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

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 (DALYs). 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. 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. Varughese and Quartey reported on four brothers with lumbosciatic syndrome due to acute LDH and associated spinal stenosis in 1979. Several papers have shown familial predisposition for LDDs. Grobler et al. reported that family history of seven adolescents with LDH. Varlotta et al. found that 32% of juvenile
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\(^6\). Frino et al. also stated that 43.8% of the patients with LDH have a positive family history\(^7\). 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\(^1\). 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 25.4% had a positive family history in the control. Richardson et al. reported that there was a familial predisposition toward lumbar disc pain and injury. Matsui et al. reported that there was a strong genetic effect for hand osteoarthritis and disc degeneration of the spine.

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

| first author | journal | year | content | reference No. |
|--------------|---------|------|---------|---------------|
| 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 positive family history. | 8 |

| 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 |
| Saftié 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 |

| 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 | 2009 | The review concluded that disc degeneration appears to be determined largely by genetic influence. | 27 |
LDDg, and those from Croatia were also at risk of LDH\(^1\). 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 offspring\(^6\). Kalichman and Hunter reviewed familial predisposition and heritability estimation of LDDg\(^7\).

As for the study using twins, Gunzburg et al. first reported the multilevel LDH in teenage twins\(^8\). Juvenile LDH cases in monozygotic twins that required operation were described by Matsui et al\(^9\). Obukhov et al. also reported multilevel LDH in 12-year-old twins\(^10\). 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\(^11\). 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\(^12\) 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\(^13,16\). 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)\(^18-17\)

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\(^13\). 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\(^14\). 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\(^15\). 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\(^16,54,64,75,114\)

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 occurs 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\(^16\). Numerous studies have been conducted since then\(^50,64,75,79,114\). 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)\(^12,32,37,42,45,47,49,102,107,118,117\)

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.

| 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     | osteophyisis, disc space narrowing                                        | 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       | Paasility 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 | MRI findings                                                              | 135 middle aged men                           | Finland       | Solovieva S      | Spine                 | 2002 | p 37          |
| 11 COL9A2 | disc herniation or disc degeneration                                       | 159 patients with sciatica                    | Finland       | Karpippen 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 | intervertebral disc degeneration                                          | 966 men and women ≥65 years                   | Holland       | Pujin 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 | osteophytes, 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 nucleus pulposus, disc bulge                                        | 135 middle aged occupationally 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         | Hiose Y          | Am J Hum Genet         | 2008 | p 54 *        |
| 28 ASPN   | lumbar disc degeneration                                                  | Chinese: 1054 cases, 1056 controls; Japanese: 1490 cases, 1216 controls | China         | Song YQ          | Am J Hum Genet         | 2008 | p 55 *        |
| 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        |
|              | disc signal intensity, bulging, height narrowing                          |                                    |               |                |                     |      |             |
| 30 Multi-gen, AGC, COL1A1, COL9A1, COL11A1, IL13RAP | lumbar disc degeneration                                                   | 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         | Connect 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 | 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         | Connect 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+lambar 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       | Kelemonti 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 Disorder | 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 patient 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 J    | 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 degeneration, 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 Rehab Cartilage  | 2014 | p 90          |
| 64 CILP, ASPN                 | lumbar disc degeneration, only male positive  | 516 Japanese collegiate athletes       | Japan       | Min SK       | J Orthop Res             | 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 ADIPQ                      | 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 | p 97          |
| 71 GDF5                       | symptomatic lumbar disc herniation            | 231 patients, 370 controls            | China       | Mu J         | Eur Spine J              | 2014 | p 98          |
| 72 multigene, COL1A1, 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         | China       | Zhang C      | Genet Test Mol Biomarkers | 2015 | n 100         |
| 74 TRAIL                      | lumbar disc degeneration                      | 153 LDD, 131 healthy subjects         | 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         | 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 |
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, COL9A2, 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) in the α2 chain of collagen IX, was associated with herniated lumbar disc disease Japan Ikechman L J Spine 2013 115

| gene                  | phenotype                               | subjects                      | country | first author | journal            | year | reference No. |
|-----------------------|-----------------------------------------|-------------------------------|---------|--------------|--------------------|------|---------------|
| 2 COL9A2, COL9A3, AGC, COL1A1, VDR, 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, osteoarthri-tis | Italy                          | Colombini A | J Steroid 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 disease                 | 1522 LDD, 1646 controls       | China      | Zhang Z       | Spine               | 2014               | 117  |

VDR: Vitamin D receptor  
AGC: Aggrekan  
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 sulfatotransferase 3  
ADAMTS: A disintegrin and metalloproteinase with thrombospondin motif's  

TRAIL: Tumor necrosis factor-related apoptosis-induced ligand  
DR4: Death Receptor 4  
ADIPOQ, adiponectin  
Trp: the tryptophan allele  
LDD: lumbar disc disease  
LBP: low back pain  
LDH: lumbar disc herniation  
TDD: total disc degeneration  
p: positive results  
n: negative results  
*: authors related work  
§: high association
with LDDs in the Finnish population. It has been reported that the Trp2 allele was associated with radial tear that was detected by MRI. However, in analyses using the Japanese population, the results were controversial. 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. The other study stated that unlike observations in the Finnish population, Trp1 was common in Japanese, and no association with LDDs was apparent; however, there was an association of a specific allele with LDDs in the Japanese population. Solovieva et al. stated that carriers of the COL1A2 minor allele have an increased risk of disc bulges compared with noncarriers. These results suggest that a specific allele of COL1A2 might be associated with LDDs. In contrast, one Japanese study revealed that SNP of c.4603C-->T [rs1676486] in COL1A1 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 COL1A1 might be a susceptible gene for LDDs.

**Collagen XI (COL11A1)**

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 COL1A2 and LDDs. Noponen-Hietala et al. analyzed 29 Finnish probands with lumbar degenerative stenosis. 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 COL1A2 minor allele have an increased risk of disc bulges compared with noncarriers. These results suggest that a specific allele of COL11A2 might be associated with LDDs.

**Collagen I (COL1A1)**

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. The other study using a small Greek population also found that TT genotype was associated with MRI-evaluated LDDs. This SNP was previously demonstrated as a susceptible gene for osteoporosis and fracture, including vertebral fracture.

**Cartilage intermediate layer protein**

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. 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. 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. 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.

**Asporin**

Asporin (ASPN) belongs to a family of leucine-rich re-
peat proteins, which are in the cartilage matrix. Previous studies have shown that the D14 allele of ASPN is associated with osteoarthritis of the knee. 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. Our team (first author Song YQ) reported that the D14 allele is also significantly associated with LDDs in Chinese and Japanese populations. Meta-analysis showed that individuals with a D14 allele of ASPN had a higher risk of DDD with a summary odds ratio of 1.70. 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

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. 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. 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 6A6 A, in 54 young and 49 elderly Japanese subjects. 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. 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.

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. 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.

Thrombospondin 2

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. Valdes et al. also reported that THBS2 was associated with the osteophyte grade in the lumbar spine using 720 women. THBSs modulate the efficacy level of MMP-2 and MMP-9, which are degradation enzymes of the intervertebral disc matrix.

Interleukin-1β

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-1α, IL-1β, and IL-1 receptor antagonist (IL-RN). Solovieva et al. wrote several papers regarding IL-1 polymorphisms and LDDs. They first found that carriers of the IL-1αT or IL-1βT alleles have a risk of disc bulging. The TT genotype of the IL-1α 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-1β T (3954) allele increased the risk of dark NP and occurrence of degenerative changes in joints. These results suggest that the effect of the COL9A3 polymorphism on LDDs might be modified by the IL-1β 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-1αT(889) or IL-1βT(3954) allele had a higher risk of and more days with LBP than noncarriers using a Finnish cohort. Using a US population, Kim et al. described that IL1RN may affect the clinical course of LDH. However, one paper from Mexico reported a negative association between LDDs and the polymorphisms of IL-1α and VDR. One additional paper using a Finnish cohort revealed that IL-1α was related to the occurrence of Modic changes, which is the endplate change of the intervertebral disc. Thus, IL-1 might be important in LDDs and LBP related to disc degeneration.

Interleukin-6

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-1α and IL-6 in early disc degeneration among Danish girls[26]. Kelemisioti et al. reported that IL-6, SKT, (KIAA1217) and CILP were involved in the etiology of disc degeneration among young Finnish adults[26]. 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[26]. 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[27,28,83,104]

One Chinese study found that promoter polymorphisms of IL-10 were associated with LDDs[76]. 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[85,83,104].

Carbohydrate sulfotransferase 3[80]

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[80]. 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[25,29,31,36,44,46,81,83,94,97,102,101,113]

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[25,29,31,36,44,46,81,83,94,97,102,101]. 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 t allele of Fok I has a risk of lower signal intensity of the disc[26]. The etiology is unknown. We speculated that this polymorphism in the VDR might alter the structural characteristics of the matrix in the intervertebral disc[26]. 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, Colombini et al. wrote a review regarding the relationship between VDR polymorphisms and osteoarthritis and intervertebral disc degeneration in 2013[77]. 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[77,100]. 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[70]. The other paper, from Brasil, described a positive association between FokI/T2C polymorphism of VDR and LDDs in 121 patients and 131 controls[70].

KIAA1217 (SKT)[80]

Skts 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 populations 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[80].

Other genes (ADH2[69], GCH1[71], COMT[87,78], HAPLN1[70], Caspase 9[74, GDF5[72], FAS[73], FASL[77], BCL-2[77], DR4[75], PARK 2[80], VEGF[76], eNOS[75], HIF-1α[75], ADAMTS4[80], ADAMTS5[80], ADIPQ[80], and TRAIL[80,80])

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**

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**

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. 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. 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, 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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