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9p21.3 Polymorphism is Not Associated with Coronary Artery Disease, But with its Severity and its Early Onset in Type 2 Diabetic Population

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Keywords

Severity of CAD; Early-onset CAD; Coronary Artery Disease; T2D; Chromosome 9p21.3; Single Nucleotide Polymorphism

Multiple large-scale genome-wide association studies found that he human 9p21.3 chromosome locus is an independent risk factor for atherosclerosis. In our previous studies, we explored the association of variant rs1333049 on chromosome 9p21.3 with CAD in Tunisian type 2 diabetic patients [1]. We also investigated the association of the severity and early onset of coronary artery disease with variant rs1333049 on chromosome 9p21.3 polymorphism and the impact of this single nucleotide polymorphism on cardiovascular risk factors in a group of type 2 diabetic patients [2]. Genotyping of variant rs1333049 on chromosome 9p21.3 was performed in type 2 diabetic patients who were undergoing coronary angiography to evaluate suspected or established CAD. Our findings demonstrated no significant association of rs1333049 polymorphism on chromosome 9p21.3 with CAD in diabetic coronarian patients, but it demonstrated that this polymorphism confers a magnified risk of early-onset and severe CAD in type 2 diabetic Tunisian population.

The association of genetics and environmental factors (such life-style) play a major role in the pathogenesis of coronary artery disease (CAD) and type 2 diabetes (T2D). The genetic architectures of CAD and T2D are dependent on multiple genetic and environmental triggers that may be specific to each disease. The chromosome 9p21.3 has been identified as the locus with strongest association to coronary artery disease in multiple independent large-scale genome-wide association studies [3-5]. Since rs1333049 polymorphism on chromosome 9p21.3 has a strong association with CAD [10], we hypothesized that such a SNP on chromosome 9p21.3 may have an amplifying impact on early onset and severity of CAD. Our studies were the first to evaluate the association between 9p21.3 and CAD in Tunisian population. Our purpose was to investigate the relationship between one SNP (Single Nucleotid Polymorphism), rs1333049, on chromosome 9p21.3 for susceptibility to CAD, the effect of this SNP on cardiovascular risk factors, severity and early onset of CAD in type 2 diabetic Tunisian population.

Many genome-wide association studies have shown that genetic variations on chromosome 9p21.3 were associated with increased risk of diabetes and CAD in the general population [3-5,6].

Interestingly, Doria et al [7]observed that the homozygous GG genotype of rs2383206 on chromosome 9p21.3 had a greater effect on the risk of CAD in diabetic patients than CC genotype in the general population. In the present study, we found that the homozygous CC genotype of rs1333049 was associated with severity of CAD in diabetic patients. Furthermore, in our population, CC genotype carriers had significantly higher smoking, hypertension, hyperlipidemia, family history of CAD and obesity percentages than non-CC genotype carriers, it's the same for BMI, LDL-C and TG levels. These observations suggest that these factors are important risk factors of CAD for the diabetic patients in the Tunisian population.

In a family-based study, Meng et al [8] observed that chromosome 9p21.3 is associated with early-onset CAD in the Irish population. In the present large-sample study, we found that, after investigating its association with traditional risk factors, homozygous CC genotype carriers were found to have an increased risk for early-onset CAD in diabetic patients. Moreover, among diabetic patients with early-onset CAD, CC genotype carriers had significantly higher Gensini scores than non-CC genotype carriers. These observations suggest that there may be a common genetic basis for diabetes and CAD in a homozygous genotype of chromosome 9p21.3 [9].

In our studies on the homozygous CC genotype of rs1333049 of 9p21.3 polymorphism, we demonstrated that it is not associated with CAD in a Tunisian population [1]. However, it confers a magnified risk of early-onset and severe CAD in type 2 diabetic patients [3].

The risk of CAD associated with 9p21.3 variant was increased in the presence of poor glycemic control in type 2 diabetes [7]. Also, as one of the risk equivalents of CAD, patients with diabetes often had an increased atherosclerotic burden and inflammatory process in the coronary artery tree [10-11]. Thus, Wang et al hypothesized that certain locus on chromosome 9p21.3 might have its effect in a common pathway of diabetes and CAD [13]. In a recent study, Chen et al revealed no association between coronary atherosclerotic plaque progression and polymorphism on chromosome 9p21.3 in Caucasian population [14]. Admittedly, this cross-section study was not designed to seek possible association of 9p21.3 with CAD in a special diabetic population. Furthermore, genetic effect of variant rs1333049 on chromosome 9p21.3 on angiographic coronary disease progression in Chinese patients remains unclear.

The mechanisms of severity of CAD and T2D in patients with acute coronary syndrome (ACS) are complex, and they are not so clear at present. While many genetic studies [15], for CAD and T2D, have identified the 9p21.3 locus as a common risk region, there are no functional variants (non-coding variants) within this region. Therefore, the link between the 9p21.3 locus and the genetic backbones of these two diseases remains poorly understood.

Case-control studies like ours have advantages for identifying disease-related genes, they have limited power to detect gene-environment interactions. Therefore, a prospective cohort study is needed to better elucidate the roles of genetic and environmental factors, and of their interactions, in CAD development [16].

Recent genome wide association studies found association of a common allele on chromosome 9p21 with coronary artery disease in the general population [17,18]. In another

study of our team, we investigated the association of variant rs1333049 on chromosome 9p21.3 with CAD in type 2 diabetic Tunisian patients and if the association is modified by the severity of hyperglycemia, the defining characteristic of diabetes [19]. We demonstrated that 9p21.3 locus and poor glycemic control interact in determining the risk of CAD in type 2 diabetes. These findings may help us to understand implications of atherogenesis in diabetes and for the design of more effective prevention strategies.

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