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Review Article

A Review on Genetics of Intervertebral Disc Disease in Indian Perspectives

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ABSTRACT

Degeneration of the Intervertebral Disc (IDD) is caused by a range of genetic variations. Although some have been reliably discovered in either phenotype, few are shared with polymorphisms leading to back pain. To properly understand the high heritability and how the genetic variations affect cell biology to cause IDD, more study is needed. It has long been recognized that IDD is largely heritable. New polymorphisms in a number of genes that increase the incidence of IDD and back pain have been found in recent study, in part due to the availability of agnostic approaches like genome-wide association analyses. The goal of this review is to highlight recent developments in our knowledge of the genetic causes of IDD.

Keywords: Intervertebral disc degeneration; Low back pain; Genetic; Genes; Spine; Indian

INTRODUCTION

Low Back Pain (LBP) is a common debilitating musculoskeletal ailment that limits activities and frequently prevents people from working [1,2]. Over 80% of people will have LBP in their lifetime, with 9.4% age-standardized point prevalence worldwide [1,3]. Long-term sick leave or unemployment caused by LBP result in a significant financial burden [4]. LBP is a serious public health concern due to its high incidence, substantial socioeconomic cost, and strain on the healthcare system [5]. Intervertebral Disc Degeneration (IDD) is a main contributor to LBP [6]. IDD is shown to be more common in LBP individuals than in controls [7]. IDD has a complicated aetiology that includes both genetic and environmental factors, but it has been evident over the past several decades that hereditary factors prevail [8,9]. The particular processes underpinning IDD are yet unknown, though. With an emphasis on the findings of study conducted in the area during the last 10 years, this review will emphasize the most recent developments in our understanding of the genetic basis of IDD.

LITERATURE REVIEW

Structure and function of intervertebral disc

In between the spinal bodies are Intervertebral Discs (IVDs) [10]. Their main function is mechanical since they are made to minimize stress and transfer forces *via* the spine. The annulus fibrosis, an outside ring of fibrous cartilage, surrounds the middle, gelatinous Nucleus Pulposus (NP), which is an avascular, complicated structure (AF). The AF is made up of 15 to 25 concentric rings or lamellae that alternate directionally, giving tensile strength and the capacity to bear stresses coming from all directions. Collagen fibers are arranged in parallel and oriented at a 60-degree angle to the vertical axis. The NP has a gel-like viscosity in contrast to the solid, stiff AF around it [11]. The collagen and elastin fibers that make up the NP are encased in a hydrated proteoglycan-containing gel that can withstand compressive stresses and deform under pressure. Early on in life, the difference between the NP and the inner layer of the AF vanishes [12]. The transition zone is a term used frequently to describe the area where the two kinds of tissue meet. A

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neighboring vertebral body's adjacent endplates and the IVD are wedged together. Bone and hyaline cartilage are bilayers on the endplates [11,13]. Only with the NP and inner AF is the cartilaginous endplate continuous. To facilitate the transfer of tensile stresses, collagen fibers of the outer AF hook directly into the apophyseal ring's bone [12]. In order to properly nourish the disc, the vertebral endplate, which serves as an interface between the neighbouring vertebral body and the IVD, must be present. The diffusion gradients created by the metabolic needs of the disc cells allow nutrients and metabolites to flow down them [14]. Forced convection is augmented by trans-endplate diffusion as IVDs are cyclically mechanically loaded and depressed [15].

Aetiology of IDD

Ageing, smoking, accidents, and hereditary factors are all contributors to the multifaceted and complicated aetiology of IDD [10]. It might be challenging to distinguish between pathogenic abnormalities and degenerative changes to the disc caused by ageing [16]. Endplate or IVD structural flaws negatively impact the mechanical environment, causing the disc to deteriorate [17]. It is believed that endplate injury causes disc degeneration through both mechanical and dietary reasons. Damage to the endplate causes the pressure in NP to drop, which disrupts the disc's feeding [18]. The feeding of the disc may also be hampered by endplate calcification [19]. Further degeneration is brought on by a progressive reduction in the disc's nutrition supply and changes to the ECM's composition, which reduce tissue strength and alter cell metabolism [20]. Endplate deficiencies are substantially linked to IDD, according to a recent study that used a sizable population-based sample [21]. It is yet unclear how these findings relate to the known genetic effect on IDD. IDD is thought to arise as a result of inflammation [22]. It is not yet known, nevertheless, whether inflammation causes or results from IDD. IDD and disc-related LBP have both been associated with local and systemic inflammation, which is caused by the overexpression of proinflammatory cytokines and chemokines. Genetic and environmental factors have a role in the complicated condition known as IDD. It may inherit a set of genes increasing their chance of having IDD that can be sporadic or familial.

Approaches to identify genetic risk factors and the heritability of IDD

Through the use of twin studies, the significance of genetic variation as a risk factor for IDD was demonstrated. Initially, male monozygotic twin pairs from the population-based Finnish Twin Cohort were used to study the heredity of IDD. Multivariate association testing revealed that familial aggregation accounted for 61% and 34%, respectively, of the Lumbar Disc Degeneration (LDD) scores in the upper and lower areas of the lumbar spine [8]. The heritability estimates for degenerative disc traits (such as disc signal, bulging, and height narrowing), which ranged between% and 54% depending on the lumbar level, were next given in a traditional twin study [23]. The Twin Suk cohort, which is predominately female, underwent the first classical twin study comparing intraclass concordance of monozygotic and RES dizygotic twin pairs [9]. They obtained heritability values that are remarkably high for a disease, 76% in the lumbar spine and 73% in the cervical spine. LBP and LDD measures showed a substantial genetic link in a subsequent investigation using Twins UK, and it was hypothesized that 11–13% of the genetic effects are shared by both LDD and LBP [24]. Finding the genetic variations responsible for a disorder after it has been proved to be heritable is the next step. The discovery of genetic markers might increase or decrease the likelihood of developing IDD.

Linkage studies of related people and candidate gene association studies were the major strategies applied in the 1990s. Co-segregation of genetic markers and phenotypes within pedigrees is used in linkage studies to pinpoint areas of the genome likely to contain genes corresponding to the characteristic. Comparatively, the candidate gene method evaluates associations between phenotypes and genetic variations within a gene of interest that is thought to be a reasonable candidate based on information about its function. In the investigation of the relationship between a gene of interest and a trait, candidate gene techniques have been a staple. This is mostly due to the fact that they are simple, quick, and inexpensive to conduct. This method needs a priori information since it selects genes linked to the illness or phenotype. The capacity to discover related genes may be constrained, though, by a lack of knowledge. The International Hap Map project made genome-wide association studies (GWAS) available starting in 2007. These investigations offer a neutral method of locating frequent variations (often single-nucleotide polymorphisms, or *SNPs*) connected to a trait. In a GWAS, an area of Linkage Disequilibrium (LD) is identified using common variations found throughout the whole genome, and its correlation with a characteristic is then examined. These tag *SNPs* are located in an LD block that also contains a causal *SNP*, and they are strongly related with the trait or phenotype. In order to attain acceptable statistical power, such investigations need well defined case and control groups with a suitable sample size. As uncommon variants linked with the trait are not regularly detected and frequently recognized variants have small effect sizes, only a tiny fraction of heritability is often explained by the GWAS identified variants related with the phenotype. Numerous top-notch evaluations have been written, mostly focusing on the vast candidate gene literature [25,26]. The studies and genetic variations that will be addressed have been chosen to highlight study that has been published in the last five years, with an emphasis on findings that have been linked utilizing agnostic approaches.

Genes in IDD

Thrombospondin: A group of glycoproteins known as Thrombospondin Proteins (*THBSs*) serve a range of purposes in the Extracellular Matrix (ECM). *THBSs* interact with cells and the matrix during tissue formation and repair via binding to collagen and tissue. c, which are believed to have a significant impact on IDD, are subject to *THBS* regulation [27]. In the Japanese and Korean populations, several functional polymorphisms in *THBS2* have been discovered to be related with lumbar disc herniation and lumbar spinal stenosis [28]. In a Chinese Han population, two *SNPs (rs6422747 and rs6422748)*

in the *THBS2* gene were recently shown to be related with IDD susceptibility but not severity, suggesting that *THBS2* gene polymorphisms may be risk factors for IDD [29].

Vitamin d receptor: One of the possible genes for IDD that has received the most study is the *vitamin D Receptor* (*VDR*) gene. Studies examining the relationship between IDD and *VDR* gene variations have produced conflicting findings. *TaqI (rs731236), FokI (rs2228570),* and *ApaI (rs7975232)* polymorphisms in the *VDR* have all been linked to IDD; however, findings from two recent meta-analyses have found no correlation between *VDR FokI* and *TaqI* polymorphisms and IDD [30,31]. However, Caucasians were shown to have a considerably decreased risk of IDD when the *FokI* mutation was included in the meta-analysis published by Chen, et al. Evidence from a meta-analysis corroborated the *FokI* polymorphism's ethnically specific protective benefits. The meta-analysis published by Jiang, et al. in Caucasian and Asian populations did not, however, reproduce the protective effect of the *FokI* polymorphism [32]. also presented proof that the ApaI polymorphism in *VDR* lowers the risk of IDD. Contradictory results from these meta-analyses show that more extensive study with sound design is needed to clarify the potential contribution of *VDR* polymorphisms to IDD and to reach a conclusive conclusion. However, it seems likely that any influence would be modest and based on ethnicity.

Collagens: The IVD contains various types of collagen, which is crucial. Type I, IX, and XI collagens are encoded by genes that have different variants [10]. The function of the type II collagen-coding genes has recently come under investigation. A significant collagen in cartilage is type II collagen, which is encoded by collagen type II, alpha 1 (*COL2A1*). Two genetic variants, *rs2276454* and *rs2070739*, were found to be IDD risk factors in a prior study [33]. The risk associated with the variant *rs2276454* has been confirmed by the discovery that the variants *rs1793953* and *rs2276454* are each associated with an elevated and decreased risk of developing IDD [34].

Aggrecan: The IVD matrix and vertebral endplate contain aggrecan, a proteoglycan with many glycosaminoglycan side chains that is encoded by the gene *ACAN* [35]. The *ACAN* gene was revealed to contain a VNTR variation that has been linked to IDD. The VNTRs range in length from 13 to 33 nucleotides, with 26, 27, or 28 repetitions being the most frequent [36]. In comparison to those who carry the normal and longer alleles, those who carry the shorter allele are 1.54 times more likely to develop lumbar disc degeneration (LDD) [35]. Asians with shorter alleles have a much higher risk of LDD, according to subgroup analyses. The findings of this study showed that shorter VNTRs are linked to a higher incidence of IDD, particularly in those of Asian heritage. The risk and characteristics of IDD in a Chinese Han population may be associated with the genetic polymorphisms of *COL2A1* and *ACAN*, according to some data

Aggrecanase: According to study, the aggrecanases may be part of what causes the ECM to alter during IDD. Aggrecanase-1 (a disintegrin and metalloprotease with thrombospondin motifs-4, or *ADAMTS4*) and aggrecanase-2 (*ADAMTS5*) are two aggrecanases that are hypothesized to be involved in IDD. Researchers have discovered a link between LDD and the *SNP rs4233367* in the exon of *ADAMTS4* [37]. With an OR of 0.69, the T-allele at this *SNP* was associated with a decreased risk of LDD, and the risk for the *TT* genotype is roughly one-fifth that of the CC genotype. The *SNP rs162509* in the *ADAMTS-5* gene was identified as a potential IDD risk factor [38]. Also discovered to be linked to LDD were the A alleles of the *ADAMTS5* gene's intronic variations *rs151058, rs229052*, and 162502 [39]. More proof that aggrecanases may be involved in mediating an environmental risk factor for IDD can be discovered in mice models where *ADAMTS5* deficiency was reported to be protective against chronic cigarette smoking-induced IDD [40].

Interleukins: Interleukins (*IL1 and IL6*) are cytokines that promote inflammation [41]. Normal IVD expression of *IL-1* results in the generation of degradative enzymes, overexpression of other cytokines, and inhibition of ECM component formation, all of which contribute to the indirect degradation of ECM components. The IL-1alpha (+889C/T) polymorphism is substantially related with risk of IDD, particularly in Caucasian populations, according to a meta-analysis [42]. Both early LDD in young females and Modic Change (MC), an MRI characteristic linked to IDD, have been linked to the *SNP rs1800587* in *IL1A* [43,44]. The variant *rs1800587* was not found to be associated with any of the three highly specific markers for IDD, including disc degeneration by Pfirrmann grading, endplate damage evaluated by total endplate damage score, and annular tears evaluated by disc herniations and hyperintense zones, more recently in a case/control study of subjects drawn from the Indian population with highly specific phenotypes for disc degeneration. The *IL1A* gene variations *rs2856836, rs1304037, rs17561*, and *rs1800587* were linked to the severity of LDD and MC in a different study. It's important to note that the PolyPhen prediction algorithm identified the *IL1A rs17561* variation as pathogenic [45]. Lumbar disc herniation is known to be significantly influenced by *IL-6* [46]. It has been shown that IL6 polymorphisms are strongly linked to IDD. Patients with *AA* or *AT* genotypes compared to the *TT* genotype had a 4.4-fold higher incidence of IDD due to a 15T/A substitution in exon 5 of *IL6* [47]. The *SNP rs1800796* was shown to confer a very high—6.7-fold—increased risk of having IDD in girls bearing the C allele compared to those who did not have the allele in a sample of Danish girls [43]. Boys did not show this relationship. Two distinct protective polymorphisms (*rs1800797 and rs180079)* in *IL6* were shown to be exclusively related with IDD in teenage boys, according to a study published in 2012 [46].

rs1800797 (genotype CC) and *rs1800795* (genotype CC) were discovered to confer an increased and decreased risk of developing IDD, respectively, in a recent meta-analysis [48]. In a sample of Indian patients, a recent study revealed no correlation between the level of *IL6* and the degree of lumbar disc herniation [45]. The relative risk of having lumbar disc herniation with the *IL-6-572* G genotype GG and CG, however, was likewise significant in a Han Chinese population it was 4.48 and 1.55 times greater than the CC genotype [49]. There is proof that lumbar disc herniation is related to genetic

variations in the *IL-6* promoter regions. However, they may be gender or demographic specific. The results on the function of *IL-6* imply that polymorphisms may be linked to a higher incidence of IDD or may give protection. It was discovered that *IL-10* promoter polymorphisms were connected to LDDs. The relationship between *IL-18RAP* and LDDs, as well as the treatment result for persistent LBP, radiographic LDDg, and adjacent segment disc degeneration following lumbar fusion, has been the subject of several articles.

Matrix metalloproteinases: IDD is hypothesized to be significantly influenced by the breakdown of the disc matrix by matrix metalloproteinases (*MMPs*). Recent study has focused on the function of *MMP3* and *MMP9* in IDD. The homozygous variation (CC) of the polymorphism *rs632478* in *MMP3* resulted in a 5-fold significant elevated risk for disc degeneration compared to the *AA* variant in a North Iranian population. Additionally, Takahashi, et al. observed that in older individuals, the *MMP3 5a5a* and *5a6a* genotype was substantially related with a higher number of degenerative discs than the *6a6a* [50,51]. *MMP-9 rs17576* was shown to significantly enhance the incidence of disc degeneration in a meta-analysis [48]. In connection to MC, the function of *MMPs* has also been investigated. The *rs17099008 SNP* of *MMP20* was discovered to be strongly linked with MC in a cohort of Indian ancestry [52]. These findings indicate that *MMPs* may play a part in IDD and MC, a characteristic of IDD.

CILP: *The Cartilage Intermediate Layer Protein (CILP)* gene's single-nucleotide polymorphism *rs2073711* has recently been linked to IDD [53]. The polymorphism was strongly related with IVD risk, according to meta-analysis. Similar ORs were discovered for both Asian and European populations after further subgroup analysis. Three *CILP SNPs* have been linked to a substantial correlation with disc bulge, a marker of IDD, according to a recent study [54]. To determine if certain IDD traits or IDD as a whole are connected with *CILP* variations, more investigation is necessary.

TRAIL: Transmembrane proteins known as tumour necrosis factor ligands are known as Tumour Necrosis Factor-Related Apoptosis-Inducing Ligands (TRAILs) [55]. Previous study on the relationship between TRAIL and IDD has yielded mixed results. Recent paper has clarified the connection between TRAIL and LDD. In the Han Chinese population, a significant correlation between TRAIL 1525/1595 polymorphisms and the risk of LDD has been documented [56-58]. In a meta-analysis that included all three studies reporting *TRAIL 1595C/T* gene polymorphisms, a substantial link between the polymorphism and a higher incidence of IDD was discovered [55]. There was a greater prevalence of the *1595TT* genotype and *1595T* allele in patients with lower degree IDD. These findings demonstrate the involvement of *TRAIL 1595C/T* polymorphisms in IDD. Both the *Death Receptor-4 (DR4)* and the *Death Receptor-5 (DR5)* are TRAIL-binding receptors that cause apoptosis in the target cell [36]. In a Han Chinese population, LDD risk and severity were related with the C626G polymorphism of the *DR4* gene with the CG and GG genotypes as opposed to CC genotypes [59]. In addition, compared to the CC genotype and the C allele, the G allele was linked to more severe forms of LDD that were degenerative. Only Han Chinese populations have had the relationships between TRAIL and DR4 studied. To ascertain if these findings are racially exclusive, more study involving diverse ethnic communities is necessary.

GDF5: *GDF5* variants were first thought to be a viable candidate for LDD because they were supposed to predispose people to osteoarthritis (OA). In five primarily female cohorts of Northern European ancestry, the *SNP rs143383* in *GDF5* was reported to be related with LDD [60]. This risk allele is also associated with knee and hip OA. The *rs143383* polymorphism and susceptibility to LDD were shown to be significantly associated, with the T allele giving risk and the C allele offering protection, according to a more recent meta-analysis [61]. Asian and Caucasian groupings showed a significant correlation in the subgroup analysis.

SKT: *SKT* is expressed in NP of IVDs, making the human *SKT* gene *(KIAA1217)* a promising candidate for lumbar disc herniation (LDH) susceptibility. In two separate Japanese case-control groups and a replicated Finnish case-control population, a substantial correlation with the *SKT* variation *rs16924573* was discovered [62]. The link between the *SNP rs16924573* and LDH was validated by meta-analysis involving more than 2200 participants from Finland and Japan.

Genome-wideassociationstudies reveal genetic variations

PARK2: In 2012, the results of the first GWAS examining disc degeneration were published [63]. Using 4683 people of European ancestry, a genome-wide association meta-analysis was carried out, and four *SNPs* linked to LDD were found. The *parkin* gene, which is encoded by the *PARK2* gene and is a member of a multiprotein E3 ubiquitin protein ligase complex, has the most important *SNP*. A small sample of individuals showed differential methylation at a CpG island in the *PARK2* promoter, suggesting that methylation of the *PARK2* promoter may affect IVD degeneration. These findings in Northern Europeans are fascinating, but they have not yet been verified despite using a hypothesis-free methodology.

CHST3: A new candidate gene *CHST3* encoding carbohydrate sulfotransferase 3 was discovered using data from a combined genome-wide linkage analysis of families with early-onset LDD and a large GWAS meta-analysis employing multi-ethnic population samples [64]. The *SNP rs4148941* and LDD were shown to be significantly correlated across the whole genome. Additionally, human participants with the A allele of *rs4148941* had considerably less *CHST3 mRNA* expressed in their IVD cells. All of this data points to a possible involvement for *CHST3* in LDD.

DISCUSSION

Genes for sciatica

Using two Finish cohorts, the first GWAS and meta-analysis of sciatica was conducted, identifying two new related loci, NFIB and *MYO5A* [65]. The *SNP rs71321981* in the regulatory area of

the transcription factor NFIB, which was the subject of the meta-strongest analysis's correlation, was reproduced in a separate population sample from Finland. The relationship with the *MYO5A* gene, however, was not repeatable. The *HLA-DRB5 SNP rs115488695* did not quite approach genome-wide significance, while *SNPs* (*rs2187689, rs7767277*) in the neighbouring gene TAP1 were linked to LDD in the meta-analysis of Northern European people mentioned above [63]. Highly linked indicators associated with LDHsurg were found at *8q24.21, SNP rs6651255*, in patients of sciatica with herniated lumbar discs that had undergone microdiscectomy (LDHsurg) and population controls [66]. Younger individuals were shown to be more responsive to its effects than older ones. The *SNP* and variations in the strong LD region are *eQTLs* that influence the expression of the neighbouring genes *CCDC26* and *GSDMC*. In order to determine whether height may be causally related to the risk of a herniated disc, a Mendelian randomisation study was conducted. Using the linked *SNPs* as an instrumental variable, the results indicated no such impact. It has been proposed that rather than the morphology connected to herniated lumbar discs, the influence of *rs6651255* on risk of LDHsurg is driven by the intensity and persistence of accompanying sciatica.

Genes for back pain

On the basis of the universal data cohorts, a sizable GWAS meta-analysis for chronic back pain has just been carried out [67]. The intronic variation *rs12310519* in the *SOX5* gene served as a new locus for persistent back pain that was discovered and reproduced in the investigation. In a two-stage meta-analysis, two additional sites were found to be of genome-wide significance: one was marked by the intronic variant *rs4384683* in *DCC* genes, and the other by the intergenic variant *rs7833174* in the *CCDC26* and *GSDMC* genes. It is surprising and encouraging to discover the same genetic variations in a highly specific group of patients receiving discectomy for MR-proven disc prolapse and in association with a relatively general back pain questionnaire. The location of the genetic variation generating the signal will be made easier with the help of bioinformatics investigation. The prospect of continuing study that does not focus just on clinical patients with highly phenotype traits is encouraging. However, in order for GWAS study to be successful, very large sample sizes are necessary, and this most recent study has brought to light the severe polygenicity linked to the backpain phenotype. Utilizing the sample of 500,000 people from the UK Biobank, more paper is being done [68].

Specific studies

Despite degenerating far more quickly than other musculoskeletal tissues, intervertebral discs are typically asymptomatic. According to some reports, lumbar disc degeneration can start as early as the second decade of life [15]. Age-related changes in disc morphology were shown by Boos, et al. [15], with discs from young children as early as 2 years of age exhibiting some very modest cleft development and granular modifications to the nucleus. With ageing, this incidence rises, such that 10% of discs in individuals 50 years old and 60% of discs in people 70 years old are badly degraded [16]. Around 20% of adults in their teens have discs with modest indications of degeneration. Even while disc degeneration begins in young adulthood, it is rare for young individuals to have severe disc degeneration, which is characterized by the presence of TDDS [2,17]. Young individuals with such extensive disc degeneration constitute a unique population of patients with potentially unique etiopathogenic processes. Results from genetic study on disc degeneration could be tainted if these patients and adult patients (who develop disc degeneration as a function of ageing) are included. We looked at young individuals with severe lumbar disc degeneration and found that five genes' *SNPs* were strongly linked to severe disc degeneration. Genetic association study on DDD has so far linked a number of *SNPs* to numerous potential genes. These *SNP* relationships, however, are not consistently repeated in other investigations.

Total disc degenerative score

Studies on disc degeneration must take into account the radiologic characteristics of all five lumbar discs rather than focusing on just a handful. All of the lumbar discs should be equally vulnerable to disc degeneration due to systemic factors such hereditary susceptibility to disc degeneration or metabolic reasons. Similar alterations may not be comparable to generalized changes occurring in all of the lumbar discs if they only occur at one or two disc levels. It's possible that a patient with Grade 3 degeneration in all of their discs is different from another patient with a single level DDD of Pfirrmann's Grade-5 and other normal discs. The five lumbar discs' separate Pfirrmann scores were added to create the TDDS, which is utilized. The severity of the patients, both low and severe, was compared. *SNPs* in possible candidate genes were investigated for their correlation with severe lumbar disc degeneration. In our investigation, it was shown that two *COX2* polymorphisms and one of each of *CALM1, ADAMTS5, COL11A1*, and *IL1F5* were strongly linked to significant disk herniation in young individuals.

CALM1 (*Calmodulin 1* gene)

In investigation, there was a substantial correlation between severe disc degeneration and the *CALM1 SNP rs3213718*. This is the first study to link the degeneration of the lumbar disc to *CALM1*. A calcium-binding protein that functions as a modulator of calcium signals is produced by the *calmodulin 1* gene. It is an intracellular protein that engages in interactions with many signal transduction-related proteins. In the Japanese population, a distinct polymorphism (functional core promoter *SNP16C/T: rs12885713)* was linked to hip osteoarthritis [18], whereas a British study found no evidence of this connection [19]. In articular cartilage and cultured chondrocytes, *CALM1* is expressed, and osteoarthritis has been linked to an increase in its expression. It is known that articular chondrocyte mechanical compression causes changes in aggrecan expression, and that these changes are reliant on *calmodulin* signalling. In addition to end plate destruction and extracellular matrix loss, disc degeneration is also characterized by osteophyte development to

variable degrees. As a result, *calmodulin* may play a key role as a mediator in the aetiology of disc degeneration.

Collagen XI (COL11A1)

The nucleus pulposus and annulus fibrosus both contain type *XI collagen*. One of the type *XI collagen* genes, *COL11A1*, and lumbar disc herniation were shown to be significantly associated in a study conducted on the Japanese population by Mio and his coworkers. The a1 chain of type *XI collagen*, encoded by *COL11A1*, is generally strongly expressed in discs, however the authors found that in patients with disc herniation, the expression was reduced [11]. The degree of disc degeneration was negatively linked with the expression level. The investigators came to the conclusion that type *XI collagen* is essential for intervertebral disc metabolism since the *COL11A1* allele *rs1676486* exhibited the strongest correlation with lumbar disc herniation. It was shown that severe disc degeneration in young individuals was substantially related with the *COL11A1* gene variant *rs1337185*.

Disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5)

Severe disc degeneration was highly correlated with the *ADAMTS5 SNP*. The *ADAMTS* (a disintegrin and metalloproteinase with thrombospondin motifs) protein family includes *ADAMTS5*. The enzyme cleaves aggrecan by acting as an aggrecanase. It is believed to be crucial to the metabolism and matrix breakdown of extracellular disc matrix. According to a recent study employing a murine model, *ADAMTS5* was predominantly in charge of the bulk of the aggrecan turnover in mouse cartilage [20]. Disc degeneration might result from the extracellular matrix of the intervertebral disc degrading more quickly than normal.

Cyclooxygenase 2 (COX2)

A significant positive correlation between severe disc degeneration and the *COX2 rs5277 SNP* was found. An enzyme called *COX2* is in charge of producing crucial biological mediators including thromboxane, prostacyclin, and prostaglandins. Interleukin 1, interleukin receptor 1, cyclooxygenase 2, and matrix *metalloprotease* gene variants have all been discovered to be related with lumbar degenerative disc degeneration [9-24]. The overexpression of prostaglandin E2 (PGE2) by the *COX2* gene may contribute to disc herniation [22]. It is also said to play a role in peripheral pain modulation [25]. The activation of degradative enzymes and the inhibition of proteoglycan production by *IL1* may contribute to degeneration. By stimulating the production of PGE2, which in turn increases the activity of *COX2* and phospholipase A2, it also controls pain. The nociceptors that innervate the disc are sensitised by *IL1, IL6*, and TNF-α that are released by herniated discs [26,27]. This may have a role in the development of pain during disc degeneration. The connections of *SNPs* in less than 20 candidate genes that have been linked to disc degeneration in young individuals with a mean age of just above 18 were examined [17]. The 538 people who were investigated had a degeneration rate of 46%, a disc degeneration rate of 54%, and a mild degeneration rate of 51%. Patients with mild disc degeneration were contrasted with those who had no degeneration. Subjects with *SNPs* of Interleukin 6 *(IL6)*, Sickle Cell Trait (SKT), and Cartilage Intermediate Layer Protein had a considerably greater chance of developing developmental delay (DD) *(CILP)*. They have found that the aetiology of disc degeneration in young adults may be related to *IL6*, SKT, and *CILP*. We examined the aforementioned *SNPs* in the current investigation but were unable to find any beneficial associations. Since both investigations used identical radiological techniques and patient groups, it is possible that ethnic differences are to blame. The strength of a study in genetic association paper is influenced by the size of the cohort.

Cartilage intermediate layer protein

The cartilage's intermediate layer contains the protein known as cartilage intermediate layer protein *(CILP)*. The intervertebral disc also contains something similar. As disc degeneration worsens, *CILP* is expressed more frequently. In the Japanese population, LDDs were linked to +1184TC in exon 8 of *CILP*. The amino acid Ile395Thr is substituted as a result of the *SNP* alteration. Another Japanese group utilising male collegiate athletes replicated the impact of the same *SNP*. Controversial study came from Finland. Both Chinese participants with MRI-defined LDD and controls as well as Finnish patients with LDD symptoms failed to demonstrate the connection. The genesis of DD in young adults was, however, described in a Finnish paper as including interleukin-6 *(IL6)*, sickle tail (SKT), and *CILP*.

Asporin

A family of repeat proteins with high leucine content includes asporin (ASPN), which is found in the matrix of cartilage. According to studies, osteoarthritis of the knee is linked to the ASPN D14 genotype. Previous functional investigations showed that ASPN inhibits Transforming Growth Factor (TGF)-signaling, which in turn suppresses *In vitro* chondrogenesis and the expression of COLA1 and AGC, with ASPN D14 having a higher inhibitory impact than other ASPNs. The D14 allele is reportedly very strongly linked to LDDs in populations of Chinese and Japanese people. With a summary odds ratio of 1.70, meta-analysis revealed that those who have the ASPN D14 allele were more likely to develop DDDg. It has also shown that ageing and degeneration enhanced the intervertebral discs' expression of ASPN. According to the findings, *ASPN* is an LDD gene in Asians, and shared risk factors for osteoarthritis (OA) and LDDs may be taken into account. Since that study, *CILP* and *ASPN* polymorphisms have also been linked to an increased incidence of LDDs in males but not in females, according to a Japanese publication.

Carbohydrate sulfotransferase

Proteoglycan sulfation is facilitated by the enzyme carbohydrate sulfotransferase 3 (CHST3). Using patients from Southern Chinese, Japanese, and Finnish populations, we were able to identify *CHST3* as a susceptibility gene for LDDs. An analysis of genome-wide association study (GWAS) data revealed that *Rs4148941* was the primary locus in this study. A possible

microRNA-513a-5p binding site is present at this locus. *In vitro*, as opposed to transcripts from other alleles, the interaction between *miR-513a-5p* and *mRNA* from the susceptibility allele of *rs4148941* was improved. Furthermore, in the intervertebral disc cells of human patients having the risk allele, expression of *CHST3 mRNA* was markedly decreased.

Parkinson protein 2, E3 ubiquitin protein ligase

Williams, et al. performed a GWAS with a meta-analysis on 4600 people to find the LDD-susceptible genes. They discovered that LDDs and a *PARK2* variation were related. They discovered differential DNA methylation at one CpG island of the *PARK2* promoter and a strong correlation between DNA methylation and LDDs during the functional analysis

Other genes

There are several genes (*ADH2, COMT, GCH1, Caspase 9, HAPLN1, FAS, GDF5, BCL-2, FASL, PARK2, DR4, eNOS, VEGF, ADAMTS4, HIF-1α, ADIPOQ, TRAIL, ADAMTS5*, etc.) whose genetic variants have been linked to LDDs. The details are both crucial and fascinating. However, replication studies for these genes are required.

Problematic issues related to genetic research regarding IDDs

The discovery of the genetic origin of LDDs faces a number of challenges in the future. The four following items are the most crucial factors to take into account:

1. There is no specified phenotype. No one agrees on phenotype. Various phenotypes are focused on in various articles. Some people are talking about the MRI modic indications LDD, LDDg, LDH, and others. It's crucial to consider what sort of intervertebral disc problem should be prioritized.

2. Too tiny of a sample size. Replication across various races is quite uncommon. Despite the fact that the exact number has not yet been decided, there is no question that the study samples should be sizable enough to confirm the analysis. The results are more accurate when the sample sizes are greater. Over 30,000 samples were only used in one study. For general understanding, samples from only one race are insufficient. Replication studies including several racial groups are required. There should be multicenter investigations including institutions from many nations.

3. it's unknown how the susceptible genes are connected. Although several studies have concentrated on multisusceptible genes for LDDs, few investigations have been carried out to elucidate the link between these many genes.

4. Not all genes have undergone functional investigations. Functional investigations are extremely difficult to conduct but are crucial for understanding the disease since they show how the vulnerable genes contribute to the pathogenesis of LDDs. The knowledge might be beneficial for illness prevention. Functional study has to be done [69].

CONCLUSION

Although sporadic LDD's high heritability was acknowledged in the 1990s, finding the mutations responsible has been a long process. This is due to a variety of reasons, including the challenge of analyzing the IVD to find viable candidate genes and the realisation that the candidate gene strategy is frequently ineffective. This is due to the fact that choosing appropriate controls frequently causes stratification of the occult population, which biases the results. There are probably a lot of false positive connections in the literature that can't bear the scrutiny of agnostic methodologies like GWAS. Although the GWAS is an effective method for finding new variations, it calls for large samples of people with uniform phenotyping and a global approach to data sharing. With the EU FP7 projects Genodisc and Pain Omics, this is already starting to happen, and new genes are being implicated in LDD. This will help to understand the pathophysiology of the disorder and might also offer potential new treatment targets. Other methods, such exome sequencing within families, which was effective in locating a new mutation in *IGFBP6* may also be useful. Studies examining the function of gene therapy, stem cell injections, and therapeutic protein injections have shown encouraging findings. To develop effective biologic and gene IVD treatments in the future, however, in an effort to treat or postpone onset in people at high risk of IDD, it will be necessary to further our understanding of IDD and identify the most crucial candidate genes.

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CONFLICT OF INTEREST

No conflict of interest is declared.

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