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Clinical Study

Two subtypes of intervertebral disc degeneration distinguished by large-scale population-based study

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Abstract

BACKGROUND CONTEXT: Lumbar disc degeneration (LDD) is a major cause of low back pain, and is a common and disabling condition worldwide. It has been defined and measured by multiple spine magnetic resonance imaging (MRI) features, but the heterogeneity among them has never been fully addressed.

PURPOSE: This study examined the intercorrelations, risk factor associations, and single nucleotide polymorphism (SNP) heritabilities of lumbar disc MRI features in a large-scale sample to classify the different intervertebral disc phenotypes associated with LDD.

STUDY DESIGN: A cross-sectional study was conducted consisting of 2,943 volunteers of Southern Chinese origin (mean age: 41.1 years; range: 15–55 years; 59.6% women).

OUTCOME MEASURES: The outcome measures were MRI phenotypic spinal patterns and their risk factor profiles in relation to developmental or degenerative origins of disc degeneration.

METHODS: Sagittal T2-weighted MRI of the lumbar spine from L1 to S1 was assessed. The MRI features of lumbar intervertebral disc changes, such as disc signal intensity loss and disc bulges or extrusions, as well as additional imaging phenotypes of end plate changes, high-intensity zones, and bone marrow changes, were evaluated. Blood samples were taken for genotyping using the HumanOmniZhongHua-8 BeadChip. Subject demographics, environmental, and lifestyle factors were assessed by questionnaires. Multivariate statistical techniques were used for phenotype evaluation. Polychoric correlations and local regression statistical analyses were performed. The genetic components contributed by common SNPs were estimated by comparing genetic correlations and phenotypic correlations using the Genome-Wide Complex Trait Analysis (GCTA) tool.

RESULTS: The study noted that lumbar disc MRI features separated into two groups with differential patterns of risk factor associations. A subset of lumbar disc abnormalities, including end plate changes but also upper lumbar disc bulging and signal intensity loss, may have a developmental origin. Subsequent degenerative changes, typically affecting the lower lumbar discs, then emerge as individuals age and are associated with body mass index.

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CONCLUSIONS: This is the first large-scale study to identify two distinct patterns of lumbar disc alterations, noting degenerative changes and a possible developmental component affecting the lumbar spine. This new classification provides a starting point for a more homogeneous phenotype definition, which may provide greater statistical power and precision in future genetic and epidemiologic studies. In addition, such insights may have direct clinical implications in the prevention, therapeutics, and prognostics of patients with disc degeneration.

Keywords: Degeneration; Development; Disc; Genetics; Intervertebral; Lumbar; MRI; Risk factors

Introduction

Lumbar disc degeneration (LDD) is a major etiologic risk factor for low back pain (LBP) [1–9], a common and disabling condition [10] affecting 80% of the general population at some time in life [11]. In the United States, the direct and indirect costs of LBP have been estimated to be over 90 billion USD per year [12], whereas 149 million work days were reported lost per year because of LBP [13]. Individuals with LBP not responsive to conservative treatment may require surgical intervention, often entailing spinal fusion [8]. However, such treatment may limit mobility and lead to degeneration of adjacent segments, causing disability and requiring further treatment [8]. Thus, understanding the etiology of LDD is imperative for improved prevention, diagnosis, and treatment.

Lumbar disc degeneration has been reported to be associated with numerous risk factors, including age [14], body mass index (BMI) [9], heavy lifting [15], cigarette smoking [16], and occupation [17]. It has a substantial genetic component with up to 77% heritability [18–20], but genetic association studies have to date identified only a few replicated susceptibility genes [21,22]. In addition to inadequate sample size, other likely reasons hindering genetic studies include phenotypic heterogeneity and methodological differences in sample recruitment and phenotype definitions across studies [23].

The definition of LDD is complicated as there are multiple features of degeneration. The current standard method for assessing LDD is magnetic resonance imaging (MRI), where degenerated discs show signal intensity loss (SIL) indicating reduced water content. Additional morphologic changes may be present in the intervertebral disc motion segment, including disc displacement (eg, bulge and herniation), osteophyte formation, subchondral vertebral marrow changes, and end plate changes. Most scoring systems for LDD simply aggregate the changes at the five lumbar discs, assuming that changes at different levels reflect the same pathological process [1]. However, the lower lumbar discs are subject to greater mechanical loading [24–27], which may explain the higher prevalence of SIL, disc narrowing, and vertebral bone marrow changes [28,29] at these levels. Conversely, end plate changes occur predominantly in the upper lumbar spine [21], and there are instances of skipped level degeneration [6] and isolated high-level LDD [22]. Previous classifications for LDD have not fully considered such differences between MRI features and disc levels [23,30–33].

In this study, we aimed to clarify the interrelationships between multiple MRI features at all lumbar disc levels, and the relationships of these features to epidemiologic factors and common genetic variants, in a large community sample. Recognizing the importance of heterogeneity, we also aimed to classify the MRI features into subtypes that are correlated and show similar relationships to risk factors. We suggest that these subtypes of lumbar spine MRI features may be appropriate phenotypes for future epidemiologic and genetic studies.

Materials and methods

Study sample

Following institutional ethics board approval, volunteers of Southern Chinese ancestry living in Hong Kong, aged 15 to 55 years, were recruited by open invitation [1,9,34,35]. Subjects with known history of spinal tumor, spinal infection, or spinal deformities were excluded. Each individual underwent MRI of the whole spine using sagittal T2-weighted fast spine echo sequences (TR 3,000 ms, TE 92 ms, slice thickness of 5 mm) [1,34]. For the current study, lumbar levels from L1 to S1 were assessed. Blood samples of each subject were obtained for single nucleotide polymorphism (SNP) chip genotyping. For those subjects who have relatives also participating in the study, only the first recruited subject within a family was selected in the current analysis. Sample sizes for each analysis are shown in Fig. 1.

Subject demographics and characteristics

Self-reported data included age (years), occupation, and the amount of smoking. Body weight (kilograms) and body height (meters) were measured. Body mass index was calculated by *body weight/body height*^{2}. Cigarette smoking pack-years was calculated by the *number of cigarettes smoked per day/20)*× *number of years smoked*. Physical workload was determined by occupation and characterized as being light, medium, moderate, or heavy, and scored for intensity on a scale of 1 to 4 [36].

MRI features

Two experienced physicians, blinded to personal data on the subjects, assessed the MRIs. Reliability estimates were good to excellent (weighted kappa statistics: signal intensity loss=0.91±0.04, disc bulging=0.70±0.10, end plate