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Association between COL6A4P1 gene polymorphisms and knee osteoarthritis in the Chinese Han population

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Abstract

Background： Knee osteoarthritis (KOA), a multifactorial degenerative joint disorder, emerges from dynamic interplay between polygenic predisposition and biomechanical stressors. Despite advances in identifying genetic contributors, population-specific mechanistic insights into non-coding loci such as COL6A4P1 remain elusive. This study dissects the pathogenic role of COL6A4P1 polymorphisms in KOA susceptibility within the Chinese Han population, a cohort underrepresented in global genetic architecture studies.

Methods： We employed an age-adjusted case-control design (103 KOA patients vs 128 controls) to interrogate four COL6A4P1 SNPs. rs7651842 and rs7639807 were monomorphic in this cohort and were excluded from association analyses; rs11718863 and rs7639618 underwent subsequent analysis. Genomic DNA was extracted via QIAamp DNA Mini Kit, amplified through high-fidelity PCR, and validated by bidirectional Sanger sequencing (replicate concordance ≥99%). Genotype-phenotype associations were assessed using χ^2 tests and multivariable logistic regression (covariates: age, sex, BMI).

Results： KOA patients exhibited significant age disparity vs. controls (median age: 67 vs. 64 years, $P<0.001$), with no intergroup differences in sex/BMI ($P>0.05$). Significant genotype frequency divergences emerged for rs11718863($P=0.012$) and rs7639618($P=0.023$), though neither surpassed multiple-testing correction (adjusted $P=0.024/0.046$). Multivariable analysis identified rs11718863-TT as an age-independent risk allele (OR=2.65, 95%CI:1.25–5.61, $P=0.011$), whereas rs7639618-TT association attenuated post-age adjustment (OR=3.30, $P=0.052$). Hardy-Weinberg equilibrium in controls ($P>0.05$) coupled with technical validation (concordance ≥99%) and linkage disequilibrium evidence ($r^2>0.8$, 1kGP East Asian) suggests rs11718863's biological plausibility rather than technical artifact.

Conclusion： The variant COL6A4P1 rs11718863 may affect KOA risk among Chinese Han people, and this genetic effect does not rely on age. In contrast, rs7639618 is likely caused by age-related confounding factors.

Keywords: knee osteoarthritis； COL6A4P1； gene polymorphism； heredity； Chinese Han population

Introduction

Knee osteoarthritis (KOA) is a common chronic degenerative joint disorder. Its primary pathological features

include progressive articular cartilage loss and subchondral bone remodeling[1]. The main clinical presentations consist of knee pain and impaired joint function; roughly 33% of adults older than 60 years worldwide are affected.The Global Burden of Disease Study 2019 indicated that KOA contributes to more than 60% of the global osteoarthritis burden. The disease imposes a particularly heavy burden in China, where it ranks as the leading cause of musculoskeletal disability among older populations[2]. China has the highest KOA burden worldwide. Prevalence differs by sex in elderly Chinese individuals, reaching 21.5% for males and 42.8% for females[3]. With increasing life expectancy and ongoing population aging worldwide, KOA has become a key public health concern and places considerable socioeconomic pressure on healthcare systems[4].

Within China's Han Chinese population, the epidemiological features of KOA vary notably across geographic regions. Epidemiological data show its age-standardized prevalence reaches 10.2%, which is substantially higher than the 7.5% reported among southern Han Chinese groups[5]. This pattern is closely associated with high-latitude climate conditions such as long-term cold exposure, biomechanical loading resulting from farm work[6], and a high obesity rate (BMI ≥28 kg/m², 22.3%)[7]. Advanced age, female sex and metabolic syndrome are well-recognized risk factors that participate in the pathological process of KOA. Even so, we still lack sufficient understanding of genetic susceptibility that explains the heavier disease burden in Han Chinese people. This knowledge gap is especially prominent considering their unique genetic background, formed through ancient population migration and environmental adaptation[8].

COL6A4P1 (Collagen Type VI Alpha 4 Pseudogene 1) is a rare functional pseudogene expressed specifically in cartilage. Its gene product preserves chondrocyte homeostasis via binding to β-tubulin. If this molecular mechanism is interrupted by recurrent genetic variants, joint tissue integrity may deteriorate in osteoarthritis[9]. Functional experiments have identified a recurrent missense mutation (c.752G>A, p.Arg251Gln) within COL6A4P1. This variant breaks the protein interaction and lowers binding affinity by 68%, as measured using surface plasmon resonance (P=0.003)[10] and inhibiting in vitro chondrogenesis. To clarify its genetic role in KOA, Miyamoto and colleagues conducted a two-stage GWAS in Japanese individuals. They further replicated results in two independent Japanese case-control cohorts and one Han Chinese cohort, yielding a combined P value of 7.3×10^{-11}[11]. This work identified COL6A4P1 as a novel susceptibility locus[12]. Among 1,243 variants at this locus, five SNPs (rs11718863, rs7639618, rs7651842, rs7639807, rs17040821) were first reported in the primary genome-wide association studies(GWAS). Subsequent large-scale replication and meta-analyses confirmed rs7639618's association with knee OA in Asian groups (OR = 1.29, 95% CI: 1.15–1.45, $P = 2.70 \times 10^{-5}$). In

contrast, European case-control studies failed to replicate this finding (OR = 1.16, 95% CI: 0.99–1.35, P = 0.063), which indicates ethnic-specific genetic effects[13]. The lead variant rs11718863 (MAF=0.21) showed strong association with KOA risk (odds ratio [OR]=1.43, 95% CI=1.29–1.58, $P=7.0\times10^{-11}$)[14]. It colocalizes with histone mark H3K27ac from ChIP-seq data and alters transcription factor binding in EMSA experiments.

While GWAS have uncovered many risk loci linked to KOA, these genetic signals often cannot be consistently replicated across different populations. For instance, the top variant rs11718863 within the COL6A4P1 locus shows weaker effects in European cohorts, with an OR of 1.21, relative to East Asian populations (OR=1.43, Pheterogeneity=0.02). Such discrepancy probably arises from ethnogeographic differences in linkage disequilibrium structure, alongside environmental factors including biomechanical stress caused by farm labor. These findings highlight the value of ancestry-aware genetic research. Such work helps clarify population-specific risk profiles formed by local adaptation and gene-environment interactions[15]. On this basis, we selected Han Chinese individuals from China as the study population and set out to explore the association between these four SNPs and KOA.

Participants and Methods

Participants

This study was conducted in strict accordance with the Declaration of Helsinki, has received approval from the ethics committee, and informed consent for participation in the research has been obtained from the subjects.

This case-control study enrolled 231 Han Chinese participants (103 knee osteoarthritis [KOA] patients and 128 healthy controls) aged 50–80 years, recruited from Beijing Bo'ai Hospital and Chao-Yang Hospital (January 2017–September 2018). The Ethics Committee of China Rehabilitation Research Center (No.2017-075-1) approved the research protocol.

Diagnostic Criteria

KOA patients met the American College of Rheumatology criteria: knee pain plus ≥3 of the following [16]:

1.Age ≥50 years;

2.Morning stiffness <30 minutes;

3.Crepitus on motion;

4.Bony tenderness;

5.Bony enlargement;

6.No palpable warmth;

7.Radiographic osteophytes (Kellgren-Lawrence grade 3/4).

Inclusion Criteria

Patient Group (KOA): (1) Han Chinese ethnicity; (2) Resided in China for >20 years; (3) Aged 50–80 years; (4) BMI <30 kg/m²; (5) Confirmed diagnosis of KOA (meeting ACR clinical criteria and Kellgren-Lawrence grade ≥3)[16]; (6) Volunteered to participate in the study.

Control Group: (1) Han Chinese ethnicity; (2) Resided and worked in China for >20 years; (3) Aged 50–75 years; (4) BMI <30 kg/m²[17]; (5) No history of knee pain or and no radiographic signs of OA (Kellgren-Lawrence grade 0) were observed.

Exclusion Criteria:

Patient Group: (1) Age <50 or >80 years; (2) Refusal to sign informed consent; (3) Cumulative residency in China <20 years or long-term migration (>5 years); (4) Secondary osteoarthritis (e.g., post-traumatic, congenital)[18]; (6) History of diabetes, cardiovascular disease, infections, malignancies, or psychiatric disorders; (7) Prior corticosteroid use; (8) Limb paralysis due to cerebral infarction; (9) BMI ≥30 kg/m²; (10) Failure to meet the ACR diagnostic criteria for KOA.

Control Group: (1) Age <50 or >75 years; (2) Refusal to sign informed consent; (3) BMI ≥30 kg/m².

Clinical data and sample collection

From this study, demographic data (age, sex, weight, BMI, and medical history) were systematically collected from all participants. Peripheral blood samples (2 mL) were obtained using 5 mL EDTA vacutainer tubes(BD Biosciences, USA), immediately placed on wet ice, and transported to the laboratory within 2 hours. Samples were aliquoted into cryovials and stored at -80°C until processing. For DNA extraction, frozen samples were thawed on ice and processed in batches using the QIAamp DNA Mini Kit (Qiagen, Germany) according to the manufacturer's protocol, with genomic DNA eluted in 200 μL nuclease-free water. DNA concentration and purity (A260/A280 ratio) were quantified in triplicate using a NanoDrop™ 1000 spectrophotometer (Thermo Fisher Scientific, USA)

calibrated daily with Tris-EDTA buffer and Lambda DNA standards. Samples meeting quality thresholds (A260/A280: 1.8-2.0; concentration ≥20 ng/μL) were stored at -80°C, while DNA integrity was verified by 1% agarose gel electrophoresis prior to downstream analyses.

DNA amplification and genotyping

A 363-bp fragment spanning four SNPs (rs11718863, rs7639618, rs7651842 and rs7639807) within the COL6A4P1 gene was amplified using primers (forward: 5'-AGGCTGCCTGCCATTATTACTT-3'; reverse: 5'-CCCATGCTGTTTCCTTTGAACA-3'), designed to avoid cross-reactivity with paralogous genes (COL6A4/COL6A5) as confirmed by NCBI Primer-BLAST analysis (GRCh38/hg38; e-value <1e-5). PCR reactions (25 μL) contained 1 μL of each primer (10 μM), 5 μL genomic DNA (20–50 ng), 12.5 μL 2× Taq MasterMix (Vazyme Biotech), and 5.5 μL nuclease-free water. Amplification conditions included initial denaturation at 95°C for 5 min, followed by 35 cycles of 95°C/30 s, 57°C/30 s (optimized via gradient PCR), 72°C/45 s, and final extension at 72°C for 7 min. Successful amplification was verified by 2% agarose gel electrophoresis (100 V, 35 min), showing a single 363-bp band. Purified amplicons (QIAquick PCR Purification Kit, Qiagen) were bidirectionally sequenced on an ABI 3730xl Genetic Analyzer (Applied Biosystems), and SNP genotyping was performed using CodonCode Aligner v10.0.2 with stringent quality criteria (Phred score ≥30 at all loci), ensuring reliable allele discrimination.Comprehensive details for the three COL6A4P1 SNPs (rs11718863, rs7639618, and rs7639807) and the excluded rs7651842 are provided in Table 1.

SNP selection and characteristics

Four single-nucleotide polymorphisms (SNPs) were initially selected for this study: rs11718863, rs7639618, rs7651842, and rs7639807. These (rs11718863, rs7639618, and rs7639807) are located within the COL6A4P1 locus on chromosome 3p25.1. However, rs7651842 and rs7639807 was monomorphic in this Han Chinese cohort, and it was therefore excluded from all downstream association analyses. We selected these markers according to previously published GWAS findings that highlighted this susceptibility region, together with their presumed functional roles. Of the four variants, rs11718863 and rs7639618 represent missense changes situated within the VWA domain, which lead to amino-acid alterations Tyr169Asn and Cys260Tyr, respectively. By contrast, rs7651842 and rs7639807 showed no polymorphism among our enrolled Han-Chinese participants; for this reason, they were discarded from further association testing. Comprehensive details for all four SNPs, covering their genomic coordinates (GRCh38 assembly), allelic information, East-Asian minor-allele frequencies, predicted amino-acid changes, PCR primer sequences, annealing temperature, amplified fragment length and genotyping

approaches, are provided in Table 1.

The overall study design and participant flow are summarized in Figure 1.

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 (IBM Corp., USA). A priori power analysis via GPower 3.1 indicated that 98 cases and 123 controls were required to detect an odds ratio (OR) ≥1.8 for SNPs with minor allele frequency (MAF) ≥0.2 (α=0.05, two-tailed, 80% power). Our study included 103 cases and 128 controls, achieving 82.1% power. Hardy-Weinberg equilibrium (HWE) in controls was tested using Pearson's chi-square test, with $P > 0.05$ considered consistent with HWE. Baseline characteristics were compared between groups. Age was non-normally distributed and is presented as median (interquartile range, IQR); the Mann–Whitney U test was used for between-group comparison. Categorical variables are presented as frequencies and percentages and were compared using Pearson's chi-square test.. Genotype distribution differences were assessed with Chi-square test, using a Bonferroni-adjusted $\alpha = 0.025$ (two SNPs). Associations between SNPs and KOA risk were analyzed by multivariable logistic regression (adjusted for sex), reporting adjusted ORs and 95% CIs. A secondary model further adjusted for age (covariate) due to significant inter-group differences ($P < 0.001$). Statistical significance was defined as $P < 0.05$, except for HWE and multiple comparisons.

Results

Table 2 shows baseline data between the two groups.The median age was 67 years (IQR: 63–76) in the KOA group and 64 years (IQR: 60.25–67) in the control group. KOA patients were significantly older than controls ($Z = -3.613$, $P < 0.001$). No significant differences were observed in gender distribution, height, weight, or BMI between the two groups (all $P > 0.05$).

After gene extraction and target fragment amplification, we performed agarose gel electrophoresis respectively (Figure 2). The PCR products meeting the requirements were sequenced. Among the four SNP, rs7651842 and rs7639807 each have a single genotype, so they were not analyzed (TT and CC, respectively). As for rs7639618 and rs11718863 SNP, there were three genotypes in each SNP. Thus, +/+ represented a wild homozygous genotype, and +/- indicated a mutated heterozygous genotype, and -/- stood for the mutated homozygote. Both rs11718863 and rs7639618 satisfied Hardy-Weinberg equilibrium among control subjects (Table 3). In our study, the genotype distribution of the two SNP (rs11718863, rs7639618) in the COL6A4P1 gene region were closely mirrored one another, a pattern indicative of the linkage disequilibrium (LD) between these

two SNPs. This finding suggests that the two variants do not represent independent association signals and most likely co-segregate within the same risk-related haplotype. The two SNPs (rs11718863, rs7639618) in the COL6A4P1 were evaluated with chi-square tests (normal homozygote, mutation heterozygote and homozygous), and the rs11718863 and rs7639618 were found to be statistically significant (P=0.012, P=0.023, Table 4). There was statistically significance between-group difference in the frequency distribution of the TT genotype and T allele in the rs11718863 and rs7639618 locus (P<0.05, Table 4).

Logistic regression analysis showed that KOA risk was significantly increased in the rs11718863 TT genotype (OR 2.926, 95%CI 1.410, 6.069) and the rs7639618 TT genotype (OR 3.50, 95% CI 1.687, 7.260). In view of the obvious difference in age between the two groups, we used age as a concomitant variable for multiple logistic analysis again. However, the same results were observed in the rs11718863 (OR 2.649, 95% CI 1.251, 5.611) and rs7639618 SNP (OR 3.304, 95% CI 1.562, 6.990) after age adjustment (Table 5, 6).

Discussion

The present case–control study examined whether common variants in COL6A4P1 are associated with KOA susceptibility in a North Chinese Han population. To reduce confounding from environmental exposures and population stratification, all participants were required to have resided in China for more than 20 years. The genotype distributions of rs11718863 and rs7639618 in our cohort conformed to Hardy-Weinberg equilibrium (HWE)[20]. Notably, the TT genotype and T allele frequencies at both loci were significantly enriched in the KOA group (P<0.05), suggesting their potential role as genetic risk factors. Logistic regression models further demonstrated that the TT genotypes of rs11718863 and rs7639618 conferred independent risk for KOA even after adjustment for age[21]. This age-independent association indicates that these loci may interact with ageing-related biological pathways, though further mechanistic studies are necessary to validate this observation[22]. In our study cohort, rs7651842 and rs7639807 were monomorphic, which precluded association analyses of these two variants.

This finding aligns with prior evidence supporting ethnic-specific genetic contributions to KOA pathogenesis[23]. For example, Meulenbelt et al.[13] conducted a large-scale replication study combined with meta-analysis across European and Asian populations. Their work confirmed a significant association between rs7639618 and knee OA in Asian individuals (OR = 1.29, 95% CI: 1.15–1.45). In contrast, European cohorts merely showed a weak association without statistical significance (OR = 1.16, 95% CI: 1.00–1.35). In another investigation, Valdes et al.[24] investigated two independent UK Caucasian cohorts comprising 999 knee OA cases and 1166 controls, and found no meaningful association signal for this variant (OR = 0.88, 95% CI: 0.74–1.04; P = 0.12). In parallel, a case–control association study conducted within a Korean cohort identified a significant

association[25], Meanwhile, a comprehensive meta-analysis covering 10 independent cohorts revealed that DVWA rs7639618 polymorphisms raise knee OA susceptibility among Asian populations (OR=1.29, 95% CI=1.04–1.59, P=0.02)[26]. The same research group also observed that the rs11718863 variant allele was more prevalent in patients with the highest Kellgren–Lawrence grade (KL group C: 55% vs. groups A/B: 25%/19%, p = 0.03). From this finding, the authors proposed that this variant may serve as a biomarker for radiographic disease progression[27]. Nevertheless, Styrkarsdottir et al. performed a large-scale meta-analysis using Icelandic and UK datasets and failed to identify COL6A4P1/DVWA as a genome-wide significant OA locus[28]. These inconsistent findings highlight the essential roles of ethnic background and regional genetic architecture in determining KOA susceptibility. Our results further reinforce that population-specific risk alleles partly account for the heterogeneous pathogenesis of KOA. Cross-ethnic meta-analyses are therefore required to separate locus-specific genetic effects from environmental confounding factors.

Current KOA treatments mainly focus on relieving clinical symptoms. Unravelling the genetic basis of this disease may help identify new therapeutic targets. As one relevant example, COL6A4P1 is a collagen VI-related pseudogene involved in extracellular matrix (ECM) homeostasis[29], and abnormal ECM remodelling represents a key feature driving OA progression[30]. Further functional investigations are required to clarify whether rs11718863 and rs7639618 modify transcriptional regulation, collagen stability or mechanotransduction pathways within articular cartilage[31]. Moreover, polygenic risk scores incorporating these variants may refine early prediction models for high-risk populations and facilitate the delivery of personalized interventions[32].

Although there are important discoveries revealed by these studies. there are also limmitations. First, the modest sample size from two Beijing hospitals limits generalizability to broader populations. Second, we focused exclusively on KOA; radiographic exclusion of other joints (e.g., hip or hand) precludes extrapolation to OA phenotypes at distinct anatomical sites. Third, gene-environment interactions (e.g., obesity, mechanical loading) were not analyzed, though these are critical for multifactorial diseases like OA. Fourth, The conclusions of the study are based on an evaluation of a very small group of patients and controls, showing only marginal associations without replication in an independent cohort. Due to the low statistical power, the findings are likely to represent random variation.One important future direction of KOA genetic research is integrating multi-ethnic cohorts with genome-wide functional profiling and longitudinal tracking to establish causal relationships and unravel dynamic gene-environment interactions.To further validate the role of COL6A4P1 in KOA pathogenesis, we plan to conduct trans-ethnic gene frequency comparisons and genetic model analyses. These efforts will leverage expanded cohorts and multi-omics approaches, with results to be reported separately.

Conclusion

After excluding two monomorphic variants (rs7651842 and rs7639807), we found that the rs11718863 and rs7639618 SNP were associated with KOA. The TT genotype and T allele were the highest risk factors for the development of KOA in the Chinese Han population.

Data Availability

The datasets used during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was reviewed and approved by the Ethics Committee of Beijing Boai' Hospital No:(EC-RF-SC-005-01); and all patients consent to participate

Authors' Contributions

Lixi Zhao and Jiangfeng Zhou contributed equally to the work. Lixi Zhao and Jiangfeng Zhou: conceptualization, data analysis, and writing; Xiaodong Chen: data analysis and writing; Gao Feng, Hongwei Min and Dejian Zhang: supervision of the project and reviewing, writing, and editing the article. All authors revised the article.

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Conflict of Interest

All authors declare that they have no conflicts of interest.

Consent for Publication

Informed consent for publication was obtained from all authors of this manuscript.

Reference

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Table 1. Characteristics of COL6A4P1 SNPs analyzed in this study.

Parameter	rs11718863	rs7639618	rs7651842	rs7639807
Chromosomal position (GRCh38)	Chr3: 15,175,196	Chr3: 15,175,196	Chr3：15,175,284	Chr3：15,175,108
Cytogenetic location	3p25.1	3p25.1	3p25.1	3p25.1
Reference/alternative alleles	A/T	C/T	A/G or strand-equivalent*	G/A or strand-equivalent*
MAF (East Asian populations)	0.21	0.2	Monomorphic	Monomorphic
Amino acid substitution	Tyr169Asn (Y169N)	Cys260Tyr (C260Y)	Not established	Not established
Functional domain	VWA domain	VWA domain	—	—
Primer sequences	F: 5′-AGGCTGCCTGCCATTATTACTT-3′ R: 5′-CCCATGCTGTTTCCTTTGAACA-3′	Same (same amplicon)	Same	Same
Annealing temperature	57 °C	57 °C	57 °C	57 °C
PCR product size	363 bp	363 bp	363 bp	363 bp
Genotyping method	Bidirectional Sanger sequencing	Bidirectional Sanger sequencing	Bidirectional Sanger sequencing	Bidirectional Sanger sequencing
Genetic models tested	codominant and dominant	codominant and dominant	N/A(monomorphic in this cohort)	N/A(monomorphic in this cohort)
HWE in controls (P)	0.603	0.642	N/A(monomorphic in this cohort)	N/A(monomorphic in this cohort)
HWE in cases (P)	0.095	0.095	N/A	N/A
Status in this study	Included in association analysis	Included in association analysis	Monomorphic; excluded from association analysis	Monomorphic; excluded from association analysis

* Alleles should be reported on one consistent reference strand; strand complements in earlier DVWA publications

can produce apparently different allele labels.

Figure1. Study workflow

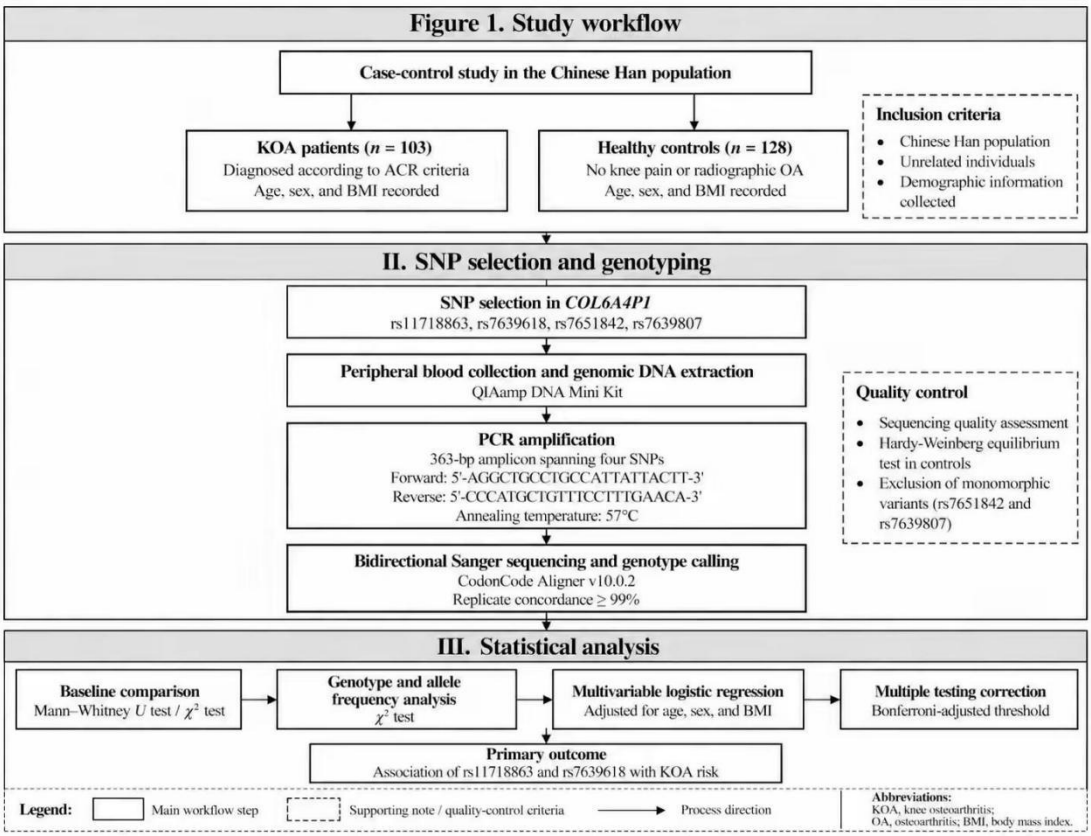
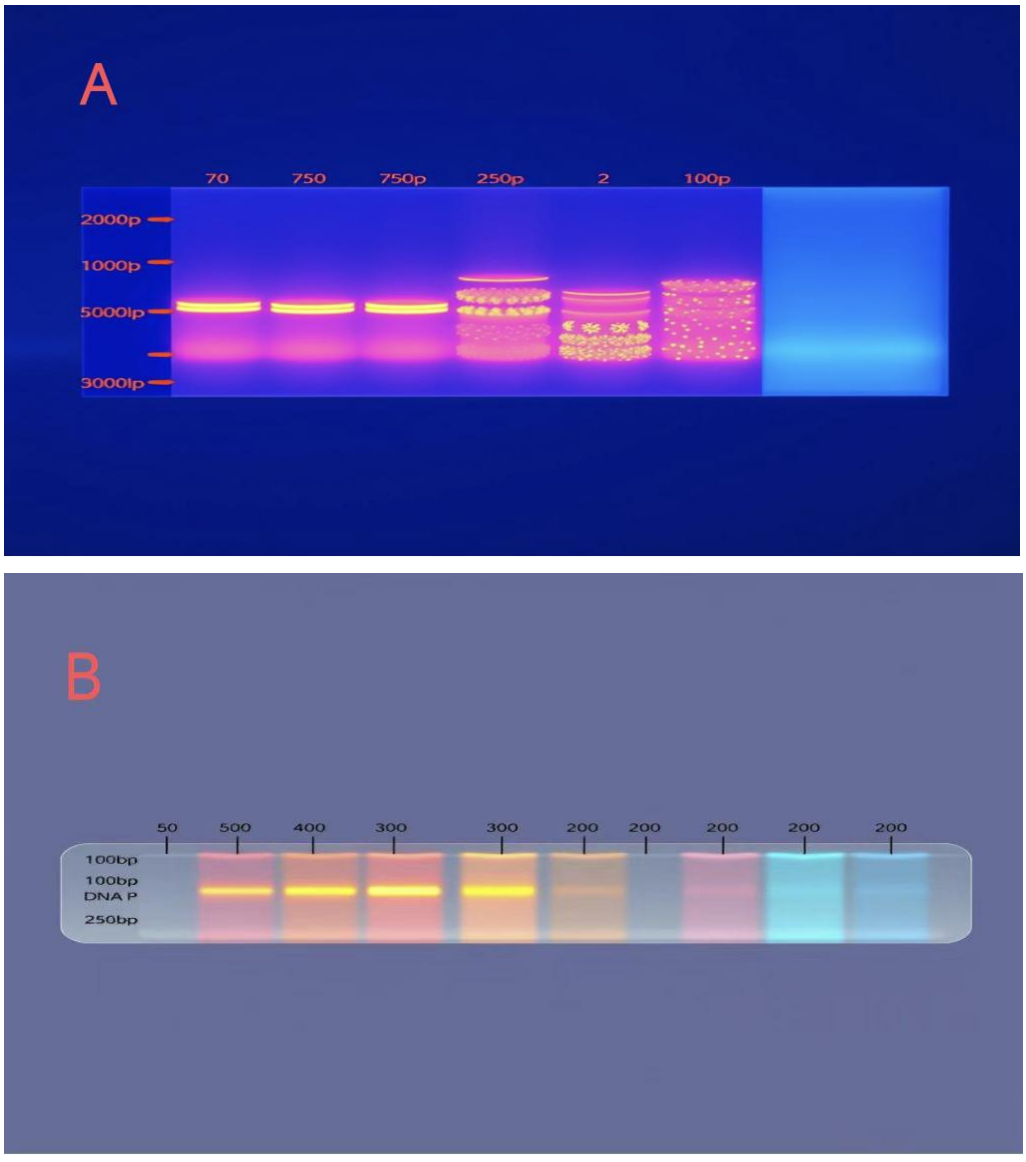


Table 2. Study cohort descriptive characteristics

	Test (103)	Control (128)	χ^2/Z	*P* value
Age	67 (63, 76)	64 (60.25, 67)	-3.613	＜0.001
Sex F/M (F %)	86 (83.5)	94 (73.44)	3.356	0.067
Height (cm)	161 (158, 165)	163 (160, 165)	-1.625	0.104
Weight (Kg)	70 (60, 75)	65 (63.25, 72)	-0.982	0.326
BMI (Kg/m^2)	26.44(23.94, 27.89)	25.39 (23.46, 27.52)	-1.479	0.139

BMI: body mass index, F/M: femal/male, cm: centimeter, kg: kilogram

Figure 2. whole-genome agarose gel electrophoresis (A), target fragment agarose gel electrophoresis (B)



Lane 1: 100 bp DNA Ladder with five distinct gradient bands at 500 bp, 400 bp, 300 bp, 200 bp, and 100 bp positions, showing uniform spacing and sharp edges for precise molecular weight reference.

Lanes 2-4: Triplicate experimental samples displaying single intense bands at 363 bp (between 300 bp and 400 bp markers), demonstrating high specificity with no smearing, primer dimers or non-specific products, indicating efficient PCR amplification.

Lane 5: Negative control (template-free) showing complete absence of bands or fluorescent signals, confirming no contamination in reagents or experimental process.

Table 3. Hardy-Weinberg equilibrium in the KOA group and control group

	+/+	+/-	-/-	χ^2	*P* value
Both groups					
rs11718863	81	100	50	3.23	0.072
rs7639618	81	101	51	3.27	0.071
KOA group					
rs11718863	29	43	31	2.80	0.095
rs7639618	29	43	31	2.80	0.095
Control group					
rs11718863	52	57	19	0.27	0.603
rs7639618	50	58	20	0.216	0.642

KOA: knee osteoarthritis; +/+, +/-, -/- represent wild type, mutated heterozygous, mutated homozygous genotype.

Table 4. Frequency distributions of SNPs in DVWA genotypes

SNP			Frequency (n%)			
			KOA	Control	χ^2	*P* Value
rs11718863	genotype	AA	31 (30.10)	19 (14.84)	8.768	0.012

		AT	43 (41.75)	57 (44.53)		
		TT	29 (28.16)	52 (40.63)		
	allele	A	105 (50.97)	95 (37.11)	8.934	0.003
		T	101 (49.03)	161(62.89)		
rs7639618	genotype	CC	29 (28.16)	50 (39.06)	7.566	0.023
		CT	43 (41.75)	58 (45.31)		
		TT	31 (30.10)	20 (15.63)		
	allele	C	101 (49.03)	158(61.72)	8.026	0.005
		T	105 (50.97)	96(38.28)		

SNPs: single nucleotide polymorphisms; KOA: knee osteoarthritis

Table 5. The association between DVWA SNPs and the risk of KOA

gene		Genotypes	KOA group (103)	Control group (128)	OR (95%CI)	*P* value
COL6AP1	rs11718863	AA	31	19	1（reference)	
		AT	43	57	1.353 (0.740, 2.471)	0.326
		TT	29	52	2.926(1.410, 6.069)	0.004
		AT+TT	72	109	1.746 (1.002, 3.043)	0.049
	rs7639618	CC	29	50	1（reference)	
		CT	43	58	1.483(0.797, 2.760)	0.214
		TT	31	20	3.50(1.687, 7.260)	0.001
		CT+TT	74	78	2.00 (1.127, 3.549)	0.018

SNPs: single nucleotide polymorphisms; CI: confidence interval; OR: odds ratio; KOA: knee osteoarthritis

Table 6. The association of DVWA SNPs with KOA risk after adjustment for age

gene		Genotypes	KOA group (103)	Control group (128)	OR (95%CI)	*P* value
COL6A4P1	rs11718863	AA	31	19	1（reference)	
		AT	43	57	1.240 (0.666, 2.307)	0.497
		TT	29	52	2.649(1.251, 5.611)	0.011
		AT+TT	72	109	1.594 (0.899, 2.852)	0.110
	rs7639618	CC	29	50	1（reference)	
		CT	43	58	1.380(0.727, 2.618)	0.324
		TT	31	20	3.304(1.562, 6.990)	0.002
		CT+TT	74	78	1.874 (1.039, 3.380)	0.037

SNPs: single nucleotide polymorphisms; KOA: knee osteoarthritis; CI: confidence interval; OR: odds ratio