

Identification of a Novel Common Genetic Risk Factor for Lumbar Disk Disease

Original Contribution

JAMA, Vol. 285 No. 14:1843-1849, April 11, 2001

Petteri Paasilta; Jaana Lohiniva; Harald H. H. Göring; Merja Perälä; S. Susanna Ränkä; Jaro Karppinen; Markku Hakala; Tiina Palm; Heikki Kröger; Ilkka Kaitila; Heikki Vanharanta; Jürg Ott; Leena Ala-Kokko

FROM ABSTRACT

Context

Lumbar disk disease (LDD) is one of the most common musculoskeletal diseases, with a prevalence of about 5%. A tryptophan (Trp) allele (Trp2) was recently discovered in the COL9A2 gene that is associated with dominantly inherited LDD but is only present in about 4% of Finnish patients with LDD.

Objective

To determine if other collagen IX gene sequence variations play a role in the pathogenesis of LDD.

Design and Setting

Case-control study conducted from February 1997 to May 1998 at university hospitals in Finland.

Participants

A total of 171 individuals with LDD (evaluated clinically and by magnetic resonance imaging or computed tomography) and 321 controls without LDD (186 healthy individuals, 83 patients with primary osteoarthritis, 31 with rheumatoid arthritis, and 21 with chondrodysplasias).

Main Outcome Measures

Frequencies of sequence variations covering the entire coding sequences and exon boundaries of the collagen IX genes, COL9A1, COL9A2, and COL9A3, which code for the 1, 2, and 3 chains of the protein, detected by conformation-sensitive gel electrophoresis and confirmed by sequencing, compared between individuals with and without LDD.

Results

Mutation analysis of all 3 collagen IX genes resulted in identification of a frequency of the Trp3 allele at 12.2% in LDD cases.

Presence of at least 1 Trp3 allele increases risk of LDD about 3-fold.

Conclusion

This study led to the identification of a novel common genetic risk factor for LDD, confirming that genetic risk factors likely play a significant role in LDD.

THESE AUTHORS ALSO NOTE:

Lumbar disk disease (LDD) is one of the most common musculoskeletal disorders in the world.

A prevalence study of persons with LDD involving a sample of 8000 persons found 5.1% of men and 3.7% of women met the diagnosis of lumbar disk syndrome, half of who were deemed to be in need of medical care.

The prevalence of sciatic pain in adult populations is between 1% and 40%.

"Clinically significant sciatica occurs in 4% to 6% of the US population."

"Disk disease is a significant problem in the western world."

"Lumbar disk disease often results in physical impairment requiring surgery, and it contributes significantly to health care costs and work disability."

"A number of environmental and anthropometric risk factors such as driving, torsional stress, smoking, and height have been implicated in the pathogenesis of LDD."

There are a number of studies that suggest disk disease, including disk herniation, sciatica, and disk degeneration "may be explained to a large degree by genetic factors."

The recent finding that the Trp2 allele is associated with dominantly inherited LDD also supports this hypothesis.

"The Trp2 allele was found in 6 out of 157 (4%) Finnish patients with LDD but in none of a series of 174 individuals without the disease."

The Trp2 allele, found on the COL9A2 gene, is associated with dominantly inherited LDD, because it was not found in the controls.

The Trp2 allele is evaluated in all families (n=23) that had LDD.

Collagen IX is a protein consisting of 3 genetically distinct chains, 1(IX), 2(IX), and 3(IX), encoded by the COL9A1, COL9A2, and COL9A3 genes.

“Collagen IX is an attractive candidate for LDD because it serves as a minor component in both main structures of the intervertebral disk, the annulus fibrosus and the nucleus pulposus, in addition to being present in cartilage and the vitreous body of the eye.”

The Trp2 allele of the 2(IX) chain is associated with dominantly inherited LDD.

Mice without the gene for the 1(IX) chain develop intervertebral disk herniation and degeneration, in addition to degenerative joint disease, which confirms a role for collagen IX in LDD.

METHODS

The case subjects consisted of 171 unrelated Finnish patients, aged 19 to 78 years, with discogenic sciatica. They all had a history of unilateral discogenic pain radiating from the back to below the knee (dermatomes L4, L5, and S1) with a duration of at least 1 month.

The clinical examination of the patients included the straight-leg-raising test, assessment of lumbar flexion, tendon reflexes, and evaluation of motor and sensory deficits.

Leg pain was assessed using 100-mm visual analog scales (VASs), disability was evaluated using the Oswestry Low Back Disability Questionnaire, and quality of life was measured using the Nottingham Health Profile (NHP).

The clinical diagnosis was supplemented with electroneuromyography and periradicular infiltration of pain provocation contrast medium, and then with corticosteroids for pain reduction, of the suspected nerve root.

152 of the patients were evaluated by magnetic resonance imaging (MRI) and the remaining 19 by computed tomography (CT).

The control sample consisted of 321 unrelated Finnish individuals without LDD. None of the controls had a history of discogenic pain or had been operated on for a herniated disk.

Blood samples were collected from all the subjects to obtain genomic DNA.

MRI and CT

Findings of MRI or CT were considered positive if they indicated disk extrusion, at least 2-level disk herniation, or at least 4-level disk bulging, or endplate degeneration at 1 or more levels in patients younger than 30 years of age, at 2

or more levels in patients aged 30 to 50 years, or at 4 or more levels in patients older than 50 years.

RESULTS

All patients had severe leg pain assessed by VAS, severe back-related disability, and decreased quality of life.

The MRI findings for the patients with LDD consisted mainly of disk herniations at interspaces L4-L5 and L5-S1.

Allele counts were obtained for LDD cases and controls.

The frequency of the Trp3 allele is significantly higher in the LDD patients than in the controls without LDD.

"This finding is in agreement with our previously published observation that another Trp allele (Trp2), located in the COL9A2 gene, is a strong risk factor for the disease."

The presence of Trp3 does not cause disease outright, but merely increases the risk of disease.

"For an individual with at least 1 Trp3 allele, the risk of disease is thus increased nearly 3-fold ($11.6\%/4.3\% = 2.7$) relative to an individual without Trp3."

COMMENT

"The difference in the frequency of the Trp3 allele between the 164 patients with LDD (12.2%) and the 321 controls (4.7%) was statistically significant."

"The results also indicated that the Trp3 allele does not itself cause LDD but increases the risk of LDD, and thus it represents the first common genetic risk factor for musculoskeletal diseases."

Collagen IX is a structural component of the annulus fibrosus and nucleus pulposus and of the endplate hyaline cartilage structures of the vertebral bodies adjacent to the intervertebral disks.

"The defects in collagen IX may thus play a role in intervertebral disk pathology."

"The mechanism by which Trp alleles may cause LDD or predispose individuals to it is not clear, but they may play a role in intervertebral disk pathology, since Trp is the most hydrophobic amino acid, and is not normally found in collagen IX."

FROM DAN MURPHY

This article makes common sense to most of us.

Remember that a gene is a section on a chromosome that encodes for a particular protein. This article is looking specifically at the protein collagen IX, which is a structural component of the annulus fibrosus, nucleus pulposus, and the hyaline cartilage endplates of the vertebral bodies.

This article notes that there are at least 2 genes identified to date that reduce the water binding ability of collagen IX protein, which in turn increases the probability of LDD and sciatica.

In my work with low impact motor vehicle collisions, the concept that there is a gene that causes a genetic risk factor for musculoskeletal diseases is very important.

In my work I emphasize the host biological uniqueness component to the motor vehicle collision.

I make an analogy with Pasteur's Germ Theory and Palmer's Chiropractic Theory, as follows:

LOUIS PASTEUR'S GERM THEORY (1822-1895)

Ill health is caused by exposure to germs, from the outside – in.

Host health is not important.

DD PALMER'S CHIROPRACTIC THEORY

Ill health is greatly influenced by an internally reduced health of the host, from the inside – out.

Host health is very important.

Palmer's theory is shared by numerous others, including Claude Bernard (1813–1878), a contemporary of Pasteur from Paris; and Harvard's Walter Cannon (1871-1945), who coined the term "homeostasis."

ACCIDENT RECONSTRUCTIONISTS IN LOW IMPACT COLLISION

Injury from motor vehicle collisions is caused by exposure to a certain magnitude of force and resulting acceleration; from the outside – in.

Host variables are not important:

Awareness, rotation, height, age, head/neck ratios, pre-existence of degenerative spinal disease, genetically encoded quantum of mu opiate preceptors (they help suppress pain perception), genetically encoded quality of type IX collagen, etc.

MURPHY PERSPECTIVE

Host variables are very important.

When assessing injury from motor vehicle collisions, factors other than magnitude of force and resulting acceleration must be considered, including the same host variables:

Awareness, rotation, height, age, head/neck ratios, pre-existence of degenerative spinal disease, genetically encoded quantum of mu opiate preceptors (they help suppress pain perception), genetically encoded quality of type IX collagen, etc.

ANOTHER RELATED STUDY

Matrix Metalloproteinase-1 And Skin Ageing

The Lancet, Vol. 357, March 24, 2001, pp 935-6.

Christine Lahmann, Jorg Bergemann, Graham Harrison, Antony Young

THESE AUTHORS NOTE:

Smokers look older than non-smokers of the same age.

Matrix Metalloproteinase-1 (MMP-1) is a protein enzyme that degrades collagen.

The authors introduce their study which showed that there is significantly more MMP-1 in the skin of smokers than non-smokers.

Collagen is the major extracellular matrix protein of the skin, accounting for at least 70% of its weight.

They conclude that smoking probably activates the gene that produces the MMP-1 protein.

FROM DAN MURPHY

Many studies continue to show that smokers have more disc degenerative disease as compared to non-smokers.

A similar mechanism of smoking causing an alteration of genetic expression resulting in accelerated collagen breakdown is a probable explanation.

I believe that this is another host variable, as discussed in the previous article.