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Review Articles

The Twin Spine Study: Contributions to a changing view of disc degeneration†

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Abstract

BACKGROUND CONTEXT: Disc degeneration was commonly viewed over much of the last century as a result of aging and ''wear and tear'' from mechanical insults and injuries. Thus, prevention strategies and research in lumbar degenerative changes and associated clinical conditions focused largely on mechanical factors as primary causes using an ''injury model.'' The Twin Spine Study, a research program on the etiology and pathogenesis of disc degeneration, has contributed to a substantial revision of this view of determinants of lumbar disc degeneration.

PURPOSE: To provide a review of the methods and findings of the Twin Spine Study project.

STUDY DESIGN/SETTING: Narrative review of the Twin Spine Study.

METHODS: The Twin Spine Study, which started in 1991, is a multidisciplinary, multinational research project with collaborators primarily in Canada, Finland, and the United States. The most significant investigations related to determinants of disc degeneration included occupational exposures, driving and whole-body vibration exposure, smoking exposure, anthropomorphic factors, heritability, and the identification of genotypes associated with disc degeneration.

RESULTS: Among the most significant findings were a substantial influence of heredity on lumbar disc degeneration and the identification of the first gene forms associated with disc degeneration. Conversely, despite extraordinary discordance between twin siblings in occupational and leisure-time physical loading conditions throughout adulthood, surprisingly little effect on disc degeneration was observed. Studies on the effects of smoking on twins with large discordance in smoking exposure demonstrated an increase in disc degeneration associated with smoking, but this effect was small. No evidence was found to suggest that exposure to whole-body vibration through motorized vehicles leads to accelerated disc degeneration in these well-controlled studies. More recent results indicate that the effect of anthropometric factors, such as body weight and muscle strength on disc degeneration, although modest, appear in this work to be greater than those of occupational physical demands. In fact, some indications were found that routine loading may actually have some benefits to the disc.

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CONCLUSIONS: The once commonly held view that disc degeneration is primarily a result of aging and ''wear and tear'' from mechanical insults and injuries was not supported by this series of studies. Instead, disc degeneration appears to be determined in great part by genetic influences. Although environmental factors also play a role, it is not primarily through routine physical loading exposures (eg, heavy vs. light physical demands) as once suspected.

Keywords: Disc; Degeneration; Heredity; Spine; Genetics

Background

A precise pathoanatomical diagnosis is not available in the vast majority of people with back pain problems [1]. Yet, theories and models of underlying pathology and its etiology have been adopted over the past half century that have had profound effects on how the problem is viewed and approached by those afflicted, their health-care providers and health and insurance policy-makers [2].

Although the specific underlying pathology is unknown in most cases of back pain, lumbar disc degeneration is a primary suspect and is commonly believed to be responsible for back symptoms, as well as being a major culprit in sciatica and lumbar spinal stenosis [3–6]. Consequently, the disc is a primary target for diagnostic and therapeutic interventions. Nachemson suggested that painful conditions may result from premature aging changes that render the disc mechanically incompetent, creating abnormal motion patterns that subject various spinal structures to undue stress [7]. Neuropathic changes, including abnormal firing in neurons innervating back tissues and nerve ingrowth into degenerated discs have been added to the list of suspected causal factors, as well [8–10]. In the case of symptomatic disc herniations, the findings of Olmarker et al. indicate that irritation of nerve roots may not only be caused by compression but also by biochemical effects of exposure to the nucleus pulposus [11]. There is also evidence that cytokines, such as tumor necrosis factor-α, may be factors in nucleus pulposus-induced neuropathy [12,13]. In addition, a possible role for bacterial infections in discs with patients with severe sciatica has been suggested [14]. Although the pain mechanisms are unclear and likely to be complex, evidence suggests that the disc plays a role in back symptoms, sciatica, and spinal stenosis [15–17], but the extent of the role remains unknown.

Before the past decade, the traditional injury or repetitive loading model of disc degeneration had dominated related prevention strategies and research for nearly half a century [18]. Such a model of disc degeneration implied that overloading from exposure to a single excessive force or repetitive loading results in structural damage (eg, accelerated disc degeneration or herniation), which in turn leads to symptomatic conditions. Among the factors most commonly suspected of accelerating degenerative changes in the discs were various occupational physical loading conditions [19]. In particular, attention has been given to heavy materials handling, postural loading, and vehicular vibration [20]. Numerous studies of the relationship between heavy materials handling and postural loading resulted in mixed findings related to the presence and degree of association with disc degeneration [21–30].

Vehicular driving had been associated with a higher incidence of back symptoms and degenerative changes, which were attributed to the effects of whole-body vibration on the intervertebral disc [31]. Yet, in an extensive review of the scientific literature, Kjellberg and others from the Swedish National Institute for Working Life [32] cautioned that although most of the studies revealed significantly higher frequencies of back symptoms and degenerative changes in the vertebrae and intervertebral discs of drivers compared with referents, ''uncontrolled confounding factors may have affected the results in all studies, and the conclusions about the causal role of whole-body vibration for the observed injuries and/or disorders, therefore, becomes uncertain.'' Buckwalter cited several mechanisms of age-related deterioration of intervertebral discs, but acknowledged that activities and agents that accelerate degeneration remain speculative [33].

Based on the studies available at the time, Frymoyer summarized the state of knowledge on determinants of ''degenerative disc disease'' 15 years ago. He wrote ''*Among the factors associated with its occurrence are age, gender, occupation, cigarette smoking, and exposure to vehicular vibration. The contribution of other factors such as height, weight, and genetics is less certain*'' [34]. A decade later Ala-Kokko conducted a literature review on the same topic, ''degenerative disc disease,'' and concluded ''*Even though several environmental and constitutional risk factors have been implicated in this disease, their effects are relatively minor, and recent family and twin studies have suggested that sciatica, disc herniation and disc degeneration may be explained to a large degree by genetic factors*'' [35]. A dramatic change in views of determinants of disc degeneration was underway.

Disc degeneration which was once viewed as a result of aging and ''wear and tear'' from mechanical insults and injuries is now viewed as being determined in great part by genetic influences [36–38], suggesting new models through which to conceptualize and study disc degeneration and associated pathology. We will summarize briefly some of our

group's research, through the Twin Spine Study, that has contributed to this substantial change in views on the etiology of disc degeneration.

The Twin Spine Study

The Twin Spine Study, which started in 1991, is a multidisciplinary and multinational research project with collaborators primarily in Canada, Finland, and the United States. Among the most significant findings related to determinants of disc degeneration were a substantial influence of heredity on lumbar disc degeneration and the identification of the first gene forms associated with disc degeneration [36,38,39]. Also, the studies on the effects of smoking and driving exposures using exposure-discordant identical twins have provided perhaps the most well-controlled studies on the effects of these exposures on human disc degeneration to date [40,41]. Among recent results are findings indicating that the effect of individual physical factors, such as body weight and muscle strength, on disc degeneration, although modest, may be greater than that of occupational physical demands [42]. Following is a brief description of the subjects and data on which the studies summarized in this article are based.

Subjects of the Twin Spine Study were recruited from the population-based Finnish Twin Cohort (with 13,888 male pairs of known zygosity) based on relevant prior information available from surveys conducted in 1975 and 1981, which had elicited response rates of 89% and 84%, respectively. The cohort has been found to be representative of the general Finnish population [43]. The Twin Spine Study subjects drawn from the Finnish Twin Cohort include 147 monozygotic (MZ) and 153 dizygotic (DZ) male twin pairs (as determined through original zygosity questionnaire data). The initial selection of 117 pairs of MZ twins was based solely on discordance between twin siblings for a specific common behavioral or environmental factor (eg, sedentary or heavy occupational physical demands, routine exercise participation, or occupational driving). The factors were selected because of their suspected importance in the etiology of spinal degeneration, back symptom complaints, and the availability of relevant information from the Finnish Twin Cohort database. In addition, a random sample of 30 MZ pairs, stratified by age, were added, as were 153 pairs of DZ twins selected using analogous criteria, yielding a total sample of 600 subjects. The volunteer rate was approximately 82%.

Study subjects were found to be quite representative of the Finnish Twin Cohort, which is representative of the Finnish population. No statistically significant differences were observed when comparing MZ twin subjects to the entire Finnish Twin Cohort for level of education, social class, smoking, level of leisure-time physical activity, or history of work-incapacitating neck, shoulder, or back pain, or sciatica. The MZ study pairs did differ from the entire Finnish Twin Cohort for work status, they were somewhat more likely to be working, and physical loading at work (slightly higher among study subjects), due to the inclusion of related factors in the selection criteria [44]. DZ pairs were selected in an analogous fashion. The validity of zygosity was studied previously in a subsample of 104 twin pairs. The agreement in classification between the questionnaire data and 11 blood markers yielded an estimated probability of misclassification of less than 1.7% [45].

Data acquisition involved transporting twins from all parts of Finland to a central location where a team of project investigators, technicians, and other staff ensured that interviews, physical examinations, and clinical testing were completed over a two-day period for each twin pair.

A structured interview was conducted by trained interviewers to obtain data on lifetime exposures of interest from adolescence through the present. Interviewers were blind with respect to the specific discordance or selection criteria for the twins, and project investigators avoided discussions with the interviewers regarding the study hypotheses. Demographic information and health history: occupational history; history of regularly performed leisure-time activities and exercise; specific recalled incidents or trauma resulting in acute ''back injury''; general dietary history, particularly related to calcium intake; and smoking and driving history were obtained from the interview. For example, for each job held during a subject's lifetime, the subject was asked to describe the job activities, including his most common lifting activity and estimate the weight lifted, the frequency of lifting, and the number of hours spent sitting during an average work day. This information along with the job title was used to appropriately categorize the job in terms of its general demands related to materials handling and postural stress. Exposure to cigarette smoking was calculated in pack-years. Optimal means of acquiring adequate estimates of lifetime exposure data is an unresolved issue in research requiring such data. However, using standardized in-depth interviews noting common life ''milestones'' to assist with recall are expected to assist in providing valid estimates of exposures of interest. Coded data were checked for congruence, outliers were identified, and in some cases phone calls were used to verify unclear or unusual recorded responses.

One year after the initial data collection, all subjects were asked to complete an additional questionnaire, which was provided by approximately 98% of subjects. The follow-up questionnaire afforded the opportunity to determine response reliability for several exposure history variables. Responses were compared with those at the time of the initial interview among those who said that there had been no change in their jobs. The intraclass correlation coefficient was 0.75 for estimates of time spent sitting, 0.77 for driving and 0.60 for total lifting per day. Also, a five-year follow-up interview and examination was conducted on a subgroup of 150 MZ subjects that allowed for reliability estimates for lifetime exercise history data.

Test-retest reliability of lifetime exercise history (using a five-year interval) yielded an intraclass correlation coefficient of 0.69 for lifetime years of exercise type and 0.73 for associated mean exercise hours per week [46].

Clinical examinations included anthropometric measurements (weight, height, % body fat using acoustic impedance) and evaluation of spinal range of motion, isokinetic lifting strength, back muscle static endurance, psychomotor reaction time, and blood and urine samples (for inflammatory mediators, connective tissue markers, and DNA analysis). The Twin Spine Study was provided extraordinary access to the 1.5-Tesla MRI scanner at Kuopio University Hospital and magnetic resonance images (MRIs) of the lumbar spine were obtained for all subjects using a set protocol. Collected blood samples were appropriately stored and transported to the Department of Human Molecular Genetics at the Finnish National Public Health Institute, where DNA was extracted.

Defining disc degeneration—The accuracy of phenotype measurement is critical in genetic epidemiology when trying to identify genes for conditions with multifactorial etiologies and in studies of gene-environment interactions. The strengths of the Twin Spine Study have been the acquisition of data on a broad spectrum of possible determinants and confounding factors, which can be controlled in analyses when appropriate, and the precision of the outcome measures, particularly with respect to degenerative and structural variations.

From the beginning of the Twin Spine Study, the research team has invested much time in methodological developments, such as in spine MRI protocols and image analysis programming. The gross qualitative ratings of spine degeneration in common use [47] were replaced or augmented when possible with quantitative measures with higher reliability and precision.

Then there is the deceptively simple issue of defining disc degeneration. The term disc degeneration is commonly used for an overall subjective impression of imaging findings, including signal loss, bulging, herniation, end plate irregularities, osteophytes, and narrowing of the disc space, but no universally accepted standard definition exists. One might expect degenerative findings to correlate with age, but such correlations have been modest within the 35-year period spanning 35–70 years of age using qualitative MRI findings (Fig. 1) [48]. The MRI finding most highly associated with age to date has been CSF-adjusted disc signal based on T2 sequence, a measure of tissue hydration. Still age explains only a minor portion of the variance in disc signal.

The various MRI findings associated with disc degeneration represent both atrophic (ie, annular tears) and proliferative (ie, osteophytes) changes and may appear at different times in the overall sequence of events collectively termed disc degeneration. Findings may also differ with respect to effects on the occurrence or severity of symptoms. Furthermore, the influence of various risk

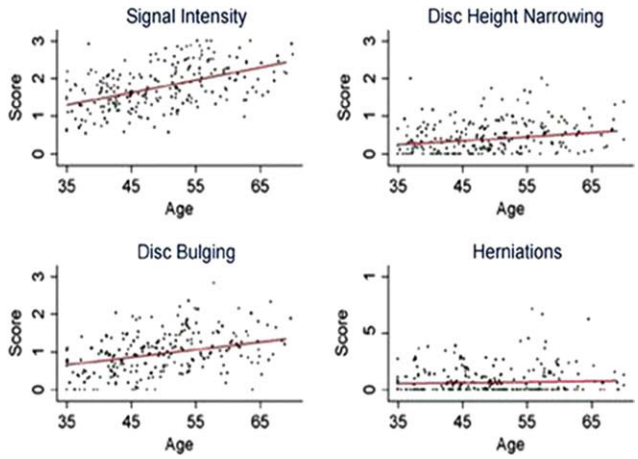

Fig. 1. Associations between age 35 and 70 years and four common findings of disc degeneration based on spine magnetic resonance imaging. The overall associations are weak (From *Spine*, Battié et al., 2004 [48]).

factors may vary in different stages of the degenerative process. Thus, a decision was made early in the Twin Spine Study to examine the distinct findings associated with disc degeneration separately, as opposed to using summary scores that aggregate different findings, which proved particularly useful for studies of genetic influences [38,49].

In an effort to refine MRI assessments of disc degeneration and explore the development of quantitative measurements using the digital data, a UNIX-based image analysis program was developed in 1994 [36], with a later version programmed to run on Windows NT to provide outcome files simultaneously for all spine levels and regions of interest. It also allowed new measures to be easily programmed, as such needs routinely arose as new questions were posed [49–52]. To obtain quantitative measurements using the program, the contours of the anatomical boundaries of lumbar discs, vertebrae, and the spinal canal are manually segmented on sagittal proton density (PD) images (Fig. 2). The evaluator follows the contour of the vertebrae, including the anterior and posterior longitudinal ligaments, and posterior wall of the spinal canal. To segment the disc from the vertebrae, the evaluator follows the boundary between the vertebral end plates and disc. Segmented areas are then adjusted using T2- and T1-weighted images, if necessary, taking advantage of different contrasts. The areas created by the intersections of those segmentation lines form the regions of interest corresponding to the disc and vertebra from which measures are derived by the software. Manual segmentation is also used in axial slices, for example, to evaluate mid-axial disc area and the central spinal canal.

Perhaps the most useful quantitative measure developed was of disc signal, adjusted for the intrabody reference of adjacent CSF. This measure has been more highly correlated with age than any of the other degenerative signs in the disc. It was also found to be the measure of disc

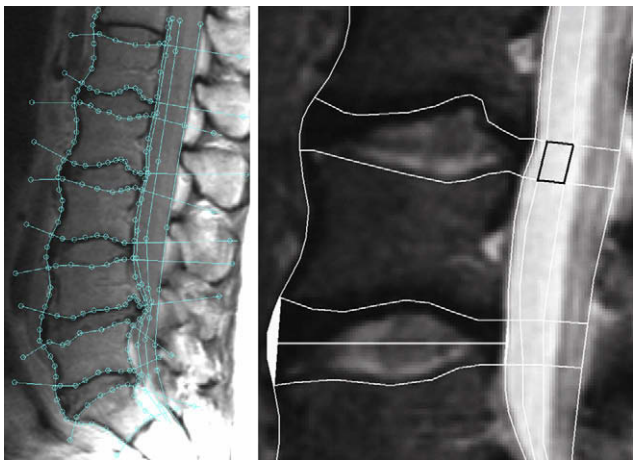

Fig. 2. The left picture shows how the manual segmentation was performed using PD-weighted images: the first and second vertical lines follow the anterior and posterior longitudinal ligaments, the fifth vertical line follows ligamentum flavum, and the third and fourth lines provide cerebrospinal fluid (CSF) samples adjacent to the disc (this is confirmed in T2-weighted images). The horizontal lines follow the disc-vertebra interface. The picture on the right shows the areas of interest created: in the upper disc level, the mean disc signal and mean signal of adjacent CSF (black lines) are obtained. The lower disc level demonstrates the "bulging" areas and the remaining disc area (minus bulging) is divided by its diameter (the horizontal "mid-disc" line) to compute mean disc height [52].

degeneration exhibiting the greatest change over a five-year follow-up period, as compared with little mean progression in disc narrowing, bulging, and other measures [52]. The importance of quantitative measures of greater reliability and precision was demonstrated in the earlier study of associations with Vitamin D receptor polymorphisms, which were identified when using the quantitative measure of signal intensity, but would have been missed using the gross ordinal scales of qualitative measurements [49].

Quantitative degenerative measures are of particular interest for longitudinal studies where more precise measurements of change are needed than available through ordinal rating scales. Quantitative measures included disc signal intensity adjusted by the signal intensity of adjacent CSF, disc volume, disc height, anthropometrics, and adjusted signal intensity of vertebrae, disc bulging, and osteophytes. Intrarater reliability coefficients for lumbar spine measurements are generally above 0.90.

Although quantitative measurements have many benefits in terms of reliability and precision, there are many findings that remain best evaluated by qualitative means. Thus, a combination of qualitative and quantitative image analysis measures have been used to depict various findings associated with degeneration. Each of the 600 subjects' films was assessed by one experienced spine specialist following a set protocol. The assessor was blinded to subject exposures and twinship. Among the specific findings assessed, either quantitatively or qualitatively, were:

From sagittal sections	From transverse sections
Disc signal (desiccation)	Disc signal (desiccation)
Disc height	Dural sac compression
Annular tears	Annular tears
Disc bulging and herniation	Disc bulging and herniation
End plate irregularities and sclerosis	Spinal canal size diameter/area
Vertebral osteophytes	

Exposure-discordant twin studies of suspected environmental and behavioral risk factors

The research program on the etiology and pathogenesis of disc degeneration began under the paradigm that disc degeneration was primarily the cumulative result of tissue injuries and degradation from trauma and repetitive loading. Yet, findings of studies of suspected physical loading risk factors were often contradictory or equivocal, possible confounding was a major concern, and dose-response relations were unclear. Also, at the time the Twin Spine Study began, MRI was just becoming available and most prior epidemiological or clinical studies had been limited to evaluating disc degeneration through radiographs. Thus, in an effort to clarify the effects of a variety of suspected risk factors, MRI and a unique study design that had been used successfully in the examination of exposure effects on cardiovascular disease were used [53]. An exposure-discordant twin model was used. Studying MZ twin siblings grossly discordant for a suspected environmental exposure of interest, controlled not only for age and gender, but also genetic influences and many other known and unknown confounding factors because of the high degree of similarity in identical twins' home and social environments and exposures. Fortunately, the onset of the study in 1992 coincided with the installation of the first 1.5-Tesla scanner in Finland, which was used to acquire study images.

As mentioned earlier, the primary suspected environmental risk factors for disc degeneration were various physical loading conditions, driving and associated whole-body vibration, and smoking. Thus, a series of investigations were conducted with identical twins discordant for a common environmental factor suspected of influencing disc degeneration or risk of back symptoms. The first "pilot" study using the exposure-discordant twin design was of 20 pairs of smoking discordant twins (mean cigarette smoking discordance, 31.6 pack-years), which revealed a lumbar disc degeneration score 18% higher, in mean, for heavy smokers as compared with their "nonsmoking" siblings (Fig. 3, top). The total amount of variance in disc degeneration scores among all subjects explained by smoking, however, was less than 2%. The statistical power to detect this small effect size attested to the efficiency of the MZ twin study design [40]. Based on this experience, recruitment and data collection protocols were established for the Twin Spine Study and the effects of various physical loading conditions at work and leisure were investigated

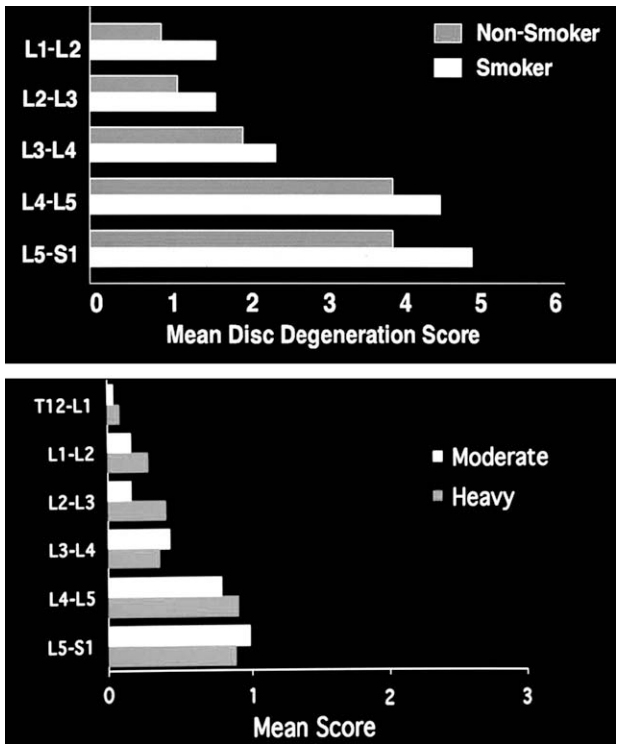

Fig. 3. (Top) The visual degeneration score for smoker and nonsmoker monozygotic siblings by disc level. Smoking had a small harmful statistically significant effect across spinal levels. (Modified from Spine, Battié et al., 1991 [40]). (Bottom) Disc height narrowing score by disc level for monozygotic siblings with physically heavy versus moderate lifetime work history. There was no consistent, statistically significant effect.

[36], including regular participation in various forms of exercise and occupational loading [54], as well as driving and associated whole-body vibration (Fig. 3, bottom) [41].

As mentioned earlier, a higher incidence of back symptom reports in driving occupations had been attributed to the effects of whole-body vibration on the intervertebral disc [31]. The investigation of 45 pairs of MZ twin siblings highly discordant for occupational driving is arguably the most well-controlled study of the effects of driving and associated whole-body vibration on human discs to date, and did not demonstrate significant differences between siblings in MRI findings of the lumbar discs. Besides qualitative measures of disc degeneration, quantitative measurements of CSF-adjusted disc signal intensity were included, which should be highly sensitive for disc degeneration [55,56]. Yet, no tendency for greater disc degeneration was seen among drivers (Fig. 4).

Despite extraordinary discordance between MZ twin siblings in occupational and leisure-time physical loading conditions throughout adulthood, surprisingly little effect on disc degeneration was observed. The findings indicated that although physical loading, that is handling heavy loads, bending, twisting, and static work in awkward postures, appears to influence disc degeneration, the effect size is very modest, which would help explain the inconsistent results of previous studies on the effects of occupational physical loading [42,52]. When the subjects from all the exposure-discordant twin studies were aggregated for analysis, occupational and leisure-time activities explained no more than 7% of the variance in disc degeneration [36]. Perhaps not surprisingly, smoking effects were not detected in this larger, independent group of twins with substantially less smoking discordance. As mentioned earlier, no evidence was found to suggest that exposure to whole-body vibration through motorized vehicles leads to accelerated disc degeneration, which was one of the primary hypotheses of possible mechanisms behind the association between driving occupations and back pain problems [57].

The findings of modest or negligible effects of the primary suspected environmental risk factors despite high exposures and gross discordance would explain the failure to demonstrate uniform, clear effects in earlier studies. It was concluded that the particular extrinsic factors studied, which had been among those most widely suspected of influencing disc degeneration, had modest effects, if any. In fact, some indications were found that routine loading may actually have some benefits to the disc. In a recent study, associations of anthropometric variables, including lifting strength and routine occupational and leisure-time physical loading with disc signal intensity and narrowing were examined in multiple regression modeling [42]. Lower disc signal (representing more disc desiccation) was associated with older age, as could be expected, but also various measures of less routine physical loading of the spine. In addition to older age, lower body mass and lifting strength, and larger disc area were associated with lower signal in multivariable analyses. Although associations were more modest, greater age and occupational loading exposures entered the multivariable model explaining disc height narrowing. The conclusion was that, ''body weight, lifting strength, and axial disc area were more highly associated with disc degeneration than occupational and leisure physical activity histories, although all had modest influences. Furthermore, higher body mass, greater lifting strength, and heavier work were all associated with more disc height narrowing, but less disc desiccation contrary to current views'' [42]. This observation may represent an important finding in better understanding the relation between various loading conditions and disc degeneration and suggests that responses of the disc may be more in keeping with other musculoskeletal structures that benefit from adaptation to routine physical loading (Fig. 5). The findings also suggest that determinants of disc degeneration and their effect sizes differ between specific degenerative findings. Thus, aggregating findings associated with disc degeneration into summary scores may mask relations.

In summary, the findings of the exposure-discordant twin studies raised questions about the adequacy of an injury model or ''wear and tear'' view of disc degeneration. Moreover, more recent findings suggest that greater routine physical loading may actually have some beneficial effects

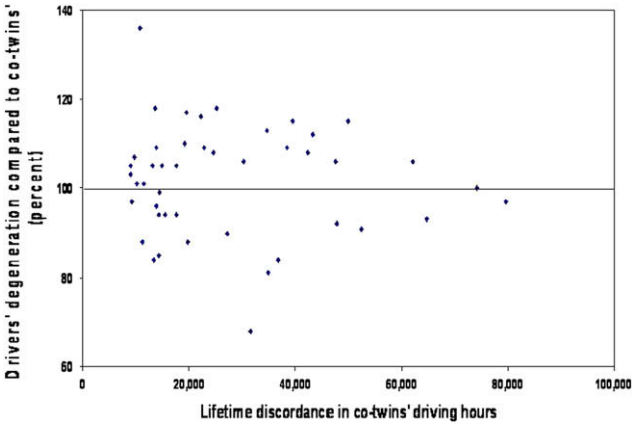

Fig. 4. The points represent the percentage difference in degeneration scores of drivers relative to their ''nondriving'' monozygotic twin siblings (scores standardized to 100). There was no indication of a dose-response relationship or threshold effect. (From the Lancet, Battié et al., 2002 [41]).

on the disc. During the course of the exposure-discordant twin studies, the striking observation of anyone who had the opportunity to view twin sibling images side-by-side was the strong resemblance in disc degeneration, not just in the degree of degeneration, but also in the types of findings and spinal levels involved. These observations led to subsequent studies of genetic influences.

Heredity as a major determinant of disc degeneration

The observations of co-twin similarities led to two studies of independent samples of MZ twins to systematically evaluate familial aggregation of disc degeneration. Familial aggregation in MZ twins can be viewed as representing the upper limit of genetic influences, as similarities can reflect both shared genes and shared early environments. Because there are very few traits that exhibit shared environmental (ie, nongenetic familial) effects in adulthood, familial aggregation is generally viewed as a proxy of total genetic effects. The resulting two articles were published in 1995 and supported a major shift in the way disc degeneration and its determinants are viewed.

Although occupational physical loading and other environmental exposures had received much attention as possible risk factors [20], detailed studies focusing on hereditary aspects of disc degeneration were lacking [58]. Before our work, there were only case series reports of similarities between twin siblings and relatives in the extent and location of degenerative changes in the spine and other joints [59,60]. We first conducted a systematic evaluation of lumbar degenerative changes blinded to twinship using the 20 twin pairs of MZ twins enrolled in the ''pilot'' study of twins discordant for smoking. We found a striking degree of similarities (matching by type of finding and spinal level) within identical twin pairs, well beyond that expected by chance or because of similarities in age (Fig. 6) [39]. This was followed by a larger, more comprehensive investigation of the role of familial aggregation and environmental influences in disc degeneration, which has been among the most important contributions to date from the research program [36]. Spine MRIs from 115 pairs of MZ twins were used to estimate the effects of commonly suspected risk factors on disc degeneration relative to the effects of age and familial aggregation, representing both genetic and early shared environmental influences. In the multivariable analysis of the T12–L4 region, 61% of the variance in disc degeneration was explained by familial aggregation, beyond that of age and occupational physical loading that together explained 16%. In the L4–S1 discs, 11% of disc degeneration was explained by physical loading and age, which rose to 43% once familial aggregation was added to the model (Fig. 7). In contrast to the upper lumbar levels, 57% remained unexplained in the lower lumbar region. These study findings led to the conclusion that lumbar disc degeneration may be explained primarily by genetic influences, early environmental exposures and yet unidentified factors, which may include complex interactions, such as between environmental factors and individual spinal anthropometrics [36].

Later, in a sample composed primarily of women from the UK and Australia, Sambrook et al. (1999) reported on heritability estimates for lumbar disc degeneration of 73%, supporting a substantial genetic influence [37]. Heritability estimates refer to the proportion of population variance in a trait attributable to genetic variation. Interestingly, although heritability estimates were high for disc bulging and narrowing (65% and 79%, respectively), a genetic influence on disc signal intensity was not apparent. Preliminary analyses from a classic twin study of 300 pairs of MZ and DZ male twins from the Twin Spine Study indicate substantial but somewhat lower heritability estimates closer to 50%, more in line with expectations from the earlier study of MZ twins [36]. Contrary to Sambrook et al.'s finding of no genetic influence on disc signal intensity using a qualitative four-point rating system, similar heritability estimates for signal intensity as for disc height narrowing were found in the Twin Spine Study when using the more reliable, precise measure of CSF-adjusted disc signal intensity. This provides an example of the importance of phenotype measurements.

The high heritability estimates for different degenerative findings in spine MRI provide motivation for identifying associated genes. Yet, disc degeneration and associated pathology likely represent complex conditions with multifactorial inheritance, presenting challenges to mapping out the genetic architecture of disc degeneration.

The search for susceptibility genes

Common diseases generally have a genetic contribution from multiple gene loci. We are interested in knowing how many alleles exist in each gene locus and their frequencies.

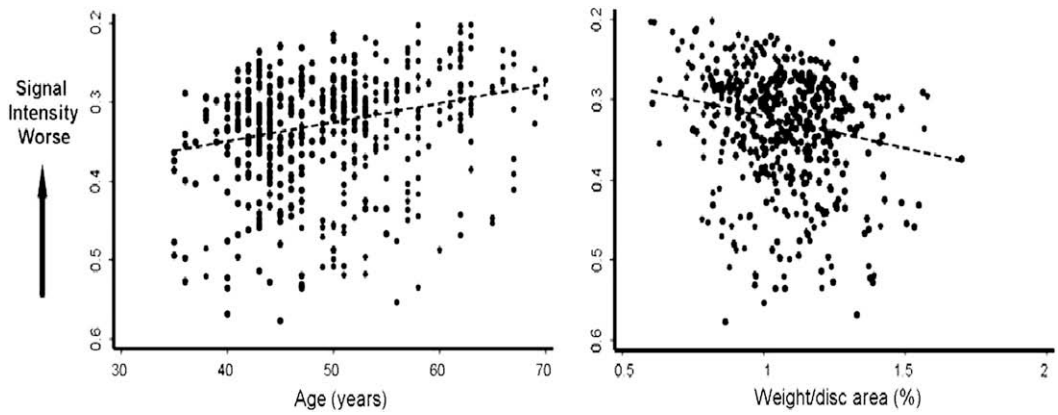

Fig. 5. Scatter plots of quantitative CSF-adjusted disc signal versus age and body weight/axial disc area. Higher body weight per disc area (and other indicators of greater routine loading on the spine) was associated with better (higher) disc signal. (From *Spine*, Videman et al. 2007 [42]).

Allele frequencies and average effects associated with the alleles determine the contribution of allelic variation to the trait of interest, which can then be partitioned into additive genetic variance (gene ''dosage'') and variance due to gene dominance [61]. Candidate genes may be used as targets, with potential genetic variation leading to differences in the proteins encoded by these genes. These proteins are part of the physiological system that, when disturbed, may give rise to the condition. Thus, the identification of associated genes, given their basic role in determining cell structure and function and hence tissue structure and function, can provide insights into mechanisms underlying disease. The candidate gene approach is promising for the analysis of common diseases, which are complex in their etiology and development, and has been used in most ''gene hunting'' studies of disc degeneration and associated pathology to date. However, undoubtedly gene-gene and gene-environment interactions are present in common polygenic conditions, such that simple linear models are unlikely to grasp the complexity. Thus, unraveling the contribution of genes and environment to etiology will be a difficult task.

After the discovery of a substantial genetic influence on disc degeneration, there has been considerable effort focused on identifying associated genes. The first gene polymorphisms associated with disc degeneration were identified through the Twin Spine Study in 1998 [38]. They were two polymorphisms of the Vitamin D receptor gene, *TaqI* and *FokI* identified in 170 MZ male twins. The associations were revealed with the phenotype of CSF-adjusted disc signal intensity. Signal intensities were 12.9% lower (more desiccation) in men with the *TaqI* tt genotype and 4.5% lower with the Tt genotype, as compared with signal intensities in men with the TT genotype. A similar pattern was seen between disc signal and *FokI* genotypes. Associations with degenerative scores using qualitative, gross ordinal scales did not reach statistical significance, emphasizing the value of more precise phenotype definition and measurement. As was written in the BackLetter [62] after the presentation of the findings at the annual International Society of the Study of the Lumbar Spine meeting in 1998, the study ''*confirmed for the first time the existence of genetic susceptibility to this progressive, age related degenerative process…This is the first step in a long process. However, this research opens the door to more accurate assessment of susceptibility to degenerative problems, and perhaps even prevention of these problems.*''

Since that time, there have been more than 30 studies of genes associated with disc degeneration and related pathology (Table 1). Among 23 studied genes, including aggrecan (AGC), collagen (COL), vitamin D receptor (VDR), inflammatory (IL), degradative (MMP), and some other genes, 17 have been associated with disc degeneration or related pathology in at least one study. However, many observed associations were based on small sample sizes and have not been replicated in other studies. Phenotypes also vary; in one quarter of studies the phenotype was based on X-ray images, which can provide only indirect evidence of disc degeneration through disc space assessment. In the studies based on spine MRI, the specific findings of disc degeneration have been assessed visually (in most studies using a four-point qualitative scale). Despite the challenges with sample sizes and phenotype definitions and associated misclassification, there is reasonable evidence suggesting associations of disc degeneration with the VDR gene (7/8 studies), with COL9A2 (8/10), and with COL9A3 (4/8). Yet, the available findings indicate that each gene has only modest effects.

DNA data for single nucleotide polymorphisms and haplotypes in 25 candidate genes, including 15 structural (aggrecan, 12 collagen, 8 interleukin, and 4 matrix metalloproteinase genes), selected for lumbar degenerative phenotypes were recently analyzed within the Twin Spine Study [63]. For genotype-phenotype associations, we used the FBAT (Family-Based Association Tests) in genetic analyses program package [64]. These tests are based on the classic transmission/disequilibrium test (TDT) [65], and permit testing of the hypotheses of no linkage and no association

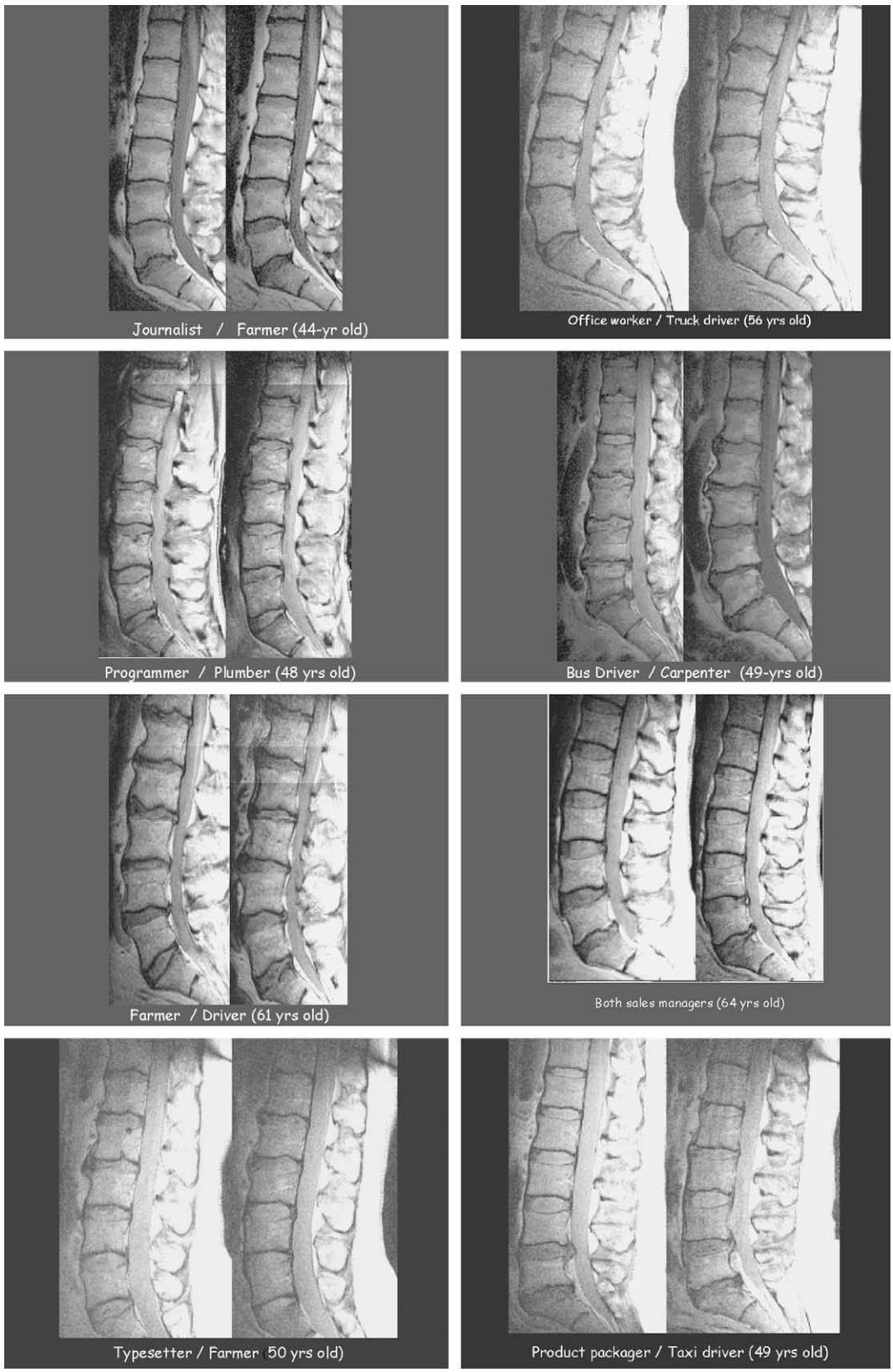

Fig. 6. High degrees of similarities in disc degeneration were noted between twin siblings, often despite high discordance in lifetime physical loading exposures. (In part from *Spine*, Battié et al., 2004 [48]).

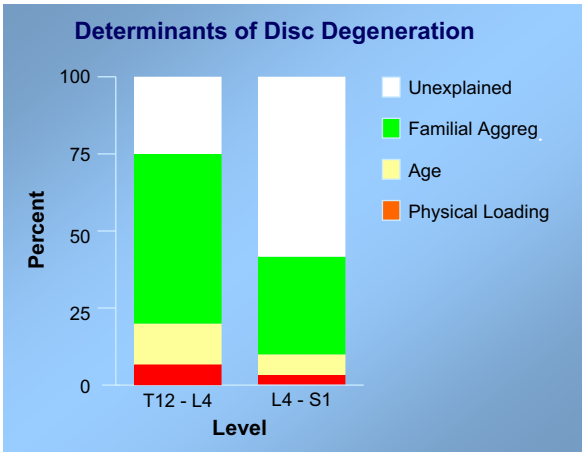

Fig. 7. The variability (adj. R^2) in qualitative disc degeneration summary scores explained by physical loading, age, and familial aggregation (proxy of heredity) demonstrated that significantly more variability remained unexplained in the L4–S1 disc levels. (Modified from *Spine*, Battié et al. 1995 [36]).

and linkage but no association. We used a strict statistical method (including 1,000 permutations) to accept an "overall gene association." The main phenotype was quantitative CSF-adjusted disc signal, in addition to the typical qualitative ordinal scores of disc height narrowing and bulging in 579 MZ and DZ twin subjects. Analyses yielded associations of lumbar disc signal, bulging, and disc height narrowing with the *AGC1* gene. Disc signal was also associated with *COL9A1* and *COL1A1* genes, and interleukin genes, *IL1RL2* and *IL18R1* [63]. Some of these findings support those of earlier analyses, whereas others await replication.

The specific interests in this study were variations in "durability" of structural proteins (disc matrix synthesis and degradation) and in inflammatory and degradative reactions. However, other mechanisms of disc degeneration may exist, such as those related to spinal morphology, muscularity, and lifting strength, which all have genetic correlations and are also included in the genetic component of disc degeneration [42].

Is the disc a pathway through which genes influence back pain problems?

Disc degeneration and back pain are clearly not synonymous and the association between the two is routinely debated. Yet, if disc degeneration does influence back pain problems, and both have a substantial genetic component, disc degeneration may be one pathway through which genes influence back pain. To examine the hypothesis that genetic influences on back pain are mediated through genetic influences on disc degeneration, a classic twin study was conducted on 300 MZ and DZ twin pairs of the Twin Spine Study using multivariate quantitative genetic models to estimate the degree to which genetic effects on back pain are correlated with genetic effects on disc degeneration [95]. Disc height narrowing was used to index disc degeneration as it was the finding most associated with back pain in earlier analyses of MZ twins [51]. In support of the hypothesis, statistically significant genetic correlations were found for various definitions of back pain and disc height narrowing. A substantial minority (up to one-fourth) of the genetic influences on pain was due to the same genetic influences affecting disc height narrowing. Yet, the substantial portion of genetic influences on pain left unexplained suggests an important role for other genetic influences that may affect pain processing, reporting, or other underlying pathological conditions.

In contrast, less than 5% of the variance in back pain outcomes explained by environmental factors was due to the same environmental factors influencing disc height narrowing. This is concordant with the earlier exposure-discordant twin studies revealing negligible or modest effects on disc degeneration of occupational activities associated with back pain complaints. This raises the question, do some of the particular environmental physical loading exposures serve primarily to exacerbate symptoms rather than cause the underlying pathology? It is also important to note that although little overlap was found between environmental factors influencing pain reporting and disc narrowing, environmental factors do appear to have a substantial role in disc height narrowing as do genes. The challenge is to refine or reconceptualize influential environmental exposures, such as biomechanical forces, which may include hypotheses on interactions with other systems, and the pathways through which they may affect lumbar disc degeneration and associated pathology.

Summary

Knowledge gained through the Twin Spine Study has added to others' efforts over more than a decade to enhance our understanding and revise views of disc degeneration. Disc degeneration is now considered a condition that is genetically determined in large part, with environmental factors, although elusive, also playing an important role. Most of the specific environmental factors once thought to be the primary risk factors for disc degeneration appear to have very modest effects, if any [34]. This advance in the understanding of disc degeneration provides a foundation from which to develop new hypotheses and more fruitful research to further elucidate the etiology of disc degeneration.

Earlier work on disc degeneration in MZ twins [36,39] established a substantial role of heredity in disc degeneration through the identification of high degrees of familial aggregation, suggesting a substantial genetic influence. This has been further substantiated by classic twin studies of MZ and DZ twins [37,95]. The initial discovery of two gene forms associated with disc degeneration [38] ushered in the

Table 1
Candidate gene studies to date seeking associations with disc degeneration, sciatica, ''lumbar disc disease'' or spinal stenosis in general population sample and patients

Authors	Genes	Sample size	Phenotype	Ethnicity
Videman et al., 1998 [38]	*VDR*	170 Population	MRI	Finnish
Jones et al., 1998 [66]	*VDR*	282 Elderly subject	Radiograph (K/L)	Australian
Jordan et al., 2005 [67]	*VDR*	291 Subjects UK	Radiograph (K/L)	
Videman et al., 2001 [49]	*VDR*	142 Population	MRI	Finnish
Kawaguchi et al., 2002 [68]	*VDR*	205 Subjects	MRI	Japanese
Cheung et al., 2006 [69]	*VDR*	804 Population	MRI	Chinese
Kawaguchi 1999 [70]	*AGC*	64 Mix	MRI	Japanese
Roughley 2006 [71]	*AGC*	44 Patients	MRI/radiograph	Canadian
Annunen et al., 1999 [72]	*COL9A2*	157 Patients +101 controls	MRI	Finnish
Paassilta et al., 2001 [73]	*COL9A1–3*	171 Patients	MRI/CT	Finnish
Solovieva et al., 2002 [74]	*COL9A3*	135 Subjects	MRI	Finnish
Karppinen et al., 2002 [75]	*COL9A2*	159 Patients +22 families	MRI	Finnish
Matsui et al., 2004 [76]	*COL9A 2–3*	107 Spondylolisthesis patients	Radiograph/MRI?	United States
Kales et al., 2004 [77]	***COL9A2–3***	105 Patients; 102 controls	Radiograph (K/L)	European
Jim et al., 2005 [78]	*COL9A2*	804 Population	MRI	Chinese
Seki et al., 2006 [79]	***COL9A2***	470 LDD Patients, 658 controls	MRI	Japanese
Higasheno 2006 [80]	*COL9A2*; *COL9A3*	84 Herniation patients	MRI	Japanese
Solovieva et al. 2006 [81]	*COL9A2–3*; ***COL2A1***; *COL11A2 IL-1β*	135 Subjects	MRI	Finnish
Noponen-H. et al., 2003 [82]	*COL9A1–2–3*; ***COL11A1***; ***AGC1***; ***VDR***; ***MMP-3***	29 Stenosis; 56 controls	MRI/CT	Finnish
Pluijm et al., 2004 [83]	*COL1A1*	966 Subjects	Radiograph (K/L) Dutch	
Tilkeridis et al., 2005 [84]	*COL1A1*	36 Subjects	Radiograph (K/L)	European
Takahashi et al., 2001 [85]	*MMP-3*	103 Subjects	MRI	Japanese
Valdes et al., 2005 [86]	*MMP-3*; *TIMP1*; *COX2*; *VDR*; *THSD2*	720 Subjects	Radiograph (K/L)	UK
Solovieva et al., 2006 [81]	*IL-1β*; ***COL9A2***; *COL9A3*; *COL11A2*; ***COL2A1***	135 Subjects	MRI	Finnish
Solovieva et al., 2004 [87]	*IL-1α*; ***IL-1β***	133 Subjects	MRI	Finnish
Le Maitre et al., 2005 [88]	***IL-1α***; *IL-1β*; ***IL1Ra–RI***	30 Tissue samples or	MRI	UK
Noponen-H. et al., 2005 [89]	*IL6*; ***IL1A***; ***IL1B***; ***TNFA***	155 Patients; 179 controls	MRI	Finnish
Min et al., 2006 [90]	*MATN3*	809 Subjects + 382 OA patients	Radiograph (K/L)	Dutch, Icelandic
Seki et al., 2005 [91]	*CILP*	467 Patients 664 controls	MRI Surg. patients	Japanese
Virtanen et al., 2007 [92]	***CIL***	602 LDD patients/602 controls	MRI	Finnish, Chinese
Koshizuka et al., 2007 [93]	*ER*; ***PTH***; ***IL1b***; *VDR*	381 Spondylosis population	Radiograph (K/L)	Japanese

K/L, Kellgren/Lawrence osteophyte—disc height classification [94].

We found 31 studies on the association of genes and spine degeneration. No association was found with genes in bold-italics. There were 12 studies with sample sizes of more than 200 subjects or cases. Half of the studies were based on population samples and half on patients with spinal disorders. The phenotypes were based on visual grading of MRI in 14 studies, on radiograph in 8–10 studies, and on back pain histories in 8 studies. Quantitative MRI measures were used in 2 studies.

current wave of studies to identify genes associated with disc degeneration, with the hope of better understanding important pathways leading to pathology. Yet, the investigation of genetic influences on disc degeneration is still in its infancy. Future research will aim to clarify the genetics of disc degeneration, identify influential environmental factors, and explore the interplay between the two.

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