902–906.

Keywords: Essential hypertension; gender dimorphism; genetic polymorphism; myeloperoxidase; oxidative stress.

Introduction

Essential hypertension (EH) represents a multifactorial disorder determined by the interaction of environmental and genetic factors.[1] Oxidative stress, a pathologic condition characterized by imbalance between the generation of reactive oxygen species and antioxidant defense systems, has been implicated to pathogenesis of EH.[2] Several oxidative stress-related enzymes are expressed in vasculature where they contribute to increased production of reactive oxygen species.[3] Myeloperoxidase (MPO), a heme-containing enzyme, catalyzes a reaction between hydrogen peroxide and chloride-producing oxidant hypochlorous acid (HOCl).[4] A common substitution −463G>A in the promoter of the MPO gene causes a loss of binding site for a transcription factor SP1 thereby decreasing gene expression.[5] Several studies reported that increased MPO activity is associated with increased risk of cardiovascular disease[6,7] It is suggested that the MPO gene may be involved in the pathogenesis of hypertension via mechanisms related to endothelial dysfunction and decreased bioavailability of nitric oxide.[8,9] A single study has been done to investigate the association between the MPO −463G>A polymorphism and EH susceptibility in a small population sample of Chinese patients.[10] This study failed to demonstrate a relationship between the polymorphism and hypertension risk. The present study was designed to investigate whether the −463G>A polymorphism of the MPO gene is associated with the risk of EH in a large Russian population from Central Russia.

Materials and Methods

The study was approved by Ethical Review Committee of Kursk State Medical University. A total of 2044 unrelated

Conflict of interest: None.

Funding: The study was supported by the Russian Research Foundation (contract No 15-15-10010).

*Corresponding author: Olga Bushueva, MD, PhD, Department of Biology, Medical Genetics and Ecology, Kursk State Medical University, Karl Marx Street, 3, 305041 Kursk, Russian Federation. Tel: +7(4712) 58-81-47; Fax: +7(4712) 58-81-47.

E-mail: olga.bushueva@inbox.ru

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2015.08.006

Russian individuals from Central Russia (predominantly from Kursk region) were recruited for this study. The participants included 1256 EH patients (663 males and 593 females) and 788 healthy subjects (385 males and 403 females) with normal blood pressure. Hypertensive patients were enrolled from Cardiology Division of Kursk Regional Clinical Hospital and Neurology Division of Kursk Emergency Medicine Hospital over two periods: from 2003 to 2006[11] and from 2010 to 2013.[12] Diagnosis of EH was verified by qualified cardiologists according to the World Health Organization criteria: Hypertensive patients had established hypertension defined by a seated systolic and/or diastolic blood pressure greater than 140 and/or 90 mmHg, respectively, on at least two separate measurements. All EH patients had no clinical signs, symptoms, and laboratory findings suggestive of secondary hypertension. Control subjects were enrolled from Kursk hospitals (patients with traumatic, surgical, or infectious diseases) and during periodic medical examinations at public institutions and industrial enterprises of Kursk region. Healthy individuals were included in control group if they had a systolic blood pressure less than 130 mm Hg and/or a diastolic blood pressure less than 85 mm Hg on at least three separate measurements and without any chronic diseases. The mean age of EH patients was 56.0 ± 10.5, and the mean age of controls was 55.8 ± 8.9. Approximately 8–10 mL of venous blood was collected and put into EDTA-coated tubes from each subject of the study and stored at −20°C until use. Genomic DNA was isolated from peripheral blood samples using a standard phenol/chloroform procedure. Genotyping of the −463G>A polymorphism (rs2333227) of the MPO gene was done by TaqMan-based assay on the CFX96 Real-Time PCR Detection System (Bio-Rad Laboratories, USA) using a protocol described in SNP500Cancer database.[13] The genotyping results were scored by two independent investigators blindly to the patient's case/control status and re-genotyping of 5% of randomly selected samples yielded 100% reproducibility. The association between the polymorphism and EH risk was estimated by odds ratio (OR) with 95% confidence interval (CI) and adjusted for confounding factors using multiple logistic regression analysis. ORs were calculated as a measure of the association of the MPO genotype with hypertension risk, with the effects of the −463A allele assumed to be additive (with scores of 0, 1, and 2 assigned for GG, GA, and AA genotypes, respectively), dominant (with scores of 0 for GG genotype and 1 for GA and AA genotypes combined), or recessive (with scores of 0 for GG and GA genotypes combined and 1 for AA genotype). The statistical significance was established at $P \leq .05$. Statistical calculations were performed with STATISTICA for Windows 8.0 (StatSoft Inc; Tulsa, OK, USA).

Results

Baseline characteristics of study population are presented in Table 1. As can be seen from Table 1, significant differences in body mass index, family history of hypertension, and smoking status were observed between the case and control groups. Data on allele and genotype frequencies are shown in Table 2. The MPO genotype frequencies were in agreement with Hardy–Weinberg equilibrium in EH and control groups ($P > .05$). No significant difference in the −463A allele frequency was found between hypertensive patients and healthy controls. Meanwhile, the frequency of heterozygote genotype −463GA was lower in EH patients than in controls (OR = 0.82; 95% CI: 0.68–1.00; $P = .05$). Taking into account the possibility of sexual dimorphism in gene-disease association,[14,15] we evaluated a gender-specific effect of the polymorphism on disease susceptibility. The gender-stratified analysis showed that a carriage of the −463GA and −463AA genotypes (dominant genetic model) is associated with decreased EH risk only in females (OR = 0.74; 95% CI: 0.56–0.96; $P = .02$). Meanwhile, additive ($P = .11$) and recessive ($P = .24$) genetic models did not show a significant effect of the −463G>A polymorphism on EH risk.

Discussion

The −463G>A polymorphism is located within an Alu-encoded hormone response element[16] of the MPO gene, and the G allele creates an SP1 binding site in the promoter,[5] whereas the A allele forms a binding site for estrogen receptor-α.[17] Functional studies showed that genotype −463GG is associated with higher expression levels of mRNA and protein compared with the −463GA and

Table 1
Baseline characteristics of study population

Baseline Characteristics	EH Patients	Controls	*P*-Values
Age, mean ± standard deviation	56.0 ± 10.5	55.8 ± 8.9	.15
Gender: number of males (%)	663 (52.8)	385 (48.9)	.08
Body mass index (kg/m^2), mean ± standard deviation	27.1 ± 6.4	26.3 ± 5.9	.005*
Positive family history of hypertension	732 (63.1)	397 (56.3)	.004*
Smokers	797 (66.4)	482 (62.0)	.04*

EH, essential hypertension.
* Means a significant difference between the groups.