GENETIC ASSOCIATION STUDIES IN LUMBAR DISC DEGENERATION
A SYSTEMATIC REVIEW

SUPPORTING INFORMATION
APPENDIX S1

Pasi J Eskola, Susanna Lemmelä, Per Kjaer, Svetlana Solovieva, Minna Männikkö, Niels Tommerup, Allan Lind-Thomsen, Kirsti Husgafvel-Pursiainen, Kenneth MC Cheung, Danny Chan, Dino Samartzis and Jaro Karppinen.

Supporting Method Information

Study inclusion criteria

Studies that are considered eligible to be included in the review have the following features:

- Relevant outcome or disease
  - Intervertebral disc changes
  - Vertebral endplate changes
  - Spondylarthrosis
- Reliable definition of outcome (MRI)
- Number of study subjects 50 or higher
- Human study
- Specific genetic variant is described

Studies considered not eligible and are therefore excluded from the review have one or more of the following features:

- Outcome or disease is not relevant
- Definition of outcome is not reliable (i.e. is other than MRI)
- Number of study subjects is under 50
- No specific genetic variant is described
- Animal study

Study quality assessment essentials

Type of bias	Criteria	Classification
Selection bias	*Major* 1. Selection of study population (inclusion and exclusion criteria well specified) 2. Representativeness (response rate, difference between participants and non-participants, and control for variables in case difference found between participants and non-participants) 3. Population stratification (confounding by ethnic origin) *Minor* 1. Awareness of study hypothesis 2. Possibility of change in the status of a risk factor as a result of low back pain	*No or minor*: Defined target population represents the general population or subgroup of the general population (e.g. women or men, certain age group, geographical area, certain occupational group) and response rate is above 60%. Ethnic origin is known. Control population is well defined and is similar to affected individuals while unaffected. *Moderate*: Defined target population represents a narrow subgroup of the general population and response rate is 80 -100%. Selection process or proper characteristics of control population are not reported. *Severe*: Defined target population represents a narrow subgroup of the general population and response rate is 60 - 80%. Control population differs from affected individuals or no information of controls is available. *Definite*: Ethnic origin of the population is not known. Study population consists of "self-selected" volunteers if suspicion of payment to non-patients. Control population is of different ethnic origin, nationality or from great geographical distance. Controls have other pathological phenotypes.
Performance bias	*Major* 1. Validity genetic analyses method 2. Quality control (genotyping error) *Minor* 1. Blinding of genetic analyses method towards the outcome	*No*: Validated method, quality control, blinding of assessors of exposure towards the outcome. *Minor:* Blinding not reported. *Moderate*: Validated method, no quality control. *Definite*: Non-validated genetic analyses method, no quality control, genotyping was not blinded towards the outcome.

Type of bias	**Criteria**	**Classification**
Detection bias	*Major* 1. Clear definition of outcome 2. Standardized validated method of assessing outcome *Minor* 1. Blinding of assessors of outcome towards genetic factors	*No or minor*: Clear definition of outcome and standardized method of assessing outcome. *Moderate*: Clear definition of outcome and not standardized method of assessing outcome. *Definite*: Unclear definition of outcome or non-systematic assessment of outcome.
Attrition bias	*Major* 1. Magnitude of missing data (including unsuccessful genotyping) 2. Completeness of follow-up (if applicable) Where the magnitude of missing data is not reported, studies are to be considered having *Possible* attrition bias.	*No:* Less than 20% of missing data. Participation rate 50-100% for follow-up time < 5 years, or comparison done for lost to follow-up regarding variables of interest. *Possible:* Missing data between 20% and 40%. Participation rate 30-50% for follow-up time < 5 years, and no comparison done for lost to follow-up regarding variables of interest and *Definite:* More than 40% of missing data. Participation rate less than 30% for follow-up time < 5 years or
Statistical analyses	1. Population stratification has been addressed 2. Hardly-Weinberg equilibrium was considered 3. Methods used for inferring genotypes and haplotypes are specified and valid 4. Multiple comparison has been addressed / risk of false positive findings was controlled	Each item should be responded as no/yes/unclear

Data extraction form (including formalized summary scoring)

Data Extraction Form		DD and Genes – A Systematic Review
STUDY DETAILS		
Title (ID)		Scoring (max. 31 points)
First author, year of publication		
Year(s) of study		1 point ☐ if reported, not the year of publication
Country of study		
Study design		
Sponsorship of study		
POPULATION		
Subjects	Clinical ☐ General ☐ Working ☐ Teenage ☐	1 point ☐ if reported
Symptoms (if reported)	LBP ☐ Sciatica ☐ Asymptomatic ☐ Other;what: Not reported ☐	
N of individuals in total	N=	1 point ☐ if reported and more than 100 individuals 2 points ☐ if reported and more than 300 individuals 3 points ☐ if reported and more than 600 individuals 4 points ☐ if reported and more than 900 individuals
N of cases	N_{case}=	
N of controls	N_{cont}=	
Gender in total population	F (%)= M (%)=	1 point ☐ if reported in all subgroups / properly, or if age and sex matched controls
Gender in cases (fill in the reported gender)	F_{case} (%)= M_{case} (%)=	
Gender in controls (fill in the reported gender)	F_{cont} (%)= M_{cont} (%)=	
Age (fill in what is reported)	Age range = Mean age and SD=	
Age in cases	Age $range_{case}$= Mean age and SD_{case}=	1 point ☐ if reported in all subgroups (population study=only one subgroup)
Age in controls	Age $range_{cont}$= Mean age and SD_{cont}=	
Ethnicity	Caucasian☐ Asian☐ American ☐ African☐ Other, specify:	1 point ☐ if reported

PHENOTYPES

MRI

Field strength (Tesla)	Field strength Not reported ☐	1 point ☐ if reported
T1/T2 /PD	Not reported ☐	
Slice orientation	Sagittal☐ Axial☐ Coronal☐ Multi-slice ☐ Other☐ Not reported☐	
Lumbar disk levels imaged	L1/L2☐ L2/L3☐ L3/L4☐ L4/L5☐ L5/S1☐ Not specified ☐	1 point ☐ if all lumbar levels
Other disk levels		1 point ☐ if other levels analysed separately
Slice thickness (mm.)	Not reported☐	
Other specific technical data on MRI	Not reported☐	
Number of MRI readers	N=	
Qualification of reader(s)	Specialist=☐ Specialist (radiology)=☐ Specialist(surgery)=☐ Researcher= ☐ Student=☐ Not reported☐ Other:	
Reader blinded to genetic data?	Yes ☐ No ☐ Not reported☐	1 point ☐ if "Yes"
Reproductibility tested?	Yes ☐ No ☐ Not reported☐	1 point ☐ if "Yes"
Intra/inter-tester	Intra☐ Inter☐ Not reported☐	
Results of reproductilibity test (methods, results: Kappa, ICC or percentage; i.e. results written open)		
Degeneration defined by (mark all that fit)	Disk space narrowing / Disk height reduction☐ Signal intensity loss☐ Presence of fissures (AT)☐ HIZ lesions☐ Bulging☐ Protrusion☐ Ligamentous signal changes☐ Endplate signal changes☐ Osteophytosis☐ Vertebral malalignment☐ Foraminal stenosis☐ Central canal stenosis☐ Nerve root displacement☐ Swelling☐ Dura impression / spinal cord affected☐	
Standardized definition of degeneration	Reference	2 points ☐ if reported and definition is well established before

GENOTYPES AND OTHER EXPOSURES			
	Genotyping methods		
	Blinding of researchers in genotyping (to degeneration data)	No☐ Yes☐ Not reported☐	
	Genes		
	Polymorphisms		(Report number if multiple variations)
	rs numbers (if reported)		(Report number if multiple variations)
	Other exposures (e.g. smoking, BMI, height, physical workload)		
QUALITY ASSESMENT			
	Selection bias	No or Minor☐ Moderate ☐ Severe☐ Definite☐	(3-0 points) 3 if No or Minor, 2 Moderate, 1 Severe, 0 Definite
	Performance bias	No☐Minor☐Moderate☐ Definite ☐	(2-0 points) 3 = ”No”, 2=”Minor” 1= ”Moderate”, 0 = ”Definite”
	Detection bias	No or Minor☐ Moderate ☐ Definite☐	(2-0 points) 2 = ”No or Minor”, 1 = ”Moderate”, 0 = ”Definite”
	Attrition bias	No☐Possible☐ Definite☐	(2-0 points) 2 = ”No”, 1 = ”Possible” , 0 = ”Definite”
	Statistical analyses		(1 points each if ”Adequate”, max. 4 points)
	Population stratification	Adequate☐ Poor☐ Unclear☐	
	HWE considered	Adequate☐ Poor☐ Unclear☐	
	Methods used for inferring genotypes and haplotypes specified and valid	Adequate☐ Poor☐ Unclear☐	
	Multiple comparison has been addressed / risk of false positive findings was controlled	Adequate☐ Poor☐ Unclear☐	
	Other exposure issue considered in analyses	No☐ Yes☐ Not reported☐	1 point ☐ if ”Yes”
FINDINGS		Genotype or haplotype or combined genotypes	
	Phenotype	Genotype (data for cases and controls, as presented in the study)	
		Measures of association (e.g. ORs and 95% CI)	
	Phenotype	Genotype (data for cases and controls, as presented in the study)	
		Measures of association (e.g. ORs and 95% CI)	

	Phenotype	Genotype (data for cases and controls, as presented in the study) Measures of association (e.g. ORs and 95% CI)
	Phenotype	Genotype (data for cases and controls, as presented in the study) Measures of association (e.g. ORs and 95% CI)
	Phenotype	Genotype (data for cases and controls, as presented in the study)
Interactions		
	Interacting phenotypes and	Genotype (data for cases and controls, as presented in the study) Measures of association (e.g. ORs and 95% CI)
SOURCE OF DATA		Publication☐ Online database☐ From correspondence with authors ☐

Categories for the credibility of cumulative epidemiological evidence

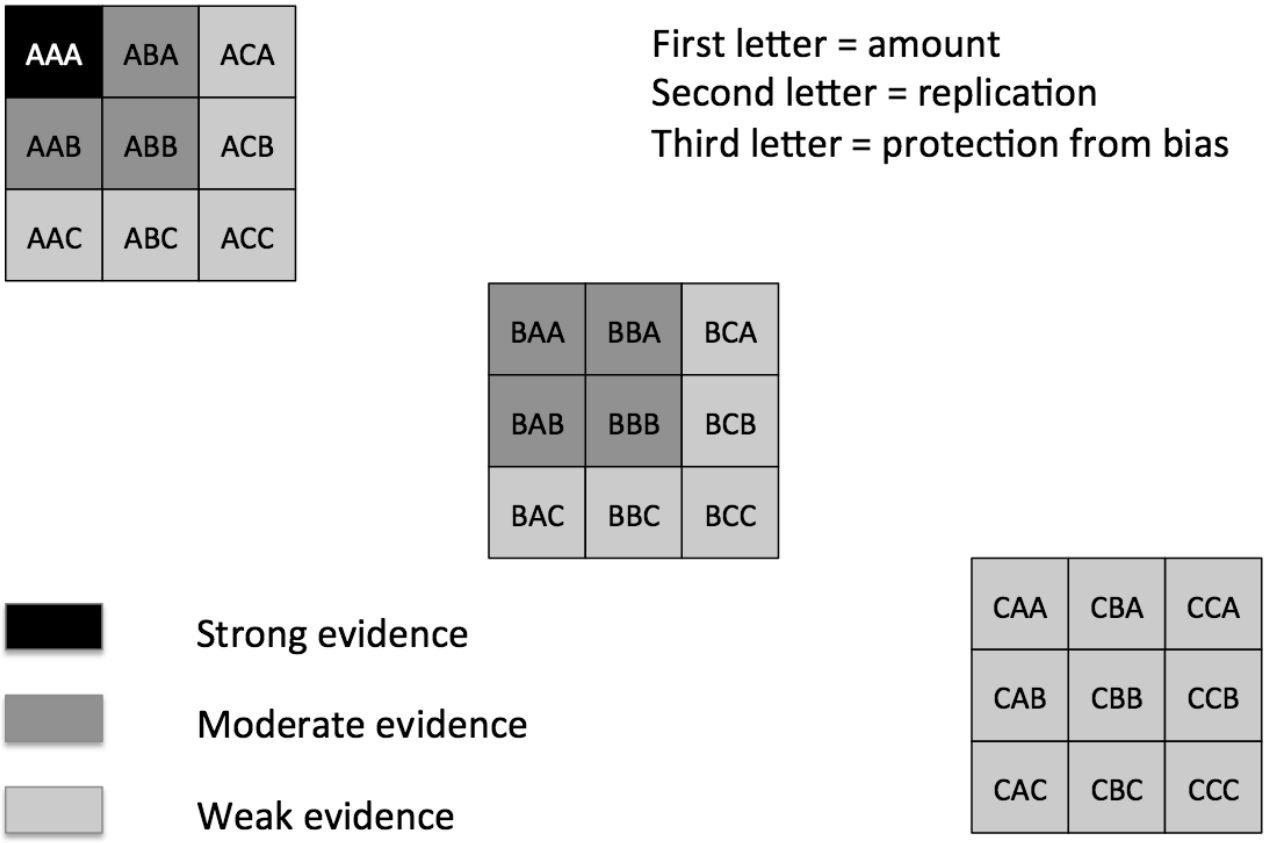

Figure S1 Categories for the credibility of cumulative epidemiological evidence. The three letters correspond (in order) to amount of evidence, replication and protection from bias. Evidence is categorized as strong, when there is A for all three items, and is categorized as weak when there is a C for any of the three items. All other combinations are categorized as moderate. From Ioannidis JP *et al*.[1] with permission from Oxford University Press.

Protein-protein interaction network analysis methods

The PPI-network was created with InWeb 2.0 [2] using all genes with a positive association to lumbar disc degeneration as input.

InWeb is based on mining of online interactiondatabses String [3], MINT [4], Bind [5], DIP [6], GRID [7], HPRD [8], Kegg [9], Reactome [10] and IntAct [11]. All experimentally based interactions from each was kept and given a score between 0 and 1 [2]. We used all interactions with a score on 0.5 or higher. To avoid highly interacting proteins (hubs) we used a network score on 0.1, which means all linker-protein (protein not in input) at most is allowed to interact with 9 other linker-proteins for each input protein they interact with [2]. P-values was calculated creating 10.000 random networks.

Supporting Results Information

Equivalent rs-numbers

Table S2. Initial abbreviations and rs-numbers searched				
Gene	Variation*	Abbreviation in the study	rs-number	Reference for the rs-number
COL9A2	c.976C>T	Trp2	rs137853213	Ensembl 64: Sep 2011
COL9A3	c.307C>T	Trp3	rs61734651	Ensembl 64: Sep 2011
COL11A2	c.877-4A>T -	IVS6^{-4} a/t G>A intron9	rs1799907 rs2744507	Ensembl 64: Sep 2011
FAS	-	-1377GA	rs2234767	Hu et al 2008[19]
FASLG	-	-844CT	rs763110	Hu et al 2008[19]
IL1A	c.1-889C>T	IL-1aT^{889}	rs1800587	Ensembl 64: Sep 2011
IL1B	c.3954C>T	IL-1bT^{3954}	rs1143634	Ensembl 64: Sep 2011
IL10	- -	-1082A/G -592A/C	rs1800896 rs1800872	Pereira et al 2008[13]
MMP1	-	-1607	rs1799750	Ju et al 2005[14]
MMP2	-	-1306C/T	rs243865	Zhai et al 2007[15]
MMP3	c.1-1171insA	5'UTR -1171a	rs3025058	Tsironi et al 2009[17]
MMP9	-	-1562C/T	rs3918242	Demacq et al 2009[16]
NOS2	-	exon22 G>A	rs1060826	Ensembl 64: Sep 2011
NOS3	-	-786T/C	rs2070744	Demacq et al 2010[18]
VDR	c.2T>C c.1056T>C	FokI TaqI	rs2228570 rs731236	Ensembl 64: Sep 2011

***** According to den Dunnen JT, Antonarakis SE. Mutation nomenclature extensions and suggestions to describe complex mutations: A discussion [12]

Included studies

Studies included in the systematic review, total **52**

Annunen S, Paassilta P, Lohiniva J, Perala M, Pihlajamaa T, Karppinen J, Tervonen O, Kroger H, Lahde S, Vanharanta H, et al. 1999. An allele of COL9A2 associated with intervertebral disc disease. Science 285(5426):409-12.

Bei T, Tilkeridis C, Garantziotis S, Boikos S, Kazakos K, Simopoulos C, Stratakis C. 2008. A novel, non-functional, COL1A1 polymorphism is not associated with lumbar disk disease in young male Greek subjects unlike that of the Sp1 site. Hormones (Athens) 7(3):251-4.

Cheung KMC, Chan D, Karppinen J, Chen Y, Jim JJT, Yip S, Ott J, Wong KK, Sham P, Luk KDK, et al. 2006. Association of the taq I allele in vitamin D receptor with degenerative disc disease and disc bulge in a Chinese population. Spine (Phila Pa 1976) 31(10):1143-8.

Cong L, Pang H, Xuan D, Tu GJ. 2010a. Association between the expression of aggrecan and the distribution of aggrecan gene variable number of tandem repeats with symptomatic lumbar disc herniation in Chinese Han of northern China. Spine (Phila Pa 1976) 35(14):1371-6.

Cong L, Pang H, Xuan D, Tu G. 2010b. The interaction between aggrecan gene VNTR polymorphism and cigarette smoking in predicting incident symptomatic intervertebral disc degeneration. Connect Tissue Res 51(5):397-403.

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Eser B, Cora T, Eser O, Kalkan E, Haktanir A, Erdogan MO, Solak M. 2010. Association of the polymorphisms of vitamin D receptor and aggrecan genes with degenerative disc disease. Genet Test Mol Biomarkers 14(3):313-7.

Eser O, Eser B, Cosar M, Erdogan MO, Aslan A, Yıldız H, Solak M, Haktanır A. 2011. Short aggrecan gene repetitive alleles associated with lumbar degenerative disc disease in Turkish patients. Genet Mol Res 10(3):1923-30.

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Higashino K, Matsui Y, Yagi S, Takata Y, Goto T, Sakai T, Katoh S, Yasui N. 2007. The alpha2 type IX collagen tryptophan polymorphism is associated with the severity of disc degeneration in younger patients with herniated nucleus pulposus of the lumbar spine. Int Orthop 31(1):107-11.

Hirose Y, Chiba K, Karasugi T, Nakajima M, Kawaguchi Y, Mikami Y, Furuichi T, Mio F, Miyake A, Miyamoto T, et al. 2008. A functional polymorphism in THBS2 that affects alternative splicing and MMP binding is associated with lumbar-disc herniation. Am J Hum Genet 82(5):1122-9.

Jim JJ, Noponen-Hietala N, Cheung KM, Ott J, Karppinen J, Sahraravand A, Luk KD, Yip SP, Sham PC, Song YQ, et al. 2005. The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. Spine (Phila Pa 1976) 30(24):2735-42.

Kales SN, Linos A, Chatzis C, Sai Y, Halla M, Nasioulas G, Christiani DC. 2004. The role of collagen IX tryptophan polymorphisms in symptomatic intervertebral disc disease in southern European patients. Spine (Phila Pa 1976) 29(11):1266-70.

Karasugi T, Semba K, Hirose Y, Kelempisioti A, Nakajima M, Miyake A, Furuichi T, Kawaguchi Y, Mikami Y, Chiba K, et al. 2009. Association of the tag SNPs in the human SKT gene (KIAA1217) with lumbar disc herniation. J Bone Miner Res 24(9):1537-43.

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Karppinen J, Paakko E, Raina S, Tervonen O, Kurunlahti M, Nieminen P, Ala-Kokko L, Malmivaara A, Vanharanta H. 2002. Magnetic resonance imaging findings in relation to the COL9A2 tryptophan allele among patients with sciatica. Spine (Phila Pa 1976) 27(1):78-83.

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Nunes, F.T.B.b , Conforti-Froes, N.D.T.a b c , Negrelli, W.F.e , Souza,D.R.S.b d. 2007. Genetic and environmental factors involved on intervertebral disc degeneration. Acta Ortopedica Brasileira 15(1):9-13.

Oishi Y, Shimizu K, Katoh T, Nakao H, Yamaura M, Furuko T, Narusawa K, Nakamura T. 2003. Lack of association between lumbar disc degeneration and osteophyte formation in elderly Japanese women with back pain. Bone 32(4):405-11.

Paassilta P, Lohiniva J, Goring HH, Perala M, Raina SS, Karppinen J, Hakala M, Palm T, Kroger H, Kaitila I, et al. 2001. Identification of a novel common genetic risk factor for lumbar disk disease. JAMA 285(14):1843-9.

Paz Aparicio J, López-Anglada Fernández E, Montes Prieto H, Pena Vázquez J, Fernández Bances I, Folgueras Henriksen V, López Fernández P, López-Fanjúl Menéndez JC, Valle Garay E, Asensi Álvarez V. 2010. Association between the genetic polymorphism of interleukin-1β (3953 T/C) and symptomatic lumbar herniated disc. Revista Espanola De Cirugia Ortopedica y Traumatologia 54(4):227-33.

Roughley P, Martens D, Rantakokko J, Alini M, Mwale F, Antoniou J. 2006. The involvement of aggrecan polymorphism in degeneration of human intervertebral disc and articular cartilage. Eur Cell Mater 11:1-7.

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Solovieva S, Kouhia S, Leino-Arjas P, Ala-Kokko L, Luoma K, Raininko R, Saarela J, Riihim\aki H. 2004. Interleukin 1 polymorphisms and intervertebral disc degeneration. Epidemiology 15(5):626-33.

Solovieva S, Lohiniva J, Leino-Arjas P, Raininko R, Luoma K, Ala-Kokko L, Riihimaki H. 2006. Intervertebral disc degeneration in relation to the COL9A3 and the IL-1ss gene polymorphisms. Eur Spine J 15(5):613-9.

Solovieva S, Lohiniva J, Leino-Arjas P, Raininko R, Luoma K, Ala-Kokko L, Riihimaki H. 2002. COL9A3 gene polymorphism and obesity in intervertebral disc degeneration of the lumbar spine: Evidence of gene-environment interaction. Spine (Phila Pa 1976) 27(23):2691-6.

Solovieva S, Noponen N, Mannikko M, Leino-Arjas P, Luoma K, Raininko R, Ala-Kokko L, Riihimaki H. 2007. Association between the aggrecan gene variable number of tandem repeats polymorphism and intervertebral disc degeneration. Spine (Phila Pa 1976) 32(16):1700-5.

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Song Y, Cheung KMC, Ho DWH, Poon SCS, Chiba K, Kawaguchi Y, Hirose Y, Alini M, Grad S, Yee AFY, et al. 2008b. Association of the asporin D14 allele with lumbar-disc degeneration in Asians. Am J Hum Genet 82(3):744-7.

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Sun Z, Ling M, Huo Y, Chang Y, Li Y, Qin H, Yang G, Lucas R. 2011. Caspase 9 gene polymorphism and susceptibility to lumbar disc disease in the Han population in northern China. Connect Tissue Res 52(3):198-202.

Takahashi M, Haro H, Wakabayashi Y, Kawa-uchi T, Komori H, Shinomiya K. 2001. The association of degeneration of the intervertebral disc with 5a/6a polymorphism in the promoter of the human matrix metalloproteinase-3 gene. J Bone Joint Surg Br 83(4):491-5.

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Excluded studies

Systematic search hits excluded after dual examination of abstracts and/or full text articles, total **72**

-the reason for exclusion

Genetic predispositions to low back pain. (2005) Medecine/Sciences 21(10): 820.

-review article

Aladin DMK, Cheung KMC, Chan D, Yee AFY, Jim JJT, Luk KDK & Lu WW (2007) Expression of the Trp2 allele of COL9A2 is associated with alterations in the mechanical properties of human intervertebral discs. Spine (Phila Pa 1976) 32(25): 2820-2826.

-number of study subjects is less than 50

Aladin DMK, Cheung KMC, Ngan AHW, Chan D, Leung VYL, Lim CT, Luk KDK & Lu WW (2010) Nanostructure of Collagen Fibrils in Human Nucleus Pulposus and Its Correlation with Macroscale Tissue Mechanics. J Orthop Res 28(4): 497-502.

-no genetic variant described

Ala-Kokko L (2002) Genetic risk factors for lumbar disc disease. Ann Med 34(1): 42-7.

-review article

Anderson JA, Ng JJ, Bowe C, Mcdonald C, Richman DP, Wollmann RL & Maselli RA (2008) Variable phenotypes associated with mutations in DOK7. Muscle Nerve 37(4): 448-456.

-not a relevant outcome

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-not a relevant outcome

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