

GENETIC INFLUENCES ON CERVICAL AND LUMBAR DISC DEGENERATION

A Magnetic Resonance Imaging Study in Twins

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Objective. Degenerative intervertebral disc disease is common; however, the importance of genetic factors is unknown. This study sought to determine the extent of genetic influences on disc degeneration by classic twin study methods using magnetic resonance imaging (MRI).

Methods. We compared MRI features of degenerative disc disease in the cervical and lumbar spine of 172 monozygotic and 154 dizygotic twins (mean age 51.7 and 54.4, respectively) who were unselected for back pain or disc disease. An overall score for disc degeneration was calculated as the sum of the grades for disc height, bulge, osteophytosis, and signal intensity at each level. A "severe disease" score (excluding minor grades) and an "extent of disease" score (number of levels affected) were also calculated.

Results. For the overall score, heritability was 74% (95% confidence interval [95% CI] 64–81%) at the lumbar spine and 73% (95% CI 64–80%) at the cervical spine. For "severe disease," heritability was 64% and 79% at the lumbar and cervical spine, respectively, and for "extent of disease," heritability was 63% and 63%, respectively. These results were adjusted for age, weight, height, smoking, occupational manual work, and exercise. Examination of individual features revealed that disc height and bulge were highly heritable at both sites, and osteophytes were heritable in the lumbar spine.

Conclusion. These results suggest an important genetic influence on variation in intervertebral disc degeneration. However, variation in disc signal is largely influenced by environmental factors shared by twins. The use of MRI scans to determine the phenotype in family and population studies should allow a better understanding of disease mechanisms and the identification of the genes involved.

Degenerative intervertebral disc disease is common with aging and is thought to be a contributing factor to pain, disability, and time lost from work in Western countries. Despite this, little is known about the pathogenesis of degenerative disc disease and the relative importance of genetic and environmental factors. Degenerative disease of the cervical and lumbar spine increases in prevalence with age, such that by the age of 60 years, most individuals have some radiographic evidence of disc narrowing and/or apophyseal osteoarthritis (OA); however, the degree of change varies considerably between individuals (1–4).

Clinical observations have long supported the concept that there is some genetic or familial contribution to OA in peripheral and axial joints. Early studies by Stecher (5) demonstrated that distal interphalangeal OA, as manifested by Heberden's nodes, was 3 times as common in the sisters of affected subjects as in the general population. Generalized OA is associated with multiple joint involvement at a rate higher than that expected by age alone (6) and is also associated with cervical and lumbar disc disease. Family studies have indicated that first-degree relatives are twice as likely as population controls to have generalized OA (7). In a recent twin study from our group, a clear genetic influence on OA of the hand and knee in women (8) was observed. OA was assessed quantitatively by determining an OA trait score, which was obtained by totaling

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osteophyte and joint narrowing scores at multiple joints from hand and knee radiographs in 307 unselected pairs of twins ages 48–70 years. Heritability estimates for both knee and hand sites combined were 0.69 for osteophytes and 0.60 for joint space narrowing, indicating a strong genetic effect on manifestations of peripheral OA (8).

Previous genetic and population-based studies of disc degeneration have been hampered by the lack of a reliable clinical phenotype (9,10). Back pain is not specific because it is reported at some time by a majority of the population over age 50, and the use of plain radiography is limited because it cannot properly assess the intervertebral disc. Magnetic resonance imaging (MRI) is generally considered the most sensitive technique for examining disc degeneration (11), and correlations have been demonstrated with biochemical changes associated with disc degeneration during aging (12). Because monozygotic (MZ; or, identical) twins have identical genes and dizygotic (DZ; or, nonidentical) twins have, on average, only half their genes in common, twin studies can provide invaluable tools for examining the influence of genetic factors on quantitative human traits by comparing similarities of MZ and DZ twins.

To examine the hypothesis that disc degeneration has a major genetic component, we examined the relative contributions of genetic and environmental effects on cervical and lumbar disc degeneration by use of MRI in MZ and DZ twin pairs.

SUBJECTS AND METHODS

Same-sex twins (males and females) ages 31–80 years were invited to participate in the study. In Australia, twins were recruited through a letter of invitation from the Australian National Health and Medical Research Council Twin Registry. British twins were recruited via a London-based twin register and a national media campaign, initially targeting only females. To avoid bias due to ascertainment of affected cases (which can lead to overrepresentation of concordant MZ pairs and misleading correlations), twins were not advised of the specific disease to be studied and were informed that the study aimed at looking at the effects of aging. Twins were neither selected nor excluded because of a history of back pain or disc disease. All study participants gave written consent, and the study was approved by the local ethics committee.

The proportion of MZ and DZ pairs recruited were similar in both countries (54% MZ in the United Kingdom and 50% MZ in Australia). Clinical details about potential confounding variables were recorded at the initial interview, including height, weight, history of smoking, history of weight-bearing exercise, and history of manual work including occupations in which some or part of the time was spent in such physical activities as cleaning or lifting (13). Zygosity was

established by a standardized questionnaire (14) and, in doubtful cases, confirmed by DNA fingerprinting.

MRI. MRI was performed using a Siemens (Munich, Germany) 1.0T superconducting magnet in London and a General Electric Signa (Milwaukee, WI) 1.5T machine in Sydney. Sagittal images were obtained using a fast spin-echo sequence of time to recovery (TR)/time to echo (TE) 5000–4500/112 msec, with a slice thickness of 4 mm. Grading was performed on T2-weighted images, although T1 images were also obtained for certain measurements. Axial sections were obtained at selected levels to assess structural changes in individuals who had features suggesting prolapse. To avoid problems related to diurnal variation in disc height (15) or differences in image quality between the 2 machines, all MRI scans were performed >1 hour after the subjects arose from sleep in the morning, with no exercise or other rest allowed between arising and the scan, and importantly, each twin pair was scanned at the same appointment and on the same machine.

Definition of phenotype. Scans were read by a single reader (PNS) who was blinded to the subjects' zygosity and clinical history; a standardized atlas (16) employing a 4-point grading system for disc height, signal change, disc bulge, and anterior osteophytes was used. These variables were graded at 6 cervical (C2–C3 to C7–T1) and 5 lumbar (L1–L2 to L5–S1) discs. Inter- and intra-observer reproducibility was tested on MRIs of a subgroup of 65 women. Images were graded on 2 occasions within 14 days by 2 radiologists and a rheumatologist (PNS) who were blinded to the clinical details. The mean intra-observer kappa value was 0.66 for both the cervical and lumbar spine, and the mean inter-observer kappa values were 0.50 and 0.60 for the cervical and lumbar spine, respectively (17) (Table 1). These kappa values are consistent with previously reported values for similar grading systems (18,19).

An exploratory analysis of the association between scores for each feature (disc height, signal, bulge, and osteophyte) at each spine level showed a strong correlation between the same measurement across all levels within the cervical and lumbar spine, but a weaker correlation when the same features were compared between the cervical and lumbar spine. A principal components analysis, using as variables the sum of the scores for each feature in the cervical and lumbar spine separately, showed that each of these variables contributed substantially to the overall variation. Accordingly, an overall measure of degenerative change at each site (score A) was determined as the arithmetic sum of the grades for each feature in the cervical and lumbar spine, similar to previously published disc degeneration summary scores (20).

Two additional scores were developed to indicate the presence of severe changes that may be of greater clinical relevance. First, a "severe disease" score (score B) was derived by summing the number of features that had been scored grade 2 or higher at all lumbar and cervical levels. For example, an individual who was graded at the C3–C4 level as grade 2 for disc height, grade 1 for signal, grade 3 for disc bulge, and grade 0 for osteophytes would have a severe disease score of 2 at that level. In addition, an "extent of disease" score (score C) was determined as the number of levels with severity scores for any feature that were grade 2 or higher.

Statistical analysis. The analysis was based on the classic twin model, which assumes that the variation in MZ and

Table 1. Weighted kappa values for individual measures of disc degeneration*

	Cervical spine				Lumbar spine			
	Upper		Lower		Upper		Lower	
	Intra	Inter	Intra	Inter	Intra	Inter	Intra	Inter
Height	0.69	0.44	0.58	0.61	0.78	0.79	0.51	0.70
Signal	0.67	0.32	0.67	0.26	0.74	0.62	0.75	0.52
Bulge	0.57	0.70	0.72	0.59	0.63	0.50	0.70	0.72
Osteophytes	0.57	0.48	0.80	0.61	0.65	0.64	0.48	0.37

* Values are for intra-observer and inter-observer agreement.

DZ twin pairs can be accounted for by additive (A) and dominance (D) genetic variance components and environmental components that are shared between members of each twin pair (common environmental variation [C]) and those that are unique to each twin pair (unique environmental variation [E]) (21). MZ twins share a common genotype; hence, variation within pairs is accounted for by their full genetic and common environmental variation (A + D + C). In contrast, DZ twin pairs have only the genetic likeness of ordinary siblings. The classic twin model assumes that the within-pair variation in DZ twins has a similar contribution from shared environment to that in MZ twins (C), but the genetic contribution is less (0.5A + 0.25D) (22). The model assumes equal MZ and DZ phenotypic variation, a similar shared environment in MZ and DZ twins, and the absence of gene–gene and gene–environment interaction. Heritability (H) was estimated as the ratio of genetic variance components to overall variation.

The potential contribution of the variance components A, C, D, and E to each of the overall degeneration scores was examined using path analysis. Nested models were fitted in sequence. Starting with a set of full models, parameters were dropped if the fit did not deteriorate significantly when they were omitted, using a threshold of $P < 0.05$. The model with the fewest significantly contributing parameters was chosen as the final model.

The approach was extended to include the effects of age and other potential confounding variables in a multivariate analysis. While age, by definition, is similar within twin pairs, imbalance in ages between the 2 zygosity groups is a potential

source of bias if the variance of each trait was age dependent. Preliminary analysis showed that all trait scores increased with age, and there was a weak negative association between intrapair variance and increasing age.

Other potential confounders may bias estimates of heritability more directly, by showing a greater association in MZ than DZ twin pairs. In this analysis, relevant potential confounding variables were considered to be height, weight, history of smoking, history of weight-bearing exercise, and history of manual work, which have been associated with degenerative intervertebral disc disease (20,23), and showed greater similarity in MZ twins than in DZ twins in our study (Table 2). Sex was not included because (a) an initial stratified analysis showed no significant effect of sex on overall score, and (b) there were too few male–male pairs to allow data from males and females to be fitted separately in the multivariate model.

The multivariate analysis accounted for the effect of age through linear regression. The influence of other confounding variables was taken into account in a Cholesky model. This approach accounts for all possible information in the confounding variables and allowed an assessment of their contribution to genetic and environmental variance separately (24). The multivariate model was fitted only to the model selected from the univariate analysis, which in all cases was an AE model. The method thus permitted apportioning of covariation into genetic and environmental variance components attributable to the main effect variable (A_{indep} and E_{indep}),

Table 2. Characteristics of the individual study subjects*

	Monozygotic twins (n = 172)		Dizygotic twins (n = 154)	
		r/ κ		r/ κ
No. (%) female	140 (81)		126 (82)	
Age, mean \pm SD years	57.7 \pm 8.3	1.0	54.4 \pm 9.3	1.0
Weight, mean \pm SD kg	66.0 \pm 11	0.81	68.5 \pm 10	0.46
Height, mean \pm SD cm	163.0 \pm 7	0.93	164.5 \pm 7.2	0.69
Smoking history		0.42		0.16
Current, %	17		16	
Past, %	23		29	
History of weight-bearing physical activity, %	21	0.82	33	0.50
History of manual work, %	40	0.51	38	0.19

* SD values are between-pair SD. r = intraclass correlation coefficient.

Table 3. Intraclass correlation coefficients (r) and heritability estimates (H) in monozygotic (MZ) and dizygotic (DZ) twins for overall disease score (score A), severe disease (score B), and extent of disease (score C)*

	rMZ	rDZ	$H_{\text{unadjusted}}$	H_{adjusted}
			(95% CI)	(95% CI)
Cervical spine				
Score A	0.72	0.36	0.69 (0.58–0.72)	0.73 (0.64–0.80)
Score B	0.80	0.50	0.85 (0.58–1.0)	0.79 (0.70–0.84)
Score C	0.70	0.22	0.65 (0.33–0.98)	0.63 (0.44–0.73)
Lumbar spine				
Score A	0.75	0.46	0.72 (0.63–0.79)	0.74 (0.64–0.81)
Score B	0.73	0.42	0.77 (0.54–0.99)	0.64 (0.48–0.74)
Score C	0.71	0.20	0.62 (0.34–0.74)	0.63 (0.44–0.73)

* See Subjects and Methods for explanations of the scores. 95% CI = 95% confidence interval.

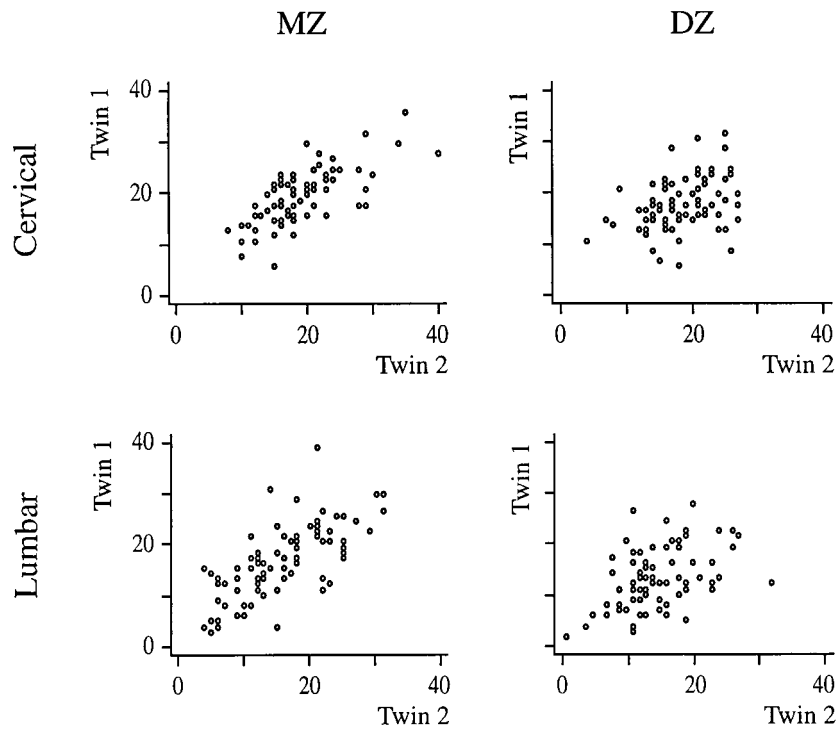


Figure 1. Overall score (score A) for each twin plotted against the score for the cotwin for monozygotic (MZ) and dizygotic (DZ) twins at each site evaluated. See Subjects and Methods for scoring system.

variance components attributable to confounding (A_{conf} and E_{conf}), and a variance component attributable to age (L). Overall variation is the sum of $A_{indep} + A_{conf} + E_{indep} + E_{conf} + L$. Adjusted heritability (H) was estimated from the ratio $A_{indep}/(A_{indep} + E_{indep})$.

In a further analysis, univariate and multivariate models were applied separately to the sum of scores for disc height, disc bulge, disc signal, and osteophytes in the cervical and

lumbar spine to examine heterogeneity in the overall degeneration score.

The path analysis was carried out using the statistical software Mx (25). Score A in the cervical and lumbar spine approximated a normal distribution, and models were fitted to the variance-covariance structure using maximum likelihood. The remaining models were fitted on correlation matrices using weighted least squares. Polyserial correlations for cate-

Table 4. Intraclass correlation coefficients (r) and heritability estimates (H) in monozygotic (MZ) and dizygotic (DZ) twins for individual features of disc degeneration

	rMZ	rDZ	Model*	H (95% CI)†	H _{adjusted} (95% CI)†
Cervical spine					
Disc height	0.62	0.17	AE	0.62 (0.55–0.68)	0.65 (0.53–0.73)
Disc signal	0.64	0.64	CE	0.0	–
Disc bulge	0.65	0.13	AE	0.64 (0.58–0.71)	0.59 (0.44–0.70)
Osteophytes	–0.04	0.04	E	0.0	–
Lumbar spine					
Disc height	0.78	0.38	AE	0.78 (0.56–0.99)	0.79 (0.71–0.84)
Disc signal	0.62	0.62	CE	0.0	–
Disc bulge	0.64	0.43	AE	0.69 (0.44–0.94)	0.65 (0.51–0.74)
Osteophytes	0.57	0.35	AE	0.59 (0.23–0.89)	0.54 (0.38–0.66)

* Variance components included in final model selected following the analytical procedure described in the text. A = additive genetic variance; C = shared environmental variance; E = random environmental variance.

† 95% CI = 95% confidence interval.

gorical data and asymptotic weight matrices were estimated using PRELIS (26).

RESULTS

The characteristics of the twins are shown in Table 2. The sample comprised 172 MZ twins (86 pairs) and 154 DZ twins (77 pairs), ~80% of whom were female. Both cotwins of each DZ pair were the same sex, and the MZ and DZ groups comprised similar proportions of female and male pairs. There were no significant differences between the MZ and DZ groups for mean height or weight, although a 3.3-year age difference was noted. There were greater correlations between MZ pairs for weight, height, smoking, and history of occupational manual work than for DZ twins. The mean disease scores and their standard errors were similar for the MZ and DZ twins (data not shown).

Heritability estimates, before and after adjustment for age, weight, height, smoking, occupation, and physical activity, are shown in Table 3. For the overall degenerative score (score A), the genetic contribution in the lumbar spine was determined to be 72% for unadjusted and 74% (95% confidence interval [95% CI] 64–81) for adjusted values, and in the cervical spine, the unadjusted value was 69% and the adjusted value was 73% (95% CI 64–80%).

A comparison of the overall scores for MZ and DZ twins is presented graphically in Figure 1. For the severe disease score (score B), genetic effects were 64% and 79%, respectively, and for extent of disease (score C), the values were 63% and 63%, respectively.

Table 4 shows the analysis of individual features of disc degeneration to examine possible heterogeneity. The data suggest that disc height and bulge score were the predominant factors contributing to the genetic determination of disc degeneration, whereas disc signal and cervical osteophyte scores did not differ between MZ and DZ twin pairs. Dominance effects were not clearly found for any trait, although a few of the DZ intraclass correlation coefficients were lower than expected. To exclude dominance effects would require the study of much larger numbers of twins. Common environmental effects on signal intensity accounted for the high and similar correlations for signal in the cervical and lumbar spine.

DISCUSSION

Using the twin model, the findings of this study suggest a strong genetic effect on disc degeneration in

the cervical and lumbar regions. Importantly, there appear to be significant differences in regard to different features of disc degeneration, with genetic influences most apparent on disc height and structural changes. Interestingly, we could find no significant genetic influence on disc signal intensity, which suggests a predominance of environmental factors (such as age-related changes in disc hydration) affecting this measure.

There have been few previous twin studies of degenerative disc disease. One early study using plain radiography examined the concordance of cervical changes in 57 twins (27). Concordance of cervical radiologic anatomy was 77.5% in 31 MZ twins compared with 42.5% in 26 DZ twins, a statistically significant difference; however, disc degeneration was not directly studied. More recently, Battie et al (20,23,28) studied male identical twins selected for discordance in suspected environmental risk factors, such as smoking. They observed that whereas age and smoking status explained only 15% of the variance in lumbar degenerative disc disease, cotwin status accounted for 54% of the variance (28), which suggested a significant genetic effect. Unfortunately, DZ twins were not evaluated in that study, making any interpretation of heritability impossible. Interestingly, decreased signal intensity was significantly related to greater leisure time physical loading, which supports an environmental influence on disc signal.

Twin studies can sometimes produce an exaggerated estimate of heritability because of certain biases, typically selection bias, whereby subjects with a disease self-select themselves. None of our subjects knew the hypothesis under investigation. Another bias could occur from an imbalance in environmental factors common to a twin pair, whereby MZ twins had greater similarity in environmental factors that were risk factors for disc disease. Table 2 shows that there was greater concordance in MZ twins for certain factors, such as occupational manual work and smoking, in the present study; however, adjustment for these factors did not diminish the estimates of heritability, which suggests that their effects were small. Moreover, for any confounder to have an impact on heritability measures of the size observed, the association between the confounder and degenerative disc disease would have to be extremely strong, even if there was a large imbalance in its distribution between MZ and DZ twins (29).

The number of males in our study was too small to assess differences between males and females; however, no systematic between-sex differences in disc degeneration were seen, a finding consistent with previous studies showing only relatively small sex differences

(4,30). Nevertheless, some caution may be necessary in extrapolating our results, which are primarily representative of women, to men. Using statistical modeling to assess the genetic contribution to a trait also has well-recognized methodologic problems (31). One is the limited power to detect the influence of common environmental and dominance variance (24). Adjusting for age and other potential confounders made little difference to the estimates of heritability in our analysis and provides reassurance that these estimates are a valid reflection of the genetic contribution to cervical and lumbar disc degeneration. To have sufficient statistical power to examine the possibility of separate additive and dominant genetic effects would require a study of many thousands of twins.

Although MRI is considered the most sensitive method for assessing disc degeneration, we did not analyze symptoms of intervertebral disc degeneration, such as pain or restriction of movement, in this study. It could be argued that since these subjects were not selected for a history of back pain or disc disease, the disc degeneration summary score (score A) does not necessarily reflect clinical pathology. Indeed, MRI findings such as prolapse or bulging do not necessarily correlate with clinical symptoms (32), although other features of disc degeneration, such as change in signal intensity or loss of disc height, have been correlated with back pain (33). However, since significant genetic effects were also observed in those twins with the most severe (score B) and widespread (score C) disease in the present study, these findings are likely to have some clinical significance. The lack of specificity of back pain as a phenotype is underscored by the fact that 75% of a sample of the twins reported having back pain lasting more than 1 week at some time. The failure to observe a significant genetic effect on signal intensity is unlikely to reflect classification error (E), since there were strong within-pair correlations in signal for both MZ and DZ twins. Our data, rather, suggest that the pathologic changes associated with diminished disc signal are influenced more by environmental factors than by genetic effects.

The biochemical and pathologic correlates of decreased signal intensity have been reported to include dehydration (12,34) and decreased proteoglycan content (12), although the latter remains a subject of controversy (34). The relationship of signal intensity to structural degenerative changes is uncertain. The influence of acute environmental influences on signal intensity is evident from diurnal variation, with changes of as much as 25% after overnight bedrest because of disc rehydra-

tion (14). To avoid this problem in our study, all MRI scans were performed >1 hour after arising from sleep, and all pairs of twins were scanned at the same appointment. With regard to osteophytosis, our findings of no within-pair correlations of cervical osteophytosis suggest that measurement error at this site may be responsible, due to the limitations of pixel size and scan resolution. In contrast, for lumbar osteophytosis, the observed intrapair differences for MZ and DZ twins suggest a modest genetic effect, which is consistent with previous studies of osteophytosis at other skeletal sites (8). It should be noted that MRI is generally not regarded as the preferred method for assessing osteophytosis.

Having demonstrated that disc height and disc bulging are genetically important phenotypes, the mechanisms of the genetic effect need to be addressed. Each disc consists of 3 major elements: the cartilaginous end plates, the annulus fibrosus, and the nucleus pulposus. The annulus fibrosus consists of concentric lamellae of highly oriented collagen fibers encapsulating the nucleus pulposus, a gel of proteoglycans (keratan sulfate, hyaluronic acid, and chondroitin sulfate) enveloped by collagen fibrils. Type II collagen comprises the major collagen component of the intervertebral disc cartilage, with lesser components including type IX and type XI collagen. It has been postulated that collagen gene mutations may play a role in some forms of familial connective tissue diseases (35). Indeed, 2 reports on 3 unrelated families have demonstrated coinheritance, with primary generalized OA of specific alleles of the type II procollagen gene on chromosome 12, the precursor of the major disc protein (36,37).

In conclusion, we have shown an important genetic influence on several specific features of intervertebral disc degeneration. The increasing use and declining cost of MRI scans for assessing specific traits should allow large-scale family and population genetic studies to be undertaken to facilitate a better understanding of these genetic mechanisms and identify relevant genes in this important area of research.

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