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Evidence for an Inherited Predisposition to Lumbar Disc Disease

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Background: A genetic predisposition for the development of symptomatic lumbar disc disease has been suggested by several twin sibling studies and subsequent genetic marker studies. The purpose of the present study was to define population-based familial clustering among individuals with a diagnosis of, or treated for, lumbar disc herniation or disc degeneration.

Methods: The Utah Population Database allows analysis of combined health and genealogic data for over one million Utah residents. We used the International Classification of Diseases, Ninth Revision, diagnosis codes entered in patient records to identify patients with a diagnosis of either lumbar disc herniation or lumbar disc degeneration and genealogic data. The hypothesis of excess relatedness (familial clustering) was tested with use of the Genealogical Index of Familiality, which compares the average relatedness of affected individuals with expected population relatedness. Relative risks in relatives were estimated by comparing rates of disease in relatives with expected population rates (estimated from the relatives of matched controls). This methodology has been previously reported for other disease conditions but not for spinal diseases.

Results: The Genealogical Index of Familiality test for 1264 patients with lumbar disc disease showed a significant excess relatedness ($p < 0.001$). Relative risk in relatives was significantly elevated in both first-degree (relative risk, 4.15; $p < 0.001$) and third-degree relatives (relative risk, 1.46; $p = 0.027$).

Conclusions: Excess relatedness of affected individuals and elevated risks to both near and distant relatives was observed, strongly supporting a heritable contribution to the development of symptomatic lumbar disc disease.

Level of Evidence: Prognostic Level II. See Instructions to Authors for a complete description of levels of evidence.

Back pain is the second most common reason for patients to seek medical treatment in the United States[1], and the lifetime risk of low back pain is estimated to be 84%[2]. The socioeconomic impact of low back pain is difficult to overstate as a recent study has shown that the total cost of low back pain in the United States exceeds $100 billion per year[3]. With low back pain, lumbar disc degeneration is a common finding. Along with disc degeneration, lumbar disc herniation may occur, resulting in back and/or leg pain symptoms. Despite the prevalence of lumbar disc disease, its etiology is not completely understood. Previous studies have suggested a multifactorial etiology including contributions from mechanical stresses to the spine[4], age-dependent disc degeneration[5], biochemical factors[6], and genetics[7]. Although several studies have suggested a familial predisposition[8-10], we are aware of no study that has evaluated the familial clustering of lumbar disc disease on a population-based, multigenerational level.

The Utah Population Database allows the combination of a computerized genealogy of the Utah founding pioneers and

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their descendents with disease diagnosis data. The Utah genealogy database was linked to the University of Utah Health Sciences Center data warehouse, a resource that contains diagnosis and procedure data on patients treated at the University Hospital. The resultant information is a unique and invaluable resource and has been previously used to evaluate familial clustering in other disease processes[11-14].

The purpose of this study was to define the familial clustering observed among individuals with a diagnosis of, or treated for, lumbar disc herniation or disc degeneration in an inpatient hospital or outpatient clinic setting. We tested the hypothesis of a heritable predisposition to lumbar disc disease, using two well-established methods: the estimation of relative risks in relatives and the Genealogical Index of Familiality (GIF).

Materials and Methods

Utah Population Database Data

The Utah Population Database and the University of Utah Health Sciences Center database were accessed, with over one million linked patients[15]. Specific International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes and Current Procedural Terminology, Fourth Revision (CPT-4) procedure codes are available for each patient. Selection of appropriate codes allowed identification of individuals who had been diagnosed as having or treated for either lumbar disc degeneration or lumbar disc herniation.

Case subjects were identified with use of the presence of ICD-9 diagnosis codes (722.52 and 722.10) and CPT-4 procedural codes (63030, 63035, 63047, 63048, 63042, and 63044) reported within the University of Utah Health Sciences Center database. The review identified 1254 patients who had at least three generations of genealogical data and at least one diagnosis of lumbar degenerative disc disease (1140 with ICD-9 code 722.52) or lumbar disc herniation (114 with ICD-9 code 722.10). Ninety-six of these individuals had, in addition to one of these diagnosis codes, one of the CPT codes listed above. The small number of patients with both ICD-9 and CPT-4 coding in their record (ninety-six) was insufficient to allow statistical analysis of patients who underwent surgical treatment.

For both analyses of familial clustering, we compared observed results among affected individuals with expected results for the Utah population; both analyses require the identification and analysis of appropriately matched controls. While all patients treated at the University of Utah Health Sciences Center have been linked to the Utah genealogical data, not all patient data could be made accessible for this analysis because of the confidential nature of the information. Instead, a set of patients representing approximately 20% of all patients at the University of Utah Health Sciences Center was randomly selected for use as controls. To allow appropriate matching for characteristics that may influence the quality and quantity of genealogical data or record-linking success, multiple cohorts for these characteristics were created and the control set of patients represented a random selection of 20% of all patients at the University of Utah Health Sciences Center who fit the characteristics of each defined cohort. All patients with at least three generations of genealogical data were assigned to a specific cohort on the basis of sex, five-year birth-year range, and presence or absence of ancestor data in the Utah population database. Two different statistical analyses were performed on all genetic relationships represented between all patients with lumbar disc herniation: the relative risks in relatives and the GIF.

Relative Risks in Relatives

Estimation of relative risks (RRs) for a phenotype among the relatives of affected individuals provides a traditional test for evidence of a genetic contribution to disease. Typically, RRs are estimated in first-degree relatives only, as this information is easily available for most affected individuals. However, although excess risk in first-degree relatives might indicate evidence of a genetic contribution, it could also simply indicate shared environment or exposure. Conversely, excess risks in second and third-degree relatives strongly support a genetic contribution to disease, given the measurable genetic sharing in these more distant relatives and the relative absence of shared household effects. Relative risks in first-degree relatives were estimated by counting the number of affected individuals among all first-degree relatives of patients (without duplication), and among all first-degree relatives of five randomly selected sets of matched controls; similar estimation was used for second and third-degree relative risks. For each degree of relative, the significance of the alternative hypothesis $RR \geq 1.0$ is calculated as a Fisher exact test and 95% confidence intervals are defined as described by Agresti and Min[16].

Genealogical Index of Familiality

The GIF analysis performs a test of the alternative hypothesis of no excess familial clustering (or relatedness) among all individuals of the phenotype of interest. The average relatedness of the set of patients with lumbar disc herniation was calculated by measuring the pairwise genetic distance between all pairs of patients. The pairwise genetic distance is estimated with use of the Malécot coefficient of kinship, or the probability that the two individuals share the same allele from a common ancestor at a given locus[17]. The same measure of average pairwise relatedness is calculated for all possible pairs among a set of randomly selected, matched controls; this process is repeated 1000 times, and the significance is measured empirically as the number of times the control relatedness exceeded the patient relatedness. The overall GIF statistic tests for excess relationships between pairs of patients versus pairs of controls; the distance GIF test statistic is calculated similarly, but ignores relationships closer than third degree, and therefore provides a strong test for a genetic contribution to a phenotype. Thus, it is not the absolute value of the GIF statistic that reveals excess relatedness of disease, but the relative value of the case-GIF to the control-GIF. In this way, the GIF statistic is able to show a difference in the prevalence of disease among relatives of individuals with lumbar disc disease and the relatives of individuals with no history of lumbar disc disease.

No patient identifiers were used in this study, and all analysis of genetic relationships between affected individuals

TABLE I Relative Risks in Relatives of Individuals with Lumbar Disc Disease

Relative	No. of Affected Individuals (Patients/Controls)	No. of Relatives (Patients/Controls)	Relative Risk	P Value	95% Confidence Interval
First	47/58	9259/47,630	4.15	<0.001	2.82-6.10
Second	20/90	25,384/131,494	1.15	0.60	0.71-1.87
Third	48/171	61,112/317,085	1.46	0.027	1.06-2.01

was nonidentifiable. This study has been approved by both the University of Utah institutional review board and the oversight body for the Utah Population Database.

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Results

Relative Risks

The estimated RRs for lumbar disc herniation in first-degree, second-degree, and third-degree relatives of patients with lumbar disc herniation are shown in Table I. The table shows the number of affected relatives of patients (and controls), the total number of relatives of patients (and controls), the estimated RR, the one-sided significance of the Fisher exact test for the 2 × 2 table of patients versus controls, and the 95% confidence interval for the RR estimate. The RR for the development of lumbar disc herniation was significantly elevated in both first-degree ($p < 0.001$) and third-degree ($p = 0.027$) relatives of affected individuals. These results strongly support a genetic contribution to a predisposition to develop lumbar disc disease.

Relative risk was elevated but was not significant (RR = 1.15, $p = 0.60$) among second-degree relatives. This may be based on limitations of our data, in that second-degree relatives are primarily in different generations from each other (for example, uncles or grandparent-grandchild), whereas first-degree and third-degree relatives are usually in the same generation (for example, siblings or first cousins).With additional years of data, this hypothesis can be tested with larger sample sizes.

GIF Test for Excess Relatedness

To test the hypothesis of no significant excess relatedness among patients, the GIF statistic was calculated for the 1254 patients with lumbar disc disease and 1000 matched controls. Table II includes the number of patients, the average relatedness of patients (overall GIF), the average relatedness of 1000 matched control analyses (mean control GIF), the p value for the overall GIF test of all relationships, and the p value for the distance GIF test, which only considers relationships beyond second degree. The overall GIF

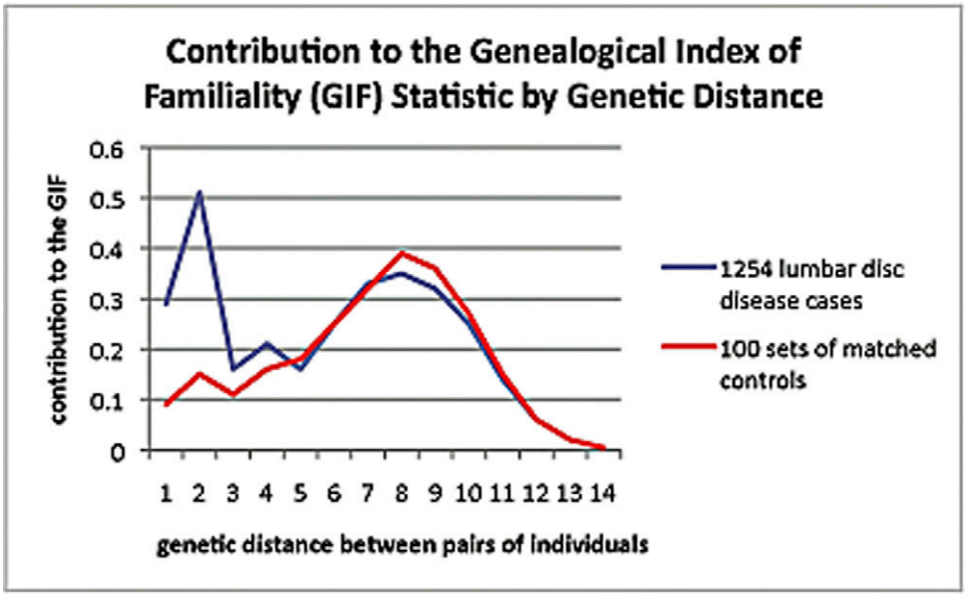

Fig. 1

The contribution to the Genealogical Index of Familiality (GIF) statistic by genetic distance. Comparison of the GIF contribution to genetic distance reveals an increased risk of lumbar disc disease in the relatives of affected individuals up to a genetic distance of four.

TABLE II GIF Test of Excess Relatedness for 1254 Individuals with a Diagnosis of Lumbar Disc Disease*

Phenotype	No. of Patients	Case Overall GIF	Mean Control GIF	Empirical P Values	
				Overall GIF	Distance GIF
Lumbar disc disease	1254	3.05	2.51	<0.001	0.760

*GIF = Genealogical Index of Familiality.

test revealed a significant excess of relationships among patients compared with controls; this supports the hypothesis of excess familial clustering. The distant GIF test ($p = 0.742$) did not show a significant excess of distant relationships (beyond second degree) among patients with lumbar disc disease.

The GIF statistic represents a sum of average pairwise distances by genetic relationship. In order to determine the genetic relationships for which patients differ from controls, we displayed the distribution of the GIF statistic for different pairs of genetic relationships observed for patients (and for controls) in Figure 1. The X axis represents the genetic distance (or relationship) between the pairs of individuals (1 = parent-offspring pairs, 2 = sibling pairs or grandparent-grandchild pairs, 3 = avuncular [aunt and uncle] pairs, 4 = first cousin pairs, etc.). The Y axis reveals the value of the GIF statistic that was contributed for each genetic distance. Figure 1 demonstrates that most of the excess relatedness of affected individuals compared with controls was observed for close relationships, which explains the finding of significant excess familial clustering ($p < 0.001$) and supports the RR results. Although we observed an excess of patient relationships that extended to a genetic distance of four (first cousins), this difference was not seen in more distant relatives and explains why the distant GIF test was not significant.

Discussion

Previous studies have suggested a familial predisposition to lumbar degenerative disc disease and disc herniation[6-10]. The results of this study support a heritable predisposition to lumbar disc disease, showing an excess relatedness of patients, and substantially elevated relative risks for close and distant relatives in the Utah genealogical database.

The preliminary data on the impact of genetics on lumbar disc disease came from case-control studies and twin studies. In a magnetic resonance imaging (MRI) study of forty identical twins (twenty pairs), Battié et al.[7] showed that, through multiple-regression analysis, approximately 26% to 72% of the variability in imaging studies was explained by their twin status. Other variables such as smoking status contributed <15% to the observed variability. In a similar study, Videman et al.[18] showed a genetic contribution to MRI-documented lumbar disc disease. In a five-year follow-up study of 150 male twins (seventy-five pairs), the authors demonstrated that familial aggregation explained 47% to 66% of the variance in the progression of degenerative findings on MRI studies of the lumbar spine. Occupational loading and physical resistance training together explained <10% of the observed degenerative changes. Several case-control studies[19,20] have described increased self-reporting of a family history of intervertebral disc disease (45% to 47%) among patients requiring surgery for disc herniations compared with controls (<33%). In a similar study, Matsui et al.[8] reported that disc herniations in patients with a positive family history were more severe than those in controls ($p < 0.03$).

Recently, genetic abnormalities in the extracellular matrix of the intervertebral disc have been implicated as a possible mechanism to explain these observations[21]. Studies have evaluated the components of the extracellular matrix and the genes that encode them as contributors to lumbar disc disease. These biochemical studies have shown an association between genes that code for type-XI collagen[21], type-IX collagen[20], and multiple intervertebral disc proteins[22] and symptomatic lumbar disc herniations.

However, population-based studies to determine the genetic influence on symptomatic lumbar intervertebral disc disease have been notably absent from the literature. Investigations such as the present study, which included an unselected subset of patients with lumbar disc disease in Utah who were uniformly identified, provide important information as they avoid the recall and ascertainment bias usually present in patient studies. The methodologies employed in this study, including the use of RR and the GIF, allow a thorough evaluation of large amounts of data. Further, they provide insight into the genetic effect in both near and distant relatives. These techniques have been previously validated and utilized to prove a familial predisposition in breast cancer[14], severe asthma[13], and rotator cuff disorders[11]. Additionally, these methods allow the identification of high-risk pedigrees that have an unusually high prevalence of disease. In breast cancer studies, researchers have collected DNA samples in individuals within such pedigrees to identify the individual genes responsible for the observed excess relatedness of affected individuals[14].

Our study used a population database of >2.4 million patients to solidify the earlier suggestions of a genetic predisposition for lumbar disc disease provided by the relatively underpowered twin studies and retrospective radiographic reviews of years past[7,8,18-20]. Additionally, the exclusion of the individuals without an appropriate diagnosis code focuses the application of the study to the individuals with symptomatic lumbar disc disease. The comparison with age-matched controls, likely to have asymptomatic disc disease[23], further supports the potential for genetic differences between symptomatic and asymptomatic individuals. By proving the familiality of lumbar disc disease, this research should promote further investigation into the

possible causes of the observed heritable predisposition for symptomatic disease. Further, the study identified a resource of high-risk pedigrees that can be used to identify and test candidate genes.

The primary limitation of our study is the use of ICD-9 data to identify affected individuals of interest. These codes are dependent on individual clinicians, and accuracy may vary depending on physician experience and specialization. The use of diagnostic codes additionally prohibited analysis of disease severity or response to treatment. Any affected individual without an appropriate ICD-9 or CPT-4 code, who had the disease diagnosed before 1993 at the University of Utah Health Sciences Center or at another facility or who was not represented in the Utah genealogy, was effectively censored from this study. Such censoring applies across the data source uniformly, to relatives of both affected individuals and controls, and thus should not affect the overall results, except to lower our power to see effects. The population of Utah has been shown to be genetically similar to the U.S. population and to the Northern European population from which of the Utah founders came[24]; therefore, the findings should be able to be generalized to this broader population.

In conclusion, lumbar disc disease likely has a multifactorial etiology, including contributions from mechanical stresses to the spine, age-dependent disc degeneration, biochemical factors, and genetics. This study identified an inheritable predisposition to the development of symptomatic lumbar disc disease. It also identified high-risk pedigrees in the Utah population, which can be studied to identify genes responsible for this predisposition. Identification of the specific genetic products responsible for lumbar disc disease may help in the development of potential biologic interventions to prevent and/or treat lumbar disc disease in the public at large. ■

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