ORIGINAL ARTICLE

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THE POLYMORPHIC VARIANT RS11646213 IN THE CDH13 GENE IS ASSOCIATED WITH SUSCEPTIBILITY TO ARTERIAL HYPERTENSION IN BULGARIAN FEMALE SUBJECTS

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Abstract. Objective: *Genome-wide scan identifies CDH13 as a novel susceptibility locus contributing to blood pressure in different European populations. The gene encodes the adiponectin receptor and the calcium-dependent cell-cell adhesion glycoprotein T-cadherin, with roles in neoangiogenesis and vascular remodeling. A meta-analysis of replication case-control studies showed significant evidence of association between the polymorphic variant rs11646213 in the CDH13 gene with arterial hypertension (AH). The aim of this study was to explore the possible association between the rs11646213 (CDH13) and the risk of AH in Bulgarians (Caucasian, Eastern European).* ***Materials and methods:*** *We performed a case-control study to determine the prevalence of rs11646213 in the CDH13 gene in Bulgarian individuals; to evaluate whether this polymorphic variant was associated with the risk of AH in the Bulgarian population, and to determine the precise direction of influence. A total of 791 subjects were included in the current study. Of them, 297 were patients with AH and 494 – population-based controls from different parts of the country. Genomic DNA was extracted from venous blood samples. The polymorphism rs11646213 in the CDH13 gene was genotyped with the TaqMan SNP Genotyping Assay platform. Non-adjusted χ^2-based analysis was applied for the evaluation of CDH13 genotype and allele association with AH by using PLINK 1.07.* ***Results:*** *The frequencies of CDH13 genotypes and alleles AA, AT, TT, A and T in the control group were 16,8%, 49,6%, 33,9%, 41,6% and 58,4% and 15,5%, 43,4%, 41,1%, 37,2% and 63,8% in the AH group, respectively. No significant genotype and allele associations were found in the general Bulgarian population. Interestingly, in subgroup analysis, the rs11646213 TA genotype showed a positive association with a decreased risk of AH (p = 0.01) in Bulgarian females.* ***Conclusions:*** *In our study, we found a positive sex–dependent association between the rs11646213 TA genotype and decreased risk of AH in the female group. The contribution of CDH13 to the risk of developing AH remains unclear, especially in this sex-dependent manner and has to be clarified by further genetic and functional analyses.*

Key words: *arterial hypertension, Bulgarian females, CDH13, polymorphism*

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INTRODUCTION

The CDH13 gene was identified as a significant genetic factor influencing blood pressure and the risk for arterial hypertension (AH). A genome-wide association study (GWAS) found a common variant, rs11646213, upstream of the CDH13 gene, associated with blood pressure traits and AH in European populations. The rs11646213 variant near CDH13 was associated with lower diastolic and systolic blood pressure, and a reduced risk of AH in several European cohorts. This discovery highlighted the potential of CDH13 as a target for understanding and treating hypertension. It is well known that CDH13 is involved in vascular wall remodelling and neoangiogenesis, important processes in vascular tone [1, 2]. It is also a receptor for adiponectin, which may play an additional role for patients with changes in their weight.

European-ancestry cohorts played a pivotal role in identifying BP-associated loci, with studies suggesting that genetic variants may have different effect sizes across ancestries due to linkage disequilibrium and environmental interactions [3]. The identification of novel loci and variants in European populations underscores the need for precision medicine approaches in defining susceptibility to and management of AH [4].

The regulation of blood pressure is a complex trait influenced by multiple genes and environmental factors. The CDH13 is one of many genes identified through GWAS that contribute to blood pressure variability [5, 6]. The genetic architecture of blood pressure involves numerous loci with small effects, and CDH13 is part of this polygenic framework [7].

In a Korean population, CDH13 variants were associated with metabolic traits and carotid atherosclerosis, suggesting a broader impact on cardiometabolic health. The study found that minor allele carriers of the CDH13 variant rs12444338 had a lower risk of hypertension, although this association was marginal after adjusting for confounders, indicating a complex relationship between CDH13 variants and AH [8].

It is of practical and scientific importance to study the possible association between CDH13 and AH, especially in a very high-risk cardiovascular population such as Eastern European.

MATERIALS AND METHODS

We performed a case-control study to determine the prevalence of rs11646213 in the CDH13 gene in Bulgarian individuals and to evaluate whether this polymorphic variant was associated with increased or decreased risk of AH in the Bulgarian population.

Genomic DNA was extracted from venous blood samples. The polymorphism rs11646213 in the CDH13 gene was genotyped by the TaqMan SNP Genotyping Assay platform. Non-adjusted χ^2-based analysis was applied for the evaluation of CDH13 genotype and allele association with AH by PLINK 1.07.

A total of 751 subjects were included in the current study. Of them, 257 were patients with AH and 494 were population-based controls from different parts of the country.

The present research included examinations of groups of individuals with AH. The subjects were referred from the USHATE „Acad. Ivan Penchev“, Department of Endocrinology, Medical University, Sofia, Bulgaria, and the Clinic of Cardiology, UMHAT “Alexandrovska”, Sofia, Bulgaria. Population controls were selected from the DNA biobank of the Molecular Medicine Center (MMC), Department of Medicinal Chemistry and Biochemistry, Faculty of Medicine, Medical University – Sofia.

The selection criteria for patients with AH were as follows:

Inclusion criteria: 1. Age between 18 and 70 years; 2. Diagnosis of AH or medication for it; 3. The duration of primary AH is at least 1 year.

Exclusion criteria: 1. Age below 18 and above 70 years; 2. Duration of the anamnesis for AH is less than one year; 3. Decline to sign an informed consent statement in genetic testing; 4. Acute coronary syndrome with or without ST-segment elevation, with indication for emergency coronary angiography; 5. Acute ischemic or hemorrhagic stroke, or within 6 months of surviving it; 6. Acute heart failure; 7. Chronic heart failure with ejection fraction ≤ 35%; 8. Acute renal failure; 9. Patients with end-stage renal failure or on hemodialysis; 10. Acute or advanced chronic liver failure; decompensated hyper- or hypothyroidism (thyroid hormone excretion in the last 6 months within normal limits); 11. Epilepsy; severe anemia or blood loss requiring blood transfusion; 12. Known deficiency of Vit. B12 – uncompensated; 13. Poorly controlled diabetes

mellitus with evidence of frequent hypo- or hyperglycemia, and hypo- or hyperglycemic coma; 14. Severe or moderately severe asthenic-dynamic syndrome; 15. Established alcohol abuse; known psychiatric illness; 16. Diagnosis of Alzheimer's disease or dementia of another type; 17. Severe Parenchymal kidney or liver damage; 18. Decompensated thyroid diseases; 19. Pituitary disorders.

The selection of patients with primary AH was performed so as to exclude cases with secondary (symptomatic) AH due to endocrine, renal or other disorders leading to elevated BP values. The strict exclusion criteria were necessary to make the studied population clearer.

The baseline characteristics of patients with AH are summarized in Table 1. It is evident from the table that the group studied had poorly controlled AH despite medical treatment and dyslipidemia.

Table 1. Basic characteristics of patients with essential AH

Indicator	Value±SD/number (percentage)
Age (years)	51.91±17.01
Sex (male)	72 (33.49%)
BMI (kg/m2)	28.31±6.5
Total cholesterol (mmol/l)	5.24±1.15
Triglycerides (mmol/l)	1.71±1.35
LDL (mmol/l)	3.79±1.11
HDL (mmol/l)	1.16±0.37
Systolic blood pressure (SBP) (mmHg)	143.40±18.33
Diastolic blood pressure (DBP) (mmHg)	89.09±12.05

RESULTS

The frequencies of CDH13 genotypes and alleles AA, AT, TT, A and T in the control group were 16,8%, 49,6%, 33,9%, 41,6% and 58,4% and 15,5%, 43,4%, 41,1%, 37,2% and 63,8% in the high blood pressure group, respectively. No significant genotype and allele associations have been found in our study of the general Bulgarian population. Interestingly, in subgroup analysis, the rs11646213 TA genotype showed a positive association with a decreased risk of AH (p=0.01) in Bulgarian females (Table 2).

DISCUSSION

The CDH13 variants were involved in the regulation of blood pressure through their effects on gene expression in tissues relevant to physiology, such as the heart, kidney, and arteries [9, 10]. The gene is part of complex regulatory networks that include interactions with other genes and pathways, such as those involved in cell adhesion and junction, which are critical for vascular function [11].

Although AH is a multifactorial disease, the CDH13 gene is a promising target for understanding its pathophysiology. Genetic predisposition, environmental factors, and lifestyle choices all contribute to hypertension risk. Additionally, the variability in genetic penetration and associations in different populations renders the transition from "bench to bedside „in molecular studies difficult [12]. Studies in rat models showed that chromosome 13, which included the CDH13 locus, played a role in blood pressure regulation, with certain genetic backgrounds associated with protection against AH [13, 14]. Experimental studies in mice lacking exon 3

Table 2. Distribution of allele and genotype frequencies for polymorphic variant rs11646213 in the CDH13 gene in the group of patients with AH and the population group of individuals with Bulgarian origin

Chr.	Polymorphic variant	Model	Allele/ genotype	Total				Male				Female			
				AH N (%)	Controls N (%)	OR	P	AH N (%)	Controls N (%)	OR	P	AH N (%)	Controls N (%)	OR	P
16	*CDH13* rs11646213 A>T	Genotypic	TT	46 (15.59)	83 (16.80)	-	0.10	8 (9.52)	40 (16.67)	-	0.27	38 (17.84)	43 (16.93)	-	**0.01**
			TA	129 (43.43)	245 (49.60)			44 (52.38)	111 (46.25)			85 (39.91)	134 (52.76)		
			AA	122 (41.08)	166 (33.60)			32 (38.10)	89 (37.08)			90 (42.25)	77 (30.32)		
		Allelic	T	221 (37.21)	411 (41.60)	0.83 (0.67-1.03)	0.08	60 (35.71)	191 (39.79)	0.84 (0.58-1.21)	0.35	161 (37.79)	220 (43.31)	0.80 (0.61-1.03)	0.09
			A	373 (62.79)	577 (58.40)			108 (64.29)	289 (60.21)			265 (62.21)	288 (56.69)		
			C	539 (95.23)	906 (92.45)			154 (95.06)	449 (93.15)			385 (95.30)	457 (91.76)		

of the CDH13 gene showed that these mice had higher resting and physical activity blood pressure, highlighting T-cadherin's role in blood pressure regulation and response to physical stress [2].

Another potential mechanism for interaction was that CDH13 promoter SNPs acted as methylation quantitative trait loci (meQTLs), influencing methylation levels and potentially affecting gene expression and hypertension susceptibility. The CDH13 gene, encoding T-cadherin, was associated with arterial hypertension through its promoter SNPs, which acted as meQTLs influencing DNA methylation and cardiometabolic traits, including diastolic blood pressure [15].

The CDH13 variants, particularly rs4783244, were strongly associated with plasma adiponectin levels, influencing both total and high-molecular-weight adiponectin. The CDH13 variants significantly influenced adiponectin levels, suggesting a unique role in metabolic health and adiponectin sensitivity, unlike other hypertension-related genetic factors that may not directly affect adiponectin. This highlights CDH13's distinct function in metabolic regulation [16, 17]. The CDH13's association with adiponectin levels suggested a unique role in modulating HDL-C levels, indicating that it may function differently from other hypertension-related genetic factors by acting as a pathway-suppressor, thereby influencing cardiovascular health through adiponectin regulation [16].

Furthermore, CDH13 variants were associated with metabolic syndrome traits, such as insulin resistance and lipid profiles, independent of visceral fat mass. The CDH13's association with adiponectin levels suggested it may contribute to an adiponectin-resistant state that promotes metabolic syndrome traits [18].

The precise association between CDH13–T cadherin and adiponectin is still under exploration. Our results have a confirmatory significance. A similar association with a protective effect on blood pressure was found in the Mexican population [19]. However, the gender-dependent manner remains unexplained for us. A similar gender-dependent manner was found for the correlation between metabolic syndrome and the variant in the Swedish population [20].

CONCLUSION

The association between CDH13 and adiponectin levels has significant implications for understanding its function in relation to hypertension and other metabolic conditions. The CDH13 encodes T-cadherin, a receptor for adiponectin, which plays a crucial role in metabolic regulation. Variants in CDH13 have been linked to adiponectin levels, influencing metabolic syndrome traits and cardiovascular outcomes. This relationship highlights the complex interplay between genetic factors and metabolic health, suggesting that CDH13 may have a unique role compared to other hypertension-related genetic factors.

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Patient consent: *Informed consent was obtained from all individual participants included in the study.*

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