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Lack of an association between matrix metalloproteinase polymorphisms and coronary heart disease in a Han Chinese population

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ABSTRACT. Coronary heart disease (CHD) has become a leading cause of human deaths worldwide. Recent studied showed that polymorphisms of the matrix metalloproteinase (MMP) genes played important roles in extracellular matrix remodeling and contribute to the pathogenesis of vascular diseases. Here, we investigated whether these MMP gene polymorphisms were associated with CHD in Han Chinese. Our case-control study was involved with 1509 unrelated individuals,

including 777 CHD cases and 732 controls. We selected a total of five polymorphisms whose genotypes were determined using Sequenom iPLEX technology. Our results showed there were no significant associations between the five MMP gene polymorphisms and CHD risk at either genotype or allele levels ($P > 0.05$). Further subgroup analyses by sex were also unable to reveal any significant association ($P > 0.05$). In conclusion, no significant associations were found between the five MMP gene polymorphisms and the risk of CHD in Han Chinese.

Key words: Coronary heart disease; Matrix metalloproteinase; Polymorphism; Han Chinese population

INTRODUCTION

Coronary heart disease (CHD) is principally caused by atherosclerosis, a progressive arterial inflammatory condition that has become the leading cause of death worldwide (Skjot-Arkil et al., 2010; Murray-Thomas et al., 2013; Sadeghi et al., 2013; Wang et al., 2014). CHD is a complex disease, involving interactions between environmental and genetic factors (Feng et al., 2014). Previous studies have found that single nucleotide polymorphisms (SNPs), important genomic elements, can affect an individual's genetic susceptibility to various diseases, including CHD (Liu et al., 2014; Muiya et al., 2014; Wu et al., 2014; Yang et al., 2014).

Mainly secreted by macrophages, matrix metalloproteinases (MMPs) are zinc-dependent enzymes that catalyze the degradation of connective tissue and extracellular matrix (Pamukcu et al., 2010; Benjamin and Khalil, 2012). MMPs are important in myocardial injury, vascular aneurysms, and remodeling (Blankenberg et al., 2003), and are thus suspected to be implicated in the pathogenesis of atherosclerosis and CHD (Yoon et al., 2002; Ketelhuth and Back, 2011).

There are 26 known MMPs that are classified into four groups based on historical assessment of their substrate specificity and cellular localization: the collagenases (including MMPs 1 and 13), gelatinases (MMPs 2 and 9), stromelysins (MMPs 3, 10, and 11), and membrane-type MMPs (MT-MMPs). Significant associations between MMP polymorphisms and CHD have been observed in previous studies, including MMP-2 rs2285053 (in the Turkish population; Alp et al., 2011), MMP-12 rs652438 (in an American population; Tanner et al., 2011), and MMP-13 rs640198 (in a European population; Vasku et al., 2012).

In the current study, polymorphisms in five MMP genes were chosen, including MMP-1, MMP-2, MMP-9, MMP-12, and MMP-13. Of these, the MMP-12 rs652438 polymorphism has been found to be associated with therapeutic outcome in the treatment of CHD (Tanner et al., 2011), while MMP-1 rs2075847 and MMP-9 rs3918250 involve CpG dinucleotides in promoters potentially regulating gene expression. This study aimed to investigate the relationship between these five polymorphisms and CHD in the Han Chinese population.

MATERIAL AND METHODS

Sample collection

We recruited a total of 1509 unrelated inpatients (777 CHD patients and 732 controls) between May 2008 and May 2014 from Ningbo Lihuili Hospital and Ningbo Yinzhou People's Hospital. All were Han Chinese diagnosed for CHD status according to the standardized coronary angiography (Higgs et al., 2005). Controls were chosen from patients with vascular stenosis of less than 50% in all coronary arteries. CHD cases included patients with a history of prior angioplasty or coronary artery bypass surgery (ISFC/WHO, 1979). Participants showed no evidence of cardiomyopathy or congenital heart, liver, or kidney disease. Discrimination between CHD and non-CHD individuals was adjudicated by at least two independent cardiologists. All blood samples were collected by the same investigator and were stored in 3.2% sodium citrate-treated tubes at -80°C. Our study was approved by the ethical committees of Ningbo Lihuili Hospital and Ningbo Yinzhou People's Hospital. Written statements of informed consent for patient-derived blood specimens and ethics statements were received from all study participants.

SNP genotyping

Human genomic DNA was extracted from peripheral blood samples using an automated nucleic acid extraction system (Lab-Aid 820, Xiamen Zeesan Biotech, Xiamen, China) and all samples were stored in Tris-ethylenediaminetetraacetic acid buffer. Polymerase chain reaction (PCR) amplification was performed on an ABI GeneAmp PCR System 9700 thermal cycler (Applied Biosystems, Foster City, CA, USA). Reactions included an initial denaturation stage at 95°C for 2 min, followed by 45 cycles of 95°C for 30 s, 56°C for 30 s, and 72°C for 30 s, before a final extension step at 72°C for 5 min. Shrimp alkaline phosphatase was then used to inactivate unincorporated nucleotides. Genotyping was conducted with an iPLEX Gold Assay using the MassARRAY platform (Sequenom, San Diego, CA, USA). We carried out a primer extension reaction using Mass-EXTEND primers, the products of which were purified on resin and then spotted using a Sequenom Nanodispenser onto a SpectroCHIP to crystalize. The polymorphisms tested were MMP-1 rs2075847, MMP-2 rs2285053, MMP-9 rs3918250, MMP-12 rs652438, and MMP-13 rs640198. Primer sequences used to genotype the five MMP polymorphisms are shown in Table 1. Data were analyzed with SpectroTYPER software (version 4.0; Sequenom).

Table 1. Sequences of the primers used togenotype the fivematrix metalloproteinasepolymorphisms.

SNP	1st primer (5' to 3')	2nd primer (5' to 3')	MassEXTEND primer (5' to 3')
rs2075847	ACGTTGGATGGTCCCATGATAATGATGGGC	ACGTTGGATGAGAGCCTTACCTGAGAAGAC	TCGTTATCTCATACTCCGCCTG
rs2285053	ACGTTGGATGCTCATCCTGTGACCGAGAAT	ACGTTGGATGAGAGCGACTCCATCTTGAAC	GTGACCGAGAATGCGGAC
rs3918250	ACGTTGGATGAGTTCCAGCTATGCAGAAGG	ACGTTGGATGTTTCGGAGAGACGGTATCAG	GGATCGCTTGAGTCC
rs652438	ACGTTGGATGCTCTTGGGATAATTTGGCTC	ACGTTGGATGTCACAGATGACAAATACTGG	TTGGCTCTGGTCTTAAA
rs640198	ACGTTGGATGTACTTAGCACAGGTGTTTGG	ACGTTGGATGTATTCTAATTCTTGGTTCC	GTTTGGTAAATTAGTGTTGAAT

SNP, single nucleotide polymorphism.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was assessed using the Arlequin software (version 3.5; Excoffier and Lischer, 2010). Differences in genotype and allele frequencies between CHD cases and controls were calculated using the CLUMP22 software with 10,000 Monte Carlo simulations (Sham and Curtis, 1995). Power analysis was performed with the Power and Sample Size Calculation software (version 3.0.43; Dupont and Plummer, 1990), while odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with Microsoft Excel (Microsoft, Redmond, WA, USA). Two-sided P values less than 0.05 were considered to be statistically significant.

RESULTS

Most SNPs were found to be in HWE. Previous research has shown that the frequency of the MMP-2 rs2285053-TT genotype is significantly lower in controls than in myocardial infarction patients in the Turkish population (Alp et al., 2011). However, our results revealed no significant associations involving this SNP (Table 2; all $P > 0.05$). A breakdown of the data by gender also failed to reveal a link between rs2285053 and CHD risk at both genotype and allele levels (Table 2; all $P > 0.05$).

Since MMP-12 rs652438 has been associated with the therapeutic outcome of antihypertensive agents in the treatment of CHD (Tanner et al., 2011), we examined whether it was also a risk factor for this disease. As shown in Table 2, there was no significant association between rs652438 and risk of CHD at both genotype and allele levels (Table 2; all $P > 0.05$). A subgroup analysis by gender also showed no connection between this SNP and CHD in male and female groups (Table 2; all $P > 0.05$).

The MMP-13 rs640198-T allele has previously been found to be associated with the severity of coronary artery disease (Vasku et al., 2012). However, we did not observe any correlation between rs640198 and CHD at either the genotype or allele level [Table 2; genotype: chi-square = 0.052, degrees of freedom (df) = 2, $P = 0.974$; allele: chi-square = 0.050, df = 1, $P = 0.823$, OR = 0.984, 95%CI = 0.853-1.134]. Analysis of the data taking sex into consideration also failed to show an association between this SNP and CHD in male and female study participants (Table 2; all $P > 0.05$).

SNPs rs2075847 and rs3918250 are located at CpG sites in the promoters of MMP-1 and MMP-9, respectively. Previous studies have demonstrated that promoter CpG SNPs contribute to CHD risk by affecting epigenetic marks (Koestler et al., 2014). However, our results revealed no significant association between rs2075847 and risk of CHD at both genotype and allele levels (Table 2; all $P > 0.05$). Sorting the data by sex also showed no link to CHD in male and female groups (Table 2; all $P > 0.05$).

In addition, our results failed to reveal a significant connection between MMP-9 rs3918250 and risk of CHD at both genotype and allele levels (Table 2; all $P > 0.05$). Categorization of the data by sex also showed no association between this SNP and CHD (Table 2; all $P > 0.05$).

Table 2. Genotype and allele distributions of the fivematrix metalloproteinasepolymorphisms.

		Genotype (N)			χ^2	P (df = 2)	HWE	Allele (N)		χ^2	P (df = 1)	OR (95%CI)
rs2075847		CC	CT	TT				C	T			
All	Cases	51	293	433			0.880	395	1159			
	Controls	45	288	399	0.466	0.792	0.463	378	1086	0.060	0.806	0.979 (0.831-1.153)
Male	Cases	35	194	305			0.581	264	804			
	Controls	28	157	234	0.156	0.925	0.811	213	625	0.120	0.729	0.964 (0.782-1.187)
Female	Cases	16	99	128			0.590	131	355			
	Controls	17	165	131	NA	NA	0.000	199	427	3.060	0.080	0.792 (0.610-1.029)
rs3918250		GG	AG	AA				G	A			
All	Cases	40	210	527			0.002	290	1264			
	Controls	26	224	482	4.090	0.129	0.997	276	1188	0.020	0.888	0.988 (0.823-1.186)
Male	Cases	29	139	366			0.002	197	871			
	Controls	16	131	272	4.023	0.134	0.963	163	675	0.310	0.578	0.937 (0.744-1.180)
Female	Cases	11	71	161			0.384	93	393			
	Controls	10	93	210	0.668	0.716	0.939	113	513	0.210	0.647	1.074 (0.793-1.456)
rs2285053		CC	CT	TT				C	T			
All	Cases	441	294	48			0.914	1176	390			
	Controls	423	266	50	0.544	0.762	0.355	1112	366	0.010	0.920	0.993 (0.842-1.17)
Male	Cases	305	197	35			0.676	807	267			
	Controls	246	149	26	0.262	0.877	0.590	641	201	0.250	0.617	0.948 (0.768-1.170)
Female	Cases	136	97	13			0.419	369	123			
	Controls	177	117	24	1.340	0.512	0.449	471	165	0.130	0.718	1.051 (0.802-1.377)
rs652438		GG	AG	AA				G	A			
All	Cases	17	160	599			0.110	194	1358			
	Controls	16	152	563	0.007	0.996	0.137	184	1278	0.010	0.920	0.992 (0.800-1.231)
Male	Cases	15	110	409			0.027	140	928			
	Controls	6	82	331	2.319	0.314	0.721	94	744	1.560	0.212	1.194 (0.904-1.578)
Female	Cases	2	50	190			0.511	54	430			
	Controls	10	70	232	4.067	0.131	0.107	90	534	2.570	0.109	0.745 (0.520-1.069)
rs640198		CC	CA	AA				C	A			
All	Cases	183	385	215			0.676	751	815			
	Controls	174	362	198	0.052	0.974	0.733	710	758	0.050	0.823	0.984 (0.853-1.134)
Male	Cases	131	267	139			0.910	529	545			
	Controls	96	203	117	0.649	0.723	0.660	395	437	0.590	0.442	1.074 (0.896-1.287)
Female	Cases	52	118	76			0.622	222	270			
	Controls	78	159	81	2.273	0.321	0.999	315	321	2.160	0.142	0.838 (0.662-1.061)

OR, odds ratio; CI, confidence interval; df, degrees of freedom; N_A, not applicable.

DISCUSSION

Previous research has established that CHD is a dynamic inflammatory process caused by atherosclerosis (Epps and Wilensky, 2011), involving numerous cells and mediators. MMPs are closely linked with atherosclerosis (Kapourchali et al., 2014) and an increase in their expression and activity has been identified in general inflammation (Creemers et al., 2001). During inflammation, MMP-12 is able to help macrophages penetrate injured tissues by the digestion of elastin and the basement membrane (Belaaouaj et al., 1995; Jormsjo et al., 2000). While not expressed in healthy tissues, elevated levels of multiple MMPs have been observed in macrophage-rich regions of human atherosclerotic plaques (Bench et al., 2011). MMP-1 may disrupt fibrous plaque by contributing to the degradation of interstitial collagens (Yoon et al., 2002). The gelatinases (MMP-2 and MMP-9) mainly degrade gelatin and collagen, and have been found to be involved in remodeling processes related to atherogenesis and plaque rupture (Blankenberg et al., 2003; Soder et al., 2009). MMP-12 is secreted by activated macrophages and not only digests elastin, but also degrades the basement membrane, inducing macrophages and smooth muscle cells to penetrate the endangium, thus accelerating the development of fatty streaks (Gronski et al., 1997; Jormsjo et al., 2000). In addition, an MMP-13 polymorphism was found to be associated with fibrous plaque in black males (Yoon et al., 2002).

Epigenetic marks such as DNA methylation of cytosine residues in CpG dinucleotides have been shown to be helpful in the advance diagnosis of CHD (Wei et al., 2014). SNPs rs3918250 and rs2075847 are promoter CpG polymorphisms and might therefore affect gene expression, although evidence is needed to support this hypothesis. MMP-12 rs652438 was found to be associated with the susceptibility of several inflammatory diseases, including lung cancer (Su et al., 2006), chronic obstructive pulmonary disease (Haq et al., 2011), diabetic nephropathy (Kure et al., 2011) and asthma (Yamaide et al., 2012). In addition, MMP-12 was critical to the progression of atherosclerosis during the transition from fatty acids to fibrous plaque (Yamada et al., 2008). Here, we investigated the relationship between MMP-12 rs652438 and CHD, although our results did not found find any association between this SNP and CHD. The MMP-2 rs2285053 CT and TT genotypes have been found to be significantly associated with increased risk of gallbladder cancer (Sharma et al., 2012), while the bile acid hyodeoxycholic acid has been shown to efficiently suppress atherosclerosis formation and plasma cholesterol levels in mice (Sehayek et al., 2001). Furthermore, the MMP-13 rs640198-T allele is associated with CHD severity, in terms of the number of stenoses and affected arteries (Vasku et al., 2012).

In the present study, we evaluated the significance of five MMP polymorphisms using a case-control study. Our results failed to reveal any significant association between these SNPs and risk of CHD in a Han Chinese population. Among five SNPs, we only found that genotype distribution of rs2075847 in females was not in HWE. We suspected that it was due to the small sample sizes or sample selection bias. Although power analysis showed that most of our association tests were moderately powerful in their ability to detect significance (power = 40.3-70.8%), future validation with larger sample sizes or meta-analysis is needed to confirm our findings. In summary, our results indicate no significant associations between MMP rs2285053, rs2075847, rs652438, rs3918250, and rs640198 polymorphisms and risk of CHD in a Han Chinese population. Future research on other MMP polymorphisms is needed since the SNPs tested herein may not be representative of the full extent to which MMP genes contribute to CHD risk.

Conflicts of interest

The authors declare no conflict of interest.

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