Association between COL11A1 (rs1337185) and ADAMTS5 (rs162509) gene polymorphisms and lumbar spine pathologies in Chinese Han population: an observational study

Hua Jiang, Qinghua Yang, Jie Jiang, Xinli Zhan, Zengming Xiao

ABSTRACT

Objectives A previous study identified a significant association between several single nucleotide polymorphisms (SNPs) and lumbar disc degeneration (LDD) in Indians. To validate the association between these SNPs and specific lumbar spine pathologies, we performed a case–control study in Chinese Han population.

Design An observational study.

Setting University Hospital in Nanning, China.

Participants This study included 428 patients with LDD and 400 normal controls.

Outcome measures Patients with LDD were classified into four subgroups, including disc herniation only (subgroup 1), discopathies or/and osteochondrosis associated with disc herniation (subgroup 2), spinal stenosis or/and spondylolisthesis (subgroup 3) and degenerative scoliosis (subgroup 4). This study was conducted by examining two aspects: environmental factors and SNP genotyping. The environmental factors were evaluated with a questionnaire survey including questions about body mass index, smoking habits, the physical demands of their job and exposure to vibrations. Rs1337185, rs5275, rs5277, rs7575934, rs3213718 and rs162509 were genotyped using a PCR-based invader assay.

Results The physical workload was significantly higher in patients with lumbar spine pathologies than in the normal controls (p=0.035). The genotype and allele frequencies of rs1337185 and rs162509 were significantly different between the patients with LDD and the normal controls. In rs1337185, a significant association was found between the C allele (risk allele) and the presence of disc herniation (OR=1.80; 95% CI 1.21 to 2.68; p=0.003, adjusted p=0.012) and the presence of spinal stenosis and spondylolisthesis (OR=1.92; 95% CI 1.29 to 2.89; p=0.001, adjusted p=0.004). In rs162509, the G allele represented a 1.58-fold increased risk to suffer from disc herniation (OR=1.58; 95% CI 1.26 to 2.09; p=0.001, adjusted p=0.004).

Conclusion The SNPs rs1337185 in COL11A1 and rs162509 in ADAMTS5 are associated with susceptibility to LDD. The C allele of rs1337185 is risky for patients who are affected by lumbar pathologies such as disc herniation, stenosis and spondylolisthesis. The G allele of rs162509 represents a risk factor for the development of disc herniation.

INTRODUCTION

Lumbar disc degeneration (LDD) is one of the most common musculoskeletal degenerative diseases, which may lead to lower back pain and unilateral or bilateral leg pain. Lower back pain affects 70%–85% of all people during their lifetime. Twenty percent of patients with lower back pain caused by LDD require surgical treatment to relieve their prolonged or aggravated back or/and leg pain. Despite decades of research, the specific factors that contribute to LDD are still not fully understood. A variety of environmental factors, such as occupation, sporting activities, smoking and obesity, have been implicated in the aetiopathogenesis of LDD. Moreover, some studies have identified associations between genetic factors and LDD. This finding suggests that genetic factors may be important in determining the risk for the occurrence and development of LDD.

To date, more than 30 candidate genes have been analysed in association with LDD.
The proteins encoded by these genes are classified into several categories based on their potential function in the disc: structural components, matrix turnover and organisation and inflammatory mediators. Recently, Rajasekaran et al. selected 58 single nucleotide polymorphism (SNP) from 35 candidate genes and performed a genetic association analysis between these SNPs and LDD in a cohort of young Indian adults. Their study identified significant associations between six SNPs in five genes (rs1337185 of COL11A1, rs5275 and rs5277 of COX2, rs7575934 of IL1F5, rs3213718 of CALM1 and rs162509 of ADAMTS5) and severe disc degeneration. According to the hypotheses of disease aetiology, the study of genetic associations is a powerful method for identifying the candidate genes or genomic regions that contribute to a specific disease. However, the lack of replication and false-positive findings are considered the main drawbacks of association studies. Thus, replicating the associations in different ethnic groups is crucial to confirm the results of association studies. Furthermore, Rajasekaran et al’s study was limited by the marginal p values, which were close to 0.05. To validate the association of rs1337185, rs5275, rs5277, rs7575934, rs3213718 and rs162509 with specific lumbar spine pathologies in an independent Chinese Han population, we conducted a genetic case-control study and performed a subgroup analysis of environmental factors in the development of LDD.

MATERIALS AND METHODS

Subjects and data collection
A total of 828 subjects were studied. Overall, 428 patients with lumbar spine pathologies (226 males and 202 females) were recruited from Spine Surgery, the First Affiliated Hospital of Guangxi Medical University between January 2012 and August 2016. The diagnosis of LDD required the following two criteria: (1) confirmed by MRI and (2) a history of lower back pain or/and leg pain for longer than 3 months. Detailed diagnoses of LDD and classification into one of four different mutually exclusive subgroups (designed subgroups 1–4) were performed by a senior spine specialist based on frontal and lateral X-ray images or CT scans and the sagittal and axial MRI images obtained using a 1.5 T MRI Achieva scanner (Philips Medical Systems, Best, The Netherlands). The classification of four subgroups was as follows: (1) subgroup 1 included 156 patients affected by disc herniation only; (2) subgroup 2 included 84 patients affected by discopathies or/and osteochondrosis associated with disc herniation; (3) subgroup 3 included 141 patients affected by spinal stenosis or/and spondylolisthesis and (4) subgroup 4 included 47 patients affected by degenerative scoliosis. The simultaneous presence of other orthopaedic diseases, such as osteoarthritis, osteoarthrosis and osteoporosis, was recorded (figure 1). Patients with an intraspinal tumour, trauma, inflammatory disease and rheumatoid arthritis were excluded from the study. Four hundred normal control subjects (224 males and 176 females) were enrolled from the Physical Examination Centre, the First Affiliated Hospital of Guangxi Medical University. In the control group, the lumbar spine MRI and CT scans were performed in 336 and 64 normal subjects, respectively. The clinical and radiographic examinations were performed by experienced orthopaedic surgeons to rule out any potential low back pain and LDD. The protocol was approved by the Ethics Review Committee of the First Affiliated Hospital of Guangxi Medical University, and signed informed consent was obtained from all subjects. All participants were Han Chinese who lived in and around the South China region.

Evaluation of environmental factors
According to the previous studies, the potential environmental risk factors of lumbar spine pathologies were evaluated based on the physical load assessment

Figure 1  Clinical assessment and classification of patients into subgroups. (A) Subgroup 1, patients who suffered from disc herniation only. (B) Subgroup 2, patients who suffered from discopathies or/and osteochondrosis associated with disc herniation. (C and D) Subgroup 3, patients who suffered from spinal stenosis (C) or/and spondylolisthesis (D). (E) Subgroup 4, patients who suffered from degenerative scoliosis. White arrows indicate the characteristic pathological features of each subgroup.
questionnaire and the occupational classification point standard. The collected information included body mass index (BMI), smoking habits, the physical workloads for the majority of the working years (evaluated by the following scoring system: score 0: \( \leq 4 \) hours/day and \( \leq 1 \) year; score 1: \( \leq 4 \) hours/day and \( \leq 2.5 \) years; score 2: \( \leq 4 \) hours/day and 1–5 years or \( \geq 4 \) hours/day and 2.5 years; score 3: \( \leq 4 \) hours/day and \( > 5 \) years or \( \geq 4 \) hours/day and \( \geq 2.5 \) years) and, over the past year, the number of hours per day spent driving or as a passenger in a motorised vehicle (exposure to vibrations).

Genotyping
Genomic DNA was extracted from peripheral blood leucocytes using genomic DNA isolation kits (Promega, Madison, Wisconsin, USA) according to the manufacturer’s instructions. The primers, probes and reaction conditions are available on request.

Genotyping was performed using a PCR-based invader assay with the probe sets designed. The genotyping results were obtained using an ABI 7900 sequence detection system (Applied Biosystems, Foster City, California, USA). Genotyping was done by laboratory personnel who were blinded to the status of the subjects. Further, 10% of the samples were tested twice to validate the genotyping results with 100% reproducibility. Two authors independently reviewed the genotyping results, data entry and statistical analyses.

Statistical analysis
A standard \( \chi^2 \)-analysis was used to examine the differences in environmental risk factors, allelic frequencies and genotype distributions between the patients with LDD and controls using the SPSS software version 17.0. Considering the type I error caused by multiple testing, \( p \) values were adjusted by using Bonferroni correction (R Software 3.3.2 for Windows). The \( p \) value was adjusted to the corresponding original 5% level by dividing by the number of subgroups. Hardy-Weinberg equilibrium was tested using a goodness-of-fit \( \chi^2 \) test. The OR and 95% CI were calculated using the reported risk allele as a reference. Statistical significance was considered at \( p<0.05 \).

RESULTS
Influence of the environmental risk factors
The characteristics of the overall population of cases and controls, including age, gender, BMI, smoking habit, physical workload, exposure to vibrations and presence of other orthopaedic conditions, are shown in table 1. The patients had an average age of 49.35±15.67 years, and the control group had an average age of 45.92±13.21 years. Among the cases, there were more males (226/428, 52.8%) than females (202/428, 47.2%), whereas among controls, there were almost equal numbers of males (224/400, 56.0%) and females (176/400, 44.0%). As the study design, the simultaneous presence of other orthopaedic diseases (13.3% of cases) was presented only in the cohort of cases. Physical workload was significantly higher in patients with lumbar spine pathologies than in the normal controls (1.61±1.31 vs 1.12±1.03, \( p=0.035 \)). However, neither groups showed a significant difference in BMI, smoking or exposure to vibrations (all \( p>0.05 \)).

Table 1
Characteristics of the study subjects and comparison of environmental risk factors of lumbar spine pathologies between controls and all cases or subgroups

<table>
<thead>
<tr>
<th>Factors</th>
<th>Controls</th>
<th>All cases</th>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
<th>Subgroup 3</th>
<th>Subgroup 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=400</td>
<td>n=428</td>
<td>n=156</td>
<td>n=84</td>
<td>n=141</td>
<td>n=47</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean±SD</td>
<td>45.92±13.21</td>
<td>49.35±15.67</td>
<td>41.56±12.42</td>
<td>43.73±9.80</td>
<td>44.13±12.93</td>
</tr>
<tr>
<td>Gender</td>
<td>Males, n (%)</td>
<td>224 (56.0)</td>
<td>226 (52.8)</td>
<td>81</td>
<td>44</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Females, n (%)</td>
<td>176 (44.0)</td>
<td>202 (47.2)</td>
<td>75</td>
<td>40</td>
<td>58</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Mean±SD</td>
<td>24.3±2.7</td>
<td>24.1±2.9</td>
<td>23.8±2.1</td>
<td>24.0±1.8</td>
<td>24.3±1.9</td>
</tr>
<tr>
<td>Past and present smoker</td>
<td>n (%)</td>
<td>102 (25.5)</td>
<td>129 (30.1)</td>
<td>51</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Physical workload (scores 0–3)</td>
<td>Mean±SD</td>
<td>1.12±1.03</td>
<td>1.61±1.31*</td>
<td>1.55±1.12*</td>
<td>1.58±1.23*</td>
<td>1.86±1.53*</td>
</tr>
<tr>
<td>Exposure to vibrations (hours/day)</td>
<td>Mean±SD</td>
<td>1.24±1.76</td>
<td>1.33±1.58</td>
<td>1.21±0.98</td>
<td>1.38±1.42</td>
<td>1.35±1.28</td>
</tr>
<tr>
<td>Other orthopaedic conditions</td>
<td>n</td>
<td>/</td>
<td>57</td>
<td>21</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

Subgroup 1, patients with disc herniation only.
Subgroup 2, patients with discopathies or/and osteochondrosis associated without disc herniation.
Subgroup 3, patients with spinal stenosis or/and spondylolisthesis.
Subgroup 4, patients with degenerative scoliosis.
*Compared with controls, \( p \) value is less than 0.05.
Associations between lumbar spine pathologies and putative conventional risk factors are also reported in table 1. Of the 428 patients with lumbar spine pathologies, 156 patients (36.4%) suffered from the disc herniation alone (subgroup 1), 141 patients (33.0%) suffered from spinal stenosis or/and spondylolisthesis (subgroup 3), 84 patients (19.6%) suffered from herniation associated with discopathies or/and osteochondrosis (subgroup 2) and 47 patients (11.0%) suffered from degenerative scoliosis (subgroup 4). A higher physical workload was exhibited in subgroup 3 (1.86±1.53) compared with the other three subgroups (all p<0.01). There was no statistical difference among subgroups 1, 2 and 4 (p>0.05). The four subgroups did not differ significantly regarding age, gender, BMI, smoking, exposure to vibrations or the presence of other orthopaedic conditions (all p>0.05).

**Genetic association analysis**

A total of 828 subjects (428 cases and 400 controls) were successfully genotyped and subjected to the statistical analysis. The distributions of alleles and genotypes for the six SNPs (rs1337185, rs5275, rs5277, rs7575934, rs3213718, rs162509) are presented in table 2. No significant deviation of genotype frequencies from the Hardy-Weinberg equilibrium was noted in the case and control groups (all p>0.05). The genotype and allele frequencies of rs1337185 and rs162509 were significantly different between the patients with lumbar spine pathologies and the normal controls.

Regarding rs1337185, a significant association was found between the C allele and the total patients. This indicated that the C allele might lead to a higher risk for lumbar spine pathologies in the Chinese population (OR=1.72; 95% CI 1.25 to 2.34; p=0.001). In accordance with the total cases, a significant association was found between the C allele and the presence of disc herniation only (subgroup 1) (OR=1.80; 95% CI 1.21 to 2.68; p=0.003). In the patients who were affected by spinal stenosis or/and spondylolisthesis (subgroup 3), the C allele was a risk factor (OR=1.92; 95% CI 1.29 to 2.89; p=0.001). After Bonferroni correction, rs1337185 showed statistical significance in abovementioned comparisons (subgroup 1 vs control, adjusted p=0.012; subgroup 3 vs control, adjusted p=0.004) (table 2).

Regarding rs162509, the risk allele (G allele) frequency of the total cases was highly significantly different from that in the controls (OR=1.38; 95% CI 1.13 to 1.69; p=0.001). Consistently, the allele distribution showed a higher frequency of the G allele in the patients with disc herniation only (subgroup 1) (OR=1.58; 95% CI 1.20 to 2.09; p=0.001, adjusted p=0.004). In the patients with degenerative scoliosis, a 1.72-fold association was found for the G allele in genetic analysis (OR=1.72; 95% CI 1.09 to 2.78; p=0.019, adjusted p=0.076). After analysis and Bonferroni correction, it revealed that rs162509 is associated with disc herniation but not with degenerative scoliosis phenotype (table 2).

Neither the genotype nor the allele frequencies of rs5275, rs5277, rs7575934 and rs3213718 were significantly different between the cases and the normal controls. Furthermore, no other significant findings in the aforementioned four SNPs were observed even when grouping subgroups 1, 2, 3 and 4.

**DISCUSSION**

It is generally recognised that LDD is a complex, multifactorial disease that is determined by genetic and environmental interactions. In this study, the patients and controls showed significant differences in the physical workload for the majority of the working years, which is consistent with previous observations. However, the two groups in our study did not show significant differences in other environmental factors, including age, gender, BMI, smoking and exposure to vibrations. Recently, genetic factors have been suggested to play an important role in the development and progression of disc degeneration. Two pivotal approaches have been used to map candidate genes and genome regions: linkage analysis and association study. Compared with linkage analysis, an association study is a more robust approach for identifying predisposition genes for common diseases and complex traits. More than 30 candidate genes related to LDD have been identified by genetic association studies. However, the most common weakness is difficulty in replicating the previous association signals.

Recently, Rajasekaran et al recruited 308 Indian subjects with mild LDD and 387 Indian subjects with severe LDD and performed a genetic association analysis for 58 SNPs of 35 candidate genes. The study detected an association between severe LDD and six SNPs in five genes including rs1337185 of COL11A1, rs5275 and rs5277 of COX2, rs7575934 of IL1F5, rs3213718 of CALM1 and rs162509 of ADAMTS5. These five genes were important candidate genes related to LDD, which could be grouped into three categories based on their potential functional zones: structural genes (COL11A1, CALM1), degradative genes (ADAMTS5) and inflammatory genes (IL1F5, COX2). To the best of our knowledge, no study has validated the associations or conducted a subgroup analysis. In this study, we identified COL11A1 (rs1337185) and ADAMTS5 (rs162509) as gene polymorphisms associated with the susceptibility of patients to LDD in a Chinese Han cohort. Furthermore, we analysed four mutually exclusive subgroups of all cases having a condition in common such as a hernia, discopathy, spinal stenosis or spondylolisthesis and degenerative scoliosis. Regarding rs1337185, the G allele was associated with a higher risk for patients suffering from disc herniation only (subgroup 1) and spinal stenosis or/and spondylolisthesis (subgroup 3). Regarding rs162509, a higher frequency of the G allele was presented in the patients with disc herniation only (subgroup 1) and degenerative scoliosis (subgroup 4). After Bonferroni correction, both SNPs (rs1337185 and rs162509) showed significantly
<table>
<thead>
<tr>
<th>SNPs</th>
<th>Genotype (%)</th>
<th>Allele (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>G</td>
</tr>
<tr>
<td>Controls (n=400)</td>
<td>285 (71.3)</td>
<td>101 (25.2)</td>
</tr>
<tr>
<td>Cases (n=428)</td>
<td>294 (68.7)</td>
<td>111 (25.9)</td>
</tr>
<tr>
<td>Subgroup 1 (n=156)</td>
<td>121 (77.6)</td>
<td>28 (17.9)</td>
</tr>
</tbody>
</table>

Continued
different allele and genotype frequencies between subgroup 1 and control group and rs1337185 showed statistically different allele and genotype frequencies between subgroup 3 and control group. Unfortunately, no detailed information was reported about the risk or protective alleles at rs1337185 and rs162509 in the Indian study. Thus, we did not evaluate the difference in the genetic associations between the Han Chinese population and Indian population.\footnote{17}

The \textit{COL11A1} gene is highly expressed in intervertebral discs and encodes the \(\alpha\)1 chain of type XI collagen, which suggests that it is critical for intervertebral disc metabolism. Mio and colleagues\footnote{26} identified a strong association between rs1676486 in the \textit{COL11A1} gene and lumbar disc herniation in Japanese patients. This study also found that \textit{COL11A1} mRNA expression in patients with lumbar disc herniation was decreased along with an increase in the severity of degeneration. This finding indicated that the functional polymorphism might produce unstable \textit{COL11A1} transcripts. Moreover, another important polymorphism in \textit{COL11A1} gene (rs1337185) was found to have significant associations with MRI-defined lumbar disc bulging in a Finnish cohort.\footnote{23} In agreement with these findings, our study confirmed that a significant association exists between rs1337185 and patients with LDD. Based on the subgroup analysis, the C allele was identified as a risk allele in the patients affected by disc herniation only (subgroup 1) and spinal stenosis or/and spondylolisthesis (subgroup 3). As a member of the large family of metalloproteases, \textit{ADAMTS5} has recently received increased attention due to its role in balancing the synthesis and degradation of the extracellular disc matrix.\footnote{27, 28} The mRNA and protein expression of \textit{ADAMTS5} has been measured in intervertebral disc tissues.\footnote{29} Furthermore, the increased expression of \textit{ADAMTS5} was correlated with degenerative changes in patients with chronic lower back pain and lumbar disc herniation.\footnote{30, 31} Correspondingly, Wu \textit{et al}\footnote{32} reported that the genetic polymorphisms in \textit{ADAMTS5} (rs151058, rs229052 and rs162502) might be associated with susceptibility to LDD. In accordance with those previous reports, the current study identified a significant association between rs162509 in \textit{ADAMTS5} gene and LDD in Chinese Han patients. The G allele represented an approximately 1.58-fold increased risk factor for developing disc herniation. It remains plausible that \textit{COL11A1} and \textit{ADAMTS5} genes may be involved in the aetiology of LDD. However, the precise role of rs1337185 and rs162509 is still unknown. Functional analysis of the \textit{COL11A1} and \textit{ADAMTS5} genes might help elucidate the real genetic effect on the aetiopathogenesis of LDD.

The previously reported association between rs5275, rs5277, rs5755934 and rs3213718 and disc degeneration disease in young Indian adults was not replicated in our study. Several factors could have led to this lack of replication. First, the discrepancy may be related to genetic differences between the Chinese and Indian populations. Second, the previous study was limited by its marginal p value, which might have led to false positive findings.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Genotype (%)</th>
<th>Allele (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 2 (n=84)</td>
<td>52 (61.9)</td>
<td>132 (78.6)</td>
</tr>
<tr>
<td>Subgroup 3 (n=47)</td>
<td>29 (61.7)</td>
<td>73 (77.7)</td>
</tr>
<tr>
<td>Subgroup 4 (n=47)</td>
<td>15 (31.9)</td>
<td>1.0 (2.1)</td>
</tr>
</tbody>
</table>

**SNPs Genotype (%) Allele (%)**

<table>
<thead>
<tr>
<th>Subgroup 1 (n=156)</th>
<th>22 (61.7)</th>
<th>106 (37.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 2 (n=84)</td>
<td>8 (9.5)</td>
<td>59 (35.1)</td>
</tr>
<tr>
<td>Subgroup 3 (n=141)</td>
<td>22 (15.6)</td>
<td>106 (37.6)</td>
</tr>
<tr>
<td>Subgroup 4 (n=47)</td>
<td>5 (10.6)</td>
<td>27 (28.7)</td>
</tr>
</tbody>
</table>

Table 2
Third, a difference in phenotype selection may have been a crucial factor that could account for this conflicting result. Genetic associations may change when different phenotypes of LDD are studied.33 There are obvious discrepancies in the clinical phenotype of patients with LDD, such as annular tears, hyperintense zones, signal intensity, disc height and disc herniation. In the current study, we selected a highly specific phenotype of LDD, which was the simultaneous presence of disc degeneration on the MRI images and leg or low back pain in a population of symptomatic patients. However, the severity of LDD in the previous study was evaluated on the basis of signal changes in the lumbar discs and was graded using the total disc degeneration score. This discrepancy corresponds well with the fact that the disease course of LDD is complicated and heterogeneous.34 Therefore, we postulate that different phenotypes in the disease course of LDD may be affected by different genetic polymorphisms.

There were several limitations in our study. First, the sample size was relatively small. Moreover, stratification by pathological subgroups reduced the number of subjects compared, which may have weakened the statistical power. We would like to enlarge the group of cases in the future, to confirm our results in a larger cohort of subjects. Second, if the original data were available, we could perform a meta-analysis of other relevant cohorts. More convincing results may be provided by a large-scale meta-analysis.

CONCLUSION

The current study showed an association between rs1337185 in COL11A1 and rs162509 in ADAMTS5 and LDD predisposition in a Chinese Han population. The C allele of rs1337185 was a risk factor for patients who are affected by lumbar pathologies such as disc herniation, stenosis and spondylolisthesis. The G allele of rs162509 represented a risk factor for the development of disc herniation.

Acknowledgements The authors thank all the participants in this study.

Contributors HJ carried out the molecular genetic studies, participated in its design and coordination and drafted the manuscript. JH participated in the molecular genetic studies and the sequence alignment. QY and XZ performed the statistical analysis and participated in the design of the study. ZK conceived of the study and participated in its design and coordination and helped to draft the manuscript.

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Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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