REVIEW ARTICLE

INTERVERTEBRAL DISC DEGENERATION LINKED TO STRUCTURAL GENE VARIATIONS

Shahzad Shoukat Nayani[1], Saeeda Baig[2]
[1]Department of Community Health Sciences, [2]Ziauddin University, Department of Biochemistry, Ziauddin University, Clifton, Karachi, Pakistan.

ABSTRACT

During the recent past focus has shifted from identifying intervertebral disc degeneration as being caused by physical exposure and strain to being linked with a variety of genetic variations. The objective of this review is to provide an up to date review of the existing research data regarding the relation of intervertebral disc degeneration to structural protein genes and their polymorphisms and thus help clearly establish further avenues where research into causation and treatment is needed. A comprehensive search using the keywords "Collagen", "COL", "Aggrecan", "AGC", "IVDD", "intervertebral disc degeneration", and "lumbar disc degeneration" from PubMed and Google Scholar, where literature in the English language was selected spanning from 1991 to 2019. There are many genes involved in the production of structural components of an intervertebral disc. The issues in production of these components involve the over-expression or under-expression of their genes, and single nucleotide polymorphisms and variable number of tandem repeats affecting their structures. These structural genes include primarily the collagen and the aggrecan genes. While genetic and environmental factors all come into play with a disease process like disc degeneration, the bulk of research now shows the significantly larger impact of hereditary over exposure. While further research is needed into some of the lesser studied genes linked to IVDD and also the racial variations in genetic makeup, the focus in the near future should be on establishment of genetic testing to identify individuals at greater risk of disease and deliberation regarding the use of gene therapy to prevent disc degeneration.

Keywords: Intervertebral Disk Degeneration; Collagen; Aggrecan.

Corresponding Author:
Dr. Saeeda Baig
Department of Biochemistry,
Ziauddin University, Clifton, Karachi, Pakistan.
Email: saeeda.baig@zu.edu.pk
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INTRODUCTION

The intervertebral disc degeneration has a complicated and multifaceted etiology, which is progressive with age and is occasionally irreversible. Although mechanical insults due to lifestyle and occupation are termed as major risk factors; yet, the dominant role of genetics cannot be ruled out. The spinal cord in humans receives a certain degree of mechanical support and safety from the 33 vertebrae, supporting ligaments, and muscles which form the vertebral column[1]. The discs account for 20-30% of the spinal length. Their primary function is to help distribute the weight, help with movement of the vertebrae, cushion the spine from loads and impacts, and allow nutrients to reach the spine and spinal cord[2]. The intervertebral discs are mostly composed of water, collagen fibers, and an aggregating proteoglycan called aggrecan which binds covalently to glycosaminoglycans chains[3]. Intervertebral discs develop macroscopic, microscopic and immunohistological changes over time, which is generally clumped together under the title of intervertebral disc degeneration (IVDD). This involves dehydration of the disc, fragmentation of collagens, and development of annular tears resulting in disc height reduction[4]. Studies conducted on degenerated discs in the past have revealed that this process of degeneration often begins in the second decade of life and is associated with modification of extracellular matrix proteins[5].

It has been determined that in the second decade of life, the relative risk of intervertebral disc herniation is approximately five times greater in patients with a family history of backache, sciatica or disc herniation[6]. In the Japanese population, a case control study resulted in a statistically relevant odds ratio of 5.61 showing the importance of family history in cases of disc herniation at age 18 years or less[7]. In 1995 a multivariate analysis of disc degeneration was done which revealed that at the upper lumbar

level familial aggregation of the model lead to an additional 61% of variability being explained compared to 7% explained by job code and 9% explained by age, while at lower lumbar level, twinship explained an additional 34% of variation compared to the 2% explained by physical loading and 7% explained by aging[8]. A major twin study comparing monozygotic and dizygotic twins revealed that heritability accounted for 74% and 73% of the variation in mild to moderate degeneration while for severe disease it was 64% and 79% at lumbar and cervical spine respectively[9]. Data from the twin spine study revealed that despite the remarkable differences in occupation and leisure time physical loading throughout adulthood, monozygotic twins showed very little difference in the extent of disc degeneration[10]. Since then multiple papers have not only established the contributions of hereditary in development of intervertebral disc disease[11] but also presented research linking the differential expression of multiple genes (either by up-regulation or down-regulation) to disc degeneration[12]. Functional polymorphisms have also been identified in several genes which are associated with the development of this disorder[4,13]. The thought process at play is that all genes that play a part in matrix turnover and organization, including collagen and aggrecan genes, are linked to the mechanical effects seen in IVDD[4].

The basis of this review is to recognize the etiology of disc degeneration with emphasis on structural gene polymorphisms associated with intervertebral disc degeneration, particularly the collagens and aggrecan genes. The goal of this paper is to establish the scope of knowledge already available and to determine areas where more research is needed to reach significant conclusions. This will eventually help the medical community reach conclusions whereby genetic interventions can be planned to halt or reverse the development of IVDD in the global population.

DISCUSSION

Table 1 offers a summary of the multiple structural components contributing to the intervertebral disc, their encoding genes, and the variations of each gene which has been explored in this review along with their proposed links to intervertebral disc degeneration. These are later discussed in further detail.

Table 1: Genetic link to IVDD.

Structural component	Encoded by gene	Variation involved	Link to IVDD	Reference
Collagen type I	COL1A1	GG, GT, TT	GT, TT: Increased risk of development of degenerative changes, decreased disc signal intensity, increased disc dessication, and disc bulging	4, 27, 28, 31
		Over-expression	Increased risk of IVDD	29
Collagen type II	COL2A1	rs1793953(A)	Decreased risk of developing disease	34
		rs2276454(C)	Increased risk of developing disease	34
		Over-expression	Seen in severely degenerated discs	29
Collagen type III	COL3A1	Over-expression	Increased risk of IVDD	4, 32, 36
		Under-expression	Increased risk of IVDD	37
Collagen type IX	COL9A2	Trp2 (G→T)	Increased risk of IVDD, endplate degeneration, disc prolapse, herniation, annular tears, and radial tears	42, 43, 44, 45, 53
		221 Haplotype	Increased risk of IVDD	
	COL9A3	Trp3 (G→T)	Increased risk of IVDD	31, 48, 49, 50, 54
Collagen type XI	COL11A1	c.4603CrT [rs1676486]	Increased severity of IVDD with decreased expression secondary to decreased stability of transcript caused by presence of this allele	58
		rs1463035	Increased risk of disc bulging	4
		rs1337185	Increased risk of disc bulging	4
	COL11A2	rs2071025(A)	Increased risk of IVDD	60
		rs986522(C)	Increased risk of IVDD in females	60
		rs2076311	Decreased disc signal intensity	4
Aggrecan	AGC1	VNTRs	Low VNTR alleles increase risk of IVDD, multilevel disc disease, and herniation	34, 61, 62, 63, 64, 65
		Under-expression	Increased risk of IVDD	29, 37
		rs1516797	Increased risk of disc height narrowing	4
		rs1042631	Decreased disc signal intensity	4

COLLAGENS

Genetic polymorphisms are variations in DNA sequence, which have a high frequency of occurrence in the population[14]. For each gene identified in the human genome, there are hundreds of variants. For COL1A1 alone, there are 729 identified variations[15]. The importance of collagen gene polymorphisms has been well established in skeletal and connective tissue disease processes in the past. COL2A1 gene mutations have been linked to skeletal dysplasias, osteoarthritis, chondrodysplasia, and achondrogenesis, while COL11A1 and COL9A gene mutations have been associated with fibrochondrogenesis and multiple epiphyseal dysplasia respectively[16]. COL1A1 polymorphisms have been proven to be linked to infantile cortical hyperostosis, Ehlers-Danlos syndrome, osteogenesis imperfect, and postmenopausal osteoporosis as well as osteoporosis in men[15,17-19]. Even in prepubertal women, COL1A1 polymorphisms have been linked to lower vertebral bone density, suggesting the strong association of genetics with a process thought to rely primarily on hormonal changes in old age[20].

Collagen Type I

Collagen type I has two a1 chains and one a2 chain. These are encoded by the COL1A1 and COL1A2 genes respectively. A functional polymorphism at the fourth Sp1 binding site in intron 1 of the COL1A1 gene (Figure 1), leading to thymidine (T) being substituted for a guanine (G), has been identified and studied for its link to IVDD[21]. Research proved that an "s" allele (representing a T substitution) has greater binding affinity for the Sp1 protein leading to primary RNA transcripts derived from the "s" allele being three times more abundant that the "S" allele derived transcripts. This lead to increased ratios of COL1A1 mRNA as compared to COL1A2 mRNA and "s" allele homozygotes and heterozygotes had lower yield strength of bone as compared to "SS" individuals[22]. Further research revealed that carriage of one copy of the "s" allele lead to a significant reduction in lumbar spinal bone mineral density and an increased risk of vertebral fracture[23-25].

In 1997 collagen type 1 was identified as appearing in increased levels in degenerated intervertebral discs[5]. After that point multiple researches showed varying results in this regard. In 2003 a study of Finnish subjects, which studied MRI proven cases of IVDD, concluded that there was no evidence of variations in Collagen 1 and 2 genes being associated with spinal stenosis[26]. In the Netherlands in 2004 research proved that people with a TT genotype had a three times higher risk of IVDD than people with a GG genotype. They also had a higher risk than those with GT genotype[27]. Greek army recruits were investigated for Sp1 polymorphisms and it was found that while "ss" genotype frequency was increased in IVDD patients, it was not present at all in controls. Further they found that the number of people in the control group who were heterozygous for this allele were significantly lesser as compared to the diseased group[28]. Videman et al. studied 25 genetic variations for a link with IVDD and concluded that COL1A1 was among the genes for which allelic variants provided the most significant evidence of being associated with disc signal intensity, disc desiccation, and disc bulging[4]. Study of degenerated disc samples obtained from discectomies in South Korea showed, in mildly degenerated discs, mRNA expressions of type I collagen were 1.41 times higher than in the samples of severely degenerated discs[29]. On the contrary to these studies, an investigation of the Indian population done in 2015 showed that cases and controls both had a similar distribution of genotypes GG, GT, and TT with no significant difference, thus concluding that the T allele had no impact on IVDD in the Indian population[30]. In Turkey a case control research into the link of single nucleotide polymorphisms with IVDD showed that not only was there statistically significant difference in the Pfirrmann score (a grading system for disc degeneration) between neutral and heterozygous cases of COL1A1 Sp1 allele polymorphism but the difference also existed between neutral and homozygous cases, and homozygous and heterozygous cases[31].

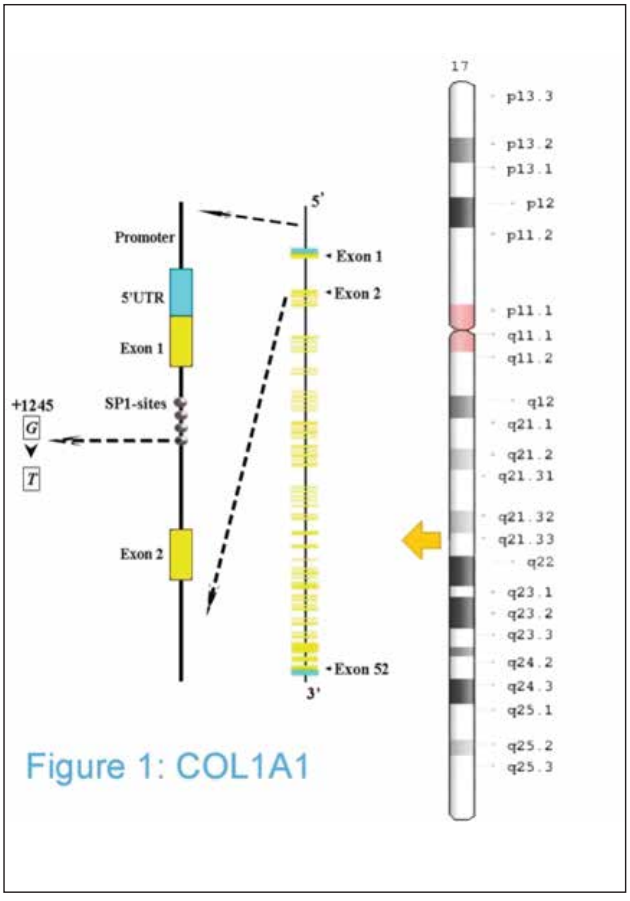

Figure 1: COL1A1

Collagen Type II

Nerlich et al. in 1997 also proposed that in the process of disc degeneration, the initial phases involved an increase in Collagen II levels, while the later phases saw a decrease in Collagen II levels[5]. Later on detailed research into the association of Collagen II genotypes with IVDD yielded no evidence of such a link[26]. However, one of the most comprehensive studies of polymorphisms related to IVDD concluded that the association of the COL2A1 gene (Figure 2) with disc signal intensity and the association of COL2A1 variants with disc bulging exhibited values close to statistical significance (p values 0.054-0.089),[4] hence demonstrating the importance of further research into this area. Study on the microarray datasets from GEO database regarding IVDD showed COL2A1 to be over-expressed in severely degenerated intervertebral discs compared to mildly degenerated ones[32]. Research into mRNA expression in IVDD showed a 1.82 times increased Collagen type II mRNA production in severe disc degeneration as compared to mild disease[29]. In 2017 a study of the Chinese population showed that Collagen type II expression was significantly down-regulated in the nucleus pulposus from patients suffering from IVDD as compared to controls. The same study found that treatment via addition of purified Collagen type II prevented the interleukin (IL)-1β induced degeneration of the nucleus pulposus cell line, while also decreasing the apoptotic rate of these cells[33]. Another study in the Chinese population concluded that two single nucleotide polymorphisms (SNPs) of COL2A1 had vastly different effects on disease. Those with an A allele in one of the SNPs (rs1793953) had a lower risk of developing IVDD than those with a T allele, and in another SNP (rs2276454) those with a C allele had higher risk of developing IVDD than those with a T allele[34].

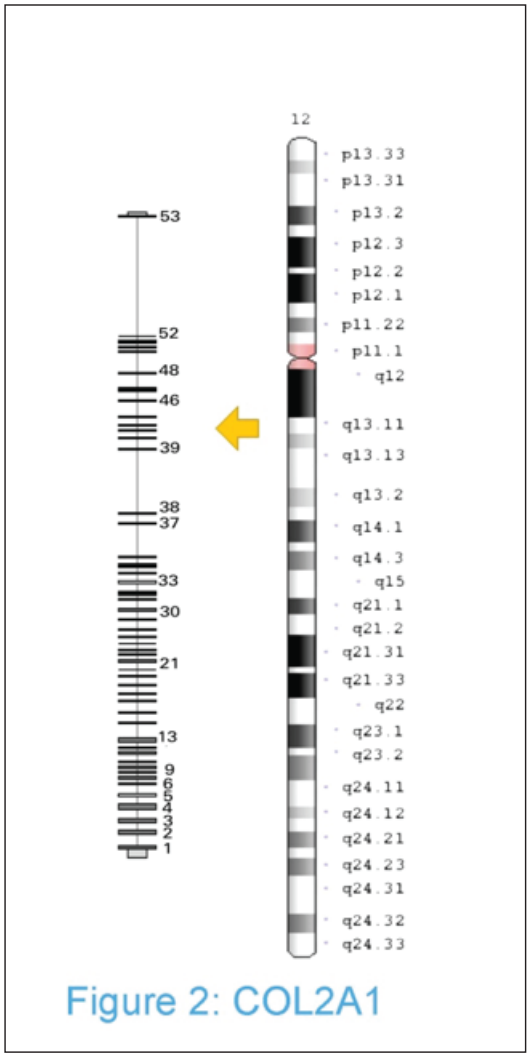

Figure 2: COL2A1

Collagen Type III

Collagen type III has been noted to be a common differentially expressed gene in the annulus cells as well as the nucleus pulposus cells, where it plays a role in the skeletal system process in the progression of IVDD[35]. The levels of Collagen III have been established to increase in the initial phases of IVDD and then finally decrease with the increasing severity of disease5. COL3A1 (Figure 3) expression was noted to be enhanced in the more severely degenerated disc samples as compared to less degenerated samples using microarray datasets from the GEO database[32]. A research in 2019 into the potential targets and signaling pathways of IVDD also identified COL3A1 as being significantly up-regulated in degenerative discs[36]. However despite these papers, there is a lack of case control studies in the different populations to determine the significance of the role of COL3A1 in IVDD. Videman et al. did report that while individual

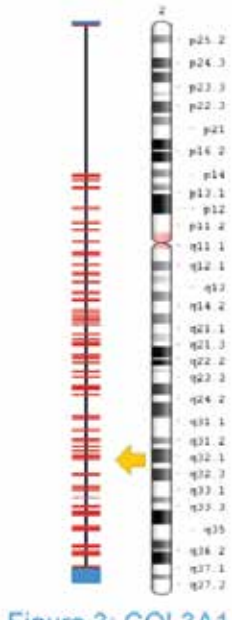
Figure 3: COL3A1

variations in the gene did not reach statistical significance, the association of these COL3A1 genes with disc bulging were close to having significant p values and a haplotype analysis showed that it was associated with disc bulging[4]. Gruber et al. noted that COL3A1 expression was significantly 3.25-fold down-regulated in IVDD[37].

Collagen Type IV

Collagen type IV has in the past been noticed to be present in the nucleus pulposus of young patients with minor disc degeneration lesions[5]. In 2005 Wang et al. concluded that Collagen type IV occurs in the intervertebral disc in a younger age group, particularly adolescents, and is an early cellular reaction in the degenerative process[38]. This raises the possibility that further work on this particular protein and its corresponding gene could have major implications in the detection and treatment of IVDD in a very early age.

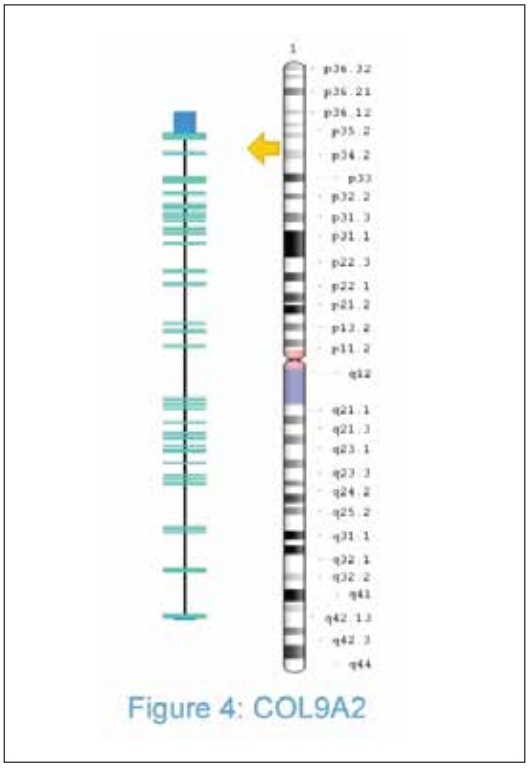

Figure 4: COL9A2

Collagen Type IX

Collagen type IX is essentially a heterotrimer made of genetically separate a1, a2, and a3 chains which functions in the cross-linkage of Collagen type II fibrils[39]. In 1996 a study on transgenic mice with mutations of Collagen type IX gene was done to see the progression of IVDD in these mice, which would develop a truncated form of Collagen IX alpha 1 chain, with age as compared to controls. This study concluded that transgenic mice not only showed more advanced degeneration and disc space narrowing, but also developed anterior and posterior herniations leading to impingement on the spinal cord, as compared to only moderate degeneration in the control group[40]. Collagen IX presence was studied in adult disc tissue regardless of the presence of any gene polymorphisms and it was found that Collagen IX deposition was not related to the genotype status and rather was linked to the presence or absence of degenerative change. Disc herniation was thus noted to result in the greatest presence of Collagen IX[41].

A specific variation was identified in COL9A2 where a codon for glutamine was converted to one for tryptophan (Figure 4). All the individuals carrying this Trp2 allele had IVDD according to Annunen et al[42]. A study done in the German population yielded results where the patients who carried the Trp2 allele suffered from IVDD, specifically prolapse, at a higher age than those without this allele[43]. Contrary to this finding, in the Japanese population it was shown that patients under the age of 40 years with a Trp2 allele had significantly more severe IVDD than those without the Trp2 allele; however patients over the age of 40 years had no significant association between IVDD and

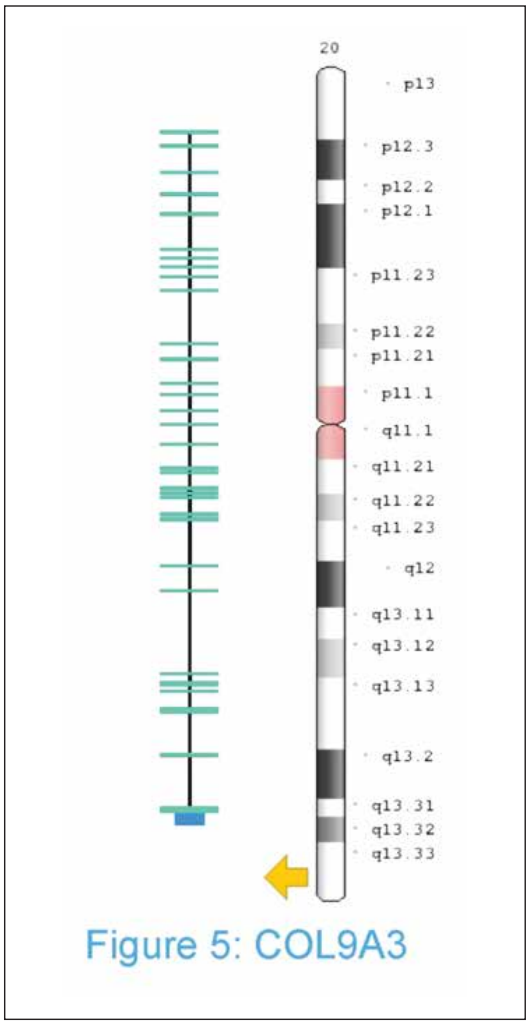

Figure 5: COL9A3

Collagen IX genotype. This indicated that the Trp2 allele is an age dependent risk factor affecting the younger age group[44]. The Trp2 allele was also studied in Finland by Karppinen et al. who studied MRI findings in patients with sciatica and their family members. They found that while clinical symptoms, disc and endplate degeneration, dorsal transverse tears, Schmorl's nodes, and high intensity zone lesions did not differ with the presence or absence of the Trp2 allele, the family members with Trp2 allele had a greater degree of disc and endplate degeneration as compared to those without, and Trp2 allele positive patients had more radial tears in non-herniated discs than those who were negative[45]. In the Japanese population, SNPs in COL9A2 were studied which included Trp2 which was found to be common in this population. The researchers concluded that while Trp2 had no association with IVDD in their study, there was significant association of a specific 221 haplotype of COL9A2 with severe lumbar disc degeneration, raising questions which will require further research[46]. Another such study from Germany looked at biopsy samples from 288 patients and found that while the Trp2 allele was not detected in these samples, homozygosity for a glutamine to arginine substitution (Arg) allele of COL9A2 was more frequent in the patients with early recurrence of IVDD. This association was not statistically significant but does warrant further research[47].

A similar variation of guanine to tryptophan was found in COL9A3 (Figure 5) where the presence of one Trp3 allele was reported to cause a threefold increase in IVDD as studied in a Finnish population[48,49]. A study regarding the link of obesity with IVDD and the role of Trp3 allele in this regard was performed in 2002 which concluded that while persistent obesity has an effect on lumbar IVDD, those who have a Trp3 allele are at greater risk with as much as 45-71% of the disc degeneration being attributable to this synergism[50]. The Greek population however, in contrast to the above papers, showed that none of the patients suffering from IVDD had a Trp2 allele present. It was found that there were more IVDD patients than controls who had at least one Trp3 allele present but this was not a statistically significant difference[51]. This difference in the effect of Trp3 allele on IVDD might be due to the modification of effect of COL9A3 polymorphism by the existence of absence of another gene polymorphism, like the IL-1βT^{3954} allele. The presence of this allele was noted to nullify the effect of a Trp3 allele on IVDD in a multivariate logistic regression analysis[52]. In 2015 a study done in Turkey found that COL9A2 Trp2 polymorphism is not linked to IVDD, however the COL9A Trp3 heterozygotes had significantly worse degeneration scores31. A Chinese population study also studied both the Trp2 and Trp3 alleles in relation to IVDD in 804 volunteers who underwent MRI scanning, and the Trp3 allele was noted to be absent in the Chinese population. The Trp2 allele was present in 20% of the population and it was found that it confers a fourfold greater risk of annular tears from 30-39 years of age, and a 2.4-fold greater risk of IVDD and herniations from 40-49 years of age[53]. In the Iranian population it was found that the Trp2 and Trp3 allele were both present in patients and controls, and patients with Trp3 allele had a 5.8-fold increase in odds of developing IVDD[54].

A study from the Finnish population conducted by Virtanen et al. however, found that neither COL9A2 nor COL9A3 had any relation to IVDD development and rather it was the occupation, and the exposure to whole body vibrations which was a risk factor[55]. Videman et al. also concluded that COL9A3 SNPs had no association with IVDD4. A meta-analysis conducted in 2018 covering 10 case control studies also concluded that COL9A2 and COL9A3 polymorphisms were not associated with IVDD[56]. Another meta-analysis in the same year reached the same conclusion regarding COL9A3 and found no link of the Trp3 polymorphism to IVDD[57].

Collagen Type XI

Collagen XI a1 chain is encoded by the COL11A1 gene. This gene has recently been studied with regards to its link with IVDD. Mio et al found that the level of its expression was inversely proportional to

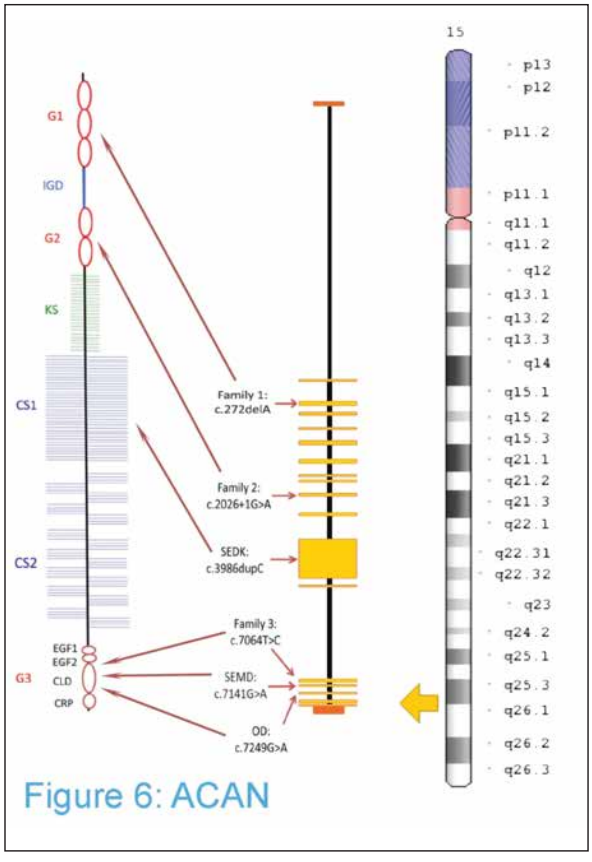

Figure 6: ACAN

the severity of disc degeneration. A specific SNP (c.4603CrT [rs1676486]) was analyzed and it was found that gene transcripts that carried this particular allele were less stable and this lead to a decrease in Collagen XI production, leading to development of IVDD[58]. The importance of Collagen XI in normal functioning of joints and cartilage was further demonstrated during a study of Zebrafish which found that those with a mutation in COL11A2 developed multiple joint pathologies[59]. A case control study to investigate COL11A2's role in IVDD in the Chinese population, studied six SNPs of the gene and found that in rs2071025, carriers of the "A" allele had a significantly greater risk of developing disease as compared to the "G" allele and that this was common to both males and females. Another polymorphism rs986522(C) was noted to significantly increase the risk of IVDD in females but not in males[60]. COL11A1 variants (rs1463035 and rs1337185) have also been linked with statistical significance to disc bulging and COL11A2 variant rs2076311 has shown significant association with disc signal intensity[4].

Aggrecan

Aggrecan, a proteoglycan, forms large aggregates with hyaluronan which restricts its movement in the extracellular matrix of cartilage. This prevents aggrecan moving away from the site under compression, and this property is utilized in the intervertebral disc. Its function relies heavily on the number of chondroitin sulfate (CS) chains present on the aggrecan core protein, primarily at the CS1 and CS2 domains (Figure 6). The CS1 domain exhibits changes with polymorphism of aggrecan gene which lead to differences in the size of CS chains on aggrecan in different people. The shorter the aggrecan allele, the lower the number of CS chains on the aggrecan molecule, the more impaired aggrecan function. This causes a decreased capacity to tolerate compression and tissue degeneration, which in turn leads to IVDD[61]. A study in American population found that severely degenerated discs had greatly decreased aggrecan immunolocalization as compared to a uniform presence in healthy discs. Gene expression analysis showed that the aggrecan gene was significantly down-regulated 1.05-fold in patients with IVDD[37].

In 1999 Kawaguchi et al. conducted a case control study to examine the variable number of tandem repeats in the aggrecan gene and their link with the development of IVDD. They concluded that study participants with short alleles had more severe disease, but none of the alleles were linked to the number or the types of herniations[62]. A study of Turkish patients also checked the VNTR polymorphisms of the aggrecan gene (AGC1). It was found that shorter alleles (13-25 repeats) were associated with severe IVDD and with multilevel disc disease and herniation, while normal (26-27 repeats) and longer (28-32 repeats) alleles were associated with herniation at only a single level[63]. In the Iranian population it was found that shorter AGC1 alleles which were ≤24 repeats occurred frequently in cases rather than in controls, such that the odds of IVDD were 3.28 times greater in shorter AGC1 allele carriers[64]. This finding was replicated in the Chinese population where shorter alleles were significantly linked to IVDD as compared to longer ones[34]. Similarly in the Korean population, it was determined that in the sample where subjects were 40 years old or less, the shortest allele (21 repeats) was significantly over-expressed in cases with IVDD as compared to controls[65]. Park et al. examined the mRNA expression of structural genes in IVDD cases and found that aggrecan expression was 1.83 times greater in those with mild disease versus those with severe IVDD[29]. Gu et al. reported that this association is specific for certain ethnicities. They found that shorter alleles had a greater risk of IVDD than normal or longer alleles. Upon analyzing the data by ethnicity, they discovered that in Asian population the shorter allele was significantly linked to developing IVDD while the normal and longer alleles were not, as compared to none of the 3 allele groups being associated with IVDD in the European population[66]. A specific allele of aggrecan (rs1516797) has also been identified as causing disc height narrowing, while the rs1042631allele has been linked to decreased disc signal intensity,[4] both of which require further study.

CONCLUSION

The degenerative process affecting intervertebral discs has long been established to be associated with multiple etiologies. A prevalent opinion regarding the importance of the role of mechanical wear and tear, and physical loading on the vertebral column has now long been challenged since it has become apparent that genetics and hereditary has a stronger role in the pathogenesis than the aforementioned factors.

As evidenced from the multiple studies mentioned in this review however, there are many areas where further work is urgently needed. One factor that needs consideration since genetics are at play is that the variances in the relationship between these factors and the disease process also rely heavily on the ethnicity or heritage of the study population. An example can be found in the research regarding COL1A1. COL1A1 expression needs to be studied further because from the studies conducted so far in different ethnic populations, while the majority report a significant linkage between IVDD and Collagen I gene polymorphisms, there are some populations where the link has not been proven and many other populations where studies have not yet been conducted. It is imperative to know the background data and conduct studies in these populations so that ways

to treat this disease preemptively can be explored and possibly implemented according to the genetic makeup of that specific racial group. The case can be made for the genes linked to Collagen types II, III, IX, XI, and Aggrecan, which have certain studies showing significant links to IVDD, while others show no association or an inverse association to IVDD partially due to the fact that certain populations do not exhibit certain alleles at all and may have other genetic markers present which need to be identified and worked on.

Another factor to consider for further research is that in many of the studies conducted to date, the sample sizes or the number of cases where genetic associations were identified have not been sufficient to help represent that association when a multivariate regression analysis or a meta-analysis was conducted later on. There are many subtypes like Collagen IV, V, VI, VIII, and X which have not been sufficiently studied. Further research in these areas is required now more than ever before, since the tools to prevent diseases like IVDD, which have significant detrimental impact on quality of life and which were previously only thought to be preventable with life style modifications, are now within the reach of modern science.

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CONFLICT OF INTEREST

There was no conflict of interest among the authors.

AUTHORS CONTRIBUTION

SB conceived the idea and finalized the manuscript. SSN did the literature review, wrote the manuscript, and crafted tables and figures.

REFERENCES

1. O'rahilly m, carpenter & swenson. Basic human anatomy. 2008 [Available from: https://www.dartmouth.edu/~humananatomy/part_7/chapter_39.htmlw.
2. Frost BA, Camarero-Espinosa S, Foster EJ. Materials for the spine: anatomy, problems, and solutions. Mater. 2019;12(2):253.
3. Muir H. The chondrocyte, architect of cartilage. Biomechanics, structure, function and molecular biology of cartilage matrix macromolecules. Bioessays. 1995;17(12):1039-48.
4. Videman T, Saarela J, Kaprio J, Näkki A, Levälahti E, Gill K, Peltonen L, Battié MC. Associations of 25 structural, degradative, and inflammatory candidate genes with lumbar disc desiccation, bulging, and height narrowing. Arthritis Rheum. 2009;60(2):470-81.
5. Nerlich AG SE, Boos N. 1997 Volvo Award winner in basic science studies. Immunohistologic markers for age-related changes of human lumbar intervertebral discs. Spine (Phila Pa 1976). 1997;22(24):2781-95.
6. Varlotta GP, Brown MD, Kelsey JL, Golden AL. Familial predisposition for herniation of a lumbar disc in patients who. J Bone Joint Surg Am. 1991;73:124-8.
7. Matsui H, Terahata N, Tsuji H, Hirano N, Naruse Y. Familial predisposition and clustering for juvenile lumbar disc herniation. Spine. 1992;17(11):1323-8.
8. Battie MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. Spine. 1995;20(24):2601-12.
9. Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. Arthritis Rheum. 1999;42(2):366-72.
10. Battié MC, Videman T, Kaprio J, Gibbons LE, Gill K, Manninen H, Saarela J, Peltonen L. The Twin Spine Study: contributions to a changing view of disc degeneration. Spine J. 2009;9(1):47-59.
11. Patel AA, Spiker WR, Daubs M, Brodke D, Cannon-Albright LA. Evidence for an inherited predisposition to lumbar disc disease. J Bone Joint Surg. 2011;93(3):225.
12. Jiang K, Li Y, Cao GY, Liu D, Liao DF, Gong K, Xie QY, Ma ZH, Pan XM. Screening of genes related with intervertebral disc disease by dynamic differential interaction network analysis. Eur Rev Med Pharmacol Sci. 2013;17(23):3186-91.
13. Mayer JE, Iatridis JC, Chan D, Qureshi SA, Gottesman O, Hecht AC. Genetic polymorphisms associated with intervertebral disc degeneration. Spine J. 2013;13(3):299-317.
14. Janeczko Ł, Janeczko M, Chrzanowski R, Zieliński G. The role of polymorphisms of genes encoding collagen IX and XI in lumbar disc disease. Neurol Neurochir Pol. 2014;48(1):60-2.
15. Information NCB. COL1A1[gene]: National Center for Biotechnology Information; 2019 [Available from: https://www.ncbi.nlm.nih.gov/clinvar/?term=COL1A1%5Bgene%5D.
16. Arseni L, Lombardi A, Orioli D. From structure to phenotype: impact of collagen alterations on human health. Int J Mol Sci. 2018;19(5):1407.
17. Harris SS, Patel MS, Cole DE, Dawson-Hughes B. Associations of the collagen type Ia1 Sp1 polymorphism with five-year rates of bone loss in older adults. Calcif Tissue Int. 2000;66(4):268-71.
18. Uitterlinden AG, Burger H, Huang Q, Yue F, McGuigan FE, Grant SF, Hofman A, van Leeuwen JP, Pols HA, Ralston SH. Relation of alleles of the collagen type Ia1 gene to bone density and the risk of osteoporotic fractures in postmenopausal women. N Eng J Med. 1998;338(15):1016-21.

19. Langdahl BL, Ralston SH, Grant SF, Eriksen EF. An Sp1 binding site polymorphism in the COLIA1 gene predicts osteoporotic fractures in both men and women. J Bone Miner Res. 1998;13(9):1384-9.
20. Sainz J, Van Tornout JM, Sayre J, Kaufman F, Gilsanz V. Association of collagen type 1 a1 gene polymorphism with bone density in early childhood. J Clin Endocrinol Metab. 1999;84(3):853-5.
21. U.S. National Library of Medicine. Collagen type I alpha 1 chain 2019 [Available from: https://ghr.nlm.nih.gov/gene/COL1A1#location.
22. Mann V, Hobson EE, Li B, Stewart TL, Grant SF, Robins SP, Aspden RM, Ralston SH. A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. J Clin Invest. 2001;107(7):899-907.
23. Keen RW, Woodford-Richens KL, Grant SF, Ralston SH, Lanchbury JS, Spector TD. Association of polymorphism at the type I collagen (COL1A1) locus with reduced bone mineral density, increased fracture risk, and increased collagen turnover. Arthritis Rheum. 1999;42(2):285-90.
24. Mann V, Ralston SH. Meta-analysis of COL1A1 Sp1 polymorphism in relation to bone mineral density and osteoporotic fracture. Bone. 2003;32(6):711-7.
25. Grant SF, Reid DM, Blake G, Herd R, Fogelman I, Ralston SH. Reduced bone density and osteoporosis associated with a polymorphic Sp1 binding site in the collagen type I a 1 gene. Nat Genet. 1996;14(2):203.
26. Noponen-Hietala N, Kyllönen E, Männikkö M, Ilkko E, Karppinen J, Ott J, Ala-Kokko L. Sequence variations in the collagen IX and XI genes are associated with degenerative lumbar spinal stenosis. Ann Rheum Dis. 2003;62(12):1208-14.
27. Pluijm SM, Van Essen HW, Bravenboer N, Uitterlinden AG, Smit JH, Pols HA, Lips P. Collagen type I a 1 Sp1 polymorphism, osteoporosis, and intervertebral disc degeneration in older men and women. Ann Rheum Dis. 2004;63(1):71-7.
28. Tilkeridis C, Bei T, Garantziotis S, Stratakis CA. Association of a COL1A1 polymorphism with lumbar disc disease in young military recruits. J Med Genet. 2005;42(7):e44-.
29. Park JY, Kuh SU, Park HS, Kim KS. Comparative expression of matrix-associated genes and inflammatory cytokines-associated genes according to disc degeneration: analysis of living human nucleus pulposus. Clin Spine Surg. 2011;24(6):352-7.
30. Anjankar SD, Poornima S, Raju S, Jaleel MA, Bhiladvala D, Hasan Q. Degenerated intervertebral disc prolapse and its association of collagen I alpha 1 Spl gene polymorphism: A preliminary case control study of Indian population. Indian J Orthop. 2015;49(6):589.
31. Toktaş ZO, Ekşi MŞ, Yılmaz B, Demir MK, Özgen S, Kılıç T, Konya D. Association of collagen I, IX and vitamin D receptor gene polymorphisms with radiological severity of intervertebral disc degeneration in Southern European Ancestor. Eur Spine J. 2015;24(11):2432-41.
32. Chen K, Wu D, Zhu X, Ni H, Wei X, Mao N, Xie Y, Niu Y, Li M. Gene expression profile analysis of human intervertebral disc degeneration. Genet Mol Biol. 2013;36(3):448-54.
33. Lian C, Gao B, Wu Z, Qiu X, Peng Y, Liang A, Xu C, Su P, Huang D. Collagen type II is downregulated in the degenerative nucleus pulposus and contributes to the degeneration and apoptosis of human nucleus pulposus cells. Mol Med Rep. 2017;16(4):4730-6.
34. Deng Y, Tan XT, Wu Q, Wang X. Correlations between COL2A and Aggrecan genetic polymorphisms and the risk and Clinicopathological features of intervertebral disc degeneration in a Chinese Han population: a case–control study. Genet Test Mol Biomarkers. 2017;21(2):108-15.
35. Yang Z, Chen X, Zhang Q, Cai B, Chen K, Chen Z, Bai Y, Shi Z, Li M. Dysregulated COL3A1 and RPL8, RPS16, and RPS23 in disc degeneration revealed by bioinformatics methods. Spine. 2015;40(13):E745-51.
36. Xunlu Y, Minshan F, Liguo Z, Jiawen Z, Xu W, Jie Y, Shangquan W, He Y, Long L, Tao H, Xuepeng L. Integrative bioinformatics analysis reveals potential gene biomarkers and analysis of function in human degenerative disc annulus fibrosus cells. BioMed Res Int. 2019.
37. Gruber HE, Hoelscher GL, Ingram JA, Bethea S, Zinchenko N, Hanley Jr EN. Variations in aggrecan localization and gene expression patterns characterize increasing stages of human intervertebral disk degeneration. Exp Mol Pathol. 2011;91(2):534-9.
38. Wang Xiang-da CB-h, HU You-gu. Expression of collagen type- in human lumbar intervertebral discs. Acta Acadimae Qingdao Umvesitatis. 2005.
39. Eyre D. Collagen of articular cartilage. Arthritis Res. 2002;4(1):30-5.
40. Kimura T, Nakata K, Tsumaki N, Miyamoto S, Matsui Y, Ebara S, Ochi T. Progressive degeneration of articular cartilage and intervertebral discs. Int Orthop. 1996;20(3):177-81.
41. Zhu Y, Wu JJ, Weis MA, Mirza SK, Eyre DR. Type IX collagen neo-deposition in degenerative discs of surgical patients whether genotyped plus or minus for COL9 risk alleles. Spine. 2011;36(24):2031.
42. Annunen S, Paassilta P, Lohiniva J, Perälä M, Pihlajamaa T, Karppinen J, Tervonen O, Kröger H, Lähde S, Vanharanta H, Ryhänen L. An allele of COL9A2 associated with intervertebral disc disease. Sci. 1999;285(5426):409-12.
43. Wrocklage C, Wassmann H, Paulus W. COL9A2 allelotypes in intervertebral disc disease. Biochem Biophys Res Commun. 2000;279(2):398-400.
44. Higashino K, Matsui Y, Yagi S, Takata Y, Goto T, Sakai T, Katoh S, Yasui N. The alpha2 type IX collagen tryptophan polymorphism is associated with the severity of disc degeneration in younger patients with herniated nucleus pulposus of the lumbar spine. Int Orthop. 2007;31(1):107-11.
45. Karppinen J, Pääkkö E, Räinä S, Tervonen O, Kurunlahti M, Nieminen P, Ala-Kokko L, Malmivaara A, Vanharanta H. Magnetic resonance imaging

findings in relation to the COL9A2 tryptophan allele among patients with sciatica. Spine. 2002;27(1): 78-82.
46. Seki S, Kawaguchi Y, Mori M, Mio F, Chiba K, Mikami Y, Tsunoda T, Kubo T, Toyama Y, Kimura T, Ikegawa S. Association study of COL9A2 with lumbar disc disease in the Japanese population. J Hum Genet. 2006;51(12):1063.
47. Knoeringer M, Reinke A, Trappe AE, Schlegel J. Absence of the mutated Trp2 allele but a common polymorphism of the COL9A2 collagen gene is associated with early recurrence after lumbar discectomy in a German population. Eur Spine J. 2008 ;17(3):463-7.
48. Paassilta P, Lohiniva J, Göring HH, Perälä M, Räinä SS, Karppinen J, Hakala M, Palm T, Kröger H, Kaitila I, Vanharanta H. Identification of a novel common genetic risk factor for lumbar disk disease. JAMA. 2001;285(14):1843-9.
49. Karppinen J, Pääkkö E, Paassilta P, Lohiniva J, Kurunlahti M, Tervonen O, Nieminen P, Göring HH, Malmivaara A, Vanharanta H, Ala-Kokko L. Radiologic phenotypes in lumbar MR imaging for a gene defect in the COL9A3 gene of type IX collagen. Radiol. 2003;227(1):143-8.
50. Solovieva S, Lohiniva J, Leino-Arjas P, Raininko R, Luoma K, Ala-Kokko L, Riihimäki H. COL9A3 gene polymorphism and obesity in intervertebral disc degeneration of the lumbar spine: evidence of gene-environment interaction. Spine. 2002;27(23):2691-6.
51. Kales SN, Linos A, Chatzis C, Sai Y, Halla M, Nasioulas G, Christiani DC. The role of collagen IX tryptophan polymorphisms in symptomatic intervertebral disc disease in Southern European patients. Spine. 2004;29(11):1266-70.
52. Solovieva S, Lohiniva J, Leino-Arjas P, Raininko R, Luoma K, Ala-Kokko L, Riihimäki H. Intervertebral disc degeneration in relation to the COL9A3 and the IL-1ss gene polymorphisms. Eur Spine J. 2006;15(5):613-9.
53. Jim JJ, Noponen-Hietala N, Cheung KM, Ott J, Karppinen J, Sahraravand A, Luk KD, Yip SP, Sham PC, Song YQ, Leong JC. The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. Spine. 2005;30(24):2735-42.
54. Bagheri MH, Honarpisheh AP, Yavarian M, Alavi Z, Siegelman J, Valtchinov VI. MRI phenotyping of COL9A2/Trp2 and COL9A3/Trp3 alleles in lumbar disc disease: a case-control study in south-western Iranian population reveals a significant Trp3-disease association in males. Spine. 2016;41(21) :1661-7.
55. Virtanen IM, Karppinen J, Taimela S, Ott J, Barral S, Kaikkonen K, Heikkilä O, Mutanen P, Noponen N, Männikkö M, Tervonen O. Occupational and genetic risk factors associated with intervertebral disc disease. Spine. 2007;32(10):1129-34.\
56. Wu H, Wang S, Chen W, Zhan X, Xiao Z, Jiang H, Wei Q. Collagen IX gene polymorphisms and lumbar disc degeneration: a systematic review and meta-analysis. J Orthop Surg Res. 2018;13 (1):47.
57. Huang D, Deng X, Ma K, Wu F, Shi D, Liang H, Chen S, Shao Z. Association of COL9A3 trp3 polymorphism with intervertebral disk degeneration: a meta-analysis. BMC Musculoskelet Disord. 2018 Dec;19(1):381.
58. Mio F, Chiba K, Hirose Y, Kawaguchi Y, Mikami Y, Oya T, Mori M, Kamata M, Matsumoto M, Ozaki K, Tanaka T. A functional polymorphism in COL11A1, which encodes the a1 chain of type XI collagen, is associated with susceptibility to lumbar disc herniation. Am J Hum Genet. 2007;81(6):1271-7.
59. Lawrence EA, Kague E, Aggleton JA, Harniman RL, Roddy KA, Hammond CL. The mechanical impact of col11a2 loss on joints; col11a2 mutant zebrafish show changes to joint development and function, which leads to early-onset osteoarthritis. Philos Trans R Soc Lond B Biol Sci. 2018;373(1759) :20170335.
60. Fang Y, Wang P, Xia L, Bai S, Shen Y, Li Q, Wang Y, Zhu J, Du J, Shen B. Aberrantly hydroxymethylated differentially expressed genes and the associated protein pathways in osteoarthritis. Peer J. 2019;7:e6425.
61. Roughley P, Martens D, Rantakokko J, Alini M, Mwale F, Antoniou J. The involvement of aggrecan polymorphism in degeneration of human intervertebral disc and articular cartilage. Eur Cell Mater. 2006;11(1):1-7.
62. Kawaguchi Y, Osada R, Kanamori M, Ishihara H, Ohmori K, Matsui H, Kimura T. Association between an aggrecan gene polymorphism and lumbar disc degeneration. Spine. 1999;24(23):2456.
63. Eser O, Eser B, Cosar M, Erdogan MO, Aslan A, Yildiz H, Solak M, Haktanir A. Short aggrecan gene repetitive alleles associated with lumbar degenerative disc disease in Turkish patients. Genet Mol Res. 2011;10(3):1923-30.
64. Mashayekhi F, Shafiee G, Kazemi M, Dolati P. Lumbar disk degeneration disease and aggrecan gene polymorphism in northern Iran. Biochem Genet. 2010;48(7-8):684-9.
65. Kim NK, Shin DA, Han IB, Yoo EH, Kim SH, Chung SS. The association of aggrecan gene polymorphism with the risk of intervertebral disc degeneration. Acta Neurochirurgica. 2011;153(1):129-33.
66. Gu J, Guan F, Guan G, Xu G, Wang X, Zhao W, Ji Y, Yan J. Aggrecan variable number of tandem repeat polymorphism and lumbar disc degeneration: a meta-analysis. Spine. 2013;38(25):E1600-7.