Intervertebral Disc Degeneration: Evaluation of Risk Factors and Familial Risk Quantification in a Large Population-Based Cohort

#683

Nikolas H. Kazmers[1], Brandon J. Rose[1], and Mick J. Jurynec[1, 2, 3]*
[1]Dept. of Orthopaedics, [2]Human Genetics, and [3]Biomedical Engineering, University of Utah, Salt Lake City, UT
*mjurynec@genetics.utah.edu

juryneclab.org

Background

Back pain is an increasingly common condition that has become a leading cause of both physical disability1 and referral for rehabilitative care. The associated economic costs are enormous; being the primary cause of work time lost and total associated expenditures exceeding $100 billion annually in the United States alone. Numerous diseases are diagnosed from the primary complaint back pain, the most common is intervertebral disc degermation (IDD), this being the breakdown of the intervertebral discs providing cushioning between the bodies of vertebrae. It is a multifactorial disease with genetic, physiological, and environmental factors contributing to risk. Understanding said risk factors is paramount to developing effective therapeutics as a means of addressing the challenges presented by.

Previous studies have identified many risk factors associated with IDD, though many of these used small cohorts or focused on a limited set of risk factors. Prior studies have identified potentially modifiable associated physiological risk factors, including altered bone mineral density (BMD), hyperthyroidism, hypothyroidism, diabetes, dyslipidemia, hypertension, and tobacco use. Case-control studies have identified family history of IDD as a significant risk factor and population-based genetic studies have identified specific genetic loci associated with IDD.. Despite these studies, our understanding of the risk factors and genetic pathways that lead to increased susceptibility to IDD remains incomplete.

Here we utilized a unique medical genetics resource, the Utah Population Database (UPDB) to 1) identify individuals diagnosed with IDD, 2) determine if IDD clusters in large, multigenerational families, 3) define the magnitude of familial risk of IDD, and 4) identify risk factors associated with IDD and quantify the magnitude of risk.

Methods

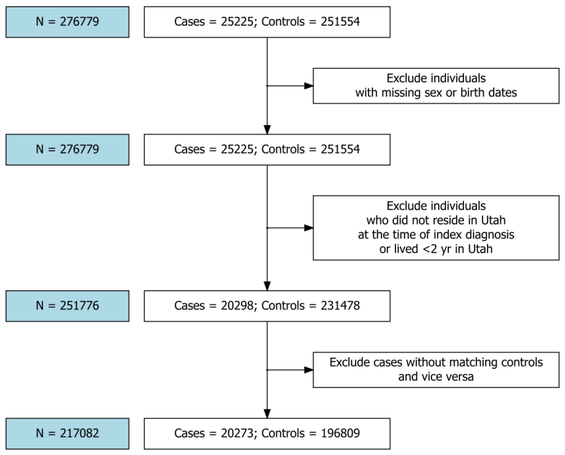
Patients diagnosed with IDD were identified in the Utah Population Database (UPDB) using related ICD-9/10 codes. The UPDB contains >8 million individuals in multigenerational pedigrees dating back to the late 1700's which are linked to >30 million medical records. IDD patients were mapped to pedigrees to identify high-risk families with an increased incidence of IDD. Logistic regression models were used to calculate familial risk of IDD in related individuals. Physiological risk factors were evaluated using logistic regression models.

Selection of cases and controls: We identified individuals with IDD in the UPDB using the following diagnostic codes: ICD-10: M51.34, M51.35, M51.36, and M51.37 or ICD-9: 722.51, 722.52, and 722.6. Inclusion as a case required the presence of at least one diagnostic code. Individuals were excluded if they were diagnosed with any of the following conditions:, congenital disorders affecting the spine, hemophilia, inflammatory conditions, Ehlers-Danlos syndrome, history of generalized ligamentous hyperlaxity, crystalline arthropathy (gout and pseudogout), and a history of spine trauma, infection, or tumors.

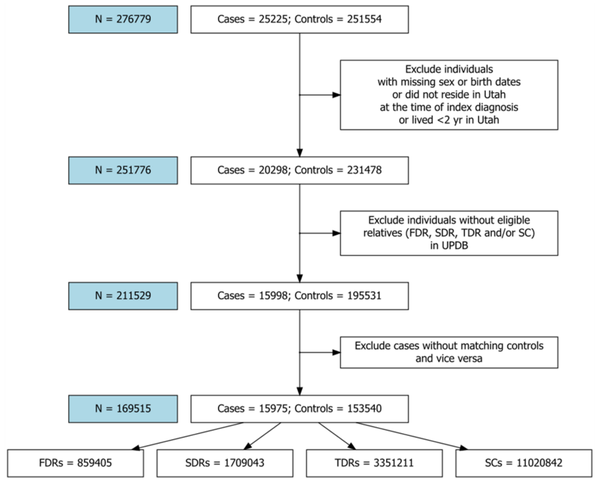
Results

We identified 614 pedigrees with an excess clustering of IDD, as defined by a familial standardized incidence ration (FSIR) ≤ 2.0. The relative risk of developing IDD was significantly elevated in the first- and second-degree relatives of affected individuals. We identified a significant association of physiological risk factors with an IDD diagnosis, including novel associations with epilepsy (OR = 1.64 [95% CI = 1.49 – 1.80]), cirrhosis/liver disease (OR = 1.84 [CI = 1.71 – 1.98]), and systemic lupus erythematosus (OR = 2.03 [95% CI = 1.31 – 3.16]). We discovered a potential new link between Gaucher Disease and IDD.

IDD Study Design



Selection and quality control of IDD cases and controls from the UPDB for risk factor analysis.



Selection and quality control of IDD cases and controls from the UPDB for familial risk analysis.

IDD Risk by Level of Familial Involvement

Table 1: Increased Familial Risk of IDD

	FDR			SDR			TDR		
Characteristic	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI[1]**	**p-value**
Sex - Male	1.18	1.12, 1.24	**<0.001**	1.26	1.20, 1.31	**<0.001**	1.25	1.22, 1.29	**<0.001**
White	2.00	1.74, 2.29	**<0.001**	2.65	2.33, 3.00	**<0.001**	2.39	2.17, 2.62	**<0.001**
Hispanic	1.08	0.98, 1.19	0.142	1.27	1.16, 1.38	**<0.001**	1.20	1.12, 1.28	**<0.001**
Relative of SDD Patient	1.50	1.39, 1.62	**<0.001**	1.08	1.01, 1.16	**0.033**	1.03	0.98, 1.08	0.270

OR = odds ratio, CI = confidence interval, FDR = first-degree relatives, SDR = second-degree relatives, TDR = third-degree relatives.

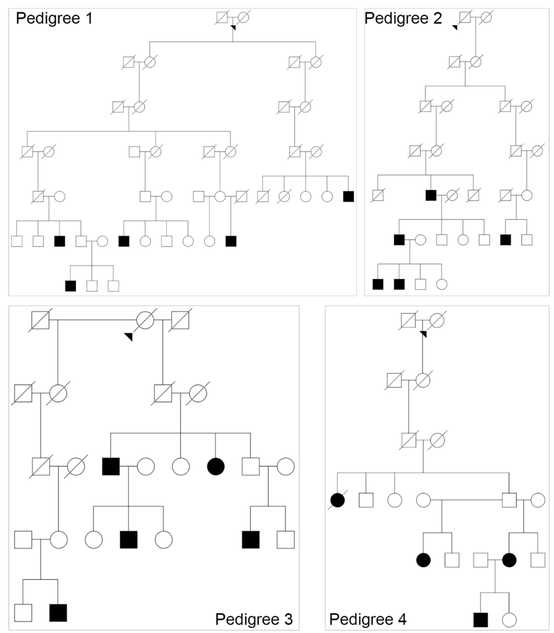
Risk Factor Analysis for IDD

Table 2: Risk Factors Associated with IDD

Characteristic	OR	95% CI	p-value
White	1.20	1.14, 1.26	**<0.001**
Hispanic	1.06	1.01, 1.11	**0.016**
Tobacco use	2.17	2.10, 2.25	**<0.001**
Obesity	1.92	1.83, 2.01	**<0.001**
Hypothyroidism	1.81	1.70, 1.93	**<0.001**
Hyperthyroidism	1.66	1.33, 2.08	**<0.001**
Alcohol Use	1.23	1.14, 1.34	**<0.001**
Diabetes	1.24	1.16, 1.33	**<0.001**
Epilepsy	1.64	1.49, 1.80	**<0.001**
Cirrhosis / liver disease	1.84	1.71, 1.98	**<0.001**
Hypertension	2.00	1.80, 2.22	**<0.001**
Dyslipidemia	2.85	2.12, 3.84	**<0.001**
Systemic lupus erythematosus	2.03	1.31, 3.16	**0.002**
HIV	1.48	1.07, 2.04	**0.017**
Gaucher Disease	9.46	3.24, 27.6	**<0.001**
Have at least one eligible FDR with IDD	1.53	1.41, 1.65	**<0.001**
Have at least one eligible SDR with IDD	1.05	0.97, 1.13	0.254
Have at least one eligible TDR with IDD	1.01	0.95, 1.07	0.830

OR = odds ratio, CI = confidence interval, FDR = first-degree relatives, SDR = second-degree relatives, TDR = third-degree relatives.

High-risk IDD pedigrees



Conclusions

Familial clustering of IDD was observed in a large, statewide population. Our data indicate that genetic, physiological, and environmental factors contribute to the disease process, further highlighting the complex and multifactorial nature of the disease. Sequencing of the highest risk families is underway to further elucidate the pathophysiology and genetics of aggressive forms of IDD.

Acknowledgements

This work was supported by funding from the the Utah Genome Project and the Skaggs Foundation for Research.