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CDKN2B-AS1 gene rs4977574 polymorphism in the severity of coronary artery disease in the Kazakh population

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Abstract

Coronary artery disease (CAD) is one of the leading diseases contributing to mortality. Although it has a hereditary nature, its genetic etiology remains unclear. Recently, many studies showed genetic risk factors using genome-wide association studies, and gene variant association with CAD. Despite the recent breakthroughs on various single nucleotide polymorphisms (SNP) linked to CAD, encompassing genes affecting metabolic disorders, influencing endothelial and smooth muscle dysfunctions, leading to plaque formation and myocardial infarction, most of those SNPs` functions remain to be pinpointed. Many studies showed significant associations between rs4977574 polymorphism of cyclin-dependent protein kinase inhibitors antisense RNA 1 (CDKN2B-AS1) gene on CAD in various ethnic groups. This review discusses the potential link between the CDKN2B-AS1 gene rs4977574 polymorphism and CAD in the Kazakh population.

Keywords: coronary artery disease, CDKN2B-AS1, rs4977574

Introduction

Genetic and environmental factors are the primary causes of pathological alterations in coronary artery endothelial tissue and vascular smooth muscle cells [1]. Advancements in coronary artery injury lead to Atherosclerotic plaque formation [2]. Despite the thorough studies on the potential causes of CAD, there is still a huge gap to fill [3]. Based on the existing scientific evidence, environmental factors such as smoking, obesity, high blood pressure, etc., and genetic factors such as single nucleotide polymorphisms are considered to explain CAD origin [4].

The hereditary influence on the development of coronary artery disease has been investigated since the mid-20th century, which was facilitated by the study of the history of cardiovascular disease within families. Remarkably hereditary effects were most pronounced in young adults [5].

Among all loci, the region of chromosome 9p21 has been studied especially well and makes up about 15-35% of carriers with an increased risk of coronary artery disease [6]. Although the exact mechanism of this locus is currently unknown, it is hypothesized that variants of this locus affect the expression of antisense non-coding RNA at the INK4 locus (inhibitors of cyclin-dependent kinase 4). The latter affect changes in the activity of CDKN2A and CDKN2B, which play an important role in the regulation of the cell cycle and proliferation of endothelial cells [7].

Previous studies have substantiated the potential protective role of CDKN2A/2B in VSMC proliferation and atherosclerotic changes. CDKN2A/2B belongs to the CDK inhibitor gene family and is considered to be a significant tumor suppressor gene [8]. The CDKN2A/2B gene comprises four exons, namely, 1α, 1β, 2, and 3, coding for two distinct proteins: P16INK4a (P16) and p14ARF (P14) and located at 9p21.3 [9]. The p21.3 band on the short arm of human chromosome 9 is broadly studied and many potential polymorphisms on this locus were linked to CAD. Specifically, human CDKN2B-AS1 gene polymorphism rs4977574 is linked to CAD onset [10]. Although this gene is located at the intron of the CDKN2A/2B gene, it has been proposed to have

a direct effect on the expression level of the CDKN2A/2B gene [11]. Although reported studies demonstrated the high prevalence of CDKN2B-AS1 gene rs4977574 polymorphism on CAD onset, there is still no commonly accepted consensus. Studies in Turkish [12] and Chinese [13] populations explored the significantly higher frequency of the G allele of the CDKN2B-AS1 gene rs4977574 polymorphism in myocardial infarction patients compared to controls, whereas the WTCCC study involving the British population showed lower G allele frequency [14]. We hypothesize this may be the result of ethnic background and, consequently any lifestyle differences of each population. Taizhanova D. et al showed a significant association of rs4977574 polymorphism in the Kazakh population (p-0.02). In this study, authors showed a significant association of four polymorphisms rs762551 (p=0.019), rs12976411 (p=0.011), rs2242480 (p=0.017), and rs4977574 (p=0.02) with CAD compared control groups [15]. However, the Bonferroni correction for multiple comparisons did not show any significant correlations in this study [15]. Although there is a lack of studies investigating on SNPs of 9p21.3 locus in the Kazakh population, other SNPs on other locus were studied. Karabayeva et al. showed a significant association of rs2407103, rs11775334, and rs2071518 polymorphisms on the 8th chromosome to myocardial and coronary artery remodeling [16]. Hua et al. showed significant relevance of the G allele of rs4977574 and the C allele of rs1333045 to CAD in the Chinese population, including Kazakh ethnic groups. The study included in total of 855 patients, where 598 patients with CAD and 297 were controls. In this study, high serum levels of apolipoprotein A (ApoA) were correlated with the AG + AA genotype of rs4977574 compared to those with the GG genotype (P=0.028) [13].

Role of CDKN2B antisense RNA 1 in CAD

The CDKN2A/2B gene is located approximately 100 kb apart from the chromosome 9p21 risk gene [17]. The p16 protein (p16INK4a), a member of the INK4 family, and p14arf are two proteins encoded from this region. The influence of p16 protein on CDK4 and CDK6 halts the transition of cells from the G1 phase to the S phase (Figure 1). Whereas the p14arf protein has a role in the activation of the p53 tumor suppressor [18]. Both proteins display widespread expression across various tissues and cell types and their somatic mutations are observed in cancer cells [19]. Suppression of cell proliferation and regulation of the cell cycle of VSMCs is one of the main mechanisms in atherosclerotic plaque formation leading to CAD. CDKN2B-AS1 gene rs4977574 polymorphism interacts with polycomb repressive complexes 1 and 2. Later leads to a decline in CDKN2A/2B expression [8,20]. Increased expression of the CDKN2B-AS1 gene upregulated in peripheral blood mononuclear macrophages carrying the G allele of the rs4977574 polymorphism has been shown [21]. Such increased expression may indicate increased cell proliferation, respectively, an increase in adhesiveness, and the appearance of atherosclerotic plaques. Another study showed that patients with CAD had reduced levels of CDKN2A and CDKN2B, again highlighting the association between this locus and CAD [17].

Other studies have shown statistically significant correlations between the level of transcription of CDKN2B-AS1 and the severity of coronary artery disease, this was justified by the fact that CDKN2B-AS1 affects the remodeling of the extracellular matrix and the modification of the vascular structure [22]. Qiao et al. showed a reliable correlation between the rs4977574 polymorphism and biomarkers, revealing a significantly increased risk of elevated HbA1c levels in individuals with the GG + GA genotype [23]. These data may indicate that rs4977574 may affect the function of pancreatic cells, and eventually lead to diabetes mellitus. Diabetes mellitus 2 increases the risk of coronary artery disease. Violation of glucose metabolism leads to the early development of coronary artery disease. It has been shown that transcription products of the CDKN2B-AS1 gene under the influence of risky SNP loci can regulate the expression of genes that are responsible for the metabolism of glucose and lipids in the blood, such as ADIPOR1, VAMP3, and C11ORF10 [24].

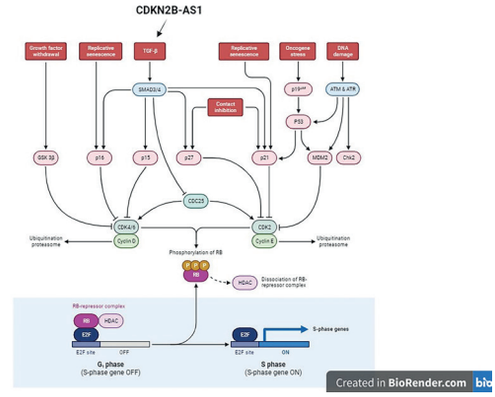

Figure 1 - Schematic representation of TGF-β signaling pathways regulated by CDKN2B-AS1 in EC and SMC. EC - endothelial cells; SMC- smooth muscle cells. Created in BioRender.com.

Huang et al. conducted a meta-analysis of the rs4977574 polymorphism in the CDKN2B-AS1 gene and its involvement in the severity of CAD. Since their case-control study deviated from the Hardy-Weinberg equilibrium (HWE), the results of the involvement of the rs4977574 polymorphism in the progression of CAD were questionable [25]. Another study showed similar results in an Asian population and confirmed the results of Huang et al., where the G allele was shown to contribute to an increased risk of CAD [26].

There were many studies conducted which are departed from HWE, although all of them showed a great association between rs4977574 polymorphism and CAD [25]. In the current understanding, rs4977574 polymorphism and CAD association should be analyzed categorizing participants into subgroups by ethnicity.

Conclusion

Despite all the existing evidence showing a significant association of rs4977574 polymorphism to CAD severity, further studies are needed to elaborate concrete mechanisms and discrepancies in different populations. Environmental factors differ in different ethnic groups, further studies are suggested to take this into account. Studies conducted among the Asian population certainly validate the potential relevance of rs4977574 polymorphism to CAD risk. However, there are very few studies published pertaining Kazakh ethnical group, therefore further studies are needed to elaborate on the significance of rs4977574 polymorphism to CAD in the Kazakh population.

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