Genetic background of degenerative disc disease in the lumbar spine

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Abstract:

This is a review paper on the topic of genetic background of degenerative disc diseases in the lumbar spine. Lumbar disc diseases (LDDs), such as lumbar disc degeneration and lumbar disc herniation, are the main cause of low back pain. There are a lot of studies that tried to identify the causes of LDDs. The causes have been categorized into environmental factors and genetic factors. Recent studies revealed that LDDs are mainly caused by genetic factors. Numerous studies have been carried out using the genetic approach for LDDs. The history of these studies is divided into three periods: (1) era of epidemiological research using familial background and twins, (2) era of genomic research using DNA polymorphisms to identify susceptible genes for LDDs, and (3) era of functional research to determine how the genes cause LDDs. This review article was undertaken to present the history of genetic approach to LDDs and to discuss the current issues and future perspectives.

Keywords:

lumbar spine, lumbar disc diseases, lumbar disc degeneration, lumbar disc herniation, discogenic low back pain, genetics, gene, polymorphism, SNP

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Introduction

Low back pain (LBP) is a very common problem that over 80% of the general population experience sometime in their life. The recent global epidemiological survey of 306 diseases in 188 countries revealed that LBP is one of the main causes of disability-adjusted life years[1]. It is speculated that lumbar disc diseases (LDDs), such as symptomatic lumbar disc degeneration (LDDg) and lumbar disc herniation (LDH), are the main cause of LBP and reportedly at least 40% of LBP may be associated with LDDs[2]. Although the incidence of symptomatic LDDg is unclear, the Japanese guideline for LDH (2005) reported the incidence of LDH as 1%, and in USA, 4.63 per 100,000 people were operated in a year. Thus, LDDs are recognized as common diseases. The causes of LDDs have been categorized into environmental factors and genetic factors. Workload, sports activity, driving, and smoking habit are the examples of environmental risk factors. Recent studies revealed that LDDs are mainly caused by genetic factors. Numerous studies have been carried out using the genetic approaches for LDDs. The history of these studies is divided into three periods: (1) era of epidemiological research using familial background and twins, (2) era of genomic research using DNA polymorphisms to identify susceptible genes for LDDs, and (3) era of functional research to determine how the genes cause LDDs. This review article was undertaken to present the history of genetic approaches against LDDs and to discuss the current issues and future perspectives.

1. Epidemiological research using familial predisposition and twins (Table 1)

The epidemiological research studies on LDDs started in 1960s. In 1966, Hurxthal reported a similar type of Schmorl's nodes in identical twins and described the probable existence of a genetic origin[3]. Varughese and Quartey reported on four brothers with lumbosciatic syndrome due to acute LDH and associated spinal stenosis in 1979[4]. Several papers have shown familial predisposition for LDDs. Grobler et al. reported that family history of seven adolescents with LDH[5]. Varlotta et al. found that 32% of juvenile

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Table 1. Epidemiological Research Using Familial Predisposition and Identical Twins Regarding Lumbar Disc Diseases.

first author	journal	year	content	reference No.
family history of juvenile lumbar disc disease				
Grobler LJ	Spine	1979	Family history of disc herniation in 7 adolescents.	5
Varlotta GP	J Bone Joint Surg Am	1991	32% of juvenile disc herniation had a positive family history for that lesion compared with 7% of the controls.	6
Matsui H	Spine	1992	The encumbrances of young patients (<18 years old) with lumbar disc herniation showing familial predisposition, with an odds ratio of 5.61 compared to the control.	7
Frino J	J Pediatr Orthop	2006	43.8% of the patients with disc herniation had a postive family history.	8
family history of degenerative lumbar disc disease				
Postacchini F	Spine	1988	There was a strong familial predisposition of discogenic low-back pain.	10
Simmons ED Jr	Spine	1996	44.6% of the patients with degenerative lumbar disc disease had a familial predisposition, whereas 25.4% had a positive family history in the control.	11
Richardson JK	Spine	1997	There was a familial predisposition toward lumbar disc pain and injury.	12
Matsui H	Spine	1998	A family history of operated lumbar disc herniation had a significant implication in lumbar degenerative disc disease.	13
Bijkerk C	Arthritis Rheum	1999	There was a strong genetic effect for hand osteoarthritis and disc degeneration of the spine.	14
Saftić R	Croat Med J	2006	Individuals with a positive family history were at risk for lumbar disc herniation.	15
Patel AA	J Bone Joint Surg Am	2011	The analysis using the Utah Population Database supported a heritable contribution to the development of symptomatic lumbar disc disease.	16
Livshits G	Eur J Epidemiol	2001	The study using Arabic pedigrees showed a predominant role of the family history as a risk factor for degenerative disc disease in offspring.	17
twin studies				
Gunzburg R	J Bone Joint Surg Br	1990	Multilevel lumbar disc herniation in teenage twins	18
Matsui H	Spine	1990	Juvenile lumbar disc herniation in monozygotic twins	19
Obukhov SK	Childs Nerv Syst	1996	Multilevel lumbar disc herniation in 12-year-old twins	20
Sambrook PN	Arthritis Rheum	1999	Using data of 172 monozygotic and 154 dizygotic twins, heritability was 74% for the lumbar spine disease.	21
Battié M	Spine	1995	Familial aggregation raised the variability in the disc degeneration score to 43%.	22
Battié M	J Bone Joint Surg Am	1995	Similarities in lumbar degeneration between co-twins were significantly greater than would be expected by chance.	23
Battié M	Spine	2004	The review indicates that heredity has a dominant role in disc degeneration, which explains 74% of the variance.	24
Battié M	J Bone Joint Surg Am	2006	Recent research indicates that heredity has a dominat role in disc degeneration.	25
Battié M	Spine	2008	The classic twin study with multivariate analysis confirmed heritability of disc degeneration, estimates varied from 29% to 54%.	26
Battié M	Spine J	2009	The review concluded that disc degeneration appears to be determined largely by genetic influence.	27

LDH had a positive family history of LDH compared with 7% of the controls[6]. The interesting report by Matsui et al. described that the encumbrances of younger patients <18 years old with LDH showed familial predisposition, with an odds ratio of 5.61 compared with the controls[7]. Frino et al. also stated that 43.8% of the patients with LDH have a positive family history[8]. The previous papers are not limited only to juvenile LDH but also in the family history of LDDg. Postacchini et al. reported that there was a strong familial predisposition of discogenic LBP using the data of the first-degree relatives (parents, siblings, and children) of 284 patients complaining of discogenic LBP (Group I), 114 patients who had undergone surgery for LDH (Group II), and 280 individuals who had never complained of LBP (Group III) by self-completed questionnaires[9]. They found that the proportion of symptomatic relatives in the affected families was higher. The study by Simmons et al. showed that 44.6% of the patients with LDDg had a familial predisposition, whereas in the controls, 25.4% had a positive family history[10]. Richardson et al. reported that there was a familial predisposition toward discogenic LBP and injury[11]. Matsui et al. conducted a case-control study using magnetic resonance imaging and plain radiography to evaluate the significance of a family history of operated LDH in the development of LDDg and LDH[12]. They found that a family history of operated LDH had a significant implication in lumbar degenerative disc disease. Based on the result, they concluded that a family history of operated LDH has a significant implication in LDDs. Bijkerk et al. found that there was a strong genetic effect for LDDg as well as hand osteoarthritis[13]. It has been reported that individuals of Arabic pedigrees[14] with a positive family history were at risk of

LDDg, and those from Croatia were also at risk of LDH[15]. The analysis using the Utah Population Database supported a heritable contribution to the development of symptomatic LDDs and a predominating role of the family history as a risk factor for LDDg in offsprings[16]. Kalichman and Hunter reviewed familial predisposition and heritability estimation of LDDg[17].

As for the study using twins, Gunzburg et al. first reported the multilevel LDH in teenage twins[18]. Juvenile LDH cases in monozygotic twins that required operation were described by Matsui et al[19]. Obukhov et al. also reported multilevel LDH in 12-year-old twins[20]. Sambrook et al. compared Magnetic Resonance Imaging (MRI) features of degenerative disc disease in the cervical and lumbar spine of 172 monozygotic and 154 dizygotic twins[21]. They found heritability was 74% at the lumbar spine and 73% at the cervical spine using their overall score. Based on the results, they concluded that there was an important genetic influence on the variation in intervertebral disc degeneration. Battié is one of the most active researchers in the particular field of investigations using twins. Battié et al. started the Twin Spine Study in Canada, Finland, and United States in 1991. In 1995, they selected 115 male identical twins[22] and investigated the effects of lifetime exposure to commonly suspected risk factors on disc degeneration using magnetic resonance imaging and estimated the effects of these suspected risk factors relative to age and familial aggregation, reflecting genetic influences. As a result, 77% of the variability at upper lumbar level and 43% of that at lower lumbar level were explained by familial aggregation in multivariate analyses. Since then, they have published numerous papers[23-27]. In their review paper, they described two key points among the most significant findings: the substantial influence of heredity on LDDg and the identification of the first gene forms with disc degeneration. They concluded that disc degeneration appears to be determined in great part by genetic influences.

2. Genomic research using DNA polymorphisms to identify susceptible genes for LDDs (Table 2)[28-117]

Many researchers have tried to find the susceptible genes and the genetic loci, which are associated with LDDs in humans. Most of them carried out an association study. This means the comparison of the gene allele frequencies between the cases and the controls. It can be called a case-control study. Another method to seek the gene loci is linkage analysis. This method uses families that have LDDs. There was only one study by Annunen et al. using linkage analysis[31]. All significant studies used the difference in single nucleotide polymorphism (SNP). SNP is a variation in a single nucleotide that occurs at a specific position in the genomic DNA, where each variation is present to some appreciable degree within a population. Association studies can determine whether a genetic variant, SNP, is associated with LDDs.

The first study to identify the specific loci was reported by Videman et al. in 1998[28]. They found that the men with TaqI tt genome and FokI ff allele of vitamin D receptor (*VDR*) gene had the worst findings of LDDg, compared with the men with TaqI TT and FokI FF allele. Then, they concluded that the specific *VDR* alleles were associated with intervertebral disc degeneration as measured by T2-weighted MRI. They demonstrated, for the first time, the existence of genetic susceptibility to this progressive, age-related degenerative process. Our team focused on the aggrecan (*AGC*) gene[30]. In 1999, we reported that the young subjects in their 20s with the shorter allele of *AGC* had severe LDDg. Since then, many candidate genes have been identified and reported. There are three groups of genes that are related to LDDs: (1) genes related to the structure of the intervertebral disc, (2) genes related to production of the degradation enzymes or cytokines for the extracellular matrix (ECM), and (3) genes related to connective tissues, such as bone and other tissues.

(1) Genes related to the structure of the intervertebral disc (Table 3)

In this category, the genes that code the structural component in the intervertebral disc are included. The polymorphism in the susceptible gene might produce structural change in the intervertebral disc component, resulting in symptomatic LDDg or LDDs.

Aggrecan gene[30,50,64,65,75,114]

AGC is a proteoglycan, which is a critical component for cartilage and intervertebral disc structure. Proteoglycans are responsible for the high water content and play a role in the load bearing function. A polymorphism has been identified in the coding region of the human *AGC*. The expressed variable numbers of tandem repeat (VNTR) polymorphism occur in exon 12, which codes for the chondroitin sulfate attachment domain. The polymorphism occurs in the highly conserved repeat region. A total of 13 alleles differing by the number of nucleotide repeats were observed. This polymorphism results in individuals having different length AGC core proteins. In 1999, we first found that multilevel and severe disc degeneration was present in the participants with shorter VNTR length of *AGC* using 64 young subjects in their 20s[30]. Numerous studies have been conducted since then[50,64,65,75,114]. Meta-analysis using the data from 1995 to 2013 suggested an increased risk of shorter alleles compared with normal alleles and longer alleles against LDDg among populations, especially among those of Asian descent[114]. However, such an association may not be statistically significant in European populations. Thus, it is still controversial whether *AGC* truly is a susceptible gene for LDDs.

Collagen IX (COL9A2 and COL9A3)[31,32,37-39,42,45,47,48,102,107,116,117]

Collagen IX is a structural protein, which consists of the cartilage collagen II/IX/XI heteropolymer. Collagen IX is

Table 2. Candidate Genes for Lumbar Disc Diseases.

							Postive or negative results	
	gene	phenotype	subjects	country	first author	journal	year	reference No.
1	VDR	lumbar disc degeneration, signal intensity, disc narrowing, bulging	85 pairs of male monozygotic twin	Finland	Videman T	Spine	1998 p	28
2	VDR	osteophytosis, disc space narrwoing	110 men, 172 women >60 years	Australia	Jones G	Ann Rheum Dis	1998 p	29
3	AGC	lumbar disc degeneration	64 young adults	Japan	Kawaguchi Y	Spine	1999 p	30 *
4	COL9A2	intervertebral disc disease	154 Trp2 (+), 174 controls	Finland	Annunen S	Science	1999 p	31
5	COL9A2	disc prolapse	3 Trp2 (+), 247 other patients	Germany	Wrocklage C	Biochem Biophys Res Commun	2000 p	32
6	VDR	lumbar disc degeneration, signal intensity, disc narrowing, bulging, annular tear, herniations, osteophytes	142 men	Finland	Videman T	Spine	2001 p	33
7	MMP-3	lumbar disc degeneration	54 young, 49 elderly Japanese	Japan	Takahashi M	J Bone Joint Surg Br	2001 p	34
8	COL9A3	lumbar disc disease	171 with LDD, 321 controls	Finland	Paassilta P	JAMA	2001 p	35
9	VDR	lumbar disc degeneration	205 young adults	Japan	Kawaguchi Y	J Bone Joint Surg Am	2002 p	36 *
10	COL9A3	lumbar disc degeneration	135 middle aged men	Finland	Solovieva S	Spine	2002 p	37
11	COL9A2	MRI findings	159 patients with sciatica	Finland	Karppinen J	Spine	2002 p	38
12	COL9A2, COL11A2	disc herniation or disc degeneration	29 Finnish probands, 56 Finnish controls	Finland	Noponen-Hietala N	Ann Rheum Dis	2003 p	39
13	COL1A1	inetrevertebral disc degeneration	966 men and women ≥65 years	Holland	Plujim SM	Ann Rheum Dis	2004 p	40
14	IL-1	disc degeneration	133 middle-aged men	Finland	Solovieva S	Epidemiology	2004 p	41
15	COL9	lumbar surgery	107 patients who underwent lumbar surgery	US	Matsui Y	J Bone Joint Surg Br	2004 p	42
16	CILP	lumbar disc herniation	467 patients, 654 controls	Japan	Seki S	Nat Genet	2005 p	43 *, §
17	MMP-3, TIMP, COX2, VDR, THBS2	osteophyte, K-L grade, osteophyte, radiographic progression of lumbar spine disc degeneration	720 women	UK	Valdes AM	Spine	2005 p	44
18	COL9A3, COL11A2, IL-1B	dark nuclues pulposus, disc bulge	135 middle aged ocuppationally active men	Finland	Solovieva S	Eur Spine J	2006 p	45
19	VDR	lumbar disc degeneration	804 Southern Chinese Volunteers	China	Cheung K	Spine	2006 p	46
20	COL9A2	lumbar disc herniation	470 patients with lumbar disc degeneration, 658 controls	Japan	Seki S	J Hum Genet	2006 p	47 *
21	COL9A2	severe disc degeneration in patients with lumbar disc herniation	84 patients having discectomy	Japan	Higashino K	Int Orthop	2007 p	48
22	ADH2	disc degeneration, osteophyte formation	387 elderly persons	Japan	Sakai Y	Spine	2007 p	49
23	AGC	dark nucleus pulposus	132 men	Finland	Solovieva S	Spine	2007 p	50
24	MMP-2	lumbar disc disease	162 younger patients with LDD, 318 healthy adults	China	Dong DM	Eur Spine J	2007 p	51
25	COL11A1	lumbar disc herniation	334 cases, 376 controls	Japan	Mio F	Am J Hum Genet	2007 p	52 *
26	CILP	lumbar disc herniation	243 Finnish patients with symptoms of LDD and 259 controls, and in 348 Chinese subjects with MRI-defined LDD and 343 controls.	Finland, China	Virtanen I	J Med Genet	2007 n	53
27	THBS2	lumbar disc herniation	847 cases, 896 control	Japan	Hirose Y	Am J Hum Genet	2008 p	54 *
28	ASPN	lumbar disc degeneration	Chinese: 1054 cases, 1056 controls; Japanese: 1490 cases, 1216 controls	China, Japan	Song YQ	Am J Hum Genet	2008 p	55 *, §

Table 2. continued

	gene	phenotype	subjects	country	first author	journal	year	reference No.	
29	IL-1, MMP-3	type II Modic change	228 subjects, 128 Modic change	Finland	Karppinen J	Spine	2008	p	56	
30	Multi-genes, AGC, COL1A1, COL9A1, COL11A1, IL18RAP	disc signal intensity, bulging, height narrowing	588 men	Finland	Videman T	Arthritis Rheum	2009	p	57	
31	MMP-9	lumbar disc degeneration	408 young patients with LDD, 451 control subjects, Northern Chinese	China	Sun ZM	Conect Tissue Res	2009	p	58	
32	CILP	lumbar disc degeneration	89 Japanese Judo athletes	Japan	Min SK	Int J Sports Med	2009	p	59	
33	KIAA1217	lumbar disc herniation, lumbar disc disease	Japanese A: 1050 cases & 1128 controls, Japanese B 674 caes & 664 controls, Finnish 514 cases & 498 controls	Japan and Finland	Karasugi T	J Bone Miner Res	2009	p	60	*, §
34	MMP-3, VDR+physical loading	lumbar disc degeneration	178 LBP with lumbar disc degeneration, 284 controls	China	Yuan HY	J Occup Health	2010	p	61	
35	IL-1A, IL-6	girl lumbar disc degenerative disease	30 boys+36 girls with LDD, 73 boys+81 girls without MRI change, Danish	Finland	Eskola PJ	Int J Mol Epidemiol Genet	2010	p	62	
36	VDR, AGC	disc degeneration and herniation	300 individual	Turkey	Eser B	Genet Test Mol Biomarkers	2010	p	63	
37	AGC	symptomatic lumbar disc herniation	70 patients vs 14 trauma+113 healthy control, Chinese Han	China	Cong L	Spine	2010	p	64	
38	AGC	lumbar disk degeneration disease	71 patients vs 108 healthy individuals	Iran	Mashayekhi F	Biochem Genet	2010	p	65	
39	IL-1RN	clinical course of lumbar herniated nucleus pulposus	54 lumbar LDH, 227 healthy adult controls	USA	Kim DH	Spine	2010	p	66	
40	CILP	lumbar disc degeneration	610 collegiate athletes	Japan	Min SK	Am J Sports Med	2010	p	67	
41	GCH1	surgical treatment success of lumbar degenerative disc disease	69 patients with LDD	USA	Kim DH	Spine	2010	p	68	
42	COMT	surgical treatment success of degenerative disc disease	69 surgical treatment	USA	Dai F	Spine J	2010	p	69	
43	HAPLN1	spinal degeneration	622 postmenopausal women	Japan	Urano T	Eur Spine J	2011	p	70	
44	Caspase 9	lumbar disc herniation, disc degeneration	387 LDH, 412 control subjects, Northern Chinese	China	Sun ZM	Conect Tissue Res	2011	p	71	
45	GDF5	lumbar disc disease	5 population cohort, 1463 northern European women	UK	Williams FM	Arthritis Rheum	2011	p	72	
46	FAS, FASL	lumbar disc disease	348 LDD, 215 healthy control, Chinese Han	China	Zhu GB	Biomarkers	2011	p	73	
47	IL-10	lumbar disc degeneration+lumbar disc herniation	320 LDD, 268 control, 134 LDH (messenger RNA analysis), Chinese Han	China	Lin WP	Genet Mol Res	2011	p	74	
48	AGC	lumbar degenerative disc disease	100 20-30 years old patients with or without LBP	Turkey	Eser O	Genet Mol Res	2011	p	75	
49	IL-6, SKT, CILP	lumbar disc degeneration	538 young adults	Finland	Kelempisioti A	BMC Med Genet	2011	p	76	
50	BCL-2	lumbar disc degeneration	325 LDD, 236 normal controls, Chinese Han	China	Shang XP	Clin Lab	2012	p	77	
51	COMT	pain after treatment for low back pain	60 lumbar fusion, 33 cognitive therapy and exercise	Norway	Omair A	BMC Musculoskeletal Disord	2012	p	78	
52	DR4	lumbar disc degeneration	296 LDD, 208 healthy controls, Chinese Han	China	Tan H	Scand J Clin Lab Invest	2012	p	79	
53	PARK2	lumbar disc degeneration	4600 individuals, Northern European	HK	Williams FM	Ann Rheum Dis	2013	p	80	
54	FAS ligand	lumbar disc herniation	475 patienst with LDH, 533 controls, Northern Chinese	China	Sun Z	Conect Tissue Res	2013	p	81	
55	MMP-12	low back pain, sciatica, disability	260 patients with LDH	Norway	Jacobsen LM	Clin J Pain	2013	p	82	

Table 2. continued

	gene	phenotype	subjects	country	first author	journal	year	reference No.	
56	IL-18RAP, IL-18R1, IL-A, MMP-3	severe degeneration, pain, disability	93 patients with chronic LBP	Norway	Omair A	BMC Musculoskeletal Disord	2013 p	83	
57	CASP-9 positive, IL-1B negative	low back pain	305 case, 587 control, Chinese soldier	China	Mu J	J Neurosurg, Spine	2013 p	84	
58	multi genes, 58 candidate gene, at least 11 genes were positive	degenerative disc disease, annular tear, disc dgeneration, endplate damage	342 subjects	Indian	Rajasekaran S	Spine J	2013 p	85	
59	MMP-2	lumbar disc degeneration	1008 LDD, 906 controls	China	Zhang Y	Eur Rev Pharmacol Sci	2013 p	86	
60	VEGF positive, eNOS negative	lumbar disc degeneration	102 LDD, 139 controls	Korea	Han IB	Genet Mol Res	2013 p	87	
61	HIF-1α	lumbar disc degeneration	320 LDD, 447 controls	Egypt	Lin WP	PLoSOne	2013 p	88	
62	CHST3	lumbar disc degeneration	4043 LDD, 28599 normal subjects	Japan, China, Finland	Song YQ	J Clin Invest	2013 p	89	*, §
63	MMP-3, VDR +occupation	lumbar disc degeneration	84 LDD, 60 controls, Egyptian	Egypt	Zawilla NH	J Occup Rehabil	2014 p	90	
64	CILP, ASPN	lumbar disc degeneration, only male positive	516 Japanese collegiate athlethes	Japan	Min SK	Cartilage	2014 p	91	
65	ADAMTS-5	lumbar disc degeneration	50 participants	Chinese Han	Wu N	J Orthop Res	2014 p	92	
66	VDR	lumbar spinal disorders	267 spinal disorders, 220 asymptomatic controls	Italian	Colombini A	PLoSOne	2014 p	93	
67	VDR	lumbar disc degeneration	121 LDD, 131 healthy controls	Brasil	Vieira LA	Genet Test Mol Biomarkers	2014 p	94	
68	ADIPOQ	lumbar disc degeneration	168 LDD, 122 healthy individuals	Jordan	Khabour OF	Ext Ther Med	2014 p	95	
69	AGC+obesity	lumbar disc herniation	61 LDH, 198 healthy	China	Cong L	Conect Tissue Res	2014 p	96	
70	IL-1A, VDR	lumbar disc degeneration	100 LDD, 100 normal MRI	Mexico	Cervin Serrano S	Int J Genomics	2014 n	97	
71	GDF5	symptomatic lumbar disc herniation	231 patients, 370 controls	China	Mu J	Eur Spine J	2014 p	98	
72	multigene, COL11A1, ADAMTS5, CALM1, IL-1F5, COX2	total disc degenerative score	308 mild TDD, 387 severe TDD	Indian	Rajasekaran S	Eur Spine J	2015 p	99	
73	TRAIL	lumbar disc degeneration	312 LDD, 196 healthy controls, Chinese Han	China	Zhang C	Genet Test Mol Biomarkers	2015 n	100	
74	TRAIL	lumbar disc degeneration	153 LDD, 131 healthy subjects, Chinese Han	China	Du H	Int J Clin Exp Pathol	2015 p	101	
75	COL1A1, COL9A3, VDR multiple mutation	lumbar disc degeneration	75 severe LDD, 25 healthy control, Southern European ancestry	Greece	Toktas ZO	Eur Spine J	2015 p	102	
76	VDR	lumbar disc herniation	110 LDH, 110 healthy control	Italian	Sansoni V	Eur Spine J	2016 p	103	
77	IL-18RAP, MMP-9	adjacent disc space narrowing, greater disc space height	208 fusion, 77 non-operative treatment	Norway	Omair A	Eur Spine J	2016 p	104	
78	ADAMTS-4	lumbar disc degeneration	482 LDD, 496 healthy controls, Chinese Han	China	Liu S	J Orthop Res	2016 p	105	
79	MMP-3	lumbar disc herniation	100 patients with LDH	Turkey	Eser B	Genet Mol Res	2016 p	106	
Review and meta-analysis papers									
1	COL9A2, COL9A3, review	lumbar disc herniation, lumbar disc degeneration		US	Ala-Kokko L	Ann Med	2002	107	

Table 2. continued

	gene	phenotype	subjects	country	first author	journal	year	reference No.
2	VDR, COL9A2, COL9A3, AGC, COL1A1, MMP-3, CILP, IL-1	lumbar disc degeneration		China	Chan D	Eur Spine J	2006	108
3	COL1A1, COL9A2, COL9A3, COL11A2, IL-1, IL-6, VDR, AGC, MMP-3, CILP, TIMP, COX2, THBS2	lumbar disc degeneration		US	Kalichman L	Joint Bone Spine	2008	109
4	COL9A2, COL9A3, COL1A1, VDR, MMP-3, IL-1	degenerative disc disease		China	Zhang Y	Int J Biol Sci	2008	110
5	GDF5, ASPN review	lumbar disc disease, osteoarthritis		UK	Loughlin J	Arthritis Res Ther	2011	111
6	COL1A1, COL9A2, COL9A3, COL11A2, IL-1, IL-6, VDR, AGC, MMP-3, THBS22	lumbar disc degeneration		US, Mexico	Kalb S	World Neurosurgery	2012	112
7	VDR review	lumbar disc degeneration, osteoarthritis		Italiy	Colombini A	J Steoroid Biochem Mol Biol	2013	113
8	AGC, meta-analysis	lumbar disc degeneration	965 LDD, 982 normal controls	China	Gu J	Spine	2013	114
9	ASPN review	degenerative disc disease		Japan	Ikegawa	Annu Rev Genomics Hum Genet	2013	115
10	COL9, COL11 review	lumbar disc disease		Poland	Janeczko Ł	Neurol Neurochir Pol	2014	116
11	COL9A2, meta-analysis	lumbar disc diesase	1522 LDD, 1646 controls	China	Zhang Z	Spine	2014	117

VDR: Vitamin D receptor
AGC: Aggrecan
MMP: Matrix metalloproteinase
COL: Collagen
IL: Interleukin
ADH2: Alcohol dehydrogenase 2
ASPN: Asporin
IL18 RAP: Interleukin 18 receptor accessory protein
GCH1: guanosine triphosphate cyclohydrolase 1 gene
COMT: Catechol-O-methyl transferase
HAPLN1: the hyaluronan and proteoglycan link protein 1
CHTS3: carbohydrate sulfatransferase 3
ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs
TRAIL: Tumor necrosis factor-related apoptosis-induced ligand
DR4: Death Recetor 4
ADIPOQ, adiponectin
Trp: the tryptophan allele
LDD: lumbar disc disease
LBP: low back pain
LDH: lumbar disc heniation
TDD: total disc degeneration
p: postive results
n: negative results
*: authors related work
§: high association

found in both the annulus fibrosus and the nucleus pulposus in the intervertebral disc. Collagen IX is a heterotrimeric protein consisting of three genetically distinct chains: α1 (IX), α2(IX), and α3(IX), encoded by the *COL9A1*, *COL9A 2*, and *COL9A3* genes, respectively. Among the three genes, *COL9A2* and *COL9A3* have been identified as susceptible genes for LDDs.

In 1999, Annunen et al. first reported that the Trp2 allele, which is induced by an amino acid substitution (Gly326Trp) mutation in the α2 chain of collagen IX, was associated

Table 3. The Classification of the Categories Among Susceptible Genes for Lumbar Disc Diseases.

1) Genes related to the structure of the intervertebral disc
Aggrecan (*AGC*)
Collagen IX (*COL9A2, COL9A3*)
Collagen XI (*COL11A2*)
Collagen I (*COL1A1*)
Cartilage intermediate layer protein (*CILP*)
Asporin (*ASPN*)
2) Genes related to enzymes for extracellular matrix
Matrix mettalloproteinase-3 (*MMP-3*)
Thrombospondin 2 (*THBS2*)
Interleukin-1 (*IL-1*)
Interleukin-6 (*IL-6*)
Other interleukins
Carbohydrate sulfotransferase 3 (*CHST3*)
3) Genes related to other connective tissues, such as bone and other tissues
Vitamin D receptor (VDR)
KIAA (*SKT*: sickle tail)
Other genes
ADH2, GCH1, COMT, HAPLN1, Caspase 9, GDF5, FAS, FASL, BCL-2, DR4, PARK2, VEGF, eNOS, HIF-1α, ADAMTS4, ADAMTS5, ADIPOQ and TRAIL

with LDDs in the Finnish population[31]. It has been reported that the Trp2 allele was associated with radial tear that was detected by MRI[38]. However, in analyses using the Japanese population, the results were controversial[47,48]. One study found that patients <40 years old with the Trp2 allele showed more severe disc degeneration at the surgical level than did those without the Trp2 allele[48]. The other study stated that unlike observations in the Finnish population, Trp 2 was common in Japanese, and no association with LDDs was apparent; however, there was an association of a *COL9 A2*-specific haplotype with LDDs[47]. The recent meta-analysis of *COL9A2* did not show the association with LDDs[117]. The paper analyzed nine previous papers in which 1522 LDD cases and 1646 controls were collected and described that *COL9A2* rs12077871, rs12722877, and rs 7533552 polymorphisms may not be associated with LDDs[117]. Thus, the issue whether the association exists or not does not lead to any conclusion regarding *COL9A2*.

As for *COL9A3* genes, there are several studies that found Trp3 is a risk of LDDs. Paassilta reported that for an individual carrying Trp3, the risk of LDDs increased threefold compared with an individual without it. Trp3 allele was also associated with radiological features of Scheuermann's disease[35]. Some studies using the Finnish population found the risk of LDDs was increased without the *IL-1betaT* (3954) and with obesity[37]. Matsui et al. carried out a similar research[42]. They found that carriers of Trp3 have a risk of development of symptomatic spinal stenosis associated with spondylolisthesis that required surgery. However, the association between Trp3 allele and LDDs was not replicated in the study using the Greek population[102].

Collagen XI (COL11A1)[39,45,52,116]

Type XI collagen is a cartilage-specific ECM protein. It is composed of three α-chains, α1(IX), α2(IX), and α3(IX), which are encoded by *COL11A1*, *COL11A2*, and *COL11A3*, respectively. Two studies from Finland found the association between *COL11A2* and LDDs. Noponen-Hietala et al. analyzed 29 Finnish probands with lumbar degenerative stenosis[39]. The frequency of the *COL11A2* IVS6(-4) t allele was 93.1% in the probands and 72.3% in controls. Solovieva et al. stated that carriers of the *COL11A2* minor allele have an increased risk of disc bulges compared with noncarriers[45]. These results suggest that a specific allele of *COL11A2* might be associated with LDDs. In contrast, one Japanese study revealed that SNP of c.4603C-->T [rs1676486] in *COL11A1* had the most significant association with LDH, and the transcript containing the disease-associated allele was decreased because of its decreased stability. This suggests that *COL11A1* might be a susceptible gene for LDDs[52].

Collagen I (COL1A1)[40,102]

Type I collagen is well known as the major protein in bone. This is also found in the outer layer of the annulus fibrosus (AF). The genes encoding collagen I, *COL1A1* and *COL1A2*, are present in both the nucleus pulposus (NP) and AF. It has been reported that a polymorphism of *COL1A1* has a risk of LDDs. The Sp1 polymorphism (TT/GT/GG) in intron 1 of the *COL1A1* gene for the binding site of the transcriptional factor Sp1 was reported to be associated with LDDs, and TT had a higher risk in the Dutch population[40]. The other study using a small Greek population also found that TT genotype was associated with MRI-evaluated LDDs[102]. This SNP was previously demonstrated as a susceptible gene for osteoporosis and fracture, including vertebral fracture.

Cartilage intermediate layer protein[43,53,59,67,76,91]

Cartilage intermediate layer protein (CILP) is found in the intermediate layer of cartilage. This is also found in the intervertebral disc. The expression of CILP is increasing as disc degeneration progresses. +1184T→C in exon 8 of *CILP* was associated with LDDs in the Japanese population[43]. The change in the SNP results in amino acid substitution Ile395 Thr. The effect of the same SNP was replicated in another Japanese group using male collegiate athletes[59,67,91]. The studies from Finland were controversial. The association was not found in 243 Finnish patients with symptoms of LDD and 259 controls, and also the association was not found in 348 Chinese subjects with MRI-defined LDD and 343 controls[53]. However, one Finnish paper described that interleukin-6 (IL 6), sickle tail (SKT), and CILP were involved in the etiology of DD among young adults[76].

Asporin[55,115]

Asporin (ASPN) belongs to a family of leucine-rich re-

peat proteins, which are located in the cartilage matrix. Previous studies have shown that the D14 allele of ASPN is associated with osteoarthritis of the knee[118]. Previous functional studies demonstrated that ASPN inhibits in vitro chondrogenesis and the expression of COLA1 and AGC through inhibition of Transforming Growth Factor (TGF)-β signaling, with a stronger inhibitory effect for ASPN D14 over others[118]. Our team (first author Song YQ) reported that the D14 allele is also significantly associated with LDDs in Chinese and Japanese populations[55]. Meta-analysis showed that individuals with a D14 allele of *ASPN* had a higher risk of DDDg with a summary odds ratio of 1.70[115]. We also demonstrated that ASPN expression in the intervertebral discs increased with age and degeneration. Based on the results, we concluded that *ASPN* is an LDD gene in Asians, and common risk factors may be considered for osteoarthritis (OA) and LDDs. Since that study, one Japanese paper also reported that *CILP* and *ASPN* polymorphisms are independent risk factors for LDDs in males but not in females.

(2) Genes related to the production of the degradation enzymes or cytokines for ECM (Table 3)

Disc degeneration is promoted by degradation enzymes and/or inflammatory cytokines. The activities of the enzymes and inflammatory cytokines are influenced by the genetic polymorphism that codes them. Thus, the strength of their activities might be related to LDDs.

Matrix metalloproteinase-3 and other MMPs[34,39,44,51,56,58,82,86,90,104,106]

Matrix metalloproteinase-3 (MMP-3, stromelysin-1) has an important role in the degeneration of the intervertebral discs. A common 5A/6A polymorphism in the promoter region of the human *MMP-3* has been identified[110]. This polymorphism was reported to be involved in the regulation of *MMP-3* expression with the 5A allele having twofold the promoter activity compared with the 6A allele[110]. Takahashi et al. found that 5A5A and 5A6A genotypes of *MMP-3* in the elderly were associated with a significantly larger number of degenerative intervertebral discs (IVDs) than the 6A6A, in 54 young and 49 elderly Japanese subjects[34]. The authors stated that the 5A allele is a possible risk factor for the acceleration of degenerative changes in the lumbar disc in the elderly. The association between the polymorphism of *MMP-3* and LDDs was replicated in another study using 720 women[44]. In that study, LDDs was evaluated by osteophytes, disc space narrowing, and summary Kellgren-Lawrence grade of X-ray findings. The results showed that the radiographic progression of spine degeneration was associated not only with the genes that encode molecules involved in inflammatory pathways, such as *MMP-3*, tissue inhibitor of metalloproteinase gene, and cyclooxygenase 2 gene but also associated with VDR gene and thrombospondin 2 (*THBS2*) gene. Since that time, there have been several papers demonstrating the association between LDDs and *MMP-3* with other genes and environmental factors[56,90]. In contrast, the study using 29 Finnish probands with degenerative spinal stenosis, which was evaluated by MRI, found no association of this finding with *MMP-3*[39]. However, they found the association with *COL9A2* and *COL11A2* in the same study.

Other inflammatory genes have been reported as candidates that have association with LDDs, LBP, and disabilities. In this category, *MMP-2*, *MMP-9*, and *MMP-12* were identified using Chinese and Norwegian populations[51,58,82,86,104,106].

Thrombospondin 2[44,54]

THBSs 1 and 2 are intervertebral disc ECM proteins that regulate the effective levels of MMP-2 and MMP-9, which are key effectors of ECM remodeling. Hirose et al. found that an intronic SNP in *THBS2* (IVS10-8C/T; rs9406328) showed a significant association with LDH in two independent Japanese populations[54]. Valdes et al. also reported that *THBS2* was associated with the osteophyte grade in the lumbar spine using 720 women[44]. THBSs modulate the efficacy level of MMP-2 and MMP-9, which are degradation enzymes of the intervertebral disc matrix[54].

Interleukin-1[41,45,56,66,97,119]

IL-1 is known as an inflammatory cytokine. IL-1 contributes to disc degeneration by increasing enzymes that degrade proteoglycan. It is also involved in mediating pain. The IL-1 gene (*IL-1*) family has three members: *IL-1*α, *IL-1*β, and *IL-1 receptor antagonist* (*IL-RN*). Solovieva et al. wrote several papers regarding *IL-1* polymorphisms and LDDs[41,45,119]. They first found that carriers of the *IL-1*αT or *IL-1*βT alleles have a risk of disc bulging[41]. The TT genotype of the *IL-1*α gene carries a more than threefold risk of disc bulges compared with the CC genotype. Second, they reported that the carriage of the *Trp3* allele in the absence of the *IL-1*β T(3954) allele increased the risk of dark NP and occurrence of degenerative changes in joints[45]. These results suggest that the effect of the *COL9A3* polymorphism on LDDs might be modified by the *IL-1*β polymorphism. Further, the polymorphism of *IL-1* might be related to LBP. The same group reported that carriers of the *IL-RN* (1812) allele had an increased risk of LBP and carriers of this allele in combination with the *IL-1*αT(889) or *IL-1*βT(3954) allele had a higher risk of and more days with LBP than noncarriers using a Finnish cohort[119]. Using a US population, Kim et al. described that *IL1RN* may affect the clinical course of LDH[66]. However, one paper from Mexico reported a negative association between LDDs and the polymorphisms of *IL-1*α and *VDR*[97]. One additional paper using a Finnish cohort revealed that *IL-1*α was related to the occurrence of Modic changes, which is the endplate change of the intervertebral disc[56]. Thus, *IL-1* might be important in LDDs and LBP related to disc degeneration.

Interleukin-6[62,76,120]

IL-6 is also an inflammatory cytokine. Two papers reported the association between *IL-6* polymorphism and

LDDs. Eskola et al's findings suggested possible roles of *IL-1A* and *IL-6* in early disc degeneration among Danish girls[62]. Kelempisioti et al. reported that *IL-6*, *SKT*, *(KIAA 1217)* and *CILP* were involved in the etiology of disc degeneration among young Finnish adults[76]. Noponen-Hietala et al. reported that genotypes AA and AT of the exon 5 SNP of *IL-6* were more common in the patients with discogenic LBP[120]. Haplotypes were found among four IL6 SNPs, G-597A, G-572C, G-174C, and T15A in exon 5. Haplotype GGGA was more common in the patients with discogenic LBP. Based on these results, they stated that these findings support the role of IL-6 genetic variations in discogenic pain.

Other ILs[57,74,83,104]

One Chinese study found that promoter polymorphisms of *IL-10* were associated with LDDs[74]. Several papers are available on the association between *IL-18RAP* and not only LDDs but also the treatment outcome of chronic LBP and radiographic LDDg and adjacent segment disc degeneration after lumbar fusion[57,83,104].

Carbohydrate sulfotransferase 3[89]

Carbohydrate sulfotransferase 3 (CHST3) is an enzyme that catalyzes proteoglycan sulfation. We identified *CHST3* as a susceptibility gene for LDDs, using 32,642 subjects consisting of 4,043 LDDs and 28,599 controls from Southern Chinese, Japanese, and Finnish populations[89]. This study showed that Rs4148941 was the main locus by a genome-wide association study (GWAS). This locus is within a potential microRNA-513a-5p (miR-513a-5p) binding site. The interaction between miR-513a-5p and mRNA, transcribed from the susceptibility allele (A allele) of rs4148941, was enhanced in vitro compared with transcripts from other alleles. Moreover, expression of *CHST3* mRNA was significantly reduced in the intervertebral disc cells of human subjects carrying the risk allele.

(3) Genes related to other connective tissues, such as bone and other tissues (Table 3)

These genes are not directly related to disc degeneration. However, for example, the genes that are responsible for osteoporosis are included in this category. Because it has been pointed out that there is an inverse relationship between osteoporosis and disc degeneration. Thus, these genes might be indirectly related to abnormal disc degeneration or disc diseases.

Vitamin D receptor[28,29,33,36,44,46,61,63,90,93,94,97,102,103,113]

VDR has an important role in normal bone mineralization and bone remodeling. It has been reported that the polymorphism of *VDR* contributes to diseases, such as osteoporosis, osteoarthritis, and LDDs. Numerous studies have focused on the relationship between the polymorphisms of *VDR* with or without other genes and LDDs[28,29,33,36,44,46,61,63,90,93,94,97,102,103]. All of the studies demonstrated that the t allele of *VDR* Taq I was associated with a high risk of LDDs. Videman et al. found that the f allele of Fok I has a risk of lower signal intensity of the disc[28]. The etiology is unknown. We speculated that this polymorphism in the *VDR* might alter the structural characteristics of the matrix in the intervertebral disc[35]. Furthermore, we further considered the possibility that *VDR* polymorphism is not directly involved in the pathogenesis of LDDs, rather it is merely a marker for other genes. *VDR* is located on chromosome 12q12. The *COL2A1* and *IGF1* are also located nearby. It is likely a genetic marker of LDDs.

Recently, Columbini et al. wrote a review regarding the relationship between *VDR* polymorphisms and osteoarthritis and intervertebral disc degeneration in 2013[113]. They checked the studies from 1997 to 2012 and found 16 reports were available for analysis. They showed the table entitled, "Characteristics of studies (case/control and population-based) analyzing *VDR* polymorphisms and LDDs." Regarding the association of *VDR* and LDDs, 10 papers showed a positive association and 6 papers showed a negative association. Since then, two papers have been published[91,100]. One Italian paper found that LDH was associated with a low plasma concentration of receptor activator of nuclear factor kappa-B ligand (RANKL) and the presence of the F allele of *VDR*[100]. The other paper, from Brasil, described a positive association between FokI/T2C polymorphism of *VDR* and LDDs in 121 patients and 131 controls[91].

KIAA1217 (SKT)[60]

Skt mice that showed sickle tail phenotype were established through a gene-trap mutagenesis in embryonic stem cells. Skt homozygous mutant mice showed late-onset abnormalities of the NP of the intervertebral disc. Skt has a human homolog, termed *KIAA1217* (accession number NM 019590). Thus, we (first author Karasugi T) focused on the gene as a candidate for LDH. We collected more than 1000 samples from Japanese and Finnish populations. Using tag SNPs, we examined the association in two independent Japanese case-control populations and found a significant association of *SKT* rs16924573 with LDH in the allele frequency model. The association was replicated in the Finnish population tested. The combined *p* value of the two population by meta-analysis was 0.00040, and the odds ratio was 1.34 (95% confidence interval (CI), 1.14-1.58). Based on the results, we concluded that SKT is involved in the etiology of LDH. The association between *SKT* and disc degeneration was also found in young adults using a Finnish cohort as described previously[76].

Other genes (ADH2[49], GCH1[68], COMT[67,78], HAPLN1[70], Caspase 9[71,84], GDF5[72], FAS[73], FASL[73], BCL-2[77], DR4[79], PARK 2[80], VEGF[87], eNOS[87], HIF-1α[88], ADAMTS4[105], ADAMTS5[92], ADIPOQ[95], and TRAIL[100,101])

There are several genes whose genetic polymorphisms are associated with LDDs. The information is very important and interesting. However, it is necessary to perform replication studies for these genes.

3. Functional research on how the susceptible genes cause LDDs

A functional study to elucidate the mechanism by which the susceptible genes lead to disc degeneration is very difficult to carry out. In fact, there are a few papers that include a functional study. However, top journals require to elucidate the mechanism by which the genes cause LDDs, and thus the papers that include a functional study are introduced here. These are the papers regarding *CLIP, THBS2, ASPN*, *CHTS*, and Parkinson protein 2, E3 ubiquitin protein ligase (*PARK2*). The mechanisms of *ASPN* and *CHTS* were described earlier.

Cartilage intermediate layer protein[43]

We (first author Seki S) found that CILP is expressed abundantly in the intervertebral discs in humans, and its expression increases as disc degeneration progresses. CILP is co-localized with TGF-β1 in chondrocytes and in the intervertebral discs. CILP inhibits TGF-β1-mediated induction of cartilage matrix genes through direct interaction with TGF-β1. Moreover, CILP inhibits TGF-β1 signaling. Further, the susceptibility allele of *CILP* shows increased binding and, therefore, inhibition of TGF-β1. It has been concluded that the ECM protein CILP regulates TGF-β signaling, and that this regulation has a crucial role in the etiology and pathogenesis of LDDs.

Thrombospondin 2[54]

The susceptible SNP of *THBS2*, located in a polypyrimidine tract upstream of the 30 splice site of intron 10, exerts allelic differences on exon 11 skipping rates in vivo. These phenomena mean that the susceptibility allele shows increased skipping of exon 11 that results in decreased THBS2 interaction with MMP-2 and MMP-9. Further, a missense SNP in *MMP-9* is also strongly associated with LDH and shows a combinatorial effect with *THBS2*. Therefore, a splicing-affecting SNP in *THBS2* and a missense SNP in *MMP-9* are associated with susceptibility to LDH. Hirose et al. proposed that the data indicate that regulation of intervertebral disc ECM metabolism by the THBS 2-MMP system plays an essential role in the etiology and pathogenesis of LDH.

Parkinson protein 2, E3 ubiquitin protein ligase

Williams et al. carried out a GWAS including meta-analysis on 4600 individuals to identify the susceptible genes for LDDs[80]. They found that a variant in the *PARK2* was associated with LDDs. In the functional analysis, they observed differential methylation at one CpG island of the *PARK2* promoter and a significant association between DNA methylation and LDDs.

Problematic issues related to genetic research regarding LDDs

There are several problems to be resolved in the future for the identification of the genetic background of LDDs. The following four points are the most important issues to be considered:

1. The phenotype is not defined.

As shown in Table 2, phenotype lacks consensus. There are various phenotypes targeted among different papers. Some are discussing on LDD, LDDg, LDH, and others on Modic signs on MRI. What kind of condition in the intervertebral disc should be focused upon is a very important issue.

2. Sample size is too small. Replication among different races is very rare.

There is no doubt that the study samples should be large enough to validate the analysis although the specific number is not yet determined. The larger sample sizes give more accurate results. Only one paper included over 30,000 samples[89]. The samples from only one race is not sufficient for universal knowledge. Replication studies among different races are needed. Multicenter studies involving institutes from different countries should be carried out.

3. The relationship among susceptible genes is unclear.

Although there are several studies that have focused on multisusceptible genes for LDDs[44,45,57,76,83,85,99,102], few studies were performed to clarify the relationship among these multiple genes.

4. Functional studies have not been carried out on all genes.

Although functional studies indicate how the susceptible genes work in the pathogenesis of LDDs, such studies are very difficult to perform, yet they are very important for the understanding of the pathology. The information might be useful for the prevention of the diseases. Functional studies should be carried out.

Summary

LDDs have a genetic background. There are numerous papers on susceptibility genes for the diseases. We should clarify the mechanism of how the genes affect and induce the pathological conditions in the intervertebral disc to establish future treatment and prevention strategies.

Conflicts of Interest: The author declares that there are no conflicts of interest.

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