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Association of *CILP*, *COL9A2* and *MMP3* Gene Polymorphisms with Lumbar Disc Degeneration in an Indian Population

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Abstract

Lumbar disc degeneration (LDD) is a multifactorial disorder caused by genetic and environmental factors. Polymorphisms in several structural and inflammatory genes like collagens, aggrecan, matrix metalloproteinases are associated with the risk of disc degeneration. In this study, we analyzed the role of a few important single nucleotide polymorphisms in cartilage intermediate layer protein (*CILP*), collagen 9A2 (*COL9A2*) and matrix metalloproteinase 3 (*MMP3*) genes in LDD from an Indian population. Two hundred patients with LDD and 200 healthy controls were recruited for the study. Genotyping was performed by allelic discrimination assay. The rs2073711 polymorphism (*CILP* gene - GG genotype) was associated with reduced risk of LDD in the Indian population (OR = 0.43, $p = 0.016$). The rs591058 polymorphism (*MMP3* gene - TT genotype) is found to be associated with lower risk among women (OR = 0.34, $p = 0.041$). No significant association was found between *COL9A2* polymorphism rs7533552 and the risk of LDD. We conclude that the *CILP* gene polymorphism (rs2073711) is associated with a lower risk of LDD, the *MMP3* (rs591058) gene polymorphism is associated with LDD among women, and the TT genotype confers a lower risk of LDD.

Keywords Lumbar disc degeneration (LDD) · *CILP* · *MMP3* · *COL9A2* · Polymorphism · Indian population

Introduction

Lumbar disc degeneration (LDD) is a common musculoskeletal disorder involving degeneration of lumbar intervertebral discs (Andersson 1999). It is a complex disease with genetic and environmental factors playing important roles (Matsui et al. 1998; Battie et al. 1995; Sambrook et al. 1999). Several genes such as collagen, aggrecan, matrix metalloproteinases (MMPs), vitamin D receptor (VITDR) play a role in the pathology of LDD. Other risk factors such as physical loading, obesity and smoking are also thought to contribute to the disease significantly (Liuke et al. 2005; Battie et al. 1991, Zitting et al. 1998).

The intervertebral disc is a specialized form of fibrocartilage divided into an outer layer, the annulus fibrosis and inner layer, and the nucleus pulposes. The annulus fibrosus has a characteristic ring-like structure consisting mainly of densely packed collagen I fibers. The nucleus pulposus is rich in collagen II (about 20% of its dry weight) and contains minor amounts of two other cartilage collagens, types IX and XI. Both layers contain small amounts of collagen VI and minor amounts of collagens III and V are present throughout the disc. Proteoglycans form almost 50% of the dry weight of the nucleus pulposus. Collagens provide tensile support for the disc and the extensively hydrated proteoglycans give the tissue its resistance to compressive forces (Ala-Kokko 2002). Collagen IX is a structural protein with an important role in connecting various types of collagens together, particularly collagen II with proteoglycans in the matrix. Previous studies have shown that a few gene polymorphisms in the collagen gene are associated with LDD risk (Pluijm et al. 2004).

Cartilage Intermediate Layer Protein (*CILP*) gene is abundantly expressed in intervertebral dics and its expression increases when degeneration occurs (Seki et al. 2005). So the SNPs in this gene may play a role in the risk of LDD. Since matrix degradation is one of the hallmarks of LDD, single

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nucleotide polymorphisms (SNPs) in matrix-degrading enzymes like MMPs and a disintegrin and metalloproteinase with thrombospondin motif (ADAMTS) may play an important role in LDD. MMP3 is one of the important enzymes present in the disc. MMP3 contributes to disc degeneration by degrading matrix proteoglycans and collagens. Polymorphisms in *MMP3* gene (rs679620, rs591058 and rs650108) have been associated with tendon/ligament injury prevalence (e.g., Achilles tendinopathy/rupture and anterior cruciate ligament rupture) (Bell et al. 2012; Laguette et al. 2011; Collins and Raleigh 2009).

In this study, we explore the role of single nucleotide polymorphisms (rs2073711 of *CILP* gene, rs591058 of *MMP3* gene and rs7533552 of *COL9A2* gene) associated with lumbar disc degeneration.

Materials and Methods

Study Population

A total of 200 patients with LDD were recruited from the Department of Neurosurgery, National Institute of Mental Health and Neurosciences, Bangalore, India, for this study during January 2016 to April 2018. Patients with low back ache with sciatica and whose MRI showed lumbar disc degeneration were considered as LDD patients and recruited to the study. Patients with physical damage to the disc and other genetic disorders were excluded from the study. The control subjects ($n = 200$) were randomly selected from general population who were healthy adults without a history of back pain in the recent past. This study was approved by the institute's ethics committee for human studies, NIMHANS, Bangalore, India (Item No.XII, Sl.No.12.04, Neurosciences). Informed consent was obtained from all participants in this study. Five-milliliter blood samples were collected from patients and control subjects for molecular analysis.

Genotyping

Genomic DNA from blood was isolated using Macherey-Nagel (MN) kits according to the manufacturer's protocol. Nanodrop ND2000c spectrophotometer was used for quantitation and purity checking. DNA with A260/280 1.75–1.85 was used for genotyping. SNP genotyping was performed using Taqman® allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) with a commercially available primer probe set (C__16027328_10 for rs2073711, C____785960_1_ for rs591058, AN7DRM6 for rs7533552). Genotyping was performed in an Applied Biosystems 7500 Fast machine.

Statistical Analysis

Statistical software R.3.3.1 was used for the analysis of data. Continuous variables were expressed as mean ± SD and categorical variables are expressed as percent values or absolute numbers, as indicated. Differences in demographic characteristics between patients and controls were compared by using the $\chi 2$ test for all categorical variables. To estimate the deviation of frequency of gene alleles in the tested population, we performed the Hardy-Weinberg equilibrium using $\chi 2$ tests. Genotypes and allele frequencies were compared by $\chi 2$ analysis. Association between risk and variables were expressed as odds ratio (OR) with 95% confidence interval (CI). The results were considered statistically significant at $p \leq 0.05$.

Results

Clinical and Demographical Details of Study Subjects

Table 1 provides the details of 200 LDD patients and 200 control subjects enrolled in the study. Median age of patients was 42 years (range 18–73 years) and controls was 40.5 years (18–80). There was no significance difference between distribution of age and sex among cases and controls.

CILP Gene (rs2073711)

The genotypic and allelic distribution of rs2073711 is given in supplementary table 1. The minor allele frequency was 0.333 for patients and 0.393 for controls. This SNP did not follow Hardy Weinberg equilibrium (HWE) in patients ($p = 0.023$) but followed HWE in controls ($p = 0.814$). Significant association was found between GG genotype and risk of LDD. GG genotype conferred significantly lower risk ($p = 0.016$, OR = 0.43, 95% CI = 0.21–0.85). In recessive model (GGvsAG + AA), significant association was found ($p = 0.009$). The genotypes were compared between different parameters like sex, smoking and alcohol consumption history. Among men, the GG genotype was found to be significantly associated (OR = 0.28, 95% CI = 0.09–0.81, $p = 0.019$). Also, among subjects with no history of smoking or alcohol consumption, the GG genotype was significantly associated with reduced risk of LDD. The data is given in supplementary table 2.

COL9A2 Gene (rs7533552)

The distribution of genotypes of rs7533552 was in HWE ($p = 0.339$). The allelic frequency for the T allele was 71.5% and for the C allele was 28.5% in patients and 72.2% for T and 27.8% for C in controls. The genotypic and allelic distribution of rs7533552 is given in supplementary table 3. Chi-square test was performed to see if there was any difference between

Table 1 Characteristics of patients and controls

Characteristics	Healthy controls ($n = 200$)	Patients ($n = 200$)	p value
Mean age (years± SD)	42.92 ± 18.23	42.94 ± 12.47	0.543
Males, n (%)	117 (58.5)	128 (64.0)	0.259
Females, n (%)	83 (41.5)	72 (36.0)	
Smoking history, n(%)			
Yes	–	48(24.0)	
No	–	152(76)	
Alcohol consumption, n(%)			
Yes	–	45(22.5)	
No	–	155(77.5)	

genotypes of patients and controls. No significant association was found between genotypes and risk of LDD. The genotypes were compared between different parameters such as sex, smoking and drinking history, and no association was found. The data is given in supplementary table 4.

MMP3 Gene (Rs591058)

The distribution of genotypes of rs591058 was in HWE ($p = 0.377$). The allelic frequency for the C allele was 70.5% and for the T allele was 29.5% in patients and 64.7% for C and 35.3% for T in controls. The genotypic and allelic distribution of rs591058 is given in supplementary table 5. Chi-square test was performed to see if there was any difference between genotypes of patients and controls. No significant association was found between genotypes and risk of LDD. The genotypes were compared between different parameters such as sex, smoking and alcohol consumption history. There was no association between genotypes and smoking history. In women, the TT genotype was found to be significantly associated (OR = 0.34, 95% CI = 0.12–0.97, $p = 0.041$). In subjects with no history of alcohol consumption, the T allele was almost associated (OR = 0.73, 95% CI = 0.53–1.00, $p = 0.052$) with LDD. The data is given in supplementary table 6.

Discussion

LDD is a disease that involves complex molecular pathological mechanisms, and many genes and other environmental factors contribute to its risk. Disc degeneration is a process that begins early in life and is a result of a variety of intrinsic and extrinsic factors, including normal aging (Min et al. 2010). Despite extensive research in this field, the etiology of the disease is still not defined clearly. Polymorphisms in collagen, matrix degradation and inflammatory genes have been studied previously as these are the key players thought to be involved in disc degradation. In this study we analyzed the association of three SNPs namely, rs2073711 (*CILP* gene), rs7533552 (*COL9A2* gene) and rs591058 (*MMP9* gene) with LDD.

rs2073711 (1184 T → C) is a polymorphism present in exon 8 of the *CILP* gene. T is the ancestral allele and C is the disease-associated risk allele. The change in allele leads to a substitution of amino acid Ile395Thr. CILP directly interacts with transforming growth factor-b1(TGF-b1) and inhibits the TGF-b1 mediated induction of extracellular matrix proteins such as collagen II and aggrecan (Seki et al. 2005). Previous studies have shown that the C allele (coding for Thr 395) of 1184 T/C increases binding and inhibition of TGF-b1, suggesting that regulation of TGF-b1 signaling by CILP plays a crucial role in the origin and pathogenesis of lumbar disc disease (Seki et al. 2005).

rs2073711 SNP has been associated with LDD in other populations. It was significantly associated with lumbar disc disease in Japanese subjects (Seki et al. 2005; Min et al. 2009, 2010). But this SNP was not associated with lumbar disc disease in Finnish or Chinese populations (Virtanen et al. 2007). However, in another Finnish population study, SNP rs2073711 was associated with disc degeneration among women (Kelempisioti et al. 2011). In an Indian study by Rajasekaran et al. (2013), this SNP was not associated with LDD. In our study, the GG genotype had a protective effect for LDD. Although the G allele is considered a risk allele, in our population it had a protective effect. Study in a larger cohort will give a clear idea about the genotypic distribution of this SNP in Indian population. Also, in our study the GG genotype showed a protective effect in men (OR = 0.28, 95% CI = 0.09–0.81, $p = 0.019$) and in subjects with no history of smoking (OR = 0.46, 95% CI = 0.22–0.97, $p = 0.042$) and no alcohol consumption (OR = 0.39, 95% CI = 0.18–0.85, $p = 0.017$).

We studied the polymorphism present in the *COL9A2* gene (rs7533552). In normal tissues collagen IX serves as a bridge between collagenous and non-collagenous proteins (Bagheri et al. 2016). The *COL9A2* gene is located in the chromosome 1p34. Collagen IX is made up of three unique polypeptides, namely α1, α2, and α3, which are encoded by genes, collagen type 9 alpha 1 (*COL9A1*), collagen type 9 alpha 2 (*COL9A2*),

and collagen type 9 alpha 3 (*COL9A3*), respectively (Toktaş et al. 2015). As collagen has an important role in maintaining the structural integrity of the intervertebral discs, genetic polymorphisms affecting the function or abundance of collagen can predispose a patient to disc degeneration. Collagen IX is an attractive candidate for LDD because it serves as a minor component in both the main structures of the intervertebral disk, the annulus fibrosus and the nucleus pulposus, in addition to its presence in cartilage and the vitreous body of the eye (Buckwalter 1995).

Several groups have studied the association of the *COL9A2* gene polymorphisms with the risk of LDD. A Finnish study reported that the *COL9A2* gene polymorphism (rs12077871) was associated with LDD (Annunen et al. 1999). Another Finnish study contradicted the previous study stating that rs12077871 was not relevant to LDD, but rs61734651 in the *COL9A3* gene was relevant to LDD (Paassilta et al. 2001).

rs7533552 is a missense variant. This is the first study involving this variant in an Indian population. rs7533552 was associated with hip osteoarthritis (Näkki et al. 2010). It was not associated with lumbar disc disease in a Japanese population (Seki et al. 2006). It was not associated with degenerative disc disease in a Han Chinese population (Song et al. 2010). No association was found between this SNP and lumbar spinal stenosis patients (Hyun et al. 2011). SNP rs7533552 was associated with disc bulging in a Finnish male twin cohort study (Videman et al. 2009). In our study this SNP was not associated with the risk of LDD.

The polymorphism rs591058 in the *MMP3* gene was also studied. MMPs are members of the zinc-endopeptidases, which can be divided into five groups: collagenases (MMP-1, MMP-8 and MMP-13), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3, MMP-7 and MMP-10), matrilysins and membrane-type MMPs (MT-MMPs) (Nagase et al. 2006; Cawston and Billington 1996). MMP-3 is involved in several functions such as extracellular matrix remodeling and degradation, cell proliferation and angiogenesis (Chakraborti et al. 2003). MMP-3 is directly involved in degradation of components of the extracellular matrix including proteoglycans, laminin, fibronectin, gelatins and collagens (Matrisian 1990). It is also indirectly involved in degradation of the extracellular matrix by activating other latent MMPs (Colombini et al. 2014; Takahashi et al. 2001). Hence, MMP-3 can mediate disc degeneration by the degradation of collagens and proteogycans.

Promoter region polymorphism in the *MMP3* gene, which produces five or six repeats of adenine (5A and 6A, respectively) was associated with degenerative disc disease (Takahashi et al. 2001). The 5A allele has twice the promoter activity compared to the 6A allele, which leads to more protein production and a potential mechanism for increased degeneration (Ye et al. 1996). This polymorphism was associated with disc degeneration in Japanese population, Chinese population and English women (Takahashi et al. 2001; Valdes et al. 2005; Yuan et al. 2010). In another study, two polymorphims in the *MMP3* gene (rs645419 and rs646910) were studied and no association was found with the disease (Videman et al. 2009). One study found that rs591058 was associated with an increased risk of Achilles tendinopathy (Raleigh et al. 2009). The T allele is the minor allele for rs591058. In our study, the T allele showed a protective effect in women (OR = 0.34, 95% CI = 0.12–0.97, $p = 0.041$). Even though the p value is only borderline significant, we can consider it since our sample size is moderately large. Also, the 95% CI is 0.12–0.97 and it does not include one. So, from the p value and CI, 95% significance can be considered. Another Indian study by Rajasekaran et al. (2013) studied rs591058 SNP and they did not find any association with lumbar disc degeneration. In that study, overall association was studied, and female subgroup analysis was not provided.

In conclusion, we studied the role of three SNPs in LDD. rs7533552 (*COL9A2*) was not associated with LDD. rs591058 (*MMP3*) showed that the TT genotype had a reduced risk of LDD in women. rs2073711 (*CILP*) results showed that the GG genotype had a reduced risk of LDD in an Indian population. Our study gives a basic understanding about the distribution of these genotypes in Indian population. Further studies in larger cohorts are needed help us understand the role of these SNPs better. Functional analysis of these genes can be a useful tool in understanding their role in LDD.

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Compliance with Ethical Standards

Conflict of Interest The authors have declared that there is no conflict of interest financially or findings specified in this paper.

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