Influence of *COL9A1* and *COL19A1* Polymorphisms on Kaschin-Beck Disease Risk

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Abstract

Objective: We aimed to determine whether COL9A1 and COL19A1 polymorphisms were associated with Kaschin-Beck disease (KBD) risk.

Methods: Five single nucleotide polymorphisms (SNPs) in COL9A1 and COL19A1 were genotyped in 316 KBD patients and 320 healthy controls. The correlation between genetic polymorphisms and KBD risk were assessed using logistic regression models by calculating odds ratio (OR) and 95% confidence interval (CI).

Results: After adjustment with age and sex, the frequency distributions of genotypes in rs3806093 and rs9346371 were significantly different between cases and controls. COL9A1 rs3806093 significantly increased KBD risk in co-dominant (OR = 14.80, p = 0.024) and recessive (OR = 16.39, p = 0.019) models. Meanwhile, COL9A1 rs555313 was associated with KBD risk in recessive model (OR = 3.80, p = 0.048). However, no strong relationships were observed after false discovery rate correction. In addition, haplotype analysis revealed two blocks (block 1: rs3806093, rs603410 and rs621347; block 2: rs9346371 and rs555313).

Conclusion: COL9A1 and COL19A1 polymorphisms were associated with KBD risk in the Chinese Han population, suggesting roles of COL9A1 and COL19A1 in the development of KBD.

Introduction

Kaschin-Beck disease (KBD) is a chronic osteochondropathy, characterized by cartilage degeneration, chondrocyte necrosis and apoptosis(Y. Shi et al., 2011; S. J. Wang et al., 2006). KBD mainly distributed from southeastern Siberia to China. There are approximately 690,000 people with KBD, and more than 10 million people may suffer from KBD in China(Lü et al., 2011). The etiology of KBD remains unclear, studies suggest that KBD is a complex disease made by interactions between environmental factors and genetic factors(F. Zhang, Guo, Wang, Yan, & Li, 2011). More than 40% of KBD risk could be attribute to genetic components(Lü et al., 2011). Certain susceptibility genes may have effects on KBD risk.

Collagens are the most abundant proteins in mammals (30% of total protein mass), the collagen family comprises 28 members (I-XXVIII)(Jiang et al., 2017; Ricard-Blum, 2011). One of the three alpha chains of type IX collagen are coded by *COL9A1* gene, which is essential for the functional longevity of joint cartilages and connected with osteochondropathy(Bönnemann et al., 2000; Czarny-Ratajczak et al., 2001). Studies in knockout mice have shown that lack of type IX collagen is associated with early onset osteoarthritis. Mutations in *COL9A1* are associated with osteoarthritis, lumbar disc disease, and multiple epiphyseal dysplasia(Jakkula et al., 2005; Lohiniva et al., 2000; Mustafa et al., 2000). Specially, it is reported that *COL9A1* polymorphism (rs6910140) was significantly associated with KBD risk in a northwest Chinese Han population(X. Shi, Zhang, Lv, Wen, & Guo, 2015). *COL19A1* encodes the alpha chain of type XIX collagen, a member of the fibril-associated collagens with interrupted helices (FACIT) collagen family. *COL19A1* was localized to 6q12-q14, the same region of *COL9A1* gene(Khaleduzzaman et al., 1997). Type XIX collagen was involved in the initial stages of skeletal muscle cell differentiation(Sumiyoshi, Laub, Yoshioka, & Ramirez, 2001). Studies reported that Type XIX collagen may contribute to brain disorders(Su, Cole, & Fox, 2017), but no data on the relationship between *COL19A1* polymorphisms and KBD risk.

In this study, we aimed to investigate whether polymorphisms of *COL9A1* and *COL19A1* affect the risk of KBD. We conducted a case-control study and focused on five polymorphisms (rs3806093, rs603410 and rs621347 of *COL9A1*; rs9346371 and rs555313 of *COL19A1*) to assess the associations of genetic polymorphisms and KBD risk.

Methods

Study subjects

A total of 636 Chinese Han individuals (316 KBD patients, 320 healthy controls) were recruited from Affiliated Hospital of Xizang Minzu University, Xianyang, China. According to the national diagnostic criteria of China (WS/T 207-2010), all KBD patients was diagnosed by two KBD experts. The exclusion criteria included patients with other clinical symptoms or radiographic changes of other osteochondropathy. The healthy controls were randomly collected from disease-free individuals who had health examination in the Affiliated Hospital of Xizang Minzu University. All study subjects were unrelated individuals. This study was in the Declaration of Helsinki and approved by the Ethics Committee of Affiliated Hospital of Xizang Minzu University, and we obtained written informed consents from all study subjects before study.

Genotyping

Combined with previous studies(F. Zhang et al., 2011), genetic polymorphisms were selected from DbSNP database (https://www.ncbi.nlm.nih.gov/SNP/) and SNP Consortium database (http://snp.cshl.org/). In addition, based on the data of the Han Chinese population in Beijing (CHB) from the 1000 Genomes project, we selected three SNPs (rs3806093, rs603410 and rs621347) of *COL9A1* gene and two SNPs (rs9346371 and rs555313) of *COL19A1*, with minor allele frequency (MAF) greater than 5%. Genomic DNA was extract from whole blood using blood DNA kit (GoldMag Co. Ltd., Xi□an, China) and was measured by Nanodrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA).We genotyped five SNPs of *COL9A1* and *COL19A1* using Agena MassARRAY platform (Agena, San Diego, CA, USA). The Agena MassARRAY Assay Design 3.0 Software (San Diego, CA USA) was used to design the primers for each SNP (Table 1). Additionally, we managed and analyzed data by the Agena Typer 4.0 Software (San Diego, CA, USA)(F. Zhang et al., 2013).

Statistical analysis

Statistical analysis was conducted with SPSS 21.0 (IBM®, Armonk, New York, USA)(X. Wang et al., 2016). $P < 0.05$ was considered statistically significant. We used Power and Sample Size Calculation software (http://sampsize.sourceforge.net/iface/s3.html#ccp) to calculate the power of the significant difference. The Hardy-Weinberg equilibrium (HWE) of each SNP was assessed by Fisher's exact test in the control group. Logistic regression analysis adjusted by age and sex was used to evaluate the association of *COL9A1* and *COL9A1* polymorphisms with KBD risk through calculating odds ratio (OR) and 95% confidence interval (CI). Allele model and genetic models (co-dominant, dominant, recessive and additive) were assessed by the chi square test and PLINK software. False discovery rate (FDR) was used to correct multiple testing. Then, haplotype analysis was performed by Haploview software (version 4.2) and PLINK software.

Results

Study subjects

A total of 316 cases (183 men and 133 women) and 320 controls (239 men and 81 women) were included in this study. The characteristics of study subjects are presented in Table 2. The mean ages of cases and controls were 54.70 ± 17.14 and 19.00 ± 1.60 years old, individually. There are significant differences in the distribution of age and sex between two groups.

Association of *COL9A1* and *COL9A1* polymorphisms with KBD risk

The loci information of five SNPs in *COL9A1* and *COL19A1* are shown in Table3. All SNPs are in HWE and the MAFs in two groups are listed in this table. HaploReg predicted that candidate polymorphisms of *COL9A1* and *COL9A1* control the regulation of Motifs changed and Selected eQTL hits. The association of *COL9A1* and *COL19A1* polymorphisms with KBD risk are presented in Table 4. The distribution frequencies of genotypes in *COL9A1* rs3806093 and *COL19A1* rs9346371 are significantly different between the two groups. Rs3806093 is significantly associated with higher risk of KBD in co-dominant (OR = 14.80, 95%CI = 1.42-154.80, $p = 0.024$, study power = 100%) and recessive (OR = 16.39, 95%CI = 1.60-168.20, $p = 0.019$, study power = 100%) models. Individuals with TT genotype of rs9346371 are associated with increased KBD risk compared with TC-CC genotype (OR = 3.80, 95%CI = 1.01-14.27, $p = 0.048$, study power = 100%). There are no significant associations between other SNPs and KBD risk ($p > 0.05$). After FDR correction, no significant associations were observed in this study (FDR-$p > 0.05$).

Haplotype analysis

We performed the haplotype analysis of *COL9A1* and *COL19A1* polymorphisms with KBD risk (Table 5). There are no significant relationship between *COL9A1* and *COL19A1* polymorphisms and KBD risk ($p > 0.05$). As shown in Figure 1 and Figure 2, we observed two blocks (block 1: rs3806093, rs603410 and rs621347; block 2: rs9346371 and rs555313).

Discussion

In this study, three SNPs in *COL9A1* (rs3806093, rs603410 and rs621347) and two SNPs in *COL19A1* (rs9346371 and rs555313) were included to explore the association of genetic polymorphisms and risk of KBD. The results showed that rs3806093 of *COL9A1* and rs9346371 of *COL19A1* were significantly associated with increased KBD risk.

KBD is an endemic multiple and deformed osteoarthropathy(W.-Z. Wang et al., 2009). Electron microscopic analysis showed that a reduction in the collagen fibril diameter and a loss of the fibril banding patterns in the cartilage matrix in patients with KBD(G. Zhang, Liu, Yu, Shi, & Zhang, 1989). Type IX collagen plays a vital role in the degradation of cartilage and bone(X. Shi et al., 2015). Several studies have revealed that genes polymorphisms encoding type IX collagen had relationship with osteoarthropathy risk(Czarny-Ratajczak et al., 2001; Jackson et al., 2010). Previous study genotyped fifteen SNPs in *COL9A1* and found rs6910140 of *COL9A1* plays an important role in the risk and severity of KBD in the Chinese Han population(X. Shi et al., 2015). Our data confirmed the association between *COL9A1* gene and KBD risk. In co-dominant and recessive models, rs3806093 of *COL9A1* had a strong association with KBD susceptibility ($p < 0.05$). *COL19A1* encodes type XIX collagen, which is mainly expressed in central neurons and is necessary for the formation of hippocampal synapses (Su, Gorse, Ramirez, & Fox, 2010). In this study, we assessed the association between *COL19A1* polymorphisms and KBD risk. We observed that rs9346371 of *COL19A1* was associated with the risk of KBD in recessive model. Combined the predictions of HaploReg, polymorphisms of *COL9A1* and *COL19A1* could affect KBD risk by regulating Motifs changed and Selected eQTL hits. It suggests that polymorphisms of *COL9A1* and *COL19A1* may be involved in the development of KBD. However, no significant associations were found after FDR analysis, further studies are needed to explore the exact relationship and mechanism of genetic polymorphisms in KBD.

Some limitations should also be considered. First, the relatively small sample size in this study. Second, we cannot do stratification analysis due to the lack of information on subjects. Third, many environmental factors (ultraviolet light and climate) and lifestyle (dietary habit, smoking and drink status) could affect the susceptibility of KBD, we could not eliminate all factors in this study. Hence, larger sample size and well-designed studies are required to validate the association of *COL9A1* and *COL19A1* polymorphisms with KBD risk.

Conclusion

In conclusion, we found polymorphisms of *COL9A1* and *COL19A1* were associated with the risk of KBD, suggesting the role of *COL9A1* and *COL19A1* polymorphisms in the development of KBD. Further studies are required to validate the influence of *COL9A1* and *COL19A1* polymorphisms on KBD risk.

Declarations

Ethics approval and consent to participate

This study was in the Declaration of Helsinki and approved by the Ethics Committee of Affiliated Hospital of Xizang Minzu University, and we obtained written informed consents from all study subjects before study.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable.

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Authors contribution

XH drafted the manuscript. JWZ and YHW performed the DNA extraction and genotyping; LW and MB performed the data analysis; DYY and MB performed the sample collection and information recording; XH and TBJ conceived and supervised the study.

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Tables

Table 1 Primers used in the study

Gene	SNP	1st-PCRP	2nd-PCRP	UEP_DIR	UEP_SEQ
COL9A1	rs3806093	ACGTTGGATGAAGGACTCCAGTTTGAACAC	ACGTTGGATGTGAACATCTAGGTTTCTGAC	R	cGGTGTTTTCAAACACAACACTTA
	rs603410	ACGTTGGATGCCTTACTATAGTCTTACTC	ACGTTGGATGGCAGTTAGCAGGAAGTTAGG	R	ggacTAATCACAACAGGCAGATCTT
	rs621347	ACGTTGGATGCCAGGACAACATGTTAGGAC	ACGTTGGATGGTCAGATGTTACAGTAACAC	F	agTATGAAATAACTATGCAGAAAACC
COL19A1	rs9346371	ACGTTGGATGCTTGTATATGGAAATCACAG	ACGTTGGATGAACTCTTGTTTGCACTCCAG	F	gACAAAATAATTATGGGCCATGA
	rs555313	ACGTTGGATGTGGGTAATTGGCTTCTGCAC	ACGTTGGATGGGTTCAGTCAGCTTGAAATG	F	TCCAAATAATCAAATCGATCA

SNP, single nucleotide polymorphism; PCRP, polymerase chain reaction primer; UEP, unextended mini sequencing primer; DIR, direction; SEQ, sequence

Table 2 Characteristics of study subjects

Characteristics	Cases (N = 316)	Controls (N = 320)	*P* value
Age	54.70 ± 17.14	19.00 ± 1.60	< 0.001
Sex			< 0.001
Man	183 (57.91%)	239 (74.69%)	
Woman	133 (42.09%)	81 (25.31%)	

Table 3 The loci information of five SNPs in *COL9A1* and *COL19A1*

Gene	SNP	Chromosome position	Alleles	SNP location	MAF (cases)	MAF (controls)	HWE test (*P*)	HaploReg
COL9A1	rs3806093	6: 70273226	A/G	intron	0.163	0.166	0.550	Motifs changed
	rs603410	6: 70274945	T/G	intron	0.214	0.214	1.000	Motifs changed
	rs621347	6: 70276646	A/G	intron	0.375	0.381	1.000	Motifs changed
COL19A1	rs9346371	6: 70210157	T/C	3'UTR	0.349	0.361	0.278	Motifs changed
	rs555313	6: 70214317	T/C	3'UTR	0.465	0.441	1.000	Motifs changed, Selected eQTL hits

SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium

Table 4 Association of *COL9A1* and *COL19A1* polymorphisms with Kaschin-Beck disease risk

SNP	Genotype	Count (case)	Count (control)	Model	OR (95%CI)	*P*	Study power	FDR- *P*
rs3806093	A/G	103/529	106/534	Allele	0.98(0.73-1.32)	0.899		0.944
	AA	8	7	Co-dominant	14.80(1.42-154.80)	**0.024**	100%	0.072
	AG	87	92		0.68(0.19-2.38)	0.542		0.813
	GG	221	221		1			
	AA-AG	95	99	Dominant	1.04(0.34-3.15)	0.944		0.944
	GG	221	221		1			
	AA	8	7	Recessive	16.39(1.60-168.20)	**0.019**	100%	0.072
	AG-GG	308	313		1			
				Additive	1.51(0.59-3.87)	0.386		0.772
rs603410	T/G	135/497	135/497	Allele	1.00(0.76-1.31)	1.000		1.000
	TT	15	14	Co-dominant	0.41(0.01-11.54)	0.599		0.784
	TG	105	107		0.70(0.24-2.05)	0.517		0.784
	GG	196	195		1			
	TT-TG	120	121	Dominant	0.68(0.24-1.94)	0.469		0.784
	GG	196	195		1			
	TT	15	14	Recessive	0.47(0.02-12.43)	0.653		0.784
	TG-GG	301	302		1			
				Additive	0.68(0.26-1.77)	0.434		0.784
rs621747	A/G	237/395	244/396	Allele	0.97(0.78-1.22)	0.818		0.941
	AA	47	46	Co-dominant	1.37(0.35-5.35)	0.649		0.941
	AG	143	152		0.49(0.16-1.49)	0.206		0.822
	GG	126	122		1			
	AA-AG	190	198	Dominant	0.66(0.25-1.78)	0.411		0.822
	GG	126	122		1			
	AA	47	46	Recessive	1.93(0.54-6.88)	0.313		0.822
	AG-GG	269	274		1			
				Additive	0.97(0.48-1.99)	0.941		0.941
rs9346371	T/C	219/409	231/409	Allele	0.95(0.75-1.19)	0.650		0.780
	TT	33	37	Co-dominant	3.69(0.85-16.00)	0.081		0.243
	TC	153	157		0.95(0.31-2.93)	0.929		0.929
	CC	128	126		1			
	TT-TC	186	194	Dominant	1.27(0.45-3.58)	0.649		0.780
	CC	128	126		1			
	TT	33	37	Recessive	3.80(1.01-14.27)	**0.048**	100%	0.243
	TC-CC	281	283		1			
				Additive	1.68(0.77-3.66)	0.192		0.384
rs555313	T/C	294/338	282/358	Allele	1.10(0.89-1.38)	0.379		0.379
	TT	74	62	Co-dominant	0.30(0.06-1.56)	0.152		0.304
	TC	146	158		0.48(0.15-1.50)	0.205		0.307
	CC	96	100		1			
	TT-TC	210	220	Dominant	0.44(0.15-1.31)	0.139		0.304
	CC	96	100		1			
	TT	74	62	Recessive	0.50(0.12-2.09)	0.345		0.379
	TC-CC	242	258		1			
				Additive	0.53(0.24-1.19)	0.124		0.304

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval

Bold data means significant difference ($p < 0.05$)

Table 5 Haplotype analysis of *COL9A1* and *COL19A1* polymorphisms with Kaschin-Beck disease risk

Gene	SNPs	Haplotype	Frequency in cases	Frequency in controls	Without adjustment		With adjustment	
					OR (95%CI)	*P*	OR (95%CI)	*P*
COL9A1	rs3806093|rs603410|rs621347	GTA	0.212	0.216	0.98(0.75-1.28)	0.876	0.66(0.26-1.69)	0.392
		AGA	0.163	0.166	0.98(0.73-1.32)	0.897	1.51(0.59-3.87)	0.386
		GGG	0.377	0.381	0.98(0.78-1.23)	0.865	0.97(0.48-1.99)	0.941
COL19A1	rs9346371|rs555313	CT	0.463	0.441	1.09(0.88-1.36)	0.424	0.53(0.24-1.19)	0.124
		TC	0.347	0.361	0.94(0.74-1.19)	0.595	1.68(0.77-3.66)	0.192
		CC	0.188	0.198	0.94(0.71-1.23)	0.640	1.15(0.48-2.77)	0.750

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval

Figures

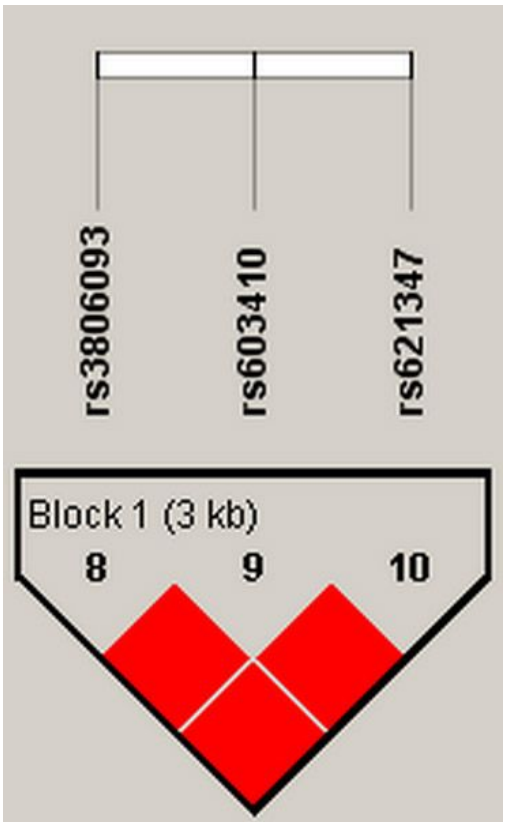

Figure 1

Haplotype block map for the SNPs of COL9A1 Block includes rs3806093, rs603410 and rs621347. The LD between two SNPs is standardized by D′.

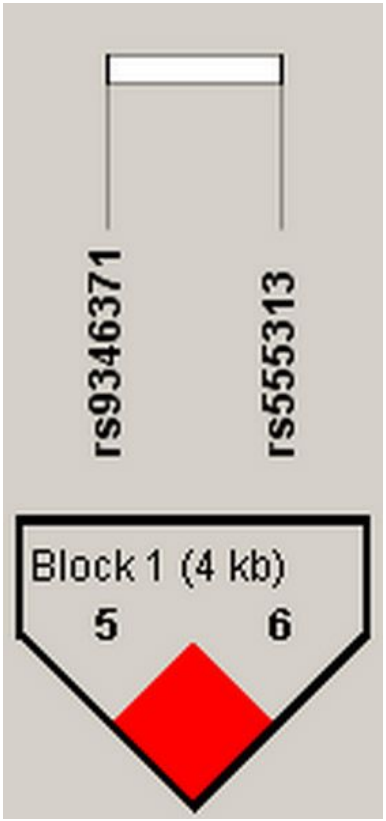

Figure 2

Haplotype block map for the SNPs of COL19A1 Block includes rs9346371 and rs555313. The LD between two SNPs is standardized by D′.