Chapter

# Pathogenesis, Pathology and Genetics of Osteoarthritis

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## Abstract

Osteoarthritis (OA) is a condition with high prevalence worldwide. OA affects not only the articular cartilage, but the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane and the periarticular muscles. Despite the fact that the risks associated with OA increase with age, it is not a part of the natural aging process. It typically involves the knee, hip, spine, hand and foot joints. Several factors play an important role in the pathogenesis of OA, including biomechanical factors, proinflammatory mediators and proteases. On the other hand, it was mostly the results of the studies conducted on the genetic, genomic and epigenetic aspects of OA, from among many of its underlying etiological factors, which shed light on the molecular processes involved in the etiopathogenesis of OA. As the mechanisms that cause joint tissue damage in OA come to light, the treatment of OA will go beyond just providing symptomatic relief. Consequentially, new treatments will emerge that will either slow or completely stop the progression of OA.

**Keywords:** Osteoarthritis, Genetics, Epigenetics, Etiopathogenesis, Pathology

## 1. Introduction

Osteoarthritis (OA) is a chronic disease that affects all structures of the joint as well as the periarticular tissues. In the past, OA was considered simply as a degenerative joint disease, yet the pathogenesis of OA is in fact much more complex than just wear and tear. Hence, the term "osteoarthritis" is indeed a pertinent term, as the suffix "itis" is indicative of an inflammatory process. It is estimated that approximately 50% of the world population over 65 years of age is affected by OA. The symptomatic treatment of this common disease provides regression of symptoms, nevertheless it often does not constitute an effective treatment option thus causing an increase in the OA-related health expenditures. The elucidation of the etiopathogenesis of OA and the molecular studies to be carried out in respect thereof are likely to allow early diagnosis of OA and also contribute to the development of new treatment options.

## 2. Pathology and pathogenesis of osteoarthritis

Articular cartilage degeneration, which develop as a result of the deterioration of the balance between the production and destruction of cartilage, new bone formation, sclerosis of subchondral bone, ligament and meniscus damage, periarticular muscle weakness, synovial inflammation and fibrosis are all involved in the

pathogenesis of OA [1]. Hence, the pathogenesis of OA would be better understood provided that the structure of the joint and the related histopathological features are reviewed.

### 2.1 Structure of the joint

Synovial joints consist of an articular cartilage that covers the ends of the opposing bones, the synovial fluid that nourishes and lubricates the tissues, the synovium that secretes the synovial fluid, the ligaments that hold the skeletal elements together, the tendons that connect the bones with the muscles, and the joint capsule surrounding the joint. In order to have normal joint functions, it is necessary that the opposing joint surfaces move over each other painlessly, that the load on the joint tissues is homogeneously distributed, and that the stability to that effect is sustained [2].

Articular cartilage is a connective tissue located at the bone ends and which has a thickness of 0.2 mm to 6 mm depending on the location. Articular cartilage provides a smooth and low-friction surface that primarily allows for normal gliding motion of the articular surfaces [3]. Cartilage consists of an extracellular matrix, 65–80% of which is water and 20–35% of which is solid matter, and of chondrocytes dispersed in this matrix. 5–6% of the tissue is composed of inorganic material consisting mostly of hydroxyapatite. The organic matter on the other hand is composed of fibrous proteins (collagen), hydrophilic sulfated proteoglycans (chondroitin sulfate, keratan sulfate I and II) and unsulfated proteins (hyaluronic acid). 90% of the collagen is type II collagen, whereas the remaining collagen consists of smaller amounts of type IX, XI, III, VI, XII and XIV collagen [4].

A proteoglycan consists of a protein and glycosaminoglycan chains attached to this protein. The most abundant type of proteoglycan is 'aggrecan' [5]. Type II collagen plays a role in maintaining the volume and shape of the content it is part of, whereas proteoglycans play a role in maintaining the hardness and elasticity [6].

Hyaluronic acid is the substance that maintains the viscosity in synovial fluid. Nonetheless, it requires the presence of a large mucinous protein, which is called lubrisin (proteoglycan-4), in order to maintain a low-friction environment and protect the surface of the joint [7].

Articular cartilage is a avascular heterogeneous structure with four different layers which has no nerve innervation and is fed by a bidirectional diffusion system. These layers are the superficial zone, transitional zone, deep zone and calcified zone. The calcified line between the deep zone and the calcified zone is called the Tide mark [8].

The extracellular matrix is synthesized by chondrocytes. Chondrocytes synthesize cartilage matrix molecules and the metalloproteinases which breakdown the matrix. The cartilage metabolism is based on the balance between the anabolic processes and the catabolic processes carried out by the matrix metalloproteinases (collagenase, gelatinase, stromelysin, cathepsin B and D) and the adamalysins [a disintegrin and metalloproteinase (ADAM), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), aggrecanase] [5]. This balance is regulated by anabolic cytokines such as transforming growth factor beta (TGF-β), insulin-like growth factor-1 (IGF-1) and bone morphogenetic proteins (BMPs) and catabolic cytokines such as interleukin 1 alpha (IL-1α), interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) [6].

The synovium, which produces the synovial fluid, consists of two layers as inner and outer layers. It is firmly attached to the joint capsule and prevents the synovial fluid from leaving the joint. The inner and outer layers of the synovium are composed of the synovial membrane and fibrous connective tissue, respectively. The

inner layer includes two types of cells. Type A synoviocytes have the characteristics of macrophages, whereas type B synoviocytes are cells with proliferative capacity and produce hyaluronic acid, collagen, lubricin and fibronectin [9].

The joint capsule is a tissue that contains vascular and nervous tissues and is rich in collagen fibers. It protects the whole joint both passively by restricting the movements of the joint and actively through the proprioceptive sensation triggered by the nerve endings.

## 2.2 Pathological changes that occur in connection with osteoarthritis

### *2.2.1 Changes that occur in the articular cartilage*

Chondrocytes are active cells that maintain cartilage through normal anabolic/catabolic activities. The earliest pathological changes observed in association with OA are the fibrillations seen on the surface of the cartilage. Fibrillations are more common at parts of the cartilage exposed to higher loads. Loosening of the collagen network and loss of aggregate occurs in the cartilage at the onset of OA. This loosening of the collagen network allows the hydrophilic proteoglycans to attract water and expand.

The activity of chondrocytes, the only cell type found in cartilage, accelerates significantly as OA develops, that is, chondrocytes begin to proliferate moderately. Nevertheless, the reasons that trigger this premature aging and changes in the chondrocyte cycle such as inflammation, proteoglycan loss, collagen degeneration and chondrocyte failure, as well as the order of occurrence of these changes are still not fully known [10].

As OA progresses, extensive matrix breakdown and loss occur due to the continued production of the proteases driven by proinflammatory cytokines. Fragmented matrix proteins give rise to the further production of cytokine and protease by chondrocytes through autocrine and paracrine stimulations. Cartilage has limited regeneration capacity, hence once collagen is broken down and lost, regeneration does not occur at a measurable degree [11].

There are various histopathological staging-grading systems that are used to categorize the changes associated with OA according to their severity, extent or order of occurrence. These classification systems classically address the changes that occur in articular cartilage, since OA primarily targets the articular cartilage. One of these systems, the histological evaluation system proposed by **Osteoarthritis Research Society International (OARSI)** is a grading, staging and a scoring system. The grades used in the said OARSI system to classify the changes occur in articular cartilage, key features of these grades and the associated criteria in terms of tissue reactions are shown in **Table 1** [12].

### *2.2.2 Changes that occur in the bone*

Thickening of the subchondral bone (bone sclerosis) occurs due to increased production of improperly mineralized collagen. Osteophytes occur at the margins of the joints, usually at the insertion sites of tendons or ligaments. Osteophytes seen in the distal interphalangeal joints of the hand are called “Heberden’s nodes”, whereas the osteophytes seen in the proximal interphalangeal joints are called “Bouchard’s nodes”. Bone cysts form in the advanced stages of the disease, but bone erosions are not typically seen. Erosive OA is commonly seen in the distal joints of the hands (distal interphalangeals and proximal interphalangeals) and central erosions are also seen as opposed to the marginal erosions seen in rheumatoid arthritis (RA) and gout [13].

| Grade # | Key features | Associated criteria (tissue reaction) |
|---|---|---|
| Grade 0 | Intact surface and cartilage morphology | Matrix: normal architecture |
| | | Cells: intact with appropriate orientation |
| Grade 1 | Intact surface | Matrix: intact superficial zone, oedema and/or superficial fibrillation (abrasion), focal superficial matrix condensation |
| | | Cells: death, proliferation (clusters), hypertrophy, superficial zone reaction must be more than superficial fibrillation only |
| Grade 2 | Surface discontinuity | As above CMatrix discontinuity at superficial zone (deep fibrillation) GCationic stain matrix depletion (Safranin O or Toluidine Blue) upper 1/3 of cartilage GFocal perichondronal increased stain (transitional zone) GDisorientation of chondron columns |
| | | Cells: death, proliferation (clusters), hypertrophy |
| Grade 3 | Vertical fissures | As above Matrix vertical fissures into transitional zone, branched fissures GCationic stain depletion (Safranin O or Toluidine Blue) into lower 2/3 of cartilage (deep zone) GNew collagen formation (polarized light microscopy, Picro Sirius Red stain) |
| | | Cells: death, regeneration (clusters), hypertrophy, cartilage domains adjacent to fissures |
| Grade 4 | Erosion | Cartilage matrix loss: delamination of superficial layer, transitional zone cyst formation |
| | | Excavation: matrix loss superficial and transitional zones |
| Grade 5 | Denudation | Surface: sclerotic bone or reparative tissue including fibrocartilage within denuded surface. Microfracture with repair limited to bone surface |
| Grade 6 | Deformation | Bone remodeling (more than osteophyte formation only) including microfracture with fibrocartilaginous and osseous repair extending above the previous surface |

**Table 1.**
*A cartilage histopathology grading methodology.*

### *2.2.3 Changes that occur in the synovium*

Four patterns have been described in OA-related synovial pathology, which are hyperplastic, inflammatory, fibrotic and detritic patterns. Hyperplastic pattern is the most common manifestation in all stages of OA. Hyperplastic pattern is considered as an early OA finding in its isolated form. Inflammatory pattern is seen equally in both the early and late stages of OA. Inflammatory cell density in the inflammatory pattern is not as much as it is in rheumatoid arthritis. Fibrotic pattern is characterized by capsular fibrosis reflecting late-stage OA. Detrital pattern is characterized by macromolecular cartilages and debris within the synovium, and reflects late-stage OA [14].

### *2.2.4 Changes that occur in the meniscus*

The changes that occur in the meniscus in connection with OA are first observed in the medial part of the meniscus. Meniscal tears are both a cause and effect of OA. Meniscal tears further increase the matrix degeneration through the inflammatory mediators which emerge as a result of the damage to the meniscus and may lead to the development of OA [15]. The regeneration capacity of the meniscus is limited. The red zone of the meniscus, which is peripherally located, is the area with the best blood supply and the best regeneration capacity, whereas the white zone of the

meniscus, which is more centrally located, is largely avascular and its regeneration is very slow and inadequate [16].

## 2.3 Etiopathogenesis of osteoarthritis

OA refers to a dynamic process, which is triggered by various biochemical and mechanical factors and in which destruction and regeneration both take place. In the past, OA was thought to be a degenerative joint disease that emerged with aging. Yet, it is known today that various factors such as biomechanical factors, proinflammatory mediators and proteases play a role in the pathogenesis of OA [17]. The release of biomarkers indicates that the findings that emerge in the earliest detectable stage of knee OA are bone and cartilage metabolisms that are impaired as a result inflammation [18].

### *2.3.1 Factors involved in the etiopathogenesis of osteoarthritis*

#### *2.3.1.1 Inflammation*

The number of proinflammatory mediators included in the synovial fluid and tissue and which play a role in OA and is increasing by the day. Early studies on OA were focused on interleukin-1 (IL1), which stimulates cartilage catabolic activity. Nevertheless, the role of IL1 in OA has been questioned over the years, since the IL1 levels in OA joints are much lower than the levels that cause cartilage deterioration. It has been shown in the relevant clinical studies that the inhibition of IL1 in knee [19] and hand OA [20] have not improved the structure and symptoms of the disease.

Cytokines such as IL6, interferon-gamma inducible-protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) and monokine induced by gamma interferon (MIG) were found to be more abundant in OA synovial fluid than IL1 or TNF-α [21]. This finding suggests that these proinflammatory cytokines play a role in inflammation. It has been demonstrated in experimental animal models that there may be a relationship between IL-6 level and increased cartilage loss. The results of all these studies support the hypothesis that IL-6, as a regulatory cytokine, plays a role in the development of OA [22]. Other cytokines and chemokines involved in cartilage degeneration caused by inhibition of the anabolic process and induction of the catabolic process are IL-7, IL-15, IL-17, IL-18, oncostatin M (OSM), growth related oncogene-alpha (GRO-alpha), chemokine (C-C motif) ligand 19 (CCL19) and macrophage inflammatory protein-1beta (MIP-1beta) [23].

It was demonstrated in some studies that there is complement activity in OA joints. In one of these studies, which was conducted on mice, it was demonstrated that complement activation was inhibited by gene deletion or pharmacological modulation and that, as a result of this inhibition, the joint is protected from surgery-induced OA [24].

Adipokines secreted by adipose tissue cause cartilage damage by activating the inflammatory cytokines along with the matrix metalloproteinases (MMPs) triggered by the inflammatory cytokines. These adipokines include leptin, adiponectin, visfatin and resistin [25].

Prostaglandin E2 (PGE-2) has been shown to inhibit proteoglycan synthesis and increase matrix degradation. Additionally, it was shown that patients with OA have high levels of PGE-2 in cartilage [26]. Furthermore, leukotriene B4, a strong leukocyte chemotaxis, has been shown to stimulate proinflammatory cytokines in human synovial fluid samples [27].

*2.3.1.2 Proteases*

Proteases are mediators that play a primary role in the catabolic process of OA. There are several proteases that have a role in the pathogenesis of OA. These proteases are collagenase-containing matrix metalloproteinases, cathepsin K-containing proteases, and serine-containing proteases. As the proteases degrade collagen, the related catabolic process results in the progression of matrix loss, since the cartilage's response to damaged matrix repair is limited [28].

'Agreccan', the largest proteoglycan, provides cartilage elasticity. The ADAMTS family of enzymes, also called aggrecanases (ADAMTS-4-5), is involved in the early stage of OA degeneration and is responsible for aggrecan degradation [28].

Type-2 collagen, the most abundant type of collagen found in the cartilage tissue, provides cartilage tensile strength. It is broken down by collagenase-containing matrix metalloproteinases. MMP13 is considered to be the main collagenase responsible for cartilage destruction in OA [28].

Aggrecanase-2 (ADAMTS-5) and MMP-13 have an important place in the pathogenesis of OA. The development of specific inhibitors to these proteases in the context of the development of potential modifying treatments for OA has been of interest [29].

*2.3.1.3 Molecular patterns associated with cartilage damage*

Damage-associated molecular patterns (DAMPs) are molecules released from the chondrocytes in the damaged cartilage. DAMPs include extracellular matrix proteins, high mobility group box 1 protein (HMGB1), advanced glycation end products (AGEs) and receptor for advanced glycation endproducts (RAGEs), and alarmins [S100 calcium-binding protein A8 (S100A8) and S100 calcium-binding protein A9 (S100A9)].

It has been demonstrated that DAMPs have important roles in the pathogenesis of OA. DAMPs activate intercellular signaling pathways such as RAGE, toll-like receptors (TLR) and mitogen-activated protein kinases (MAPKs), thereby inducing the expression of catabolic proteases and inflammation-related genes [30]. DAMPs give rise to the increase in MMPs and activated macrophages which in turn lead to chondrocyte apoptosis and cause damage to the extracellular matrix (ECM) and cartilage [31, 32].

Fragmented matrix proteins such as cartilage oligomeric matrix protein (COMP), fibromodulin, proteoglycan, collagen, tenascin C, fibronectin, biglycan and aggregate are released from the damaged matrix. These fragmented matrix proteins stimulate the immune response. Consequentially, TLR and integrin are activated and the upregulation of the degenerative pathway is achieved [23, 33–35].

RAGE is a member of the immunoglobulin family. It is expressed in chondrocytes and macrophages. RAGE has been demonstrated to increase in OA joints. This increase causes the production of MMPs, which play a direct role in the pathogenesis of OA [36].

Alarmins are intracellular proteins secreted from bone cartilage or synovium in OA. It is an important member of DAMP family that has a role in the pathogenesis of OA [33].

HMGB1 is a nonhistone nuclear protein. Its release from the nucleus is associated with the apoptosis or necrosis or inflammatory stimulation of cells [37]. A significant increase occurs in the secretion of proinflammatory cytokines, chemokines and MMPs with the increase in HMGB1 secretion [38].

S100A8 and S100A9 are secreted from granulocytes, macrophages and monocytes. There is evidence that these proteins play a role in the cartilage damage and

OA progression [39]. In addition to their catabolic effect, S100A8 and S100A9 lead to the formation of bone/osteophyte [40].

It has been demonstrated in the literature that the basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) crystals, from among the inorganic calcium crystals, accumulate in the synovial fluid [41]. Calcium-containing crystals trigger the inflammatory process by either directly stimulating the chondrocytes or indirectly stimulating the immune system [30]. Additionally, it has been reported in the literature that monosodium urate crystals also trigger inflammation and cause cartilage damage [42].

*2.3.1.4 Free oxygen radicals*

The amount of free oxygen radicals and the extent of the DNA damage they cause are higher in OA cartilages than in cartilages without OA. Free oxygen radicals have an important place in OA progression, since they increase the synovial inflammation and cartilage destruction [43].

*2.3.1.5 Biomechanical factors*

Abnormal mechanical loading has an important role in the onset and progression of OA [44]. Abnormal mechanical loading may be caused by various factors such as obesity, joint alignment disorders or joint instability. Abnormal mechanical loading leads to mechanical damage in the joint and result in an increase in the release of matrix-degrading enzymes. Cartilage destruction products trigger inflammation and damage to the joint cartilage occurs through cytokine activation.

## 2.4 Genetics of osteoarthritis

The molecular processes underlying OA, which have a complex etiology, have become clearer through genetic and epigenetic studies. OA has been categorized as early-onset OA and late-onset OA. Genetic factors are more prominent in the early-onset OA. Genetic studies on the early-onset OA will provide a better understanding of the etiopathogenesis of the disease.

Family and twin studies have been conducted to reveal the genetic factors in OA [45]. To give a few examples, in the family studies conducted by Kellgren in UK and US, it was determined that there is a genetic component of the hand and knee OA [46], whereas in the study conducted by Lanyon et al., it was shown that the risk of radiographic hip OA is higher in the siblings of the patients with advanced hip OA [47].

Studies, in which monozygotic (MZ) and dizygotic (DZ) twins were compared, have shown that genetic factors are effective in OA. In one of these studies, it was shown that genetic factors are 39–65% effective on hand and knee OA radiographs, independently of environmental and demographic factors [48]. In another study, knee OA progression was investigated in 114 MZ and 195 DZ female twin couples. Consequentially, a higher correlation was found in the MZ twins than in the DZ twins in terms of both osteophyte and joint space narrowing, and the heritability was calculated as 62% for osteophyte progression and 72% for joint space narrowing progression. Additionally, it has been reported that the genetic effect on knee OA progression is more prominent in the medial compartment [49]. Furthermore, it has also been reported that the genetic effect differs according to the affected area in OA. Accordingly, the heritability was reported as 40%, 60%, 65% and 70% in the knee, hip, hand and spine regions, respectively [48].

Candidate gene studies have focused on many gene groups such as cartilage structural genes [collagen type II alpha 1 (COL2A1), collagen type IX alpha 3 (COL9A3), collagen type XI alpha 1 (COL11A1)], genes associated with bone mineral density (BMD) [vitamin D receptor (VDR), estrogen receptor 1 (ESR1)], genes associated with chondrocyte cell signal transduction (bone morphogenetic protein 5 (BMP5), frizzled-related protein B (FRZB), interleukin-4 receptor alpha (IL-4Rα)], inflammatory cytokine genes (IL-1, IL-10, TGFβ1, IL-6, TNFα) [50].

The finding that VDR gene polymorphism is associated with BMD lead to the studies on the possible relationship of VDR gene polymorphism with OA [51]. In this context, it was shown in a study conducted on 543 women in Finland that VDR polymorphism plays a role in the etiology of symmetrical hand OA [52].

The prevalence of knee OA is significantly higher in women than in men. This difference was atrributed to the estrogen receptor α (ERα), which is encoded by ESR1. Several polymorphisms in ESR1 [PvuII (rs2234693) and BtgI (rs2228480)] have been confirmed as risk factors for OA [53].

FRZB is a glycoprotein and plays a role in chondrocyte maturation and bone development. In Rotterdam and Genetics, Osteoarthritis and Progression (GARP) studies, R324G single nucleotide polymorphism (SNP) of the FRZB gene was found to be associated with generalized OA, whereas rs7775 and rs2888326 SNPs were found to be associated with knee and hip OA [50]. BMPs are bone-derived factors that can induce new bone formation. In a study conducted by Sharma et al. on BMP5 gene, rs1470527 and rs9382564 polymorphisms were shown to be significantly associated with knee OA [54].

The hypothesis put forward in candidate gene studies is still being investigated in terms of the genetic variant. Researchers favor genome-wide association studies (GWAS), which is a hypothesis-free approach, in the event that they think that candidate gene studies do not contribute much to the etiopathogenesis of the disease. GWAS allows the identification of genetic loci and the discovery of new genetic variants. In this context, GWAS contributes to the discovery of prognostic biomarkers that can contribute to early diagnosis and the identification of new areas that can be targeted by medical treatments [55–58]. The number of OA genetic risk loci, most of which have small effect sizes, has increased to 90 in the GWAS studies carried out up till 2019 [59]. 56 new loci were identified in the two major OA analyzes published recently [59, 60]. First of these two studies, that is the deCODE (Decode Genetics, Iceland)-UKBB (UK Biobank, England) study, was conducted with more than 650,000 British and Icelandic citizens. 11.6 million genotype variants were examined within the scope of the said study, and 23 significant variants were detected in 22 loci [60]. Second of these studies, that is the Arthritis Research UK Osteoarthritis Genetics (arcOGEN)-UKBB study, was conducted with more than 455,000 British citizens. 17.5 million genotype variants were examined within the scope of the said study, and 65 significant variants were detected in 64 loci [61]. These studies, which were conducted via performing separate meta-analyses for the hip and knee OAs, are the largest OA GWAS studies published to date (**Figure 1**) [59].

Genetic variations are grouped into single nucleotide substitutions (mutations and single nucleotide polymorphisms (SNPs)], insertions and deletions, copy number variations or short tandem repeats [62]. Variations in the genome underlie the differences between the individuals. The most common of these variations are SNPs. SNPs are considered to be associated with susceptibility to diseases [63]. The majority of the common diseases that give rise to SNPs, including OA, are considered to affect the transcription of nearby genes by altering the transcription factor binding [59].

Epigenetics plays an important role in the regulation of gene expression and is associated with the pathogenesis of a number of human diseases. The term

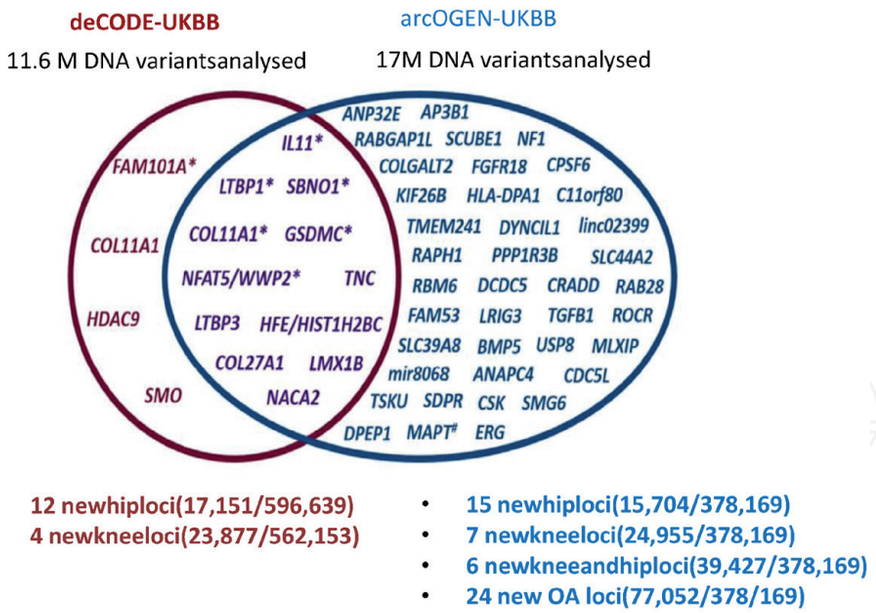


**Figure 1.**
*The new OA risk loci identified in either or/both of the deCODE-UKBB and arcOGEN-UKBB studies.*

epigenetics encompasses DNA and chromatin modifications and the functions related thereto, in addition to non-coding RNAs (ncRNAs). Epigenetic control of gene expression is necessary and essential for typical organism development and cell control [63]. Epigenetic changes are transmissible and reversible changes that do not change the nucleotide sequence but cause changes in gene expression [64]. Changes that occur within the gene itself cause structural changes in some synthesized proteins. These changes lead up to early onset-OA. Given the above considerations, epigenetics is a very important area in the diagnosis, prognosis and treatment of OA [63]. Three different epigenetic regulation are involved in the molecular pathogenesis of OA. These include DNA methylation, expression of non-coding RNAs [ncRNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small nucleolar RNAs (snoRNAs)], histone modifications that regulate gene expression at transcriptional and/or post-transcriptional levels [65]. DNA methylation is the most studied epigenetic control mechanism. 5-methylcytosine is formed as a result of the addition of a methyl group to the 5′ position of cytosine in the CpG dinucleotide by DNA methyltransferase [DNA Mtase (DNMT)]. Methylation at gene promoter regions is associated with suppression of gene expression. On the other hand, methylation within the gene bodies is associated with increased gene expression [66, 67]. The candidate gene study conducted to examine DNA methylation of matrix-degrading proteases such as MMP3, MMP9, MMP13 and ADAMTS4 was the first study to describe the possible effect of DNA methylation in OA. In the said study, hypomethylation was demonstrated in the promoter regions of selected catabolic genes in OA chondrocytes, and it was found that this hypomethylation was associated with increased expression of the gene [68].

miRNAs are small ncRNAs, which consist of 19 to 25 nucleotides and function at the post-transcriptional level by binding and repressing the expression of specific mRNA targets. miRNAs are involved in different cellular pathways and play a role in OA and in maintaining cartilage homeostasis [69]. Despite the constantly increasing number of publications and miRs related to the pathogenesis of OA, there is still no miR biomarker, which has been validated for use in the early diagnosis of the disease. This has been atrributed in part to the fact that OA is a multifactorial heterogeneous disease [63].

lncRNAs are large RNA molecules comprising more than 200 nucleotides. Deregulated expression of lncRNAs plays an important role in inflammatory diseases. lncRNAs have been shown to be associated with OA progression and cartilage degeneration [70]. LncRNAs regulate gene expression at the post-transcriptional level via micro-RNAs and modulate transcriptional gene silencing through chromatin regulation [71].

### 2.5 New treatments and future in osteoarthritis

Since chronic low-severity inflammation is involved in OA, the development of drugs that act on pro-inflammatory cytokines has also become a new hope in the treatment of OA [72]. In a study, an intra-articular (IA) IL-1 receptor antagonist (IL-1Ra) was applied to the canine knee and it was reported that it reduced the number and size of osteophytes in the femoral condyle in the follow-ups [73]. However, in another study, anakinra, which is IL-1Ra, was applied IA to the knees of patients with OA. In this randomized controlled trial, they found no superior effect to placebo on pain and WOMAC scores [74].

It has been reported that the serum TNF levels of patients with OA are elevated. The positive results obtained with the use of TNF-α inhibitors especially in erosive hand osteoarthritis are promising. In the study of Magnano et al., 12 patients with erosive hand OA were treated with adalimumab (ADA) and reported a significant improvement in symptoms after 3 months [75].

Proteases are mediators that play a primary role in the catabolic process of OA. 'Agreccan', the largest proteoglycan, provides cartilage elasticity. The ADAMTS family of enzymes, also called aggrecanases (ADAMTS-4-5), is involved in the early stage of OA degeneration and is responsible for aggrecan degradation [28]. Preclinical studies of the molecule GSK2394002, which effectively inhibits ADAMTS 4 and 5, were discontinued because serious cardiovascular side effects were encountered in animal experiments with systemic use [76]. However, phase II studies on 114810, an IA administration molecule developed to reduce systemic side effects, are ongoing [77].

OA is a dynamic process triggered by various biochemical and mechanical factors, where destruction and repair are together. The fibroblast growth factor 3 (FGF-3) family, especially FGF 18, has an anabolic effect on human chondrocytes [78]. In a study including 549 patients with stage 2 and 3 knee OA, FGF-18 (sprifermin) IA was administered. An increase in tibiofemoral joint cartilage thickness has been reported up to 12 months. In the light of this information, it can be said that Sprifermin is currently one of the promising candidates for disease-modifying OA drug (DMOAD) [79].

The mechanism of action of platelet-rich plasma (PRP) is suggested to be that bioactive growth factors released from α granules in platelets stimulate tissue healing at high concentrations. In a meta-analysis of 16 studies, 1543 patients were examined; PRP and IA hyaluronic acid (HA) were compared. In terms of pain and functionality, it was found to be more effective than intra-articular HA injection [80]. However, the 2019 OARSI guidelines state that there is low-level evidence of the use of PRP in patients with knee, hip, and polyarticular OA and should not be used [81]. Larger randomized controlled studies with long-term follow-up are needed to elucidate its effects on tissue regeneration and delaying surgery.

In the light of these, the aim of OA treatment is to prevent disease formation or to provide regeneration of damaged tissue rather than eliminating the symptom. It would be more logical for DMOADs to be developed in the future to target the early stages of disease pathogenesis. For this reason, randomized double-blind controlled studies will contribute to the development of OA treatment.

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