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MMP20 Single-Nucleotide Polymorphisms Correlate with Susceptibility to Alcohol-Induced Osteonecrosis of the Femoral Head in Chinese Males

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E 1,2 Feimeng An*
E 3 Jieli Du*
B 1,2 Jiaqi Wang
C 3 Liang Zhao
F 2 Chao Ma
B 2 Jian Zhao
AG 2 Jianzhong Wang

1 Inner Mongolia Medical University, Hohhot, Inner Mongolia, P.R. China
2 Department of Trauma Orthopedics, The Second Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, P.R. China
3 Department of Orthopedics, Cangzhou People's Hospital, Cangzhou, Hebei, P.R. China

* Feimeng An and Jieli Du are co-first author

Corresponding Author: Jianzhong Wang, e-mail: wangjianzhong0503@126.com

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Background: Alcohol-induced osteonecrosis of the femoral head (ONFH) is caused by the interaction of genetic and environmental factors. Genetic variations of matrix metalloproteinase (*MMP*) system are associated with ONFH development and progression. In this study, we aimed to evaluate the relationships between *MMP20* gene polymorphisms and the risk of alcohol-induced ONFH in Chinese Han males.

Material/Methods: In this case-control study, genotypes of 14 selected SNPs in the *MMP20* gene were assayed using MassARRAY in 299 male cases with alcohol-induced ONFH and in 197 healthy males. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the influence of gene polymorphism on occurrence of alcohol-induced ONFH by allelic model analysis, genotype model analysis and haplotype analysis.

Results: After allelic model analysis, the minimum alleles of rs10895322, rs1784424, rs3781788, and rs1573954 correlated with an increased risk of alcohol-induced ONFH ($P<0.05$). Genetic model analysis revealed significant associations of 9 SNPs with alcohol-induced ONFH occurrence even after adjustment for age ($P<0.05$): 2 protective SNPs (rs1711423 and rs1784418) and 7 high-risk SNPs (rs10895322, rs1784424, rs3781788, rs7126560, rs1573954, rs1711399, and rs2292730). Moreover, 8 SNPs showed a statistically significant association with different clinical phenotypes ($P<0.05$). Beyond that, haplotype "CGGTTCCA" in *MMP20* was discovered to correlate with a 1.63-fold increased risk of alcohol-induced ONFH (OR: 1.63, 95% CI: 1.15–2.30, $P=0.0058$).

Conclusions: Our data sheds new light on the associations of *MMP20* gene polymorphisms with alcohol-induced ONFH predisposition in Chinese Han males.

MeSH Keywords: Genetic Association Studies • Matrix Metalloproteinase 20 • Osteonecrosis • Polymorphism, Genetic

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Background

Alcohol-induced osteonecrosis of the femoral head (alcohol-induced ONFH) caused by excessive and chronic alcohol consumption is an intractable orthopedic disease that is characterized by the progressive collapse of the femur head and loss of hip joint function. Although there are a variety of clinical treatments, the prevalence of alcohol-induced ONFH and resulting disability in the Chinese population continues to increase, particularly among young men. Data demonstrate that 30.7% of ONFH cases in China are alcohol induced [1]. For these reasons, identifying risk factors and taking primary prevention measures are necessary to prevent alcohol-induced ONFH.

Recent research into the molecular biology and genetic underpinnings of alcohol-induced ONFH has provided new information about gene polymorphisms, which has opened up novel avenues of research to uncover the risk factors of this condition [2]. In the past few years, genome-wide association studies (GWAS) have identified several susceptibility genes such as *APOA1*, *PAI-1*, *SREBF1*, *VEGF MTHFR*, and *TFPI* that are associated with ONFH [3–8]. Chondrocytes from a femoral head with osteonecrosis lose their phenotype during ONFH, revealed by reducing of extracellular matrix production in glycosaminoglycan (GAG) and type 2 collagen excretion [9]. In addition, our previous studies demonstrated that *NOS3*, *ABCB, IL23R*, *APOA1*, *APOB*, *TIMP2*, *MMP2*, *MMP3*, and *MMP8* single-nucleotide polymorphisms were related to the risk of alcohol-induced ONFH and clinical outcomes or other clinical characteristics in the Chinese population [10–13]. Although multiple gene variants have been proposed as risk factors for alcohol-induced ONFH, the molecular etiology and pathogenesis have remained indistinct.

The *matrix metalloproteinase-20 (MMP20)* gene is located in an *MMP* cluster with 7 other *MMPs* at chromosomal location 11q22.3. *MMP20*, which has been well established as an essential participant in amelogenesis, is expressed in ameloblasts and odontoblasts during dental enamel development and is responsible for cleaving and removing most of the protein components of the extracellular enamel matrix such as amelogenin (the most abundant extracellular matrix (ECM) protein in developing enamel) thus facilitating enamel mineralization [14,15]. *MMP20* is a relatively newly identified member of the *MMP* family and was also named “human enamelysin” because it was originally thought that *MMP20* expression was restricted to enamel. In recent years, the expression of MMP20 has also been reported in other tissues. A study in 2015 confirmed the expression of *MMP20* in the retina and RPE/choroid [16]. Kraus et al. [17]investigated the expression of *MMP20* in 3 major human tumor entities: colon, breast, and lung tumors. They found that *MMP20* was identified at both the mRNA and the protein level in breast MCF-7, colon HT-29, and lung A549 cell lines. Thus, they concluded that *MMP20* was a potential new candidate for tumor diagnosis or therapy.

In this case-control study, 14 SNPs on the *MMP20* gene were selected to shed light on possible correlations with the occurrence of alcohol-induced ONFH and the clinical phenotypes in a Chinese male population.

Material and Methods

Study participants

There were 496 males (299 patients with alcohol-induced ONFH and 197 healthy males) among Han Chinese, sequentially enrolled in this study. All of the patients were selected randomly from the Zhengzhou Traditional Chinese Medicine Traumatology Hospital without restriction of disease severity. The patients were diagnosed with ONFH after using plain radiographs in stage II, III, and IV of the Ficat Classification system. Patients with traumatic osteonecrosis and other hip diseases were excluded. Alcohol-induced osteonecrosis was defined by a history of consumption of more than 400 mL of alcohol per week [18]. As well, enrolled patients had not received systemic treatment before the blood samples used for the study were collected. Control study participants were genetically irrelevant healthy males who were enrolled from Zhengzhou Medical Center and lived in or near Zhengzhou without hip pain, without lesions found on hip joint plain radiographs, and without relationship to the enrolled patients. Those who had a chronic metabolic disorder or who needed steroid treatment were also excluded from this study.

A normative questionnaire was used to collect personal information. Our research was approved by the ethics committee of Zhengzhou Traditional Chinese Medicine Traumatology Hospital and The Second Affiliated Hospital of Inner Mongolia Medical University (No. YKD2016138). Signed informed consent documents were obtained from all candidates.

SNP selection and genotyping

A total of 14 SNPs were selected from the NCBI dbSNP (*http://www.ncbi.nlm.nih.gov/snp*) and the 1000 Genomes Project databases (*http://www.internationalgenome.org/*) with minor allele frequencies (MAFs) >5% in the 1000 Genomes Chinese Han Beijing population. Genomic DNA was extracted from the peripheral blood of the participants using the GoldMag whole blood genomic DNA purification kit (GoldMag Co. Ltd., Xi’an, China). DNA concentration was determined using a NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA, USA). Primers for amplification process and single base extension reactions were designed using the Assay Design Suite

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Table 1. Characteristics of the male individuals in controls and alcohol-induced ONFH patients.

Variables	Cases (n=299)	Controls (n=197)	*P* value
	N (%)	N (%)	
Age, years			
Mean ±SD	43.24±13.07	49.76±8.83	*P*<0.001*
≤50	215 (71.9)	113 (57.4)	
>50	84 (28.1)	84 (42.6)	
Clinical stages			
Stage II	74 (24.7)		
Stage III	121 (40.5)		
Stage IV	104 (34.8)		
Hip lesions			
Unilateral	70 (23.4)		
Bilateral	229 (76.6)		
Course, months			
>12	151 (50.5)		
≤12	148 (49.5)		

P<0.05 indicates statistical significance. * Independent samples *t*-test.

V2.0 (*https://agenacx.com/online-tools/*). SNP genotyping was performed by Agena MassARRAY iPLEX (Agena Bioscience, San Diego, CA, USA). Genotyping results were output by Agena Bioscience TYPER version 4.0 software.

Statistical analysis

SPSS 19.0 (version 19.0, Chicago, IL, USA) was used to do the statistical analysis. All the *P*-values were 2-sided, and *P*<0.05 was considered to be statistically significant. The *t*-test were used to compare the age difference of cases and controls. An exact test was used to assess the variation in each SNP genotype frequency from the Hardy-Weinberg equilibrium (HWE) in the control participants before analysis. Differences in SNP genotype and allele distribution between cases and controls were compared by the χ^2 test/Wald test. Four models including the codominant, dominant, recessive, and log-additive model were used to assess the association between each genotype and the risk of alcohol-induced ONFH. Finally, both the SHEsis software platform (*http://analysis.bio-x.cn/myAnalysis.php*) and the Haploview software (version 4.2) were used to estimate the linkage disequilibrium (LD) patterns and construct haplotypes. The risk associated with individual genotypes and allele was calculated as the odds ratio (OR) with their 95% confidence interval (95% CI) based on logistic regression model analysis with an adjustment for age.

Results

Altogether, 299 eligible cases with alcohol-induced ONFH (mean age ±SD: 43.24±13.07) and 197 controls (mean age ±SD: 49.71±8.85) were recruited for our study. All of the individuals were males. The results of *t*-tests showed that the cases and controls were not matched for age (*P*<0.05), so we adjusted the age factor in the subsequent analysis (Table 1).

The detailed information about the 14 selected SNPs on the *MMP20* gene including band, alleles, minor allele frequency (MAF), and HWE results. The *P*-values of alleles were calculated by chi-square test. All SNPs did not deviate from HWE (*P*>0.05). Comparing the differences in MAF distributions between cases and controls, we found that 4 SNPs may significantly correlate with the risk of alcohol-induced ONFH under the allele model (rs10895322G/A, OR=1.422, 95% CI=1.069–1.892, *P*=0.015; rs1784424T/G, OR=1.368, 95% CI=1.059–1.767, *P*=0.016; rs3781788T/C, OR=1.345, 95% CI=1.031–1.755, *P*=0.029; rs1573954C/T, OR=1.328, 95% CI=1.028–1.716, *P*=0.030) (Table 2).

Subsequently, by unconditional logistic-regression analysis, we further identified the correlation between selected SNPs and alcohol-induced ONFH risk under 4 gene models (codominant, dominant, recessive, and log-additive). Meanwhile, all results were adjusted by age (Table 3). Rs10895322 and rs1784424 notably increased the risk of alcohol-induced ONFH under all of the gene models, including codominant, dominant, recessive,

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Table 2. Basic information of candidate SNPs in this study.

SNP ID	Gene	Band	Alleles A/B	MAF		HWE P^a value	ORs	95% CI		P^b value
				Case	Control					
rs2292730	MMP20	11q22.2	A/G	0.296	0.254	0.192	1.24	0.93	1.64	0.147
rs1784410	MMP20	11q22.2	C/A	0.401	0.424	1.000	0.91	0.70	1.18	0.474
rs1711399	MMP20	11q22.2	G/T	0.462	0.418	0.559	1.19	0.92	1.54	0.181
rs1711437	MMP20	11q22.2	T/C	0.385	0.413	1.000	0.89	0.69	1.16	0.379
rs1711433	MMP20	11q22.2	C/T	0.010	0.005	1.000	1.99	0.40	9.89	0.623
rs10895322	MMP20	11q22.2	G/A	0.326	0.254	0.851	**1.42**	**1.07**	**1.89**	**0.015***
rs1784424	MMP20	11q22.2	T/G	0.575	0.497	0.775	**1.37**	**1.06**	**1.77**	**0.016***
rs3781788	MMP20	11q22.2	T/C	0.403	0.334	0.521	**1.35**	**1.03**	**1.76**	**0.029***
rs1711423	MMP20	11q22.2	G/T	0.425	0.487	1.000	0.78	0.60	1.00	0.053
rs17174327	MMP20	11q22.2	T/C	0.062	0.087	0.370	0.69	0.43	1.13	0.138
rs1784418	MMP20	11q22.2	T/C	0.428	0.487	0.670	0.79	0.61	1.02	0.067
rs7126560	MMP20	11q22.2	A/G	0.404	0.343	1.000	1.30	0.10	1.69	0.053
rs2245803	MMP20	11q22.2	G/A	0.002	0.005	1.000	0.33	0.03	3.64	0.717
rs1573954	MMP20	11q22.2	C/T	0.555	0.485	0.317	**1.33**	**1.03**	**1.72**	**0.030***

A – minor alleles; B – major alleles; * $P<0.05$ indicates statistical significance; [a] P was calculated by exact test; [b] P was calculated by Pearson chi-squared test. Bold values indicate a significant difference.

and log-additive. Rs3781788 also revealed an increased risk under both the dominant and the additive model. Meanwhile, both rs7126560 and rs2292730 revealed an increased risk under the log-additive model, rs1573954 exhibited an increased risk under 2 models (recessive and log-additive), and rs1711399 revealed an increased risk under the recessive model. In addition, rs1711423 showed a negative effect under the recessive and log-additive models, and rs1784418 also showed a decreased risk under both the dominant model and the log-additive model.

Next, we completed the correlation analysis of alleles and genotypes of SNPs with the clinical phenotypes (unilateral or bilateral hip lesions, >12 months or ≤12 months course, and clinical stages of alcohol-induced ONFH), respectively (Table 4). Regarding rs10895322, some significant association was found between the G allele and the patients with different clinical phenotypes. In patients who had bilateral hip lesions, >12 months course, and/or stage II/III alcohol-induced ONFH, the G allele was a risk factor. Likewise, the rs3781788 T allele showed the same results. Among patients who had bilateral hip lesions, >12 months course, and/or stage III alcohol-induced ONFH, the G allele of rs1784424 showed significantly increased risk, and the G allele of rs1711423 showed significantly decreased risk, relative to controls. In addition, the allele distribution showed a higher frequency of the rs1573954 C allele in the patients with unilateral hip lesions, ≤12 months course, and/or stage II alcohol-induced ONFH. Rs1784418 showed a decreased risk in patients with >12 months course or/and stage III of alcohol-induced ONFH. Regarding rs7126560 and rs2292730, these 2 SNPs only revealed the increased risk for >12 months course and stage IV alcohol-induced ONFH, respectively.

Finally, using parameter D', we detected the extent of linkage disequilibrium between SNPs, and then determined the haplotype LD block according to the control group data. We observed that 2 blocks existed strong linkage disequilibria in *MMP20* (Figure 1). Block 1 included 8 SNPs: rs1711437, rs10895322, rs1784424, rs3781788, rs1711423, rs17174327, rs1784418, and rs7126560; block 2 includes 2 SNPs: rs1784410 and rs11711399. In block 1, compared with the "TATCGCTG" wild-type, the "CGGTTCCA" haplotype was found to be associated with an increased alcohol-induced ONFH risk after adjustment for age (OR=1.63, 95% CI=1.15–2.30, P=0.0058) (Table 5). However, we did not find any association between alcohol-induced ONFH and the haplotype of block 2.

Discussion

In this study, we have attempted to show the correlation between MMP20 polymorphisms and alcohol-induced ONFH and the different clinical phenotypes in Chinese Han males. Nine susceptibility SNPs in the *MMP20* gene revealed a statistically significant association with the alcohol-induced ONFH occurrence: 2 protective SNPs (rs1711423 and rs1784418) and 7 high-risk

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Table 3. Genotypic model analysis of relationship between SNPs and alcohol-induced ONFH risk adjusted for age.

SNP ID	Model	Genotype	Control	Case	OR (95% CI)	*P*[a]-value	AIC	BIC
rs10895322	Codominant	AA	109 (55.9%)	136 (46%)	1	**0.018***	625.9	642.6
		GA	73 (37.4%)	127 (42.9%)	1.44 (0.97–2.14)			
		GG	13 (6.7%)	33 (11.2%)	**2.47 (1.21–5.04)**			
	Dominant	AA	109 (55.9%)	136 (46%)	1	**0.016***	626.1	638.7
		GA-GG	86 (44.1%)	160 (54%)	**1.58 (1.09–2.31)**			
	Recessive	AA-GA	182 (93.3%)	263 (88.8%)	1	**0.029***	627.1	639.7
		GG	13 (6.7%)	33 (11.2%)	**2.10 (1.05–4.19)**			
	Log-additive	–	–	–	**1.51 (1.13–2.03)**	**0.0051***	624	636.6
rs1784424	Codominant	TT	48 (24.5%)	52 (17.4%)	1	**0.018***	629.8	646.6
		GT	101 (51.5%)	150 (50.2%)	1.43 (0.88–2.33)			
		GG	47 (24%)	97 (32.4%)	**2.18 (1.26–3.77)**			
	Dominant	TT	48 (24.5%)	52 (17.4%)	**1**	**0.032***	631.2	643.8
		GT-GG	148 (75.5%)	247 (82.6%)	**1.66 (1.05–2.63)**			
	Recessive	TT-GT	149 (76%)	202 (67.6%)	**1**	**0.014***	629.9	642.5
		GG	47 (24%)	97 (32.4%)	**1.69 (1.10–2.58)**			
	Log-additive	–	–	–	**1.48 (1.13–1.94)**	**0.0046***	627.8	640.4
rs3781788	Codominant	CC	89 (45.4%)	104 (34.8%)	1	0.072	632.6	649.4
		CT	83 (42.4%)	149 (49.8%)	1.53 (1.02–2.29)			
		TT	24 (12.2%)	46 (15.4%)	1.66 (0.92–2.99)			
	Dominant	CC	89 (45.4%)	104 (34.8%)	1	**0.023***	630.7	643.3
		CT-TT	107 (54.6%)	195 (65.2%)	**1.56 (1.06–2.28)**			
	Recessive	CC-CT	172 (87.8%)	253 (84.6%)	1	0.310	634.8	647.4
		TT	24 (12.2%)	46 (15.4%)	1.33 (0.77–2.29)			
	Log-additive	–	–	–	**1.35 (1.02–1.78)**	**0.032***	631.3	643.9
rs1711423	Codominant	TT	51 (26%)	97 (32.4%)	1	0.052	631.9	648.7
		GT	99 (50.5%)	150 (50.2%)	0.74 (0.48–1.16)			
		GG	46 (23.5%)	52 (17.4%)	0.51 (0.30–0.88)			
	Dominant	TT	51 (26%)	97 (32.4%)	1	0.057	632.2	644.8
		GT-GG	145 (74%)	202 (67.6%)	0.67 (0.44–1.02)			
	Recessive	TT-GT	150 (76.5%)	247 (82.6%)	1	**0.042***	631.7	644.3
		GG	46 (23.5%)	52 (17.4%)	**0.62 (0.39–0.98)**			
	Log-additive	–	–	–	**0.72 (0.55–0.94)**	**0.016***	630	642.6
rs1784418	Codominant	CC	50 (25.4%)	96 (32.1%)	1	0.066	633.5	650.3
		CT	102 (51.8%)	150 (50.2%)	0.71 (0.45–1.10)			
		TT	45 (22.8%)	53 (17.7%)	0.53 (0.31–0.91)			
	Dominant	CC	50 (25.4%)	96 (32.1%)	1	**0.043***	632.8	645.4
		CT-TT	147 (74.6%)	203 (67.9%)	**0.65 (0.43–0.99)**			
	Recessive	CC-CT	152 (77.2%)	246 (82.3%)	1	0.082	633.9	646.5
		TT	45 (22.8%)	53 (17.7%)	0.66 (0.41–1.05)			
	Log-additive	–	–	–	**0.73 (0.55–0.95)**	**0.020***	631.5	644.1

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Table 3 continued. Genotypic model analysis of relationship between SNPs and alcohol-induced ONFH risk adjusted for age.

SNP ID	Model	Genotype	Control	Case	OR (95% CI)	*P*[a]-value	AIC	BIC
rs7126560	Codominant	GG	85 (43.1%)	104 (35.1%)	1	0.130	633	649.8
		AG	89 (45.2%)	145 (49%)	1.35 (0.90–2.02)			
		AA	23 (11.7%)	47 (15.9%)	1.73 (0.95–3.13)			
	Dominant	GG	85 (43.1%)	104 (35.1%)	1	0.068	631.7	644.3
		AG-AA	112 (56.9%)	192 (64.9%)	1.43 (0.97–2.09)			
	Recessive	GG-AG	174 (88.3%)	249 (84.1%)	1	0.170	633.1	645.7
		AA	23 (11.7%)	47 (15.9%)	1.47 (0.84–2.54)			
	Log-additive	–	–	–	1.32 (1.00–1.75)	**0.045***	631	643.6
rs1573954	Codominant	TT	48 (24.6%)	59 (19.8%)	1	0.050	628.4	645.2
		TC	105 (53.9%)	147 (49.3%)	1.31 (0.81–2.11)			
		CC	42 (21.5%)	92 (30.9%)	1.95 (1.13–3.37)			
	Dominant	TT	48 (24.6%)	59 (19.8%)	1	0.081	629.4	642
		TC-CC	147 (75.4%)	239 (80.2%)	1.50 (0.95–2.36)			
	Recessive	TT-TC	153 (78.5%)	206 (69.1%)	1	**0.030***	627.7	640.3
		CC	42 (21.5%)	92 (30.9%)	**1.61 (1.04–2.49)**			
	Log-additive	–	–	–	**1.40 (1.06–1.84)**	**0.015***	626.5	639.1
rs1711399	Codominant	TT	64 (32.6%)	90 (30.1%)	1	0.071	631.9	648.7
		GT	100 (51%)	142 (47.5%)	1.02 (0.67–1.57)			
		GG	32 (16.3%)	67 (22.4%)	1.78 (1.02–3.10)			
	Dominant	TT	64 (32.6%)	90 (30.1%)	1	0.390	634.4	647.1
		GT-GG	132 (67.3%)	209 (69.9%)	1.19 (0.80–1.79)			
	Recessive	TT-GT	164 (83.7%)	232 (77.6%)	1	**0.021***	629.9	642.5
		GG	32 (16.3%)	67 (22.4%)	**1.75 (1.08–2.85)**			
	Log-additive	–	–	–	1.29 (0.99–1.68)	0.063	631.7	644.3
rs2292730	Codominant	GG	106 (53.8%)	140 (46.8%)	1	0.120	634.7	651.5
		GA	82 (41.6%)	141 (47.2%)	1.39 (0.94–2.04)			
		AA	9 (4.6%)	18 (6%)	1.94 (0.81–4.66)			
	Dominant	GG	106 (53.8%)	140 (46.8%)	1	0.058	633.3	645.9
		GA-AA	91 (46.2%)	159 (53.2%)	1.44 (0.99–2.09)			
	Recessive	GG-GA	188 (95.4%)	281 (94%)	1	0.240	635.5	648.1
		AA	9 (4.6%)	18 (6%)	1.66 (0.71–3.90)			
	Log-additive	–	–	–	**1.39 (1.01–1.91)**	**0.041***	632.7	645.3

* $P<0.05$ indicates statistical significance. [a] *P* values were calculated by Wald test by unconditional logistic regression adjusted for age. Bold values indicate a significant difference.

SNPs (rs10895322, rs1784424, rs3781788, rs7126560, rs1573954, rs1711399, and rs2292730). Among these SNPs, 8 SNPs showed a statistically significant association with different clinical phenotypes. In particular, the haplotype "CGGTTCCA" in *MMP20* was also founded to be correlated with a 1.63-fold increased risk of alcohol-induced ONFH. As far as we know, this is the first report to reveal the correlation between these *loci* and ONFH susceptibility.

MMPs devastate the cartilaginous extracellular matrix (ECM) production during chondrogenesis [19,20] and ONFH [9]. And ECM, including GAG and collagen type 2, are commodities not only in normal chondrocytes but also in chondrocytic differentiation [21]. MMP20 may inhibit the synthesis of ECM of chodrocytes in the femoral heads under osteonecrosis. But studies on these risk *loci* are relatively rare. A recent GWAS reported

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Table 4. Stratification analysis for association of *MMP20* gene polymorphism with the clinical phenotypes of alcohol-induced ONFH.

SNPs	Genotype (%)				Allele (%)					
rs2292730	**GG**	**GA**	**AA**	***P*[a]**	**G**	**A**	***P*[b]**	**OR**	**95% CI**	
Controls	106 (53.8)	82 (41.6)	9 (4.60)		294 (74.6)	100 (25.4)				
Unilateral	32 (45.7)	32 (45.7)	6 (8.60)	0.320	96 (68.6)	44 (31.4)	0.166	1.35	0.88	2.06
Bilateral	108 (47.2)	109 (47.6)	12 (5.20)	0.190	325 (71.0)	133 (29.0)	0.232	1.20	0.89	1.63
Stage II	32 (43.2)	39 (52.7)	3 (4.00)	0.320	103 (69.6)	45 (30.4)	0.239	1.28	0.85	1.95
Stage III	66 (54.5)	51 (42.1)	4 (3.30)	0.780	183 (75.6)	59 (24.4)	0.948	0.65	1.37	0.78
Stage IV	42 (40.4)	51 (49.0)	11 (10.6)	**0.023***	135 (64.9)	73 (35.1)	**0.012***	**1.59**	**1.10**	**2.29**
>12 months	76 (50.3)	67 (44.4)	8 (5.30)	0.710	219 (72.5)	83 (27.5)	0.532	1.11	0.79	1.56
≤12 months	64 (43.2)	74 (50.0)	10 (6.80)	**0.043***	202 (68.2)	94 (31.8)	0.065	1.37	0.98	1.91
rs1784410	**AA**	**CA**	**CC**	***P*[a]**	**A**	**C**	***P*[b]**	**OR**	**95% CI**	
Controls	65 (33.0)	97 (49.2)	35 (17.8)		227 (57.6)	167 (42.4)				
Unilateral	25 (35.7)	30 (42.9)	15 (21.4)	0.710	80 (57.1)	60 (42.9)	0.923	1.02	0.69	1.51
Bilateral	84 (36.8)	109 (47.8)	35 (15.3)	0.310	277 (60.7)	179 (39.3)	0.354	0.88	0.67	1.16
Stage II	25 (34.2)	32 (43.8)	16 (21.9)	0.880	82 (56.2)	64 (43.8)	0.762	1.06	0.72	1.56
Stage III	45 (37.2)	65 (53.7)	11 (9.1)	**0.012***	155 (64.0)	87 (36.0)	0.108	0.76	0.55	1.06
Stage IV	39 (37.5)	42 (40.4)	23 (22.1)	0.350	120 (57.7)	88 (42.3)	0.985	1.00	0.71	1.40
>12 months	57 (38.0)	71 (47.3)	22 (14.7)	0.520	185 (61.7)	115 (38.3)	0.282	0.84	0.62	1.15
≤12 months	52 (35.1)	68 (46.0)	28 (18.9)	0.570	172 (58.1)	124 (41.9)	0.897	0.98	0.72	1.33
rs1711399	**TT**	**GT**	**GG**	***P*[a]**	**T**	**G**	***P*[b]**	**OR**	**95% CI**	
Controls	64 (32.6)	100 (51)	32 (16.3)		228 (58.2)	164 (41.8)				
Unilateral	22 (31.4)	31 (44.3)	17 (24.3)	0.230	75 (53.6)	65 (46.4)	0.346	1.20	0.82	1.78
Bilateral	68 (29.7)	111 (48.5)	50 (21.8)	0.120	247 (53.9)	211 (46.1)	0.215	1.19	0.90	1.56
Stage II	19 (25.7)	41 (55.4)	14 (18.9)	0.450	79 (53.4)	69 (46.6)	0.317	1.21	0.83	1.78
Stage III	32 (26.4)	60 (49.6)	29 (24.0)	**0.013***	124 (51.2)	118 (48.8)	0.088	1.32	0.96	1.83
Stage IV	39 (37.5)	41 (39.4)	24 (23.1)	0.120	119 (57.2)	89 (42.8)	0.822	1.04	0.74	1.46
>12 months	43 (28.5)	70 (46.4)	38 (25.2)	0.088	156 (51.7)	146 (48.3)	0.087	1.30	0.96	1.76
≤12 months	47 (31.8)	72 (48.6)	29 (19.6)	0.280	166 (56.1)	130 (43.9)	0.585	1.09	0.80	1.48
rs1711437	**CC**	**TC**	**TT**	***P*[a]**	**C**	**T**	***P*[b]**	**OR**	**95% CI**	
Controls	67 (34.4)	95 (48.7)	33 (16.9)		229 (58.7)	161 (41.3)				
Unilateral	26 (37.1)	30 (42.9)	14 (20.0)	0.800	82 (58.6)	58 (41.4)	0.976	1.01	0.68	1.49
Bilateral	87 (38.7)	107 (47.6)	31 (13.8)	0.230	281 (62.4)	169 (37.6)	0.270	0.86	0.65	1.13
Stage II	28 (38.4)	33 (45.2)	12 (16.4)	0.540	89 (61.0)	57 (39.0)	0.638	0.91	0.62	1.34
Stage III	46 (38.0)	65 (53.7)	10 (8.30)	**0.005***	157 (64.9)	85 (35.1)	0.123	0.77	0.55	1.07
Stage IV	39 (38.6)	39 (38.6)	23 (22.8)	0.240	117 (57.9)	85 (42.1)	0.852	1.03	0.73	1.46
>12 months	59 (39.6)	69 (46.3)	21 (14.1)	0.480	187 (62.8)	111 (37.2)	0.284	0.84	0.62	1.15
≤12 months	54 (37.0)	68 (46.6)	24 (16.4)	0.440	176 (60.3)	116 (39.7)	0.682	0.94	0.69	1.28

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Table 4 continued. Stratification analysis for association of *MMP20* gene polymorphism with the clinical phenotypes of alcohol-induced ONFH.

SNPs	Genotype (%)				Allele (%)					
rs10895322	**AA**	**GA**	**GG**	***P*[a]**	**A**	**G**	***P*[b]**	**OR**	**95%CI**	
Controls	109 (55.9)	73 (37.4)	13 (6.70)		291 (74.6)	99 (25.4)				
Unilateral	34 (49.3)	26 (37.7)	9 (13.0)	0.110	94 (68.1)	44 (31.9)	0.140	1.38	0.90	2.10
Bilateral	102 (44.9)	101 (44.5)	24 (10.6)	**0.022***	305 (67.2)	149 (32.8)	**0.018***	**1.44**	**1.06**	**1.94**
Stage II	30 (41.1)	36 (49.3)	7 (9.60)	**0.049***	96 (65.8)	50 (34.2)	**0.041***	**1.53**	**1.02**	**2.31**
Stage III	54 (45.0)	51 (42.5)	15 (12.5)	**0.007***	159 (66.3)	81 (33.8)	**0.024***	**1.50**	**1.05**	**2.13**
Stage IV	52 (50.5)	40 (38.8)	11 (10.7)	0.410	144 (69.9)	62 (30.1)	0.218	1.27	0.87	1.84
>12 months	63 (41.7)	69 (45.7)	19 (12.6)	**0.016***	195 (64.6)	107 (35.4)	**0.004***	**1.61**	**1.16**	**2.24**
≤12 months	73 (50.3)	58 (40.0)	14 (9.70)	0.092	204 (70.3)	86 (29.7)	0.216	1.24	0.88	1.74
rs1784424	**TT**	**GT**	**GG**	***P*[a]**	**T**	**G**	***P*[b]**	**OR**	**95% CI**	
Controls	48 (24.5)	101 (51.5)	47(24.0)		197 (50.3)	195 (49.7)				
Unilateral	15 (21.7)	33 (47.8)	21(30.4)	0.490	63 (45.7)	75 (54.3)	0.140	1.38	0.90	2.10
Bilateral	36 (15.7)	117 (51.1)	76(33.2)	**0.006***	189 (41.3)	269 (58.7)	**0.009***	**1.44**	**1.10**	**1.89**
Stage II	13 (17.6)	35 (47.3)	26(35.1)	**0.035***	61 (41.2)	87 (58.8)	0.061	1.44	0.98	2.11
Stage III	14 (11.7)	65 (54.2)	41(34.2)	**0.001***	93 (38.8)	147 (61.3)	**0.005***	**1.60**	**1.15**	**2.21**
Stage IV	24 (23.1)	50 (48.1)	30(28.9)	0.650	98 (47.1)	110 (52.9)	0.464	1.13	0.81	1.59
>12 months	25 (16.6)	73 (48.3)	53(35.1)	**0.031***	123 (40.7)	179 (59.3)	**0.013***	**1.47**	**1.09**	**1.99**
≤12 months	26 (17.7)	77 (52.4)	44(29.9)	0.060	129 (43.9)	165 (56.1)	0.098	1.29	0.95	1.75
rs3781788	**CC**	**CT**	**TT**	***P*[a]**	**C**	**T**	***P*[b]**	**OR**	**95% CI**	
Controls	89 (45.4)	83 (42.4)	24 (12.2)		261 (66.6)	131 (33.4)				
Unilateral	27 (39.1)	29 (42.0)	13 (18.8)	0.340	83 (60.1)	55 (39.9)	0.173	1.32	0.88	1.97
Bilateral	76 (33.2)	120 (52.4)	33 (14.4)	**0.028***	272 (59.4)	186 (40.6)	**0.031***	**1.36**	**1.03**	**1.80**
Stage II	23 (31.1)	37 (50.0)	14 (18.9)	0.061	83 (56.1)	65 (43.9)	**0.024***	**1.56**	**1.06**	**2.30**
Stage III	36 (30.0)	68 (56.7)	16 (13.3)	**0.023***	140 (58.3)	100 (41.7)	**0.037***	**1.42**	**1.02**	**1.98**
Stage IV	44 (42.3)	44 (42.3)	16 (15.4)	0.720	132 (63.5)	76 (36.5)	0.444	1.15	0.81	1.63
>12 months	50 (33.1)	74 (49.0)	27 (17.9)	**0.048***	174 (57.6)	128 (42.4)	**0.015***	**1.47**	**1.07**	**2.00**
≤12 months	53 (36.0)	75 (51.0)	19 (12.9)	0.310	181 (61.6)	113 (38.4)	0.174	1.24	0.91	1.70
rs1711423	**TT**	**GT**	**GG**	***P*[a]**	**T**	**G**	***P*[b]**	**OR**	**95% CI**	
Controls	51 (26.0)	99 (50.5)	46 (23.5)		201 (51.3)	191 (48.7)				
Unilateral	23 (32.9)	31 (44.3)	16 (22.9)	0.560	77 (55.0)	63 (45.0)	0.449	0.86	0.58	1.27
Bilateral	74 (32.3)	119 (52.0)	36 (15.7)	**0.021***	267 (58.3)	191 (41.7)	**0.040***	**0.75**	**0.57**	**0.99**
Stage II	25 (33.8)	34 (46.0)	15 (20.3)	0.140	84 (56.8)	64 (43.2)	0.255	0.80	0.55	1.17
Stage III	42 (34.7)	65 (53.7)	14 (11.6)	**0.001***	149 (61.6)	93 (38.4)	**0.011***	**0.66**	**0.47**	**0.91**
Stage IV	30 (28.9)	51 (49.0)	23 (22.1)	0.860	111 (53.4)	97 (46.6)	0.626	0.92	0.66	1.29
>12 months	52 (34.4)	75 (49.7)	24 (15.9)	0.081	179 (59.3)	123 (40.7)	**0.036***	**0.72**	**0.53**	**0.98**
≤12 months	45 (30.4)	75 (50.7)	28 (18.9)	0.120	165 (55.7)	131 (44.3)	0.245	0.84	0.62	1.13

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Table 4 continued. Stratification analysis for association of *MMP20* gene polymorphism with the clinical phenotypes of alcohol-induced ONFH.

SNPs	Genotype (%)				Allele (%)					
rs1784418	**CC**	**CT**	**TT**	***P*[a]**	**C**	**T**	***P*[b]**	**OR**	**95% CI**	
Controls	50 (25.4)	102 (51.8)	45 (22.8)		202 (51.3)	192 (48.7)				
Unilateral	25 (35.7)	29 (41.4)	16 (22.9)	0.280	79 (56.4)	61 (43.6)	0.294	0.81	0.55	1.20
Bilateral	71 (31.0)	121 (52.8)	37 (16.2)	**0.044***	263 (57.4)	195 (42.6)	0.072	0.78	0.60	1.02
Stage II	25 (33.8)	34 (46.0)	15 (20.3)	0.150	84 (56.8)	64 (43.2)	0.254	0.80	0.55	1.17
Stage III	40 (33.1)	67 (55.4)	14 (11.6)	**0.001***	147 (60.7)	95 (39.3)	**0.020***	**0.68**	**0.49**	**0.94**
Stage IV	31 (29.8)	49 (47.1)	24 (23.1)	0.700	111 (53.4)	97 (46.6)	0.624	0.92	0.66	1.29
>12 months	52 (34.4)	74 (49.0)	25 (16.6)	0.096	178 (58.9)	124 (41.1)	**0.044***	**0.73**	**0.54**	**0.99**
≤12 months	44 (29.7)	76 (51.4)	28 (18.9)	0.140	164 (55.4)	132 (44.6)	0.281	0.85	0.63	1.15
rs7126560	**GG**	**AG**	**AA**	***P*[a]**	**G**	**A**	***P*[b]**	**OR**	**95% CI**	
Controls	85 (43.1)	89 (45.2)	23 (11.7)		259 (65.7)	135 (34.3)				
Unilateral	27 (38.6)	29 (41.4)	14 (20.0)	0.220	83 (59.3)	57 (40.7)	0.172	1.32	0.89	1.96
Bilateral	77 (34.1)	116 (51.3)	33 (14.6)	0.100	270 (59.7)	182 (40.3)	0.072	1.29	0.98	1.71
Stage II	23 (31.1)	38 (51.4)	13 (17.6)	0.089	84 (56.8)	64 (43.2)	0.053	1.46	0.99	2.15
Stage III	37 (30.6)	67 (55.4)	17 (14.1)	0.051	141 (58.3)	101 (41.7)	0.058	1.37	0.99	1.91
Stage IV	44 (43.6)	40 (39.6)	17 (16.8)	0.440	128 (63.4)	74 (36.6)	0.566	1.11	0.78	1.58
>12 months	51 (34.2)	72 (48.3)	26 (17.4)	0.130	174 (58.4)	124 (41.6)	**0.048***	**1.37**	**1.00**	**1.86**
≤12 months	53 (36.0)	73 (49.7)	21 (14.3)	0.350	179 (60.9)	115 (39.1)	0.191	1.23	0.90	1.69
rs1573954	**TT**	**TC**	**CC**	***P*[a]**	**T**	**C**	***P*[b]**	**OR**	**95% CI**	
Controls	48 (24.6)	105 (53.9)	42 (21.5)		201 (51.5)	189 (48.5)				
Unilateral	13 (18.8)	31 (44.9)	25 (36.2)	**0.046***	57 (41.3)	81 (58.7)	**0.039***	**1.51**	**1.02**	**2.24**
Bilateral	45 (19.7)	116 (50.9)	67 (29.4)	0.082	206 (45.2)	250 (54.8)	0.065	1.29	0.98	1.69
Stage II	12 (16.2)	31 (41.9)	31 (41.9)	**0.005***	55 (37.2)	93 (62.8)	**0.003***	**1.80**	**1.22**	**2.65**
Stage III	18 (15.0)	69 (57.5)	33 (27.5)	**0.010***	105 (43.8)	135 (56.3)	0.058	1.37	0.99	1.89
Stage IV	28 (27.2)	47 (45.6)	28 (27.2)	0.440	103 (50.0)	103 (50.0)	0.721	1.06	0.76	1.49
>12 months	30 (19.9)	76 (50.3)	45 (29.8)	0.130	136 (45.0)	166 (55.0)	0.090	1.30	0.96	1.75
≤12 months	28 (19.2)	71 (48.6)	47 (32.2)	0.084	127 (43.5)	165 (56.5)	**0.037***	**1.38**	**1.02**	**1.87**

* $P<0.05$ indicates statistical significance. [a] *P* values were calculated by Wald test adjusted for age; [b] *P* was calculated by Pearson chi-squared test. Bold values indicate a significant difference.

a susceptibility locus (rs10895322) for 11q-deletion neuroblastoma, and 11q deletion is an inversely correlated prognostic factor in neuroblastoma [22]. In 2015, another GWAS identified association between rs10895322 and neovascular lesion size in age-related macular degeneration (AMD), which suggests the possibility of using *MMP20* as a novel target to control the growth of choroidal neovascularization (CNV) after the onset of AMD [16]. Similarly, in this study, we found that rs10895322 may be a high-risk factor of alcohol-induced ONFH, implying that the risk attributed to rs10895322 in ONFH and neuroblastoma may be mediated through a comparable angiogenesis process that is regulated by *MMP20*.

In a family-based association study, Jeremias et al. [23] concluded that rs1711399 and rs1711423 were associated with the susceptibility to molar-incisor hypomineralization (MIH). Our study showed that rs1711399 played a risk-heightening role in the occurrence of alcohol-induced ONFH, while rs1711423 may be a protective SNP. We hold the opinion that there are genetic differences between the 2 diseases.

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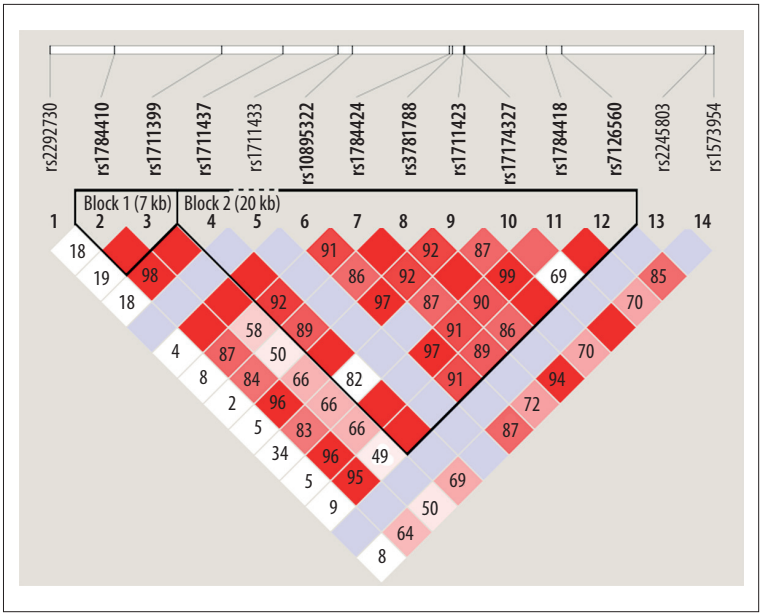

Figure 1. Haplotype block map for SNPs of the *MMP20* gene.

Table 5. The haplotype frequencies of *MMP20* polymorphisms and their association with alcohol-induced ONFH risk.

	Haplotype								Freq	OR[b] (95% CI)	*P*[b]
	rs 1711437	rs 10895322	rs 1784424	rs 3781788	rs 1711423	rs 17174327	rs 1784418	rs 7126560			
1	T	A	T	C	G	C	T	G	0.377	1	–
2	C	G	G	T	T	C	C	A	0.278	1.63 (1.15–2.30)	0.006*
3	C	A	G	C	T	C	C	G	0.088	1.68 (1.00–2.82)	0.051
4	C	A	G	T	T	C	C	A	0.074	0.89 (0.51–1.53)	0.670
5	C	A	G	C	T	T	C	G	0.062	1.14 (0.63–2.07)	0.670
6	C	A	T	C	G	C	T	G	0.055	0.79 (0.44–1.43)	0.440

* *P*<0.05 indicates statistical significance. [b] Adjusted by age. Bold values indicate a significant difference.

In our study, rs1784418 was also a protective SNP concerning the occurrence of alcohol-induced ONFH in both dominant and log-additive genetic models. In 2012, Tannure et al. [24] speculated that rs1784418 C>T may be involved with caries susceptibility in primarily Caucasian patients with poor oral health habits. A similar study by Filho et al. in 2016 explored the association of rs1784418 C>T and dental caries experience. Their conclusion is that the rs1784418 T allele can potentially be used as a marker for lower caries risk in certain populations [25]. The latest report from Brazil by Antunes et al. [26] suggested that *MMP20* rs1784418 C>T may contribute to the occurrence of white spot lesions in the primary dentition. The aforementioned conclusions are consistent with our results; though the function of rs1784418 is unknown, there is a possibility that the variant affects the transcription of *MMP20*. In the study by Han et al. [27], they analyzed the correlations between polymorphisms of rs1711437 (G>A) and kidney transplantation outcomes in 235 transplant recipients. The conclusions suggest that *MMP20* polymorphisms may influence the long-term outcome of kidney allografts. Beyond that, the *MMP20* gene also has been shown to be related to kidney aging by Wheeler et al. [28]. They showed that the A allele at rs1711437 was associated with high glomerular filtration rate (GFR). However, our study found no relationship between this locus and alcohol-induced ONFH. The study by Wang et al. [29] in 2015 suggested that *MMP20* rs2292730, rs12278250, and rs9787933 might be associated with ovarian cancer risk in a group of 417 ovarian cancer cases and 417 controls. In contrast to this conclusion, a comprehensive meta-analysis by Zhu and Sun [30] in 2017 found that these 3 *loci* might not be associated with ovarian cancer risk. Our present study only indicated that rs2292730 is a risk SNP of alcohol-induced ONFH

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among these 3 SNPs. In the study by Kanna et al. [31], genetic polymorphisms of *MMP20* (rs17099008) were significantly associated with Modic changes, which are vertebral endplate signal changes predominantly observed in the lumbar spine. Our study did not include this site. It is necessary to conduct larger-scale, multicenter, and high-quality studies in the future.

Up to now, the other 4 high-risk sites (rs1784424, rs3781788, rs7126560, and rs1573954) have not been described in other diseases. Collectively, our study provides insight into the pathogenesis of alcohol-induced ONFH. Although this study had an adequately sufficient statistical power, some intrinsic limitations may still exist. First, our study did not perform a functional study of these SNPs. To clarify the function of *MMP20* in alcohol-induced ONFH, SNPs functional study is essential. Second, the sample capacity was relatively small; a larger sample capacity will be more persuasive. Finally, participants' ethnicity was limited to the Han Chinese population. Hence, the associations identified in this study should be confirmed in further studies with other ethnic groups.

Conclusions

We demonstrated in this study that *MMP20* polymorphisms can play both risk-heightening and risk-mitigating roles and that *MMP20* may serve as a marker to predict the occurrence of alcohol-induced ONFH. These findings were in agreement with the multifactorial etiology of alcohol-induced ONFH. However, because of the lack of functional studies and the fact that most intronic SNPs are nonfunctional, these results more likely suggest that other coding SNP(s) tagged by these positive SNPs might be causal to alcohol-induced ONFH.

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Conflict of interest

None.

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