The genetics behind osteoarthritis: Asian focus

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Osteoarthritis (OA), a degenerative disease of the joints, is the most common form of arthritis in the elderly. It is one of the major causes of disability in developed countries and causes physical, mental, social, and economical problems [1]. OA is characterized by degradation of articular cartilage, accompanied with sclerosis of the subchondral bone, joint space narrowing, and osteophytes (bony outgrowths at the joint margins). The affected joints include the hand, spine, knee, and hip. It can be local, which is restricted to one joint, or generalized, which involves more than three joints or a group of joints.

Known risk factors of OA are obesity, female gender, advancing age, injury to the joints, and genetics. Several epidemiological studies have demonstrated a strong genetic contribution to primary OA, with hand OA at the highest estimated heritability of 65%, while that of the knee and hip OA are 40% and 60% respectively [2]. The finding of genetics involvement with OA pathogenesis has significant clinical importance. Firstly, the associated genes can improve knowledge on the molecular pathway underlying the disease incidence and progression. This information is necessary for development of prevention and therapeutic intervention. Secondly, physicians can identify individuals at risk of developing severe or progressive OA and allow them to monitor better the disease progression and to target the interventions.

Approaches taken in genetic studies of osteoarthritis

Studies in the past decades have made a great step toward the understanding of genetic influences on the disease. The approaches include sib recurrent risk and familial aggregation studies, twin studies, linkage analysis, candidate gene association studies, and differential expression studies.

For the twin studies, sib recurrence risk and familial aggregation, the common phenotypes are not exclusively resulted from genetics but may be the consequence of shared environmental factors that the family members are exposed to. Therefore, large studies that include several families are very important. These studies include the Genetics, Arthrosis, and Progression study (GARP) in the
Netherlands, the Multicenter Osteoarthritis Study (MOST, of Boston University Medical Campus) and the Osteoarthritis Initiative (OAI, of University of California, San Francisco, USA).

Linkage analysis is employed to identify chromosomal regions that contain OA genes by investigating polymorphic loci that are inherited along with the trait of interest. If a polymorphic locus (marker) is close to the disease locus on the same chromosome, it is inherited jointly with the disease. With the advancement of technology, it is possible to analyze polymorphic markers of the entire genome. Studies in the United Kingdom, Finland, Iceland, and the United States (reviewed in Valdes and Spector, 2009 [3]), along with a meta-analysis [4] provided delineated regions of harboring OA susceptibility genes on chromosomes 7q34-7q36.3, 11p12-11q13.4, 6p21.1-6q15, 2q31.1-2q34, and 15q21.3-15q26.1. These regions include some candidate genes for having roles in OA incidence and progression, such as IL-1 cluster, FRZB, BMP5 and MATN3. The roles of these genes’ protein products will be discussed.

Another approach to identify OA genes is genetic associations. This strategy analyzes the effect of a gene variant on disease occurrence. If the incidence of a variant occurring in the affected group more than in the control, higher than it can be found by chance, that gene is highly possible to associate with the disease. Some genes encoding for cartilage components, extracellular matrix, and bone density, such as collagen and aggrecan, were chosen as candidate genes to be analyzed. By this approach, polymorphisms in genes encoding estrogen receptor alpha (ESR1) and the vitamin D receptor (VDR) were found to be associated with OA [5].

Another approach employs a differential expression of genes taken from cartilage and synovium of OA patients and normal control [5]. Single nucleotide polymorphisms (SNPs) in genes with significantly different expression profiles between the two groups are analyzed for the association with OA in the population. Several SNPs were identified by this method.

Pathways and molecules involved in osteoarthritis

Several genes involving developmental processes or maintenance of cartilage and bone were found to associate with OA susceptibility and progression. Understanding the gene functions has improved understanding towards the disease pathogenesis. Valdes and Spector [3] categorized molecules involved with OA into five broad classes. Interplay between molecules in these classes further complicates the analysis of OA pathogenesis as shown in Fig. 1.

Inflammation

Synovial inflammation is seen in early OA [6]. Some cytokines, such as interleukin 6 (IL-6) was found to involve in the cartilage degradation. The chromosome region of 2q12-2q21 where the IL-1 gene cluster resides was also found to be involved with distal inter-phalangeal joint OA by linkage analysis [7]. Sclerotic osteoblasts express IL-6, IL-8, and TGF-β1 at a significantly higher level than non-sclerotic counterpart expresses, and suggested that the subchondral bone had a pro-inflammatory environment.

Extracellular matrix (ECM) molecules

As one of OA hallmarks involves the degradation of ECM, genes encoding for these molecules, particularly collagen and cartilage oligomeric matrix protein (COMP), were excellent candidates of genetic association studies. Mutations in COMP cause pseudoachondroplasia and multiple epiphyseal dysplasias. Recently, COMP serum level was found to be promising as a biomarker for OA [8], but so far no polymorphism in COMP was found to be associated with OA [9, 10].

Similar to COMP, COL2A1 had been a focus of many association studies. COL2A1 encodes for the alpha 1 polypeptide chain of type II collagen, the major component of articular cartilage. It has increased expression in early and late-stage OA [11], while chondroprogenitor cells are normally expressed during development. Polymorphisms in the gene were found to be associated with knee and hip OA in Caucasian and with hip OA in Japanese [10]. However, no such association was found in cohorts from the US [12] and Finland (with primary early-onset hip and/or knee OA) [13].

Along with the type II collagen, aggrecan is also the major component of the cartilage ECM. To add another layer of complexity into the effect of genetics on OA, polymorphisms in genes controlling the expression of COL2A1 and the aggrecan gene AGC1 are also linked to the disease. A Japanese group demonstrated that a variant of ASPN gene, encoding for asporin, with a polymorphic stretch of 14 aspartic
acid residues (D14) within exon 2 is more common in patients with the knee and hip OA than the unaffected [14]. The investigators also reported that the variant with 13 repeats of aspartic acid residues (D13) was under-represented in the knee and hip OA patients. It has been shown that transforming growth factor (TGF)-β induces transcription of AGC1 and COL2A1. D14 asporin inhibits TGF-β, and subsequently lowers the synthesis of aggrecan and type II collagen, whereas the D13 asporin has a weaker inhibitory effect to TGF-β [14].

Another gene controlling AGC1 and COL2A1 expression is also found to be associated with OA susceptibility. CALM1, encoding for calmodulin 1, was identified as a hip OA susceptibility loci in Japanese cohort by a genome-wide association analysis [15]. The T allele at the core promoter SNP of CALM1 lowers the synthesis of aggrecan and type II collagen. A combinatorial effect of polymorphisms of calmodulin 1 and asporin in regulating the expression of AGC1 and COL2A1 was also demonstrated. Taken together, it is highly possible that genes encoding for ECMs are associated to OA.

ECM = Extra Cellular Matrix  
BMP = Bone Morphogenic Protein  
Wnt = Wingless-type
**Wnt signaling proteins**

Wnt signaling pathway is involved in cartilage and bone development and degeneration (reviewed in detail in Corr, 2008 [16]). It functions in developmental processes and organogenesis. Wnt signaling molecule inhibits the transcription activity of β-catenin, which was suggested to contribute to cartilage loss, as areas of degenerative cartilage in OA was found to have increased levels of β-catenin [17]. This pathway also plays role in endochondral ossification that causes osteophytes [18]. As bone growth in OA is characterized by osteophyte and subchondral sclerosis, re-activation of Wnt pathway fits with the theory that unbalanced growth processes is a cause of OA.

Polymorphisms associated with OA susceptibility were found in some Wnt-signaling genes: Two non-synonymous SNPs in FRZB, encoding for secreted frizzled-related protein 3 (sFRP3), were found to associate with hip and knee OA in Caucasian, predominantly in female [19]. The association was confirmed by subsequent replication studies [10]. sFRP3 is expressed in adult articular chondrocytes. Functional analysis of the two SNPs in FRZB suggested that the Arg324Gly substitution and the Arg200Trp/Arg324Gly double substitution reduced the ability of sFRP3 to antagonize Wnt signaling [19].

Moreover, a SNP in the 3’ untranslated region of Wnt-1-induced secreted protein 1 (WISP-1) gene was associated with spinal OA in postmenopausal Japanese women [20], suggesting site-specific and sex-specific effects of the pathway.

**Proteins related to modulation of osteocyte or chondrocyte differentiation**

Proteins in this class, such as estrogen receptor alpha (ESR1), the vitamin D receptor (VDR) and osteoprotegerin (OPG), are related to bone density and osteoporosis. Therefore, they are good candidates for genetic association studies. In fact, several variants in genes encoding for these proteins have been reported to be associated with OA in several populations [5, 21-26]. While some negative findings have also been reported [12, 27-29].

Bone morphogenetic proteins (BMPs) are a group of growth factor and cytokine in the TGF-β superfamily. Microsatellite in intron 1 of BMP5 and SNPs in BMP2 were suggested to be associated with OA [5, 26, 30]. Protein encoded from the growth and differentiation factor 5 (GDF5) gene belongs to the BMP family and functions in chondrogenesis and bone repair. A SNP in the 5’ untranslated region of GDF5 has been reported to associate with OA in several populations [31, 32] and to cause significant decrease in transcriptional activity [31].

It was found that the BMP-7 level was elevated in plasma and synovium fluid of Thai OA patients [33]. BMP-7 is under investigation for being a potential inhibitor of OA progression [34].

The thyroid pathway was also implicated in OA at multiple joints. DIO2 gene encoding for an enzyme converting T4 (inactive thyroid) into T3 (active thyroid) was found to associate with the disease in UK, Dutch, and Japanese [35]. T3 in the growth plate functions in chondrocyte differentiation and bone formation.

**Proteases and their inhibitors**

Proteins in this class include A disintegrin and metalloproteinase domain (ADAM) and ADAM with thrombospondin motif (ADAMTS). ADAM and ADAMTS are metalloproteinase involved in osteoclast formation, chondrocytes maturation, and proliferation. Polymorphisms in ADAM12 were reported to associate with prevalence and progression of knee OA [5, 26, 36]. While Rodriguez-Lopez (2009) found no association of these polymorphisms with OA, they found a SNP in ADAMTS14 associated with the knee OA in women [37].

Moreover, levels of some matrix metalloproteinases (MMPs) are elevated in synovial fluid of OA patients and a polymorphism in MMP-1 was found to associate with knee OA in Turkish [38]. MMPs and aggrecanases involve in chondrocyte maturation by degrading the cartilage matrix, to be filled with bone-specific collagen. MMP-3 interacts with sFRP3 of the wnt signaling pathway and MMP-3 level is increased in Frzb knockout mice [39].

In addition to genes belonging to these five categories, epigenetic control, such as DNA methylation, may be important in determining complex gene expression pattern found in arthritic chondrocytes [40]. Methylation of leptin, a gene involved in obesity, directly effects the expression of MMP-13 [41]. Some microRNAs, whose function is to silence their target genes, were identified to be differentially expressed in osteoarthritic chondrocytes compared with normal chondrocytes [42].

**Site-specific, sex-specific, and ethnic-specific nature of osteoarthritis genetic effects**

It is obvious that some genes and variants are
controversial on being related to OA. The reason may be that effects of genetic variations on OA are mostly site-specific and some are ethnic-and sex-specific (Table 1). For example, haplotypes in genes encoding for the cartilage intermediate layer protein (CILP) and ADAM12 were found to be associated with knee OA, especially in men [5]. Moreover, while a variation in the promoter of the calmodulin gene, CALM1, was reported to be associated with hip OA in Japanese [15], studies in Han Chinese and Caucasian were not able to replicate the results [10, 43, 44]. Another variation in GDF5 was found to be associated with susceptibility to OA in Japanese and Chinese [31], and Europeans [32], but not in Greek [45]. Similarly, genetic predisposition of rheumatoid arthritis is difference between population of European and Asian ancestries [46]. The ethnic-specific nature of the findings may not exclusively due to genetic factors, as shared environmental factors are important in the disease incidence and progression.

Challenges in genetic studies of osteoarthritis
There are a few challenges in studies of genetic effects on OA, in addition to the disease being multifactorial, which is the interplay between several genes and environmental factors.

Lack of good animal models
Conducting experiment in animal model is the gold standard in functional study of disease-causing genes. However, thus far, there is no “ideal” model for OA genetic research. For example, articular cartilages of mouse and human have considerable differences, both in cartilage metabolism and histology. The reason impedes the functional analysis of ADAMTS5, a gene encoding for major aggrecanase in articular cartilage, was proved involved in OA as deletion of this gene prevents cartilage degradation in a mouse model of OA [47]. Moreover, cystatin 10, a gene implicated in OA in a mouse model, has no human counterpart. This challenge makes it difficult to analyze functionally the role of susceptibility genes.

Low rate of replication
This problem is of particular for studies that include different ethnic groups. A standard inclusion criterion is crucial for a global collaboration. Some countries, like Thailand, have population from mixed ethnic background. Thus, it is one of the major causes of the low rate of replication.

Small sample size in specific studies
This problem arises from OA being site- (e.g., hip, hand, and knee), sex-, and ethnic-specific. Therefore, it is difficult to recruit enough cases and controls for each subgroup to conduct reliably the studies.

Inclusion criteria
While some studies used radiographic OA (ROA) as an inclusion criterion, some used symptomatic OA with radiographic evaluation, or used total joint replacement as a condition for terminal stage of the disease. Both have advantages and disadvantages. ROA, usually accompanied with evaluation scores, such as Kellgren-Lawrence (K-L) score, allows detection of early changes in the anatomy. However, ROA is very common and most ROA are not symptomatic [48]. Universal agreement of disease phenotypes of OA must be generated in order to conduct global collaboration and cross-reference.

Clinical implications
Several studies have focused on developing reliable biomarkers that can identify individual at risk of developing OA or at early stage of the disease. Protein levels in serum and synovial fluid were tested; some were successful and some were not. Among the promising candidates are collagen type II, glycoprotein 39, COMP, BMP-7, osteopontin, and endoglin [33, 49-53]. Markers to identify OA in its early stages are very important as they enable early interventions. Further knowledge on molecular pathways underlying the disease will allow direct and effective therapy.

Thus far, clinical implications of OA had been on obesity. This is because of the biomechanical overloading and the biomolecular effects. Leptin, an obesity gene, regulate MMP-13 expression in chondrocytes [41] and a microRNA differentially expressed in OA is also associated with high body mass index [42]. Weight control may modulate the adipokine profile and delay the disease incidence or progression [54].

Conclusion
While the Human Genome Project and the HapMap Project help uncovering many of the genetic determinants of complex disorders, to fully understand the genetics underlying OA pathogenesis, a global, or at least, a continental collaboration is crucial to overcome these challenges. From Table 1, it is clear
that many candidate genes have not been studied in Asian cohort, whose genetic compositions are undoubtedly different from that of European. While most studies of Asian cohort were performed in Japanese and Han Chinese, very few were on Southeast Asian. It is estimated that more than one million senior citizens in Thailand are suffering from OA [55], though not many studies have been done on genetics of OA in Thais. Moreover, replication associations for a complex disease like OA are crucial in understanding the disease etiology. It is also important to distinguish between the true and false positives.

Table 1. Selected genes associated with osteoarthritis.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>OA association</th>
<th>Association in Asian subjects*</th>
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<tbody>
<tr>
<td><strong>Inflammation</strong></td>
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<tr>
<td><strong>CCL2</strong></td>
<td>Chemokine (C-C motif) ligand 2</td>
<td>Immunoregulatory and inflammation. Binds to chemokind receptors CR2 and CR4</td>
<td>Differentially expressed in OA bone [56]</td>
<td>A polymorphism in the promoter is associated with primary knee OA in Korean [57] -</td>
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<tr>
<td><strong>COX2</strong> (PTGS2)</td>
<td>Cyclooxygenase 2 (Prostaglandin G/H SYNTHASE2)</td>
<td>Osteogenesis and bone repair</td>
<td>Associated with hip and knee OA [58, 59]</td>
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<tr>
<td><strong>IL-1 gene cluster</strong></td>
<td>Interleukin 1-α, β, interleukin 1 receptor antagonist (IL1RN)</td>
<td>Stimulate osteoclast activity in vitro, increase production of metalloproteinases and aggrecanases, in turn stimulate cartilage degredation</td>
<td>Polymorphisms in IL1RN are associated with disease severity in knee OA [60] and implicated in a meta-analysis [61] Negative finding in Turkish population [62]</td>
<td>-</td>
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<tr>
<td><strong>IL-6</strong></td>
<td>Interleukin-6 Interferon β-2</td>
<td>Stimulates osteoclasts, a polymorphism involved in BMD</td>
<td>Increased expression in radiographic knee OA in British women [63] and in osteophytes [64]. A polymorphism is associated with osteolysis [65] and distal interphalangeal OA [66]</td>
<td>-</td>
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<tr>
<td><strong>IL-10</strong></td>
<td>Interleukin-10</td>
<td>Anti-inflammatory, prevents cartilage destruction by reducing IL-1β and TNF-β expression in articular chondrocytes in a mouse model [67]</td>
<td>Associated with knee OA in Greek [68] and distal interphalangeal OA [69]</td>
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<tr>
<td><strong>HLA</strong></td>
<td>Human leukocyte antigen system</td>
<td>Antigen presentation, associated with rheumatoid arthritis</td>
<td>HLA-DRB1 alleles are associated with OA in Italian [70] and German [71] and distal interphalangeal OA in Dutch [72]</td>
<td>HLA class I is associated with generalized OA in Japanese [73]</td>
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Table 1. Selected genes associated with osteoarthritis (Continued).

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<tr>
<td><strong>Extracellular matrix molecules</strong></td>
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<tr>
<td><strong>CILP</strong></td>
<td>Cartilage intermediate layer protein</td>
<td>Inhibits TGFβ 1-mediated induction of cartilage matrix genes. Increase in synthesis in early OA cartilage</td>
<td>Associated with knee OA prevalence and progression [26] and knee OA in men [5]</td>
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<tr>
<td><strong>MATN3</strong></td>
<td>Matrilin 3</td>
<td>Cartilage extracellular matrix protein. Involved in development and homeostasis of cartilage and bone</td>
<td>Increased expression in OA [83] Associated with hand OA, but not knee OA [84, 85]. Activates the expression of OA-associated genes [86]</td>
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</table>
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<tbody>
<tr>
<td><strong>Genes/proteins in Wnt signaling pathway</strong></td>
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<tr>
<td><strong>CALM1</strong></td>
<td>Calmodulin 1</td>
<td>A member of calcium-modulated protein family. Functions in growth, cell</td>
<td>Negative findings in Caucasian [10] and UK Caucasian women with hip OA [43]</td>
<td>Associated with hip OA in Japanese [15]. Negative finding in Han Chinese [44]</td>
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<tr>
<td></td>
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<td>cycle and signal transduction. Regulates COL2A1 expression</td>
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<td><strong>ENG</strong></td>
<td>Endoglin, CD105</td>
<td>Receptor for members of TGF-β superfamily. Involves in angiogenesis,</td>
<td>Up-regulated in RA and OA synovial fluid and tissues [89]</td>
<td>Elevated level in plasma and</td>
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<td></td>
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<td>inflammation and wound healing</td>
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<td>synovial fluid associated with</td>
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<td>knee OA severity in Thais [50]</td>
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<tr>
<td><strong>FRZB</strong></td>
<td>Secreted frizzled-related protein 3 (sFRP)</td>
<td>Antagonist in Wnt-signaling pathway, modulates chondrocyte maturation</td>
<td>Associated with hip OA [19, 90], generalized OA, multiple joints OA [10, 91, 92]. These SNPs may lead to elevated serum sFRP level, which can be used as a biomarker.</td>
<td></td>
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<tr>
<td><strong>WISP-1</strong></td>
<td>Wnt-1-induced secreted protein 1</td>
<td>A target of the Wnt pathway and is directly regulated by beta-catenin</td>
<td>Increased expression in synovium and cartilage of mice with experimental OA and human OA, and induces expression of MMPs and aggrecanase [93]</td>
<td>Associated with spinal OA in post-menopausal Japanese women [20]</td>
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<tr>
<td><strong>Proteins related to modulation of osteocyte or chondrocyte differentiation</strong></td>
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<tr>
<td><strong>BMP2</strong></td>
<td>Bone morphogenetic protein 2</td>
<td>A member of TGF-β superfamily. Involved in chondrogenesis and</td>
<td>Associated with prevalence of knee OA [5, 26]. mRNA localized in OA tissues [94]</td>
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<tr>
<td></td>
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<td>osteogenesis, induces the formation of ectopic cartilage</td>
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<tr>
<td><strong>BMP5</strong></td>
<td>Bone morphogenetic protein 5</td>
<td>A member of TGF-β superfamily. Induced endochondral osteogenesis in vivo</td>
<td>Mapped for a primary OA susceptibility locus with a functional microsatellite [30, 95]</td>
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<tr>
<td><strong>BMP7</strong></td>
<td>Bone morphogenetic protein 7</td>
<td>A regulator of cartilage and bone induction activity with roles in</td>
<td>Detected in synovial fluid of RA and OA patients [96]</td>
<td>High level in plasma and synovial fluid relative to knee OA severity in Thais [33]</td>
</tr>
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<tbody>
<tr>
<td>*ESR1</td>
<td>Estrogen receptor alpha</td>
<td>Associates with BMD. Modulates proteoglycan degradation and matrix metalloproteinase expression in chondrocytes</td>
<td>Radiographic knee and hip OA [5, 21, 24]</td>
<td>Associated with primary knee OA in Korean [22]</td>
</tr>
<tr>
<td>*GDF5</td>
<td>Growth differentiation factor 5</td>
<td>A member of TGF-β superfamily. Required for normal formation of bones and joints in the limbs, skull, and axial skeleton [97]</td>
<td>A functional SNP in the 5’ UTR, which reduces the gene expression, is associated with OA in European, Spanish, and Asian population [32], but not in Greek population [45]</td>
<td>Associated with OA in Japanese and Chinese [31]</td>
</tr>
<tr>
<td>*OPG</td>
<td>Osteoprotegerin (osteoclastogenesis inhibitory factor)</td>
<td>A secreted glycoprotein that regulates bone resorption, inhibits osteoclast differentiation</td>
<td>Associated with knee OA progression [5, 26]</td>
<td>-</td>
</tr>
<tr>
<td>*VDR</td>
<td>Vitamin D receptor</td>
<td>Mediates effects of VitD, regulates osteoclastogenesis, involved in BMD and osteoporosis</td>
<td>Associated with hand OA (Finnish women) [98], osteophytes in knee and lumbar spine OA [23, 25] Some negative studies [12, 29]</td>
<td>Japanese: no association to hand, hip, knee OA [28]</td>
</tr>
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</table>

Protease/protease inhibitors

| AACT     | Alpha-1-antichymotrypsin                    | a plasma protease inhibitor involved in cartilage proteoglycan degradation | Associate with knee OA progression [5, 26]              | -                             |
| ADAM12   | A disintegrin and metalloproteinase domain 12 | A metalloproteinase involved in osteoclast formation, chondrocytes maturation and proliferation | Associated with prevalence and progression of knee OA [5, 26, 36] | -                             |
| ADAMTS14 | ADAM with Thrombospondin motif (ADAMTS) 14   | A metalloproteinase                                                      | Associated with knee OA in women [37]                  | -                             |
| *MMPs    | Matrix metalloproteinase                     | Major enzyme responsible for collagen and aggrecan degradation in articular cartilage | Elevated expression in serum, cartilage and synovial tissues of OA patients [99] | A polymorphism in MMP-1 is associated with knee OA in Turkish [38]. |
| TNA      | Tetranectin                                 | Extracellular matrix degradation. Induced during the mineralization phase of osteogenesis | Associate with knee OA progression [5, 26]              | -                             |

* indicates that, to the author’s knowledge, no association study of the gene and OA in Asian subjects has been reported at the time of this manuscript submission. Genes associated to OA are divided into five categories, as suggested by Valdes and Spector, 2009 [3].
Knowledge gained from studies in the last few years prompted researchers to look at OA as a systematic musculoskeletal disorder involving cell differentiation and metabolism, rather than a disease of articular cartilage as previously thought. Genetic component is exceedingly probable as an underlying cause of phenotypic variation, making some people more susceptible in developing OA or having the disease progress more rapidly than others. Reversion in gene expression in OA suggests that the cause of generalized OA may be unbalance bone metabolism. Some proteins are selected as candidate biomarkers for OA; some are therapeutic targets. Information gathered from clinical and basic research is highly significant in understanding and tackling this disabling and costly disease.

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