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Original Article

Association of MMP3 COL5A1 and COL1A1 gene polymorphisms with ACL geometric size in Chinese population

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Abstract: Introduction: The anterior cruciate ligament is one of the most frequently injured structures within the knee joint. Previous study reported positive relationship between small anterior cruciate ligament (ACL) and injury risk. The major structural constituents of ligaments are collagens, but no study reported the relationship between the size of ACL and the genes encoding collagens. This study was conducted to investigate whether the gene polymorphisms of MMP3, COL5A1, COL1A1 are associated with the size of anterior cruciate ligament in Chinese. Materials and methods: 106 Chinese participants without any history of previous ligament or tendon injuries have been recruited. All participants received 1.5-T magnetic resonance imaging of both knees and the length and width of the anteromedial (AM) and posterolateral (PL) bundle of ACL were measured. Meanwhile, all participants were genotyped for MMP3 variant (rs679620), COL5A1 variant (rs12722) and the COL1A1 variant (rs1107946). Results: The t-test showed longer AM bundle (39.27 ± 1.24 versus 37.16 ± 2.06 mm, P<0.001) and thicker PL bundle (3.29 ± 0.68 versus 2.76 ± 0.70 mm, P=0.007) in male. Among three genotypes of the MMP3 rs679620, the GG genotype had longest AM bundle (38.92 ± 1.96 mm, P=0.024) and widest PL bundle (3.39 ± 0.54 mm, P<0.001), while the AG had the widest AM bundle (3.10 ± 0.58 mm, P=0.002). The genotypes of COL1A1 rs1107946 were distributed by sex. Most men had a TT genotype (77%) with longer AM and PL bundle (38.67 ± 1.43 mm, 20.59 ± 1.39 mm). TT genotype had longest AM and PL bundle (38.67 ± 1.43 mm, 20.59 ± 1.39 mm), while GG genotype had shortest AM and PL bundle (37.28 ± 1.57 mm, P=0.039; 19.22 ± 1.34 mm, P=0.015, respectively). Conclusion: The geometric size of ACL was influenced by the MMP3 rs679620 and the COL1A1 rs1107946 variant.

Keywords: ACL, gene polymorphism, magnetic resonance imaging, statistics

Introduction

The anterior cruciate ligament (ACL) is an important stabilizer in maintaining the normal biomechanics of the knee and is the most commonly injured knee ligament. Every year, an estimated 80,000 to more than 250,000 ACL injuries occur, many in young athletes 15 to 25 years of age [1]. The risk factors of ACL injury have been identified, such as trauma, anatomical, hormonal, and neuromuscular. Uhorchak JM. *et al* reported the positive relationship between small ACL and injury risk [2], because the stresses in a smaller ACL will be greater for a given applied load. In addition, geometric differences in the size and shape of the ACL had not been well charcterized so far, limited by lacking of standardized methods to obtain the data.

The ACL consists of two distinct functional bundles known as the anteromedial (AM) and posterolateral (PL) bundle named by their tibial insertion. The measurements in cadaveric specimens suggest that the AM bundle is 36.9 ± 2.9 mm in length, while the PL bundle is 20.5 ± 2.5 mm in length [3]. The diameters are similar, with an average size of 7.1 mm and 6.7 mm, respectively [4]. For previous experience, to demonstrate to the two bundles, coronal image of 1.5-T magnetic resonance imaging (MRI) reported to be the common choice. Cohen et al sug-

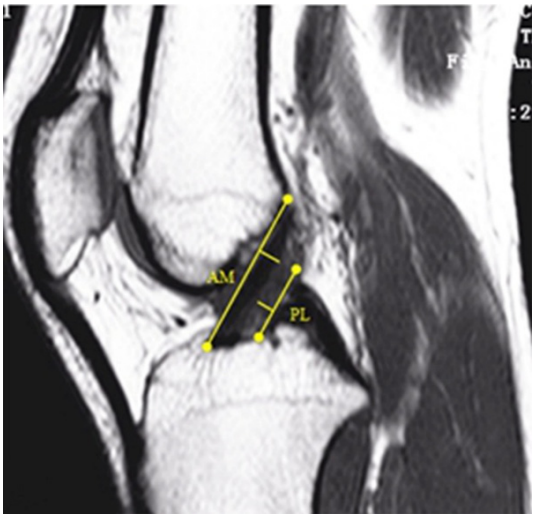

Figure 1. Sagittal 1.5-T T1-weighted MRI showing AM and PL bundle length and width. The vertical lines are examples of the measurements (length) taken for the AM and PL bundles. The horizontal lines are examples of the measurements (width) taken for the AM and PL bundles.

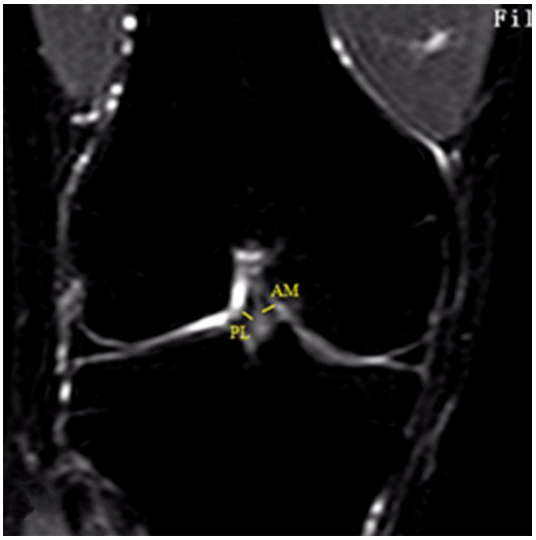

Figure 2. Coronal 1.5-T T2-weighted MRI showing AM and PL bundle width measurements. The horizontal lines are examples of the measurements (width) taken for the AM and PL bundles.

gested that the size of both bundles could be reliably detected using MRI in standard sagittal and coronal viewing planes [3, 5].

Moreover, to investigate the relationship between the genetic polymorphisms and the size of ACL, we selected three genes associated with the ligament and tendon injuries or lower body growth-MMP3 gene (rs679620), COL5A1 gene (rs12722) and COL1A1 gene (rs1107946). The relationship between ACL rupture and MMP3, COL5A1, COL1A1 gene has been mentioned previously [6-8]. MMPs are members of the zine-endopeptidases synthesized by fibroblasts. MMP3 is a member of the MMPs responsible for collagen degradation. Malila S. *et al* reported the 5A+ genotype of the MMP-3 -1612 promoter polymorphism was represented in ACL ruptures [9]. COL1A1 gene encodes type 1 collagen which is the major component of tendons. COL5A1 is also known to be fibrillar in structure, and the COL1A1/COL5A1 interactions affect fibrillogenesis [10]. Meanwhile, COL1A1 gene (rs1107946) was previously reported to be associated with lower body growth or bone mineral density [11-13].

In the present study, we demonstrate the effect of specific genetic changes (single nucleotide polymorphisms [SNPs]) within the genes coding for MMP3, collagen types I, V previously shown to be associated with tendon and/or ligament injuries on the length and width of ACL, and explore familial predisposition for ACL injury risk.

Materials and methods

Subjects

Blood samples for this study were obtained from 106 Chinese subjects (54 male: 32.6 ± 12.2 years, 173.3 ± 7.5 cm, 80.9 ± 13.3 kg; 52 female: 39.3 ± 15.1 years, 160.0 ± 5.9 cm, 59.9 ± 8.6 kg) without any history of previous ligament or tendon injuries. Female participants had normal menstrual cycles and used no hormone-based medications for the past 6 months. Participants signed a consent form approved by the university institutional review board prior to enrollment. MRI of the knee were prospectively collected for all patients during 5 weeks in April and May 2015, using a closed 1.5-T magnet (PHILIPS ACHIEVA 1.5; PHILIPS Healthcare, Netherland) with the knee positioned in full extension.

MRI measurements

The intact ACL was measured on T1- and T2-weighted sagittal and coronal views for the AM and PL bundle. In addition, the difference between male and female measurements was assessed. Based on the documented literature [14], and for the purposes of this study, on the

Table 1. Age, physical characteristics and MRI measurement of all participants according to sex

		Male	Female	*P* value
n		54	52	-
Age (years)		32.60 ± 12.17	39.27 ± 15.09	0.282
Height (cm)		173.26 ± 7.50	160.00 ± 5.60	**<0.001**
Mass (kg)		71.90 ± 11.24	59.92 ± 8.61	**<0.001**
BMI (kg/m^2)		22.89 ± 3.19	22.49 ± 3.97	0.673
Sagittal Length (mm)	AM	39.27 ± 1.24	37.16 ± 2.06	**<0.001**
	PL	19.90 ± 1.24	19.28 ± 1.64	0.125
Sagittal Width (mm)	AM	2.68 ± 0.76	2.48 ± 0.86	0.363
	PL	3.29 ± 0.68	2.76 ± 0.70	**0.007**
Coronal Width (mm)	AM	2.21 ± 0.32	2.18 ± 0.43	0.771
	PL	2.01 ± 0.30	1.90 ± 0.26	0.141

Boldface type indicates significance (P<0.05).

sagittal plane, the AM bundle was defined as the oblique fibers inserting at the anterior border of the ACL on the tibia and the proximal aspect of the femoral insertion on the lateral femoral condyle. This was readily visible and corresponded to the AM bundle appearance seen arthroscopically. Similar to the AM bundle, the PL bundle was defined as the oblique fibers inserting posteriorly on the tibia insertion and on the distal aspect of the femoral insertion on the lateral femoral condyle. There is a septum or dividing line on MRI where the bundles can be identified for measurement (**Figure 1**). In the coronal plane, the AM and PL bundle widths were measured by delineating the 2 bundles and measuring the transverse measurement or width of each bundle (**Figure 2**).

DNA extraction and genotyping

Total DNA was isolated from Blood (5 ml) using Blood samples were collected from the subjects forearm vein during the morning hours and stored at -80°C. DNA was isolated with the UltraPure blood kit (SBS Genetech Co. Ltd., Shanghai, China) according to the manufacturer's instructions. Genotyping of MMP3, COL1A1 and COL5A1 polymorphisms were determined by Real-time PCR allelic discrimination TaqMan assay (AB), which is used for genotyping analysis, as previously published [15-17]. All PCR reactions contained 10 ng of DNA, 5.0 μl TaqMan Universal Master Mix (AB) (2×), 0.25 μl primers and probes (10×) and water for a final volume of 10 μl, including the appropriate negative controls in all assays. For the all polymorphisms, the assay used probes and primers designed by assay-on-demand services from Applied Biosystems. We used the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/) to extract the available information on the SNPs in all genes Real-time PCR was performed on an ABI Prism 7500 Fast (Applied Biosystems, Foster City, CA, USA). Conditions for the three polymorphisms were 95°C for 10 min and 50 cycles of amplification (95°C for 5 s and 60°C for 30 s). For each cycle, the software determined the fluorescent signal from the VIC-or FAM-labeled probe (Applied Biosystems). Allelic discrimination was performed using specific primers and probes for each allele. A 5% random sample from each genotype was independently verified twice for quality control.

Statistical analysis

Data were analyzed using SPSS 22.0 (IBM Corp., Armonk, USA). Quantitative data were expressed as mean ± SD. Statistical analysis of differences between two groups was performed by unpaired t test, and the statistical analysis of differences among three or more groups was assessed using ANOVA and multiple comparison tests. A *p*-value of less than 0.05 was considered statistically significant.

Results

Participant characteristics

All participants were compared with age, height, weight, body mass index (BMI) by sex, and the length and width of the AM and PL bundles were measured by MRI. There were no significant differences in age between the male and female (P=0.282), but the height and weight were significantly higher in male (P<0.001). There was no significantly difference the body mass index (BMI) either. The average length and width of the AM and PL bundles in the sagittal plane and width in the coronal plane are summarized as well. The length of AM bundle (39.27 ± 1.24 mm) in male was longer than that (37.16 ± 2.06 mm) in female (P<0.001). The averaged sagittal width of PL bundle was 3.29 ± 0.68 mm for male, while 2.76 ± 0.70

Table 2. Age, physical characteristics MRI measurement for the MMP-3 rs679620 genotyping

n=106		MMP-3 rs679620 genotype			
		AA (n=22)	AG (n=32)	GG (n=52)	*P* value
Sex (male %)		54%	43%	53%	0.798
Age (years)		30.00 ± 12.55	36.69 ± 15.35	37.85 ± 13.47	0.289
Height (cm)		170.82 ± 7.65	166.06 ± 10.62	165.46 ± 9.02	0.271
Mass (kg)		68.35 ± 11.83	66.56 ± 12.69	64.71 ± 11.16	0.675
BMI (kg/m^2)		22.38 ± 3.44	24.22 ± 4.69	23.54 ± 2.88	0.791
Sagittal Length (mm)	AM	38.07 ± 1.87	37.23 ± 1.74	38.92 ± 1.96	**0.024**
	PL	19.46 ± 0.99	19.92 ± 1.92	19.45 ± 1.34	0.576
Sagittal Width (mm)	AM	2.09 ± 0.25	3.10 ± 0.58	2.46 ± 0.92	**0.002**
	PL	3.35 ± 0.65	2.22 ± 0.31	3.39 ± 0.54	**<0.001**
Coronal Width (mm)	AM	2.07 ± 0.24	2.17 ± 0.37	2.27 ± 0.41	0.312
	PL	1.93 ± 0.26	1.82 ± 0.30	2.05 ± 0.26	**0.035**

Boldface type indicates significance (P<0.05).

Table 3. Age, physical characteristics MRI measurement for the COL5A1 rs12722 genotyping

n=106		COL5A1 rs12722 genotype			
		CC (n=43)	TC (n=16)	TT (n=47)	*P* value
Sex (male %)		36%	63%	64%	0.210
Age (years)		33.86 ± 14.89	40.13 ± 13.27	36.30 ± 13.50	0.552
Height (cm)		164.68 ± 8.98	164.88 ± 3.48	169.39 ± 10.68	0.203
Mass (kg)		63.64 ± 12.53	62.56 ± 6.24	69.52 ± 11.61	0.157
BMI (kg/m^2)		22.32 ± 3.16	22.02 ± 2.23	24.32 ± 4.27	0.547
Sagittal Length (mm)	AM	37.99 ± 2.28	37.86 ± 1.65	38.59 ± 1.80	0.517
	PL	19.83 ± 1.48	19.14 ± 1.17	19.53 ± 1.56	0.511
Sagittal Width (mm)	AM	2.67 ± 0.94	2.80 ± 0.94	2.41 ± 0.65	0.384
	PL	3.07 ± 0.76	2.68 ± 0.59	3.11 ± 0.74	0.336
Coronal Width (mm)	AM	2.19 ± 0.42	2.26 ± 0.36	2.18 ± 0.34	0.871
	PL	1.94 ± 0.24	1.97 ± 0.25	1.96 ± 0.34	0.955

mm for female (P=0.007). There was no significant difference between other measurements for male and female (**Table 1**).

Genotype analysis

The allele frequency of MMP-3 rs679620 genotype was assessed (AA: 20.8%, GG: 30.2%, AG: 49.1%). There were no significant differences in sex, age, height, mass, and BMI between the three genotype groups, indicating that no growth or sex-specific effects exist. On sagittal view, individuals with the GG genotype exhibited longer length of AM bundle (38.92 ± 1.96 mm) than those with either the AA (38.07 ± 1.87 mm) or AG genotype (37.23 ± 1.74 mm, P=0.024). The AM was wider on sagittal view in individuals with the AG genotype for the MMP3 rs679620 variant (3.10 ± 0.58 mm) compared to the AA genotype (2.09 ± 0.25 mm) and GG genotype (2.46 ± 0.92 mm; P<0.002), while the coronal width of AM was similar in the three genotype groups. The sagittal width of PL was shorter in individuals with the AG genotype (2.22 ± 0.31 mm) compared to the AA genotype (3.35 ± 0.65 mm) and GG genotype (3.39 ± 0.54 mm; P<0.001). The PL on coronal view was wider in individuals with GG genotype (2.05 ± 0.26 mm) than those with either AA genotype (1.93 ± 0.26 mm) or AG genotype (1.82 ± 0.30 mm, P=0.035) (**Table 2**).

No significant association was observed between rs12722 COL5A1 and measurement of both bundles (**Table 3**).

When stratified by sex, for COL1A1 rs1107946 variant genotype, more male subjects had TT

Table 4. Age, physical characteristics MRI measurement for the COL1A1 rs1107946 genotyping

n=106		COL1A1 rs1107946 genotype			
		TT (n=26)	GT (n=48)	GG (n=32)	*P* value
Sex (male %)		77%	50%	31%	**0.050**
Age (years)		30.15 ± 12.12	36.79 ± 16.48	39.13 ± 10.0	0.209
Height (cm)		173.92 ± 9.21	166.79 ± 8.64	160.88 ± 6.42	**<0.001**
Mass (kg)		73.00 ± 11.40	65.40 ± 12.44	61.31 ± 7.83	**0.022**
BMI (kg/m^2)		23.06 ± 2.71	22.55 ± 4.52	22.67 ± 2.60	0.918
Sagittal Length (mm)	AM	38.67 ± 1.43	38.63 ± 2.31	37.28 ± 1.57	**0.039**
	PL	20.59 ± 1.39	19.34 ± 1.42	19.22 ± 1.34	**0.015**
Sagittal Width (mm)	AM	2.67 ± 0.67	2.58 ± 0.84	2.49 ± 0.89	0.839
	PL	3.18 ± 0.71	3.10 ± 0.75	2.90 ± 0.75	0.480
Coronal Width (mm)	AM	2.25 ± 0.32	2.13 ± 0.33	2.25 ± 0.47	0.549
	PL	2.02 ± 0.33	1.99 ± 0.28	1.90 ± 0.27	0.436

Boldface type indicates significance (P<0.05).

genotypes (77%), compared with the GT (50%) and GG (31%, P=0.050). The height and bodyweight was associated with different genotype. The individuals with TT genotype was significantly higher and heavier than GT genotype and GG genotype (P<0.001, P=0.002). The sagittal length of AM (38.67 ± 1.43 mm) and PL (20.59 ± 1.39 mm) in individuals with TT genotype were both longer than GT (AM: 38.63 ± 2.31 mm, PL: 19.34 ± 1.42 mm) and GG genotype (AM: 37.28 ± 1.57 mm; PL: 19.22 ± 1.34 mm), P=0.039 and P=0.015 respectively. No significant association was detected between COL1A1 genotype and other measurements (**Table 4**).

Discussion

The principal finding of this study is the association between the MMP3 and COL1A1 gene variant and ACL size in Chinese population. To our knowledge, our study is the first report that indicates an association between the gene polymorphisms and the geometric size of ACL.

ACL ruptures are multifactorial disorders that are associated with several intrinsic and extrinsic risk factors. The small size of ACL may be the potential risk factor of ACL ruptures. There were many previous studies had reported the association between gene polymorphisms and ACL ruptures before [18, 19]. To date, no studies have investigated the size of ACL among gene polymorphisms. In our study, the length and width of AM and PL bundles were measured by 1.5-T magnetic resonance imaging. The MRI measurement was based on the experience of the previous study, using sagittal and coronal imaging planes to show the AM and PL bundles. Our study offers new possibility of gene polymorphisms relating to ACL size, even to the risk of ACL ruptures. An asymptomatic group of participants with a limited range of age, BMI and no history ligament or tendon injuries were studied to explored the association between ACL size and gene polymorphism. To our knowledge, this is the first study to demonstrate the relationship between size of tendon and a gene polymorphism in vivo.

Many previous studies had reported that both the AM and PL bundles of males were longer than those of females in Caucasia cadaveric specimens [14, 20, 21]. In our study, we found longer AM bundle and thicker PL bundle in males in sagittal plane (**Table 1**). According to this finding, we need to consider the sexual effect exists in different genotype analysis. Therefore, we established comparison of sex, height, weight and BMI data in front of measurement of the ACL, in order to determine growth or sex-specific effects.

Previous studies have reported MMP-3 rs-679620 gene polymorphism was associated with injuries in tendons and ligaments [6], but no association was found in the mechanical properties of tendon structures [22]. Our study confirmed that this gene polymorphism was significantly associated with the length and width of AM bundle, and width of PL bundle, without the effect on sex or growth (**Table 2**). The GG genotype had longer and thinner AM bundle and thicker PL bundle compared to sub-

jects with other genotypes. This result suggest that the GG genotype had more extensible AM bundle, which brought more range of motion, and more stable PL bundle, which brought more stability against vertical force acted on ACL.

The association between the COL5A1 rs12722 polymorphisms and tendon pathologies in female were reported [8, 23]. The COL5A1 rs12722 gene was not associated with the measures of patellar tendon properties in an asymptomatic cohort [24]. The COL5A1 rs12722 was recently found to be associated with severity of musculoskeletal injuries [25]. O'Connell K. *et al* reported significant interaction between the COL5A1 rs12722 T/C and COL12A1 rs970547 A/G variants and risk of ACL injury [10] [17]. However, in this study, we found no significant difference in sex, height, weight and measures of ACL size with three different genotype groups in Chinese (**Table 3**). Above all, this gene may influence the fibril property of ACL instead of size in Chinese population.

A recent study showed the GG genotype of COL1A1 rs1107946 has negative biologic effects on BMD (bone mineral density) and mineral turnover related to pubertal stage [13, 17]. The studies before never identify whether the ligaments is affected by this polymorphism before. In our study, there is an association between the genotype of COL1A1 rs1107946 and measurement of ACL size, especially the length of AM and PL bundles (**Table 4**). We also found the distribution of genotypes or alleles associated with sex. Most male had a TT genotype, while most female had a GG genotype. However, the results of measure were not extremely consistent with sex group. The AM and PL bundles with TT genotype were both longer than GT and GG genotype, but the width of the bundles had no significant difference, while **Table 1** showed the sex influenced the length of AM bundle and width of PL bundle. This difference may suggest that there was genetic effect on ACL size existing.

Potential limitations of this study were the relatively small sample size (n=106) for a genotype association study. Further research on an independent population is required to confirm the findings of this study, and to identify the variant within this chromosomal region. Another limitation was that our study was limited to uncertainty of observation and measurement.

Conclusion

To our knowledge, our study is the first report that indicates an association between the gene polymorphisms and the geometric size of ACL. The geometric size of anterior cruciate ligament is influenced by the MMP3 rs679620 and the COL1A1 rs1107946 variant. For these, DNA sequence variants within genes can be responsible for size of ACL. Genotyping can be an available approach to find potential risk of ACL rupture.

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Disclosure of conflict of interest

None.

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