Asian Biomedicine Vol. 5 No. 1 February 2011; 23-36 DOI: 10.5372/1905-7415.0501.003

Review article

The genetics behind osteoarthritis: Asian focus

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Osteoarthritis (OA), a degenerative joint disease, is the most common form of arthritis in the elderly. Problems arising from the condition are not only health, physical, and psychological, but also economical and social. OA is a complex disease causes by environmental factors (obesity, female gender, advancing age) and genetics. A strong genetic contribution to primary OA has been observed in several studies. Asian population is undoubtedly genetically different from European, whom most studies have been performed. This review systematically compares results of molecules involved with OA from studies performed on Asian and Caucasian populations. The clear differences between Asian and Caucasian populations may be from the sex- and ethnic-specific nature of the disease, as well as from the inclusion criteria of the studies. Global collaboration is highly significant in understanding genetic underlying OA. Knowledge gained from genetic study is important to the development of prevention and therapeutic intervention, and to identify individuals at risk of developing severe or progressive OA.

Keywords: Asian, genetics, osteoarthritis

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.

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Approaches taken in genetic studies of osteoarthritis

Researches 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

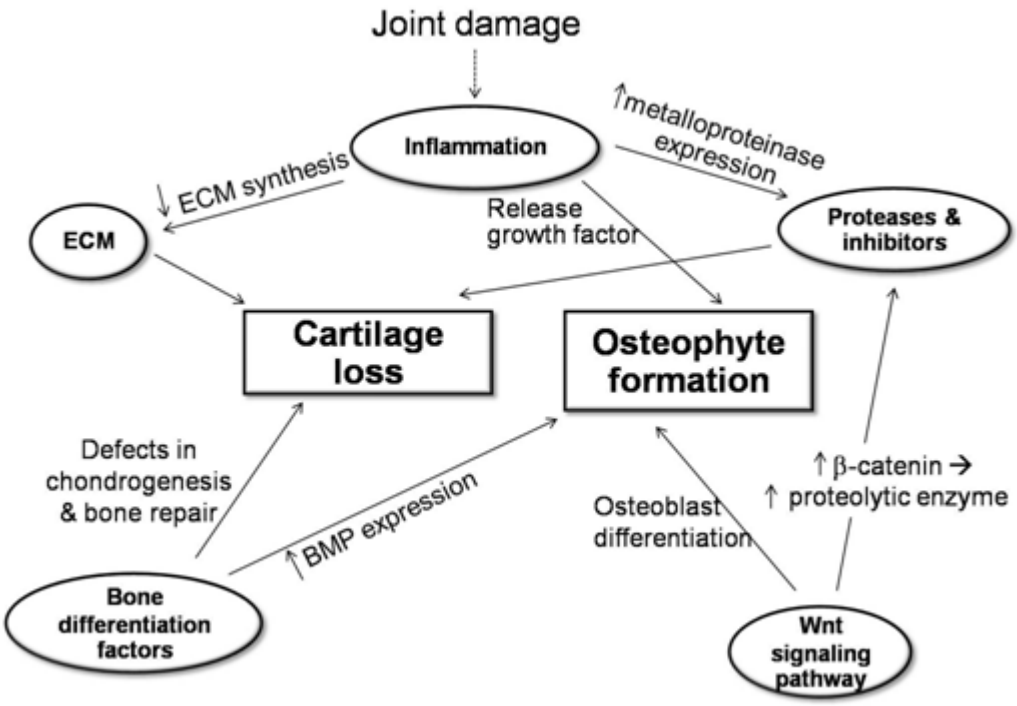
Synovial inflammation is seen in early OA [6]. Some cytokines, such as interleukin 6 (IL-6) was found to involve in the cartilage degradation. The chromosome region of 2q12-2q21 where the IL-1 gene cluster resides was also found to be involved with distal inter-phalangeal joint OA by linkage analysis [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



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

Fig. 1 Interaction between molecular pathways associated with OA pathophysiology. Gene/proteins associate with OA phenotypes (in rectangular boxes) are categorized into five classes (in oval boxes). Interconnection between these pathways further complicates studies in OA pathogenesis. Inflammation that is caused by imbalance between the pro- and anti-inflammatory factors increases metalloproteinase expression. The imbalance between the proteolytic enzymes (e.g. matrix metalloproteinase, a disintegrin and metalloproteinase domains) and their inhibitors, in turn, causes cartilage degradation. Inflammation also causes cartilage loss by inhibiting ECM synthesis and chondrocyte proliferation. Genes encoding for ECM molecules and bone differentiation factors directly regulate cartilage homeostasis. Uncontrolled cell proliferation and maturation lead to another OA hallmark, osteophytes. Inflammation, the villain in OA pathogenesis, activates releases of growth factors such as Vascular Endothelial Growth Factor (VEGF) and causes angiogenesis that contributes to osteophyte formation. β-catenin level, controlled by Wnt pathway, also effects VEGF expression, matrix mineralization, and matrix degrading enzyme, and is involved in OA phenotype development.

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-□[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 calmodulin1 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.

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 ostophyte 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 multi-factorial, 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.

Gene	Protein	Function	OA association	Association in Asian subjects*
Inflammation				
CCL2	Chemokine (C-C motif) ligand 2	Immunoregulatory and inflammation. Binds to chemokind receptors cCR2 and CCR4	Differentially expressed in OA bone [56]	A polymorphism in the promoter is associated with primary knee OA in Korean [57]
COX2 (PTGS2)	Cyclooxygenase 2 (Prostaglandin G/H SYNTHASE 2)	Osteogenesis and bone repair	Associated with hip and knee OA [58, 59]	-
IL-1 gene cluster	Interleukin 1-α, β, interleukin 1 receptor antagonist (IL1RN)	Stimulate osteoclast activity in vitro, increase production of metalloproteinases and aggrecanases, in turn stimulate cartilage degredation	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]
IL-6	Interleukin- 6 Interferon β -2	Stimulates osteoclasts, a polymorphism involved in BMD	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]	-
IL-10	Interleukin -10	Anti-inflammatory, prevents cartilage destruction by reducing IL-1β and TNF- β expression in articular chondrocytes in a mouse model [67]	Associated with knee OA in Greek [68] and distal interphalangeal OA [69]	-
HLA	Human leukocyte antigen system	Antigen presentation, associated with rheumatoid arthritis	HLA-DRB1 alleles are associated with OA in Italian [70] and German [71] and distal interphalangeal OA in Dutch [72]	HLA class I is associated with generalized OA in Japanese [73]

Table 1. Selected genes associated with osteoarthritis (Continued).

Gene	Protein	Function	OA association	Association in Asian subjects*
Extracellular matrix molecules				
ASPN	Asporin, Periodontal ligament-associated protein 1	Associated with cartilage matrix. Suppresses TGF- β -mediated effects and reduces proteoglycan accumulation [14]	Knee OA and hip OA [14, 74-76] Found associated by meta-analyses [10, 77] Negative finding in Spanish Caucasians [78]	Associated with knee and hip OA in Japanese [14], knee OA [74] and age at onset [79] in Chinese, female-specific knee OA in Korean [76]
COL2A1	Collagen, Type II α -1	Cartilage collagen	Increased expression in OA [11]. Associated with hip and knee OA in the Rotterdam Study [80], Dutch [25] and Caucasian men [10]. Negative finding in US [12] and Finnish with primary early-onset hip and/or knee OA cohort [13]	Associated with hip OA in Japanese [81]
COMP	Cartilage oligomeric matrix protein	Chondrocytes territorial matrix , a candidate gene for pseudoachondroplasia and hereditary osteochondral dysplasias with early-onset OA	Lower serum levels in hand and knee OA [82]. Negative finding in Caucasian [10]	Negative finding in Japanese [9]
CILP	Cartilage intermediate layer protein	Inhibits TGFβ 1-mediated induction of cartilage matrix genes. Increase in synthesis in early OA cartilage	Associated with knee OA prevalence and progression [26] and knee OA in men [5]	-
MATN3	Matrilin 3	Cartilage extracellular matrix protein. Involved in development and homeostasis of cartilage and bone	Increased expression in OA [83] Associated with hand OA, but not knee OA [84, 85]. Activates the expression of OA-associated genes [86]	-
SPP1	osteopontin (secreted phosphoprotein 1)	A bone matrix protein involving bone maturation and fracture repair.	Up-regulated in human OA chondrocytes [87]	High level in plasma and synovial fluid relative to knee OA severity in Thais [49] and Chinese [88]

Table 1. Selected genes associated with osteoarthritis (Continued).

Gene	Protein	Function	OA association	Association in Asian subjects*
Genes/proteins in Wnt signaling pathway				
CALM1	Calmodulin 1	A member of calcium-modulated protein family. Functions in growth, cell cycle and signal transduction. Regulates *COL2A1* expression	Negative findings in Caucasian [10] and UK Caucasian women with hip OA [43]	Associated with hip OA in Japanese [15]. Negative finding in Han Chinese [44]
ENG	Endoglin, CD105	Receptor for members of TGF-β superfamily. Involves in angiogenesis, inflammation and wound healing	Up-regulated in RA and OA synovial tissues [89]	Elevated level in plasma and synovial fluid associated with knee OA severity in Thais [50]
FRZB	Secreted frizzled-related protein 3 (sFRP)	Antagonist in wnt-signaling pathway, modulates chondrocyte maturation	Associated with hip OA [19, 90], generalized OA, multiple joints OA [10, 91, 92]. These SNPs may leads to elevated serum sFRP level, which can be used as a biomarker.	-
WISP-1	Wnt-1-induced secreted protein 1	A target of the wnt pathway and is directly regulated by beta-catenin	Increased in expression in synovium and cartilage of mice with experimental OA and human OA, and induces expression of MMPs and aggrecanase [93]	Associated with spinal OA in post-menopausal Japanese women [20]
Proteins related to modulation of osteocyte or chondrocyte differentiation				
BMP2	Bone morphogenetic protein 2	A member of TGF-β superfamily. Involved in chondrogenesis and osteogenesis, induces the formation of ectopic cartilage	Associated with prevalence of knee OA [5, 26]. mRNA localized in OA tissues [94]	-
BMP5	Bone morphogenetic protein 5	A member of TGF-β superfamily. Induced endochondral osteogenesis in vivo	Mapped for a primary OA susceptibility locus with a functional microsatellite [30, 95]	-
BMP7	Bone morphogenetic protein 7 (osteogenic protein-1)	A regulator of cartilage and bone induction activity with roles in stimulation of proteoglycan synthesis and cartilage repair	Detected in synovial fluid of RA and OA patients [96]	High level in plasma and synovial fluid relative to knee OA severity in Thais [33]

Table 1. Selected genes associated with osteoarthritis (Continued).

Gene	Protein	Function	OA association	Association in Asian subjects*
ESR1	Estrogen receptor alpha	Associates with BMD. Modulates proteoglycan degradation and matrix metalloproteinase expression in chondrocytes	Radiographic knee and hip OA [5, 21, 24]	Associated with primary knee OA in Korean [22]
GDF5	Growth differentiation factor 5	A member of TGF-β superfamily. Required for normal formation of bones and joints in the limbs, skull, and axial skeleton [97]	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]	Associated with OA in Japanese and Chinese [31]
OPG	Osteoprotegerin (osteoclastogenesis inhibitory factor)	A secreted glycoprotein that regulates bone resorption, inhibits osteoclast differentiation	Associated with knee OA progression [5, 26]	-
VDR	Vitamin D receptor	Mediates effects of VitD, regulates osteoclastogenesis, involved in BMD and osteoporosis	Associated with hand OA (Finnish women) [98], osteophytes in knee and lumbar spine OA [23, 25] Some negative studies [12, 29]	Japanese: no association to hand, hip, knee OA [28]
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.

Acknowledgement

This study was supported by Research Funds from the Faculty of Science, Chulalongkorn University, and the Thailand Research Fund. The author has no conflict of interest to report.

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