The effect of single nucleotide polymorphism on susceptibility of osteoarthritis: recent progression and implications

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Abstract: Osteoarthritis (OA) is a disabling and malformation disease that affects multiple joints, especially hip and knee joint, which is characterized by degeneration and progressive loss of articular cartilage with pathological changes in bone, synovium, and soft tissues of affected joints. Polymorphisms in several genes, such as TIMP3, interleukin-6 (IL-6), IL-16, CDH2, HIF1A, and WISP1, have been demonstrated to be protective factors of OA. However, polymorphisms in other genes including ADAM12, DWA and ACE were considered to be correlated with increased risk of OA. The present review focuses on the association between single nucleotide polymorphisms (SNPs) locus and susceptibility of OA.

Keywords: Single nucleotide polymorphism (SNP); susceptibility; osteoarthritis (OA); review

Introduction

Osteoarthritis (OA) is a incapacitating and deformation disease which affects multiple joints, especially hip and knee joint. Prevalence of OA increases with age. The disease affects 10% of the males and 18% of the females aging more than 45. It is expected that 20% of adults in North America and Western Europe will be affected with OA by 2030 (1). The characteristic of OA is degeneration and gradual deprivation of articular cartilage with pathological changes in bone, synovium, and parenchyma of relevant influenced joints (2). Patients with OA bring about a serious medical, social and economic pressure, thus it is crucial to carry out investigations to illuminate the etiology. OA is a complicated disease which changes the homeostasis of articular cartilage and subchondral bone by biomechanical and metabolic ways (4). At present the main treatment method of OA focuses on controlling symptoms, such as pain of the joint (5,6). Ren et al. (7) systematically reviewed the relation in ERα and the risk of OA by a meta-analysis. Their study selected 17 researches which involve 10 Europeans and 7 Asians. The study manifested that there was a weak association in ERαXbaI polymorphism and the risk of OA in Europeans rather than in the Asians, and that ERαPvuII polymorphism had no connection with the disease in either population. Kerkhof et al. (8) conducted large-scale meta-analysis to identify the effect of common genetic polymorphism in the interleukin-1b (IL-1B) and interleukin-1R antagonist (IL1RN) genes in danger of knee OA. Their study selected 17 researches which involve 10 Europeans and 7 Asians. The study manifested that there was a weak association in ERαXbaI polymorphism and the risk of OA in Europeans rather than in the Asians, and that the ERαPvuII polymorphism had no connection with the disease in either population. Claessen et al. (9) investigated the relation in radiographic OA and insulin-like growth factor-1 (IGF-1) gene variation...
in primary OA invalids in a systematic review. They involved 11 researches which surpass 3,000 primary OA patients. Observational result suggested a direct correlation between IGF-1 gene variation and radiographic OA.

Although there are a number of literatures in this field, such as meta-analysis and systematic review, regarding effect of single nucleotide polymorphism (SNP) on susceptibility of OA, reviews regarding this topic are relatively scarce. Therefore, this review summarized the effect of both of protective factors and risk factors of SNP on susceptibility of OA.

**Protective factor for OA**

**Interleukin-6 (IL-6) gene**

Chronic inflammatory procedure includes the manufacture of cytokines which exist in the synovial liquid, inducing hyperalgesia and is in relation to the destruction of chondrocyte. Tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) can highlight among the major mediators. Generated by chondrocytes, the cytokines promote the production of proteolytic enzymes and they bring about the generating of other mediators (10). IL-6 has a complicated biochemical reaction, exerting a basilic part as a regulator of assimilatory and dissimilatory effect in OA. Researches have indicated that the IL-1β and stroma metalloproteinases can up-regulate the generation of IL-6, which decreases the generation of collagen-2, accelerating the injury of joint. IL6 resides in 7p21-24, and the promoter region is 303 bp (11). Fernandes et al. (12) determined to investigate the association between the SNP in the section 572 located in the promoter region (572G/C) of IL6 in the elderly patients which have hip and knee OA. The study involved 257 physically independent elderly people, 92 individuals with OA of case group and 165 individuals with no OA of control group. The level of joint injury was evaluated by radiographic categorization in the standard with Kellgren and Lawrence (KL) and the functional health status was assessed by Lequesne and WOMAC. The result of the research shown that individuals with the C allele had a statistically significantly lower susceptibility of OA (OR: 0.51; 95% CI: 0.32–0.80; P=0.004) and less radiological damage of both hip (P=0.04) and knee joints (P=0.03). As to functional status, individuals which carry the C allele had a lower level of functional lesion assessed by WOMAC (P=0.04), although Lequesne questionnaire showed no difference (P>0.05). Therefore, they regarded IL6 572G/C as a protectin affecting the onset and severity of both hip and knee OA in the elderly invalids. The research by Chua et al. (13) examining the variation 572G/C also revealed that allele C plays a protective role in the systemic lupus erythematosus.

**IL-16 gene**

IL-16 is localized to chromosome 15q26.3, which is initially translated into a precursor protein including 631 amino acids. IL-16 is a CD4-specific ligand which is needed for the initial steps of CD4 bioactivity. IL-16 activates CD4+ T cells, monocytes, and dendritic cells in alternative by binding to the CD4 molecule. Besides, IL-16 which is a proinflammatory cytokine can increase the secretion of cytokines, such as IL-15, inducing inflammatory response. IL-16 dysregulation is closely related to rheumatoid arthritis (14). Liu et al. (15) examined the relation between IL-16 rs11556218, rs4778889, and rs4072111 and the risk of knee OA in the Chinese population. The study included 228 subjects, half of whom presented with knee OA; the others were healthy controls. They found that the T/G genotype reduced the risk of knee OA in comparison with the T/T genotype in rs11556218. There was linkage disequilibrium between rs4778889 and rs11556218. The results are consistent with the following researches. Luo et al. (16) assessed the correlation between IL-16 variation and sensitivity of knee OA in the Chinese. This research included 150 knee OA patients and 147 healthy subjects. The results showed that the polymorphisms in IL-16 rs11556218 were related to the reduced knee OA risk. Otherwise, the C allele and genotype CC+CT of rs4778889 were associated with the decreased susceptibility of knee OA. IL-16 rs11556218 and rs4778889 have found to be protective factors of OA onset, which suggests other SNPs may be associated with OA.

**TGF-β/Smad3 signaling pathway**

Many studies including candidate gene researches and meta-analyses show that ASPN and GDF5 are in relation to OA (17). The gene coding for growth differentiation factor 5 belongs to the TGF-β superfamily, which plays crucial part in osseous and joint progression with mutations causing a series of skeletal diseases. Biological researches suggest that the SNP rs143383 in GDF5 causes the reduction in GDF5 transcription in joint tissues, which may be essential
for OA progress (18). Functionally, aspirin binds to TGF-β, suppressing its binding to the TGF-β type II receptor, thus inhibiting TGF-β-induced expression of anabolic cartilage molecules involving type II collagen and aggrecan. Allele-specific influences the TGF-β activity, which have the D14 allele related to OA, suppressing TGF-β activity more efficiently than other alleles. This consists TGF-β-induced productions of TIMP3 by the PI3K/Akt signaling pathways. Su et al. (19) aimed to investigate whether SNPs of TGF-β1, TGF-βRI, Smad3, and TIMP3 are related to knee OA. They conducted a study and genotyped 518 patients with knee OA and 68 healthy individuals. All projects were genotyped for TIMP3, TGF-β1, TGF-βRI, and Smad3 polymorphisms. They observed significant associations with TIMP3 rs715572G/A existed in knee OA patients and healthy controls. The GA in TIMP3 rs715572G/A was related to OA significantly (P=0.007). Patient indicated significant differences in TIMP3 rs715572G/A genotypes between grade 4 knee OA and healthy individuals. So TIMP3 rs715572G/A may be a protective factor for serious knee OA. TIMP-3 absence in mice leads to cartilage degeneration which resembles to change observed in OA patients, revealing TIMP-3 may play a physiopathologic role in the onset and progress of OA (20).

**CDH2 gene**

Cadherins are calcium-dependent cell-cell adhesion proteins which exert crucial parts in cell adhesion and migration (21). Human vitro studies have found a vital part of cadherin 11 in the progression and architecture of the synovium and in adjusting the capacity of synovial fibroblasts (SFs) to express inflammatory factors, such as cytokines, chemokines. Ruedel et al. (22) explored to establish the part of genetic polymorphism of N-cadherin in OA of the knee and hip. This study composed of 312 cases with OA and 259 healthy individuals. The results showed the minor allele of rs11564299 had a protective effect on OA. Compared to subjects of the major allele, the individuals of the minor allele of rs11564299 displayed promoted N-cadherin levels in SFs. The minor allele was predicted to have a new transcription factor binding site. Therefore, a CDH2 promoter polymorphism affected the risk of OA and hnRNP K was detected to be associated with the modulation of enhanced N-cadherin expression in patients with OA which carried the minor allele of rs11564299.

**Risk factor for OA**

**ADAMTS14 gene**

The joints of OA patient have an imbalance between synthesis and degradation of ECM which leads to cartilage destruction. And metalloproteinases have been regarded as the major groups of enzymes responsible for this undermined cartilage. A disintegrin and metalloproteinases with thrombospondin motifs (ADAMTSs), which are members of the Zn²⁺-metalloprotease superfamily (metzincins), are known as novel genetic factors of OA. ADAMTSs have a thrombospondin type 1 (TSP1) motif, followed by a spacer region and a variable number of TSP1 repeats, which appear to be associated with binding to ECM components consisting of procollagen and aggrecan (23). ADAMTS14, belonging to ADAMTS, which has been recently reported to be a novel OA candidate gene, is located on chromosome 10q22.1. Poonpet et al. (24) investigated the association between genetic polymorphism of the SNP rs4747096 in ADAMTS14 and knee OA susceptibility in the Thai population. Comparing the genotype distributions, allele frequencies and inheritance patterns between patients and controls, they found that the frequency of both the AA genotype and the A allele were obviously higher in female patients of knee OA than in controls. Compared to GG, genotypic AA and AG were showed to have obviously increased risk for knee OA. While no significant relations were discovered in males. They concluded that the SNP rs4747096 in ADAMTS14 had relation to knee OA in the female Thai; for his reason, the function of ADAMTS14 in OA appears to be gender-determination. The positive results of both A and G alleles originated from the present and previous studies may suggest that the amino acid substitution determined by rs4747096 in ADAMTS14 is not the direct detrimental factor contributing to OA. However, this polymorphic locus may be related to the OA causative gene on the same chromosome and the SNP is inherited jointly with disease onset.

**ADAM12 gene**

ADAM, which belongs to the Zn-dependent metzincin superfamily, has been demonstrated to have relation to some severe diseases like rheumatoid arthritis, heart disease, and tumor (25). Twenty-three human ADAMs have been identified and ADAM12 gene is a candidate of OA. Human ADAM12 locates on chromosome 10q26 encoding two
ways, one is a transmembrane form and the other is an alternatively spliced secreted form. There is a moderating effect of human ADAM12 on frame formation, cartilage cells proliferation, and maturation. Furthermore, ADAM12 is increased in OA chondrocyte and giant cells with multiple uncles which are surround incompact hip implants. Poonpet et al. (26) evaluated whether there was a relation between the ADAM12 rs3740199 variation and the risk of knee OA in Thai population. The significant relations were suggested from the C allele and the CC genotype in men with knee OA. However, there seemed to have no significant relation to female patients. The researchers proved that the rs3740199 in ADAM12 was related with the risk of knee OA in Thai men. Comparing with the GG and GC genotypes, the CC genotype carried the biggest risk. Similar study was conducted in a Chinese Han population. Lou et al. (27) tried to assess rs3740199, rs1871054, rs1278279, and rs1044122 of ADAM12 for their relation with knee OA susceptibility in a Chinese Han population. This case-control study included 152 subjects who were diagnosed as knee OA and 179 healthy individuals. They observed that rs1871054 was significantly related with increased risk of OA. However, no statistically significant relations with OA for other SNPs were found. Although the correlated polymorphic locus in the Thai and the Chinese Han population was different, both studies indicated ADAM12 SNPs were linked to the risk of OA.

**DVWA gene**

DVWA gene, which is particularly expressed in chondrocyte, codes for a protein appearing double von Willebrand factor A domains (VWA domain), including protein-protein interactions and cellular adhesion (28). Both DVWA rs11718863 and rs7639618 variations reside on the exonic third area, causing missense variants with a resulting amino acidic alternative. The SNPs were identified as associated with the reducing of the interplay between the DVWA protein and the β-tubulin. This protein-protein conjugated is essential to the adjusting of cartilage differentiation, which plays a key role in protecting artculated joints from OA pathogenesis. Bravata et al. (29) explored weather the DVWA rs11718863, rs7639618, rs7651842, rs7639807, and rs17040821 would cause protein functional changes. This case-control study involved 61 Sicilian cases with knee OA and 100 healthy controls. Clinical and radiographic assessment was carried out according to AKSS scores and KL. They detected that all DVWA SNPs’ Minor Allele Frequencies (MAF) were more than in the European and the rs7639618 SNP indicated a statistical relation with KL. The researchers have showed that rs11718863 was a statistically significant predictor of KL values in Sicilian OA invalids; also, this genetic variation was more representative with more severe knee OA.

**IL-7 gene**

IL-7 resides on chromosome 8q12q13, spanning 72 kb, and involves six exons. It encodes a 177-amino-acid protein with a 25-amino-acid-long signal peptide. IL-7, a non-redundant cytokine, is crucial for T cell survival and development in humans. Studies have indicated that IL-7 is present in several diseases, such as leukaemia, lymphoma and some types of solid tumours (30). It has been identified that IL-7 contributes to joint tissue destruction in OA in an autocrine manner. Long et al. (31) have certified that IL-7 protein is produced by articular chondrocytes, and endogenous production of IL-7 by cartilage tissue in patients with OA is higher than the control projects. Zhang et al. (32) performed a retrospective, case-control study to evaluate the action of variants of IL-7 in OA susceptibility in the Chinese Han population from 2013 to 2015. Four SNPs rs2583764, rs2583760, rs6993386, and rs2583759 were genotyped in 602 OA patients and 454 healthy volunteers. Among these polymorphisms, rs2583764, rs2583760, and rs6993386 indicated no significant association with OA, while the rs2583759 polymorphism was significantly related with OA in the Chinese. The study represents the first attempt to explore the relation between polymorphisms in IL-7 and OA. However, the present study is only based on subjects of the Chinese Han population. Larger samples with more markers in other ethnic groups will be essential to clarify the apparent association of IL-7 to OA.

**IL-8 gene**

IL8, which belongs to the CXC chemokine gene family, is a proinflammatory mediator, playing a pivotal role in chemoattractant for neutrophilic granulocytes, and is a beneficial angiogenic factor (33). The IL-8 located on 4q12-q13 encode IL-8. The positions of IL-8 variations at rs4073 -251 and rs2227306 +781 are demonstrated to regulate IL-8 expression. The variations have been assessed in several clinical managements and have been identified to the risk of a great quantity of inflammatory disorders, involving disease severity and clinical development. He et al. (34)
designed a study to assess the effect of IL-8 variations located on rs4073 -251 and rs2227306 +781 on the risk of OA. They found that patients with OA are more likely to carry IL-8 -251 TT genotype, IL-8 -251 T allele, IL-8 +781 TT genotype and IL-8 +781 T allele than controls. Hence, the researchers concluded that the TT genotype and T allele of the IL-8 gene variations at -251 and +781 might have a high susceptibility of OA. Study of IL-8 +781 C/T polymorphism showed it was also linked with other system disease of human. A research including 45 patients and 137 healthy individuals identified that IL-8 +781 C/T was related to irritable bowel syndrome (35).

**IL-17 and IL-17F**

The family of IL-17 cytokine consists six members of IL-17A, B, C, D, E, and F IL-17A, which is a proinflammatory cytokine involving in a large number of inflammatory diseases consisting of systemic lupus erythematosus, ankylosing spondylitis, and rheumatoid arthritis (RA) (36). IL-17F is detected to have great similarity to IL-17A. Both of them lead to the producing of different adhesion molecules, chemokines, and cytokines, which suggests overlapping function occur in IL-17A and IL-17F. Microsatellite association mapping indicates that OA susceptibility gene locates on chromosome 6p12.3-q13. Similarly, both IL-17A and IL-17F locate on chromosome 6p12.3-q13. Han et al. (37) investigated the association between polymorphisms of IL-17A G-197A and IL-17F T7488C and the susceptibility of knee OA in 302 OA patients and 300 healthy individuals of a Korea population. It suggested that there were significant differences in frequencies of allele and genotype of IL-17A G197A between OA cases and healthy individuals. However, for IL-17F T7488C, the two groups did not differ significantly in the genotype and allele distribution. In this study, the allelic and frequencies of IL-17F T7488C in the controls were conformity in Chinese and Japanese populations (38).

**Angiotensin-converting enzyme (ACE) gene**

ACE is crucial to renin-angiotensin system (RAS), which exerts a vital role in maintenance of water, electrolyte and homeostasis in human (39). ACE can adjust the physiological functions of vessel. It can catalytically convert angiotensin I into angiotensin II which narrows small blood vessel and stimulates aldosterone, as well as vasodilator bradykinin inactivated to influence neurotransmitter metabolism. ACE (about 21 kb) resides on chromosome 17q23, consisting 26 exons and 25 introns. Qing et al. (40) designed a study to evaluate the relation of ACE rs4343 and rs4362 variations with the risk of OA. The results showed that both ACE rs4343 and rs4362 variations were related to the significantly highly risk of OA. In an Indian population study (41), the researchers investigated the relation between ACE I28005D variations and clinically, radiologically diagnosed as primary knee OA. This study involved 100 OA patients and 100 healthy individuals. They found that the primary knee OA patients manifested a higher frequency of the DD genotype and the D allele. Therefore, this research suggested the ACE gene variation I28005D was related to primary knee OA in Indian. Subjects of the two studies equally belong to the Asian population, and the results should be validated in other ethnicity.

**A[sporin (ASPN) gene**

Asporin belongs to the family of small leucine-rich proteoglycans, constituting a main non-collagen component of the ECM. Some researchers suggested that ASPN combines to TGF-β receptor and thus restrains the expression of TGF-β-induced gene. A research indicated that the minor allele of ASPN SNP rs13301537 was related to hand OA development (42). Liang et al. (43) evaluated correlations between ASPN SNP rs13301537 and knee OA susceptibility in Chinese. The study included 510 cases with knee OA and 520 healthy controls. This study revealed that genotypes CT and CC of rs13301537, and allele C were related to a significantly highly risk of knee OA. Compared with TT genotype, the relation between the susceptibility of OA and genotype CT of rs13301537 was stronger in females and those aged more than 65 years old. However, a Greek study showed that the D13 allele and the D14 allele had a low susceptibility of knee OA (44).

**ESR1 gene**

Human estrogen receptor includes two subtypes consisting of ESR1 and ESR2, which belong to the steroid/thyroid hormone superfamily of nuclear receptors. ESR1 is expressed in chondrocytes, osteoblasts and stromal cells, which may suggest that ESR1 can adjust bone and cartilage. It is observed that women have a high risk of severe knee OA especially after the menopause. Some researchers hypothesize that estrogen is likely to have association with the pathogenesis or development of knee OA. Dai et al. (45)
aimed to investigate whether the \textit{ESR1} SNPs rs2234693 and rs9340799 were related with primary knee OA in Chinese. This case-control study involved 469 patients and 522 healthy individuals. Results indicated that the female patients with OA have a high frequency of T allele. Moreover, rs2234693 was related to knee OA in the model (TT + TC versus CC). Genotype TT + TC and T allele were associated with knee OA. In all participants, rs9340799 A allele was related to knee OA. The difference of dominant genetic model (AA + AG versus GG) in women was statistically significant. The combined genotype (AA + AG) and A allele were only related to knee OA. Thereby, \textit{ESR1} is significantly related to knee OA etiology in Chinese. There have been many researches examining the relations between the two frequent common \textit{ESR1} rs2234693 and rs9340799 and OA, but the outcome was controversial. Various published reports (46-54) have suggested a significant relation of \textit{ESR1} variation and susceptibility of knee, hip, or generalized OA in different populations, although the potential pathogenesis remains to be further elucidated.

**BDKRB2** +9/-9 bp gene

Bradykinins are inflammatory mediators, which belong to oligopeptides family that originate from the promotive effect of kallikreins proteolytically cleaving prokinins and are vasodilators produced by the synovium. Bradykinins contribute to both the initiation and maintenance of inflammation, causing the production of pain, promotion of the hypercatabolic state, followed the apoptosis of chondrocyte and the articular cartilage degeneration (55). Most of the process is mediated by the receptor BDKRB2. BDKRB2 mediates the majority of the inflammatory events induced by bradykinin, which is extensively dispersed among most tissues of the human body, involving the tissues of the joints affected by OA. The BDKRB2 is regarded as a strong mediator of inflammation and vasodilation which promote production and release nitric oxide (NO). Chen et al. (56) explored the part of BDKRB2 polymorphisms in OA, 245 cases with primary knee OA and 264 controls included. The result indicated that individuals with -9/-9 genotype had an apparently increased risk for knee OA when compared to the +9/+9 genotype. The +9/-9 genotype was associated with the radiographic severity of OA. The existence of -9 bp was related to serious OA. However, the -58 T/C polymorphism had no association with susceptibility and seriousness of OA. The study firstly indicated the role of genetic polymorphisms of BDKRB2 in OA. This study shows that the BDKRB2 +9/-9 polymorphism is likely to be regarded as a genetic marker for the OA initiation and development.

**Secreted phosphoprotein 1 (SPP1) gene**

\textit{SPP1} gene codes a phosphorylated acidic glycoprotein, expressed extensively in different tissues and cells. \textit{SPP1} gene plays roles in regulating cell adhesion and mutation, chemoattraction and immunoregulation (57). \textit{SPP1} protein was also a number of the crucial non-collagenous bone matrix proteins secreted by cartilage cells, synoviocytes and osteoblasts, and this protein exerts a role in bone remodeling and in cartilage-to-bone converting in repair of fracture. Several studies proved that SPP1 mRNA production was increased in osteoarthritic cartilage cells when compared to normal cells, and the expression of \textit{SPP1} protein in plasma and synovial fluid were also significantly related to the seriousness of knee OA (58). Lv et al. (59) tried to testify if \textit{SPP1} rs17524488 and rs11730582 are related with susceptibility of hip OA. They conducted a study enrolling 389 patients with hip OA and 315 controls. The study indicated that rs17524488 delG/insG had an increased susceptibility of hip OA. However, with regard to rs11730582, the adjusted ORs was 1.18 for allele C, 1.26 for TC, and 1.31 for CC, revealing no relation between rs11730582 and the susceptibility of hip OA. Otherwise, the rs17524488 delG/insG and insG/insG genotypes both related to the increased expression of \textit{SPP1} in articular chondrocyte and synovial fluid, while rs11730582 played no part in the expression of \textit{SPP1}. The researchers concluded that the genetic polymorphisms chrs17524488 in \textit{SPP1} promoter conferred high susceptibility of hip OA in Chinese, probably through stimulating the expression of \textit{SPP1}.

**Fibronectin (FN)**

The catabolism of ECM degradation products, particularly FN, have been exerted a role in regulating the degradation of chondrocyte (60). Chondrocytes produce respective integrin which serves as receptors of FN consisting of integrins \(\alpha\beta_1\), \(\alpha\beta_3\), and \(\alpha\beta_5\). \textit{FN-I} is located on chromosome 2q34-36, which encodes FN. FN is a multiple functional glycoprotein which is associated with a large number of biological processes like cell differentiation, damage repair, and angiogenesis. Integrins, as receptors on cell surface, are comprised of \(\alpha\) and \(\beta\) chains. Integrin \(\alpha\V
(ITGAV) is a member of the most disordered α integrins binding to five different β subunits consisting of β1, β3, β5, β6, and β8. Secretion of ITGAV indicates to have an increased risk of OA chondrocytes. Yang et al. (61) established whether FN-1 polymorphisms and genes of integrin are related with risk or knee OA seriousness in Chinese population. Two independent researches include 928 cases with knee OA and 693 controls, consisting of ten SNPs of FN-1 and ITGAV. FN-1 rs940739A/T was detected to have a significant relation to knee OA in both phases of this research. FN-1 rs6725958C/A and ITGAV rs10174098A/G were merely related to knee OA. It also showed major differences in the FN-1 rs6725958C/A and rs940739 A/T genotypes between patients with level 4 OA and healthy individuals. Consequently, they suggested that the FN-1 rs940739A/T is likely to have a crucial susceptibility of knee OA in Chinese population. Such polymorphisms probably account for the reason why some subjects are at a higher susceptibility of knee OA.

RAGE and S100A8

The receptor for advanced saccharification endproducts (RAGE) is a pattern-recognition receptor, binding to internal S100/calgranulins and amyloid-b-peptide, affects gene expression via activating signal transduction pathways. S100A8, which belongs to the family of S100, is mainly expressed by phagocyte cell and is related to pro-inflammatory disorders. The relation between RAGE and S100A8 promotes the production of matrix metalloproteinase (MMP) and increases the level of MMPs involved in regulating extracellular matrix destruction. MMP-1 plays a critical part in the type II collagen regression, which is a composition of primary extracellular matrix. In the cartilage of OA, MMP-1 expression is considered to have an increase in frequency. Yang et al. (62) explored the potential genetic effect of RAGE, S100A8, and MMP-1 on OA. They conducted a matched research involves the cases of OA genotype and control groups in a Chinese population. The result indicated that RAGE −429T/C and 557G/A had a meaningful relation to OA cases compared with control individuals.

Concluding remarks

This review summarizes the progression and implications of the effect of SNP on susceptibility of OA. The effect includes protective factor and risk factor for OA. Polymorphisms in the genes, such as TIMP3, IL-6, IL-16, CDH2, HIF1A and WISP1, have been proved to be protective factors of OA. Nevertheless, polymorphisms in other genes, such as ADAM12, DVWA, ACE were considered to be correlated with increased risk of OA.

However, most of the studies only focused on the association between SNP and susceptibility of OA. It is necessary to assess the effects of each allele and genotype on folding of protein, activity of enzyme, and localization of cell. In addition, large-scale investigations in different populations with OA are needed to elucidate the exact part of gene polymorphisms. And we should explore the potential function of these genes for preventing and curing disease.

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Footnote

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