

Genetics May be a Factor – What Does the Literature Say?

How to Determine the Percentage of Impairment

Jeffrey D. Coe, MD



Los Gatos, CA

Disclosures

Benvenue Medical, Consulting Agreement, Research Support
NuVasive, Consulting Agreement, Research Support
Providence Medical Technology, Consulting Agreement
Alphatec, Ownership Interest

Disclaimers

The opinions expressed in this presentation are strictly my own.

I am an Orthopaedic Spine Surgeon and not a Medical Geneticist.

Introduction

- Case example
- Science and literature
 - Overview of genetics
 - Genetics of orthopaedic diseases
 - Genetics and disc degeneration
- Definition/identification of degenerative disc "disease"
- Rationale for apportionment, including genetic factors
- My take on *Rice v. City of Jackson*

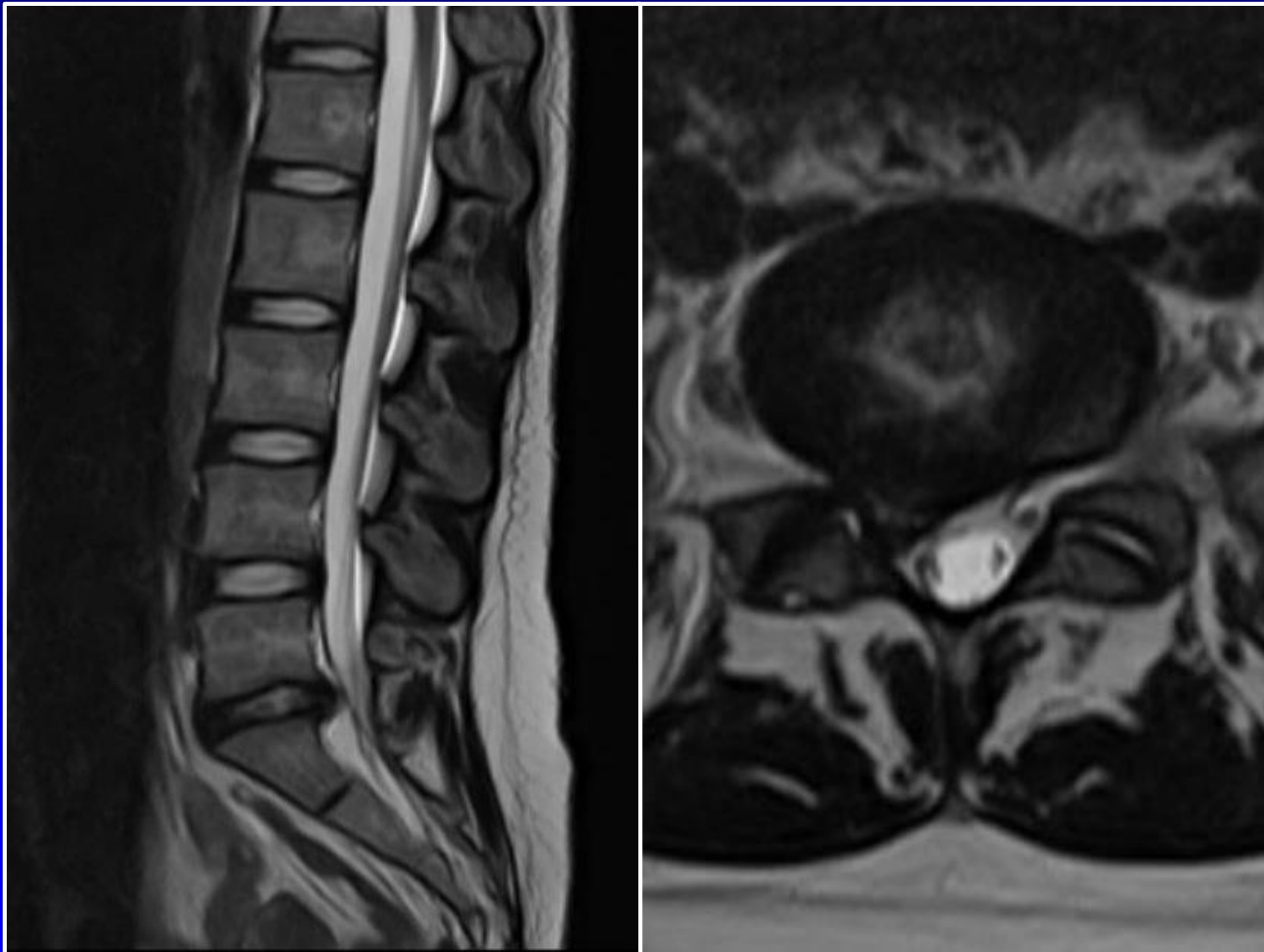
Case Presentation

- 21 female college student was “power lifting” while weight training 15 months before presentation
- She noted the immediate onset of low back pain with the subsequent development of right lower extremity pain
- Her symptoms improved after initial non-surgical treatment but then recurred when she attempted to return to the gym
- Non-surgical treatment: PT, activity modification, medications, heat/ice, core strengthening and a lumbar ESI (temporary relief)
- Pain distribution: right buttock posterior thigh and calf associated with intermittent paresthesias
- Neurologically intact on examination but had a + right SLR at 45 degrees & right sciatic notch tenderness
- + Family history for lumbar spine issues, no surgery

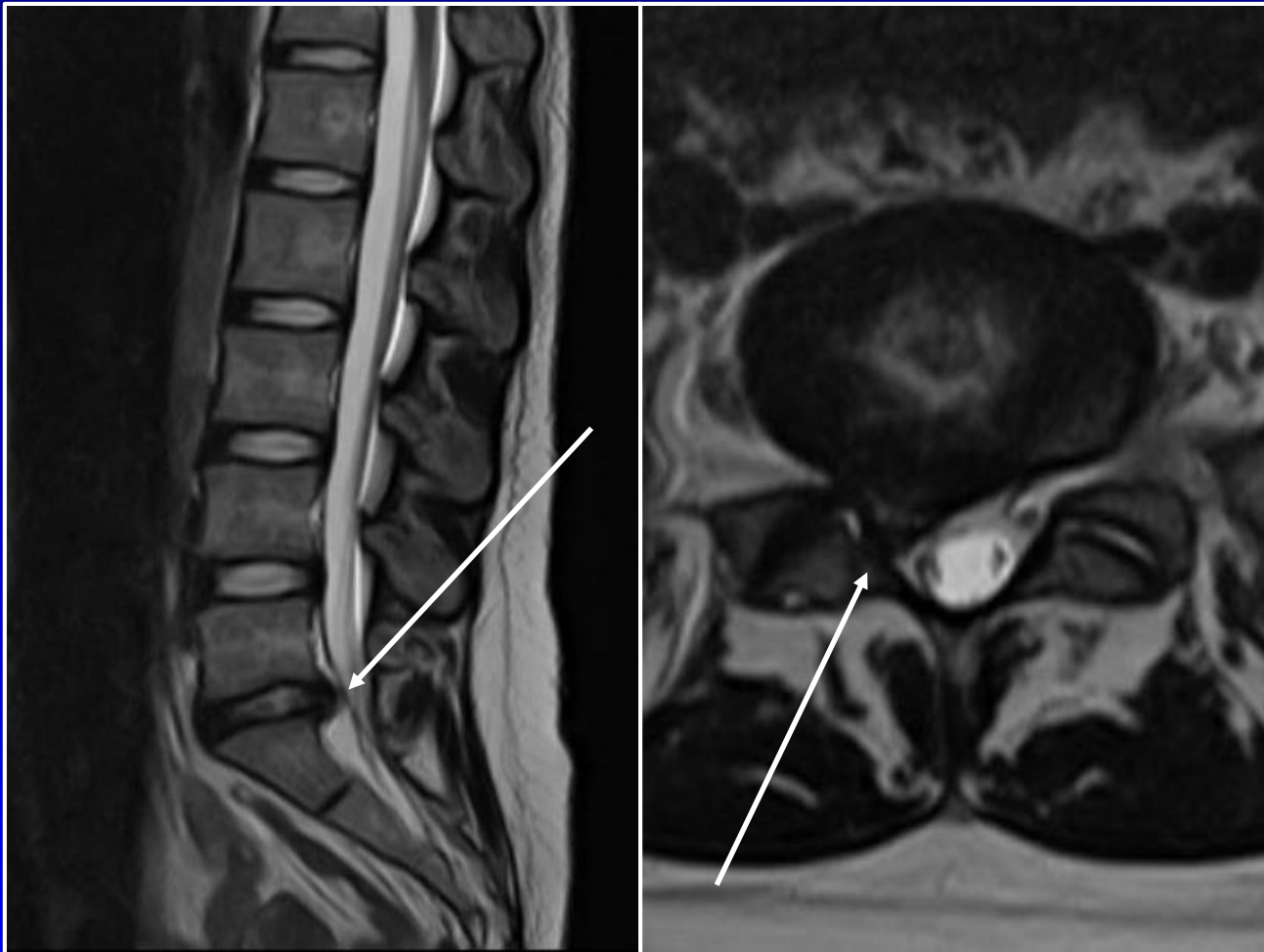
Case Presentation



Case Presentation



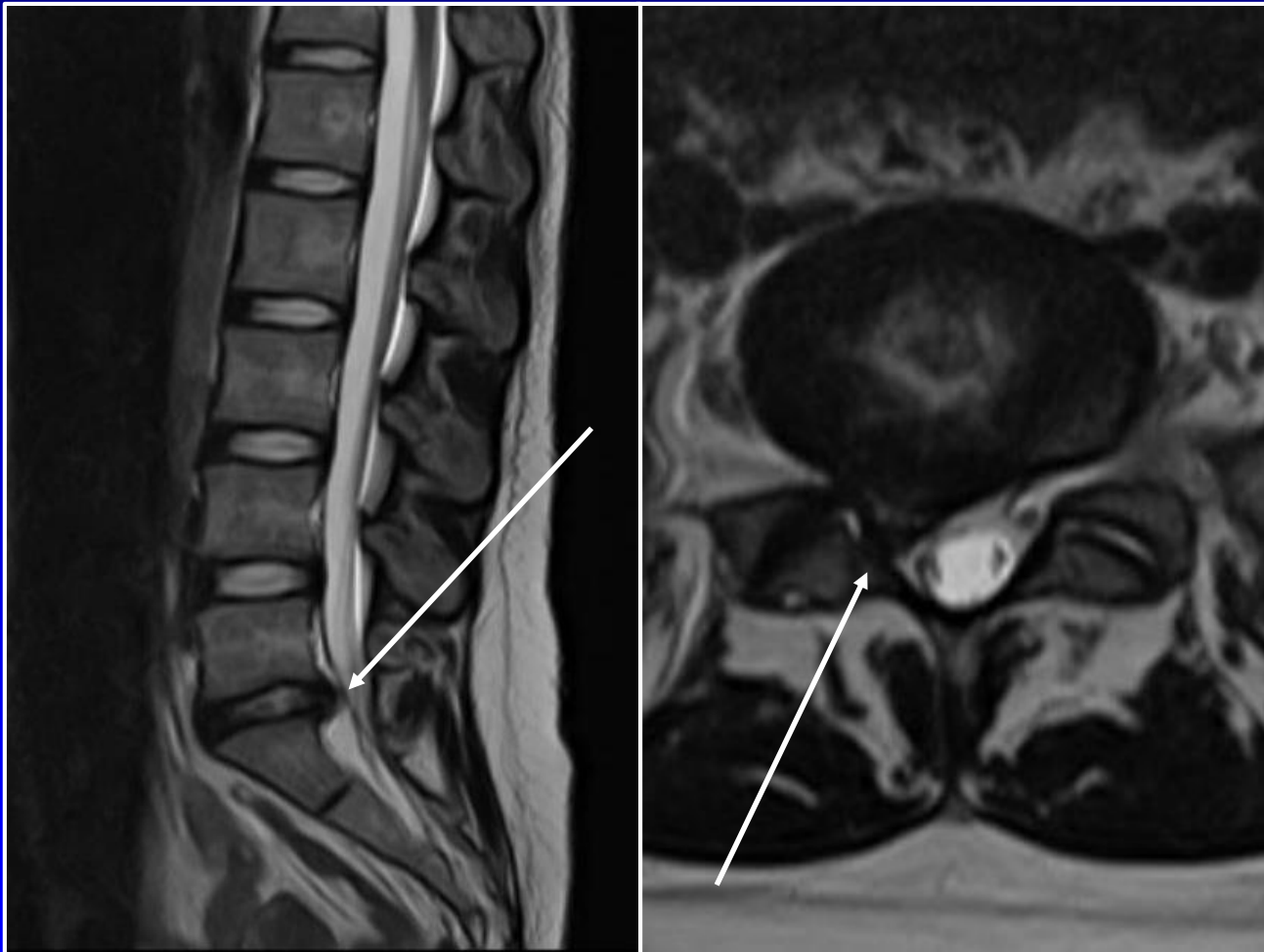
Case Presentation



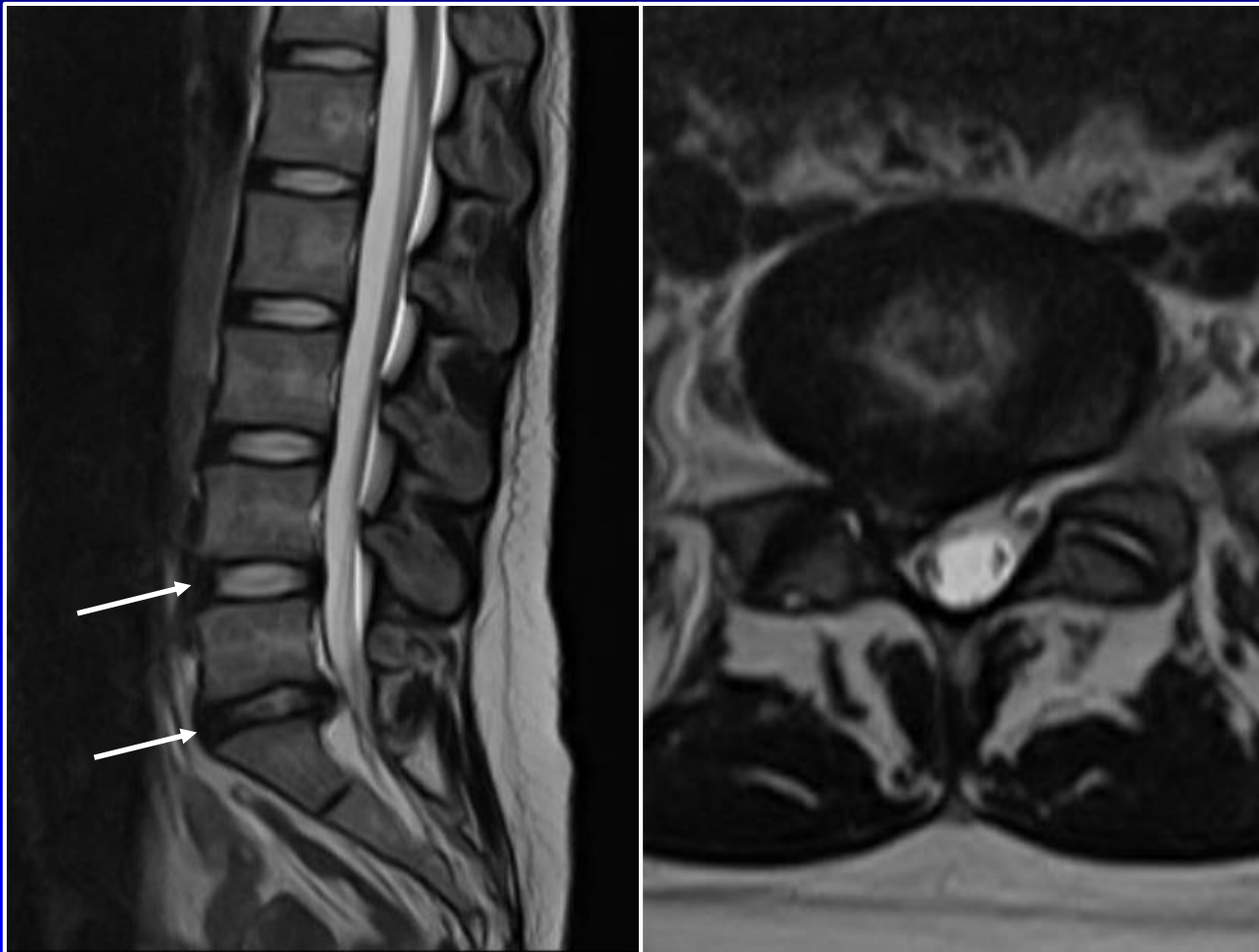
Case Presentation

- The patient underwent an outpatient right-sided L5-S1 microdiscectomy
- She was back in the gym and pain-free at 6 weeks postoperative
- She continues to do well 3 months postoperative

Case Presentation



Case Presentation



Case Presentation

- What if this young woman was not a 21-year-old college student but a 21-year-old kitchen worker who developed symptoms after lifting a 50 pound bag of sugar?
- Although impossible to prove, the disc desiccation/degeneration at L5-S1 was likely present at the time of symptom onset, probably on a genetic basis
- Most would consider the degree of disc desiccation/degeneration as abnormal in a 21-year-old which likely predisposed her to a lumbar disc herniation subsequently triggered with heavy lifting
- If she had persistence of symptoms after surgery and could not return to work, would you apportion any of her impairment to genetic factors?

Genetics Terminology

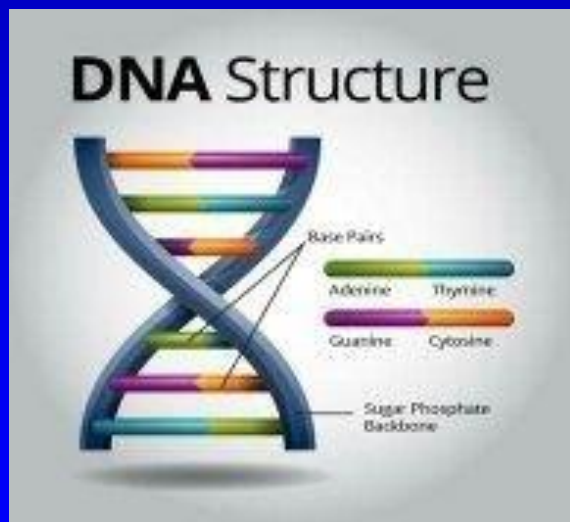
- **Gene**: A set of segments of the nucleic acid molecule that contains information necessary to produce a functional RNA transcript in a controlled manner, it is the basic unit of heredity that is encoded in DNA
- **Locus**: The specific location of a gene on a chromosome which can aid in the determination of mechanism of action
- **Allele**: One of multiple alternative forms of a single gene, at a single locus, homozygous if the same and heterozygous if different
- **Genome**: The entire complement of genetic material in the chromosome set of an organism
- **Genotype**: The complement of alleles present in the particular individuals genome which gives rise to the individuals phenotype

Genetics Terminology

- Single nucleotide polymorphism (SNP): A single base change (e.g., A → T) that may influence the action of a gene (some SNPs have been shown to account for some of the variation and complex disease processes)
- Haplotype: A group of SNPs inherited together that can have a greater predictive value (and be more clinically relevant) than a single SNP
- Phenotype: The observable physical or behavioral traits of an organism largely determined by the organisms genotype.
- Epigenetic: Relating to or arising from nongenetic influences on gene expression
- Heritability: That portion of outcome explained by genes alone

Genetics Terminology

- Genetics focus primarily on the DNA code and the influence of single genes
- Genomics is the search for understanding of how different genes and alleles interact and affect expression and phenotypes



Genetics in Medicine

- **Until relatively recently, the focus of genetics research has been on mendelian or monogenic traits & diseases**
 - Traits: Eye color, ear lobe shape
 - Diseases: Cystic fibrosis, sickle cell anemia, osteogenesis imperfecta
- **Recent research has focused on understanding disease processes with multiple genetic influences**
 - Patient is at risk can be identified
 - Treatments can be tailored
- **Examples of multifactorial disease processes with genetic influences include:**
 - Cancer (i.e. breast and colon)
 - Diabetes
 - Asthma
 - Cardiovascular disease

Genetics of Orthopaedic Diseases

- **Osteoporosis:**
 - Bone mineral density estimated to have a heritability of greater than 70%
- **Osteoarthritis (Spector et al, *Osteoarthritis Cartilage*, 2004):**
 - Hip: 60% heritability
 - Knee: 65% heritability
 - Hand: 39% heritability
- **Adolescent Idiopathic Scoliosis (AIS):**
 - A single polymorphism (CHD7) is linked to AIS (not confirmed in all studies)
 - Applied orthogenomics (ScoliScore): Analysis of 53 genetic markers combined with analysis of presenting Cobb angle can predict risk of progression in subset of AIS patients
- **Pain and Analgesia**
 - Research has shown that absence of the gene CYP2D6 (encodes cytochrome P450) can lead to opiate ineffectiveness

Genetics in Disc Degeneration

Copyright 1995 by *The Journal of Bone and Joint Surgery, Incorporated*

Similarities in Degenerative Findings on Magnetic Resonance Images of the Lumbar Spines of Identical Twins*

BY MICHELE CRITES BAITTIÉ, PH.D.†, DAVID R. HAYNOR, M.D., PH.D.‡, LLOYD D. FISHER, PH.D.‡, KEVIN GILL, M.D.§,
LAURA E. GIBBONS, M.S.‡, SEATTLE, WASHINGTON, AND TAPIO VIDEMAN, M.D., DR.MED.SCI.¶, JYVÄSKYLÄ, FINLAND

- Study of 20 male identical twin pairs evaluated with MRI
 - One twin a smoker, the other a non-smoker in each pair
 - Incidence of LBP was the same
 - 36 to 60 years of age
- A subset of the Finish Twin Cohort that included nearly all pairs of twins born in Finland before 1958 that were still living in 1967
- MRIs evaluated by two observers (two rounds) that were blinded as to twin status

Genetics in Disc Degeneration

Copyright 1995 by *The Journal of Bone and Joint Surgery, Incorporated*

Similarities in Degenerative Findings on Magnetic Resonance Images of the Lumbar Spines of Identical Twins*

BY MICHELE CRITES BAITTIÉ, PH.D.†, DAVID R. HAYNOR, M.D., PH.D.‡, LLOYD D. FISHER, PH.D.‡, KEVIN GILL, M.D.§,
LAURA E. GIBBONS, M.S.‡, SEATTLE, WASHINGTON, AND TAPIO VIDEMAN, M.D., DR.MED.SCI.¶, JYVÄSKYLÄ, FINLAND

- Multiple regression analysis performed
- Similarities between co-twins MRI findings were greater than what could be explained by chance alone
- 26 to 72 percent of MRI variability explained by co-twin status
- Smoking status explained 0 to 15 percent of MRI variability

Genetics in Disc Degeneration



Genetics in Disc Degeneration

Copyright 1995 by *The Journal of Bone and Joint Surgery, Incorporated*

Similarities in Degenerative Findings on Magnetic Resonance Images of the Lumbar Spines of Identical Twins*

BY MICHELE CRITES BAITIÉ, PH.D.†, DAVID R. HAYNOR, M.D., PH.D.‡, LLOYD D. FISHER, PH.D.‡, KEVIN GILL, M.D.§,
LAURA E. GIBBONS, M.S.‡, SEATTLE, WASHINGTON, AND TAPIO VIDEMAN, M.D., DR.MED.SCI.¶, JYVÄSKYLÄ, FINLAND

“It is probably rare for degenerative changes and other structural variations in the spine to have a purely genetic or environmental etiology; instead, they are the effect of environmental forces acting on structures whose strength and morphology have been partially genetically predetermined.”

Genetics in Disc Degeneration

Copyright 1995 by *The Journal of Bone and Joint Surgery, Incorporated*

Similarities in Degenerative Findings on Magnetic Resonance Images of the Lumbar Spines of Identical Twins*

BY MICHELE CRITES BAITTIÉ, PH.D.†, DAVID R. HAYNOR, M.D., PH.D.‡, LLOYD D. FISHER, PH.D.‡, KEVIN GILL, M.D.§,
LAURA E. GIBBONS, M.S.‡, SEATTLE, WASHINGTON, AND TAPIO VIDEMAN, M.D., DR.MED.SCI.¶, JYVÄSKYLÄ, FINLAND

“It is possible, however, that biological processes underlying the rate of degeneration of connective-tissue constituents also may be genetically predetermined to some extent.”

Genetics in Disc Degeneration

The Spine Journal 9 (2009) 47-59

Review Articles

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

Michele C. Battié, PhD^{a,b,*}, Tapio Videman, MD, PhD^{a,b}, Jaakko Kaprio, MD, PhD^b,
Laura E. Gibbons, PhD^c, Kevin Gill, MD^d, Hannu Manninen, MD, PhD^e,
Janna Saarela, MD, PhD^f, Leena Peltonen, MD, PhD^{g,h,i}

- Expansion of the original Finish twin spine study
- Found a substantial influence of heredity on lumbar disc degeneration
- Identified first gene forms associated with disc degeneration
- Noted surprisingly little effect on physical loading conditions (including exposure to whole-body vibration) on disc degeneration

Genetics in Disc Degeneration

The Spine Journal 6 (2006) 624–635

2006 Outstanding Paper Award: Medical & Interventional Science
Are first-time episodes of serious LBP associated
with new MRI findings?

Eugene Carragee, MD^{a,*}, Todd Alamin, MD^a, Ivan Cheng, MD^a, Thomas Franklin, MD^a,
Erica van den Haak, BS^a, Eric Hurwitz, DC, PhD^b

- 200 subjects evaluated with MRI, radiographs and clinical evaluation
- No prior lifetime history of significant LBP but at high risk for future LBP episodes
- Followed over 5 year period
- 51 subjects (25%) developed subsequent significant LBP episodes
 - 3% of these had radicular pain primarily
 - 16% of these had new MRI findings (possibly age related)
 - “Injury” or not → no difference in incidence of new findings

Genetics in Disc Degeneration

The Spine Journal 6 (2006) 624–635

2006 Outstanding Paper Award: Medical & Interventional Science
Are first-time episodes of serious LBP associated
with new MRI findings?

Eugene Carragee, MD^{a,*}, Todd Alamin, MD^a, Ivan Cheng, MD^a, Thomas Franklin, MD^a,
Erica van den Haak, BS^a, Eric Hurwitz, DC, PhD^b

- **Questions raised**

- Was there any secondary gain to participate in the study?
- How certain were the authors (and even the subjects) that they did not have prior LBP episodes?
- Was this sample representative of “at risk” low back pain patients?
- Is MRI 100% sensitive in detecting symptomatic structural changes in the spine?
 - Probably not!

Disc Degeneration vs “Disease”

- The epidemiologic genetic studies evaluate disc degeneration regardless of symptoms
- No consensus definition for "degenerative disc disease" (DDD)
 - Discography no longer in widespread usage
 - DDD is generally a "clinical" diagnosis in patients with symptomatic low back pain that also have imaging findings of disc degeneration
 - Newer tests: SPECT/CT
- Several multicenter RCTs of lumbar total disc replacement have demonstrated significant improvement in low back pain in carefully selected DDD patients in both the control (fusion) groups and disc replacement groups at 5 or more years
- Active-L TDR study (5 year data)
 - 64.7% were using opiates at time of surgery
 - Only 1.5% still on opiates at 5 years (98.5% opiate free!)
 - $P < 0.0001$

Apportionment Issues

- **Monogenic disease**
 - Relatively straightforward (e.g., fractures in an Osteogenesis Imperfecta patient)
- **Polygenic disease with environmental influences**
 - Degeneration may be a predisposition to symptoms possibly associated with injury (despite the Carragee paper)
 - How can you fairly apportion to a genetic predisposition to a symptomatic condition?
 - Does every injured worker with disabling LBP get some apportionment to genetics because genetics may explain up to 72% disc degeneration?

How I Apportion

- My best estimate of that portion of the injured worker's factors of impairment (including causation factors) that is attributable to the work exposure
- My best estimate of that portion of the injured worker's factors of impairment (including causation factors) that is attributable to other factors
 - Pre-existing disease
 - Prior injury
 - Genetic factors assessed individually
 - Subsequent injury
- I do not use epidemiological data to indicate that any given individual has genetically-based spinal disease

My Take On *Rice v. City of Jackson*

- **Caveat: I have seen the WCAB decision & the Appeals Board decision and part (but not all) of the original QME report**
- **29 year old police officer with history of:**
 - 1998 vehicle roll-over
 - 2004 shoulder surgery
 - Family history of low back “problems” and THR (father)
 - Prior ACL and meniscus injury
- **CT injury claimed**
- **Logical flaws**
 - The QME used epidemiological studies combined with family history to infer that the applicant had an apportionable genetic predisposition (bad collagen) to disc degeneration
 - The QME implicated hip degeneration as correlating genetically with lumbar degenerative disc disease (not scientifically established)

Summary

- Case example
- Science and literature
 - Overview of genetics
 - Genetics of orthopedic diseases
 - Genetics and disc degeneration
- Definition/identification of degenerative disc "disease"
- Rationale for apportionment, including genetic factors
- My take on *Rice v. City of Jackson*

A high-angle, wide shot of the ancient Inca city of Machu Picchu, perched on a steep mountain ridge. The ruins, including terraced stone walls, a central green field, and various stone structures, are bathed in the warm, golden light of late afternoon. In the background, a massive, jagged mountain peak rises sharply against a clear sky, with other mountain ranges visible in the distance. The overall scene is one of majestic natural beauty and historical significance.

THANKS!