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Matrix metalloproteinase-1 and matrix metalloproteinase-12 gene polymorphisms and the risk of ischemic stroke in a Tunisian population

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ABSTRACT

Matrix metalloproteinases (MMPs) play an important role in early atherosclerosis, extracellular matrix remodeling, plaque rupture and myocardial infarction. MMP gene polymorphisms contribute to the risk of developing cardiovascular diseases. In this study, we investigated, for the first time, the association between MMP-1-16071G/2G, MMP-12 -82A/G and MMP-12 1082A/G genotypes and haplotypes and the risk of ischemic stroke (IS) among patients with type 2 diabetes mellitus (T2DM). To examine whether these genetic polymorphisms are associated with susceptibility to IS, 196 patients with IS and 192 controls were examined by PCR-based RFLP. When the analyses were adjusted for multiple risk factors, no interaction between T2DM and MMP-1-1607 1G/2G polymorphism on the risk of ischemic stroke was found ($p = 0.074$). However, MMP-12 polymorphisms genotypes were associated with the higher risk of IS in diabetic patients compared with total patients. The -82G-1082G haplotype of MMP-12 polymorphisms was associated with higher risk of ischemic stroke in diabetic patients [AOR = 2.33; 95% CI (1.25–3.62), $P = 0.032$]. These findings showed that there was an important joint effect of the MMP-12 polymorphisms and T2DM on the risk of IS and therefore it can be considered as a potential marker of cerebrovascular disorders in diabetic patients.

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1. Introduction

Stroke physiopathology is complex at the molecular level and involves a wide variety of proteins, including the matrix metalloproteinases (MMPs) [38]. Extracellular matrix (ECM) remodeling is an essential process in the pathogenesis of atherosclerosis and coronary heart diseases (CHD). Matrix metalloproteinases (MMPs) a family of peptidase enzymes are secreted by many types of cells as proenzymes. On activation by proteolytic cleavage, activated enzymes are capable of degrading many extracellular matrix components, resulting in weakening the fibrous cap and predisposing the atherosclerotic plaques to disruption and embolic events. Because MMPs appear to be involved in monocyte invasion and vascular smooth muscle cell migration, derangement of MMP regulation is considered to be a critical factor in the development of vascular lesions [46] and remodeling which is recognized as a determinant of major vascular pathologies including atherosclerosis and restenosis [29]. MMP expression can vary among individuals due to genetic diversity, which could influence the susceptibility of presenting with vascular disease [14]. Genetic polymorphisms located in the promoter region of the MMP genes could lead to increased gene expression and could be associated with predisposition to various diseases [55]. Overexpression of MMPs enzymes in advanced lesions may contribute to the thinning of the plaque cap and to the development of ischemic events resulting from plaque rupture [3]. MMP-1 and MMP-12 genes contain single nucleotide polymorphisms. Most of the investigated polymorphisms have previously been shown to alter the gene expression [26,47]. MMP-1 is the only MMP that can cleave native collagen types I and III, which are major structural components of the fibrous plaque cap. MMP-1 might play a significant role in fibrous plaque disruption by contributing to the degradation of interstitial collagens and thinning of the fibrous cap [39]. A single-guanine (1G)-to-(2G) polymorphism located at the MMP-1 promoter region (MMP-1-1607 1G/2G, rs1799750) that affects the transcription level of the gene has been identified. It has been demonstrated that the promoter comprising the 2G allele has significantly greater transcriptional activity compared with the 1G promoter, because the 2G allele creates an E26 (Ets) transcription factor binding site and increases transcription capacity [47]. MMP-12 displays a broad substrate specificity, including ECM proteins such as fibronectin,

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laminin, vitronectin, type IV collagen, and heparan sulfate [5,15]. MMP-12 not only digests elastin, but also degrades the basement membrane, which enables macrophages to penetrate injured tissues during inflammation. The A allele of the MMP-12 -82A/G polymorphism (rs2276109) shows a higher affinity for the transcription factor activator protein-1 (AP-1) and higher gene expression in reporter gene assays [26]. The MMP-12 1082A/G (357Asn/Ser, rs652438) polymorphism is located in the coding region of the hemopexin domain that is responsible for MMP-12 activity, while the function of this polymorphism remains unknown [25]. Studies have found that polymorphisms in MMP genes that modulate their transcription or activity are associated with the outcome of the coronary artery disease (CAD). Studies assessing the effects of polymorphisms in the MMP-1 on cardiovascular events have found inconsistent associations [16,43]. The MMP-1-16071G/2G variant has been associated with the risk of coronary heart disease and with several cancers also [22,27,40,41,56,57]. The 2G allele has been linked to increased incidence or progression of several diseases, including periodontitis [1,7,21,31,45], cardiovascular disorders [43,57], coronary heart disease in diabetes mellitus patients [10], arteriosclerosis [42], degenerative disc disease [50], endobronchial tuberculosis [29], arthritis [37] and lung conditions [24,36]. -1607 2G allele is also the independent significant risk factor for carotid plaque presence [9]. In addition, a common functional MMP-12 (-82A/G) promoter polymorphism that increases expression of MMP-12 is associated with increased coronary artery stenosis in diabetic patients [26] and it has been associated with coronary atherosclerosis [54,55]. MMP-12 -82A/G was also associated with coronary artery aneurysm formation in patients with Kawasaki disease with the G allele conferring increased risk [48]. The MMP-12 rs2276109 gene polymorphism may contribute to susceptibility to systemic sclerosis (SSc), and in particular to diffuse cutaneous SSc (dcSSc) and pulmonary fibrosis in an Italian population [34]. The functional significance of the second single-nucleotide polymorphism MMP-12 1082 A/G (rs652438), is unclear, but has been correlated with breast cancer outcome [49]. MMP-12 expression levels were found to be upregulated in recurrent versus non-recurrent stage IB lung cancer [6] and correlated with local recurrence and metastasis [20]. Haplotype analysis was performed to investigate the combined effect of some linked MMP polymorphisms and some diseases. A study showed that haplotypes of MMP-1 and MMP-12 were associated with the decline of lung function [27]. Some MMP polymorphisms were shown to be associated with both atherosclerosis and chronic obstructive pulmonary disease [17,52]. In addition, a trend of the GG-A haplotype of MMP-1 -16071G/2G and MMP-12 1082A/G towards the prediction of future clinical events was found in patients with CAD (coronary artery disease) [23]. We hypothesized that the joint effects or haplotypes of MMP polymorphisms are stronger than the individual effect of each polymorphism and because MMP-1 and MMP-12, genes are clustered on chromosome 11q22.3, we therefore addressed, for the first time, whether there were any associations between MMP-1-16071G/2G, MMP-12 -82A/G and MMP-12 1082A/G genotypes and haplotypes and the risk of ischemic stroke in a Tunisian population among patients with and without diabetes.

2. Material and methods

2.1. Subjects

Blood was sampled from 196 patients (102 males, 94 females; ages ranging from 40 to 85 years, with an average age of 63.52 ± 11.45 years) who presented to the emergency department at Fattoyuma Bourguiba University Hospital in Monastir, Tunisia with ischemic stroke (117 diabetic and 79 nondiabetic) from March 2011 to March 2012. In addition to age, the other inclusion criterion was clinical diagnosis of ischemic stroke, causing a measurable neurological deficit (defined as impairment of language, motor function, cognition, gaze, or vision, or as neglect). Ischemic stroke was defined as the rapid development of focal or global disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than vascular origin after exclusion of hemorrhage by computed tomographic scan or magnetic resonance imaging of the brain. Diabetic subjects were defined by a fasting plasma glucose ≥7.0 mmol/l, or by the use of anti-diabetic drugs [12]. Patients were considered diabetic if diabetes was previously known. Exclusion criteria for cases included clinical presentation suggestive of subarachnoid hemorrhage, even if the initially computed tomography scan is normal. In addition, none of the subjects had any of the following conditions: transient ischemic attack, cerebral infarction due to cardiogenic events, cerebral hemorrhage, cerebral venous thrombosis, systematic inflammatory and autoimmune diseases, brain tumors, valvular heart disease, cancers, rheumatoid arthritis, heart failure, acute coronary syndrome, peripheral vascular disease, arteriovenous malformation, or aneurysm, presumed pericarditis or presence of either ventricular thrombus or aneurysm related to recent acute myocardial infarction and no anti inflammatory or oral anticoagulants drugs has been taken by any patient. Concomitant liver and kidney diseases and thyroid disease were not also found in these patients. After at least brain computed tomography or magnetic resonance imaging scan was performed to rule out hemorrhagic stroke, patient recruitment from 3 to 6 h was enrolled since onset of stroke. Medical personnel of the emergency department provided ischemic stroke care within the first hours to time of initial diagnosis, treatment, and initial hospitalization. 192 healthy subjects consisting of blood donors were recruited as controls (110 males, 82 females; ages ranging from 40 to 85 years, with an average age of 61.69 ± 7.0 years). Matching is required for case control study for the elimination of bias in comparison between cases and controls. It assures that no large imbalance between cases and controls occurs. Controls were matched with cases for age and sex. Before sampling, it was verified by direct interview by two experienced neurologists if they had neurological disorders. All participants completed a structured questionnaire as performed previously by [37] in order to verify the stroke free-status. In addition, physical examination and complete clinical history, including stroke risk factors, were taken for all participants. Controls had no history of stroke who were symptomatically normal (had no history of arterial or venous thrombosis); all free of any history of obesity, hypertension, dyslipidemia, diabetes mellitus, or CAD were included in the study. Cerebrovascular diseases, brain aneurysms, Alzheimer's disease, dementia or Parkinson's disease, kidney/liver diseases, hematological diseases, tumors, peripheral vascular diseases, and autoimmune diseases were excluded from these controls. Hypertension was defined as systolic pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg in at least two separate measurements, or in the case of a hypertension history [53]. Obesity was defined as BMI ≥30 kg/m^2. Hypercholesterolemia was considered present if total cholesterol serum levels were ≥5 mmol/l or if the subject was undergoing a treatment with cholesterol lowering drugs. As ethnic differences may influence conclusions reached in SNP-association studies, all participants were of Tunisian origin and were consented to participate in the study. This study was approved by our hospital ethical committee.

2.2. Genotyping

For each polymorphism, a DNA sequence containing the polymorphic site was amplified by PCR using primers described in supplemental Table 1. The primers, probes and reaction conditions are available upon request. Genotyping was performed by laboratory personnel blinded to case–control status. As a quality control measure, and to assess reliability of genotyping, we performed double-sampling restriction fragment length polymorphism-PCR in more than 10% of the samples and the results were consistent. Negative control reactions without DNA were included in each well in all the genotyping steps (PCR amplification and enzymatic digestions). No PCR product was detected from any of the negative control reactions. The amplicon was digested with an appropriate restriction enzyme that cleaves only 1 of the 2 alleles. The methods

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