Review Article

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

Wenxiang Chen, Yiying Wang, Jianning Zhao, Nirong Bao

Department of Orthopedics, Jinling Hospital, Nanjing 210002, China

Contributions: (I) Conception and design: W Chen, N Bao; (II) Administrative support: J Zhao, N Bao; (III) Provision of study materials or patients: W Chen, Y Wang; (IV) Collection and assembly of data: W Chen; (V) Data analysis and interpretation: Y Wang, J Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nirong Bao. Department of Orthopedics, Jinling Hospital, 305 Zhongshan East Road, Nanjing 210002, China.
Email: bnrbnr@sina.com.

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*, *DVWA* 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

Received: 28 March 2017; Accepted: 24 July 2017; Published: 25 August 2017.
doi: 10.21037/aoj.2017.08.01
View this article at: http://dx.doi.org/10.21037/aoj.2017.08.01

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 predominantly divided into two types, primary OA and secondary OA. The characteristic of primary OA is late onset, while the characteristic of secondary OA is early onset with established causes. However, the etiology of primary OA has not yet been fully illuminated. The causes of OA are gene, obesity, aging, and inflammation (3). 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 *ER*α 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 *ER*α *XbaI* polymorphism and the risk of OA in Europeans rather than in the Asians, and that the *ER*α *PvuII* 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 and hip OA. They found that the genetic polymorphism in the *IL-1B* had no correlation in danger of hip or knee OA, however, *IL1RN* was likely to act on severity of knee OA. 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 susceptivity 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 susceptivity 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 Zn^{2+}-metalloproteinase 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 articulated joints from OA pathogenesis. Bravatà *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.

Asporin (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 *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, *ESR1* is significantly related to knee OA aetiology in Chinese. There have been many researches examining the relations between the two frequent common *ESR1* rs2234693 and rs9340799 and OA, but the outcome was controversial. Various published reports (46-54) have suggested a significant relation of *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 vasodilatation 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 –58T/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

SPP1 gene codes a phosphorylated acidic glycoprotein, expressed extensively in different tissues and cells. *SPP1* gene plays roles in regulating cell adhesion and mutation, chemoattraction and immunoregulation (57). 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 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 *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 susceptivity 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 susceptivity of hip OA. Otherwise, the rs17524488 delG/insG and insG/insG genotypes both related to the increased expression of SPP1 in articular chondrocyte and synovial fluid, while rs11730582 played no part in the expression of SPP1. The researchers concluded that the genetic polymorphisms chrs17524488 in *SPP1* promoter conferred high susceptivity of hip OA in Chinese, probably through stimulating the expression of *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 αvβ1, αvβ3, and αvβ5. *FN-1* 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 α and β chains. Integrin αV

(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.

Acknowledgments

The authors thank their colleagues at the Department of Orthopedics, Jinling Hospital, Southern Medical University, Nanjing, China and would like to thank Editage (www.editage.cn) for English language editing.

Funding: This study was supported by the Medical Scientific Research Foundation of Jiangsu Province (BL2012002).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoj.2017.08.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Samuels J, Krasnokutsky S, Abramson SB. Osteoarthritis: a

tale of three tissues. Bull NYU Hosp Jt Dis 2008;66:244-50.
2. Litwic A, Edwards MH, Dennison EM, et al. Epidemiology and burden of osteoarthritis. Br Med Bull 2013;105:185-99.
3. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2013;39:1-19.
4. Kuettner KE, Cole AA. Cartilage degeneration in different human joints. Osteoarthritis Cartilage 2005;13:93-103.
5. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010;18:476-99.
6. Khatod M, Inacio M, Paxton EW, et al. Knee replacement: epidemiology, outcomes, and trends in Southern California: 17,080 replacements from 1995 through 2004. Acta Orthop 2008;79:812-9.
7. Ren Y, Tan B, Yan P, et al. Association between polymorphisms in the estrogen receptor alpha gene and osteoarthritis susceptibility: a meta-analysis. BMC Musculoskelet Disord 2015;16:44.
8. Kerkhof HJ, Doherty M, Arden NK, et al. Large-scale meta-analysis of interleukin-1 beta and interleukin-1 receptor antagonist polymorphisms on risk of radiographic hip and knee osteoarthritis and severity of knee osteoarthritis. Osteoarthritis Cartilage 2011;19:265-71.
9. Claessen KM, Ramautar SR, Pereira AM, et al. Relationship between insulin-like growth factor-1 and radiographic disease in patients with primary osteoarthritis: a systematic review. Osteoarthritis Cartilage 2012;20:79-86.
10. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011;7:33-42.
11. Goldring MB, Otero M, Tsuchimochi K, et al. Defining the roles of inflammatory and anabolic cytokines in cartilage metabolism. Ann Rheum Dis 2008;67 Suppl 3:iii75-82.
12. Fernandes MT, Fernandes KB, Marquez AS, et al. Association of interleukin-6 gene polymorphism (rs1800796) with severity and functional status of osteoarthritis in elderly individuals. Cytokine 2015;75:316-20.
13. Chua KH, Kee BP, Tan SY, et al. Interleukin-6 promoter polymorphisms (-174 G/C) in Malaysian patients with systemic lupus erythematosus. Braz J Med Biol Res 2009;42:551-5.
14. Blaschke S, Schulz H, Schwarz G, et al. Interleukin 16 expression in relation to disease activity in rheumatoid arthritis. J Rheumatol 2001;28:12-21.
15. Liu Z, Ma L, Qiu S, et al. Genetic polymorphisms of interleukin-16 are associated with susceptibility to primary knee osteoarthritis. Int J Clin Exp Med 2015;8:1401-5.
16. Luo SX, Li S, Zhang XH, et al. Genetic polymorphisms of interleukin-16 and risk of knee osteoarthritis. PLoS One 2015;10:e0123442.
17. Evangelou E, Chapman K, Meulenbelt I, et al. Large-scale analysis of association between GDF5 and FRZB variants and osteoarthritis of the hip, knee, and hand. Arthritis Rheum 2009;60:1710-21.
18. Daans M, Luyten FP, Lories RJ. GDF5 deficiency in mice is associated with instability-driven joint damage, gait and subchondral bone changes. Ann Rheum Dis 2011;70:208-13.
19. Su SL, Yang HY, Lee HS, et al. Gene-gene interactions between TGF-β/Smad3 signalling pathway polymorphisms affect susceptibility to knee osteoarthritis. BMJ Open 2015;5:e007931.
20. Sahebjam S, Khokha R, Mort JS. Increased collagen and aggrecan degradation with age in the joints of Timp3(-/-) mice. Arthritis Rheum 2007;56:905-9.
21. Becker SF, Langhe R, Huang C, et al. Giving the right tug for migration: cadherins in tissue movements. Arch Biochem Biophys 2012;524:30-42.
22. Ruedel A, Stark K, Kaufmann S, et al. N-cadherin promoter polymorphisms and risk of osteoarthritis. FASEB J 2014;28:683-91.
23. Apte SS. A disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin type 1 motif (ADAMTS) superfamily: functions and mechanisms. J Biol Chem 2009;284:31493-7.
24. Poonpet T, Honsawek S, Tammachote N, et al. ADAMTS14 gene polymorphism associated with knee osteoarthritis in Thai women. Genet Mol Res 2013;12:5301-9.
25. Kveiborg M, Albrechtsen R, Couchman JR, et al. Cellular roles of ADAM12 in health and disease. Int J Biochem Cell Biol 2008;40:1685-702.
26. Poonpet T, Tammachote R, Tammachote N, et al. Association between ADAM12 polymorphism and knee osteoarthritis in Thai population. Knee 2016;23:357-61.
27. Lou S, Zhao Z, Qian J, et al. Association of single nucleotide polymorphisms in ADAM12 gene with susceptibility to knee osteoarthritis: a case-control study in a Chinese Han population. Int J Clin Exp Pathol 2014;7:5154-9.
28. Minafra L, Bravatà V, Saporito M, et al. Genetic, clinical and radiographic signs in knee osteoarthritis susceptibility.

Arthritis Res Ther 2014;16:R91.
29. Bravatà V, Minafra L, Forte GI, et al. DVWA gene polymorphisms and osteoarthritis. BMC Res Notes 2015;8:30.
30. Lundström W, Fewkes NM, Mackall CL. IL-7 in human health and disease. Semin Immunol 2012;24:218-24.
31. Long D, Blake S, Song XY, et al. Human articular chondrocytes produce IL-7 and respond to IL-7 with increased production of matrix metalloproteinase-13. Arthritis Res Ther 2008;10:R23.
32. Zhang HX, Wang YG, Lu SY, et al. Identification of IL-7 as a candidate disease mediator in osteoarthritis in Chinese Han population: a case-control study. Rheumatology (Oxford) 2016;55:1681-5.
33. Rizzo A, Losacco A, Carratelli CR. Lactobacillus crispatus modulates epithelial cell defense against Candida albicans through Toll-like receptors 2 and 4, interleukin 8 and human β-defensins 2 and 3. Immunol Lett 2013;156:102-9.
34. He Y, Liang X, Wu X, et al. Association between interleukin 8 -251 A/T and +781 C/T polymorphisms and osteoarthritis risk. Immunol Lett 2014;162:207-11.
35. Romero-Valdovinos M, Gudiño-Ramírez A, Reyes-Gordillo J, et al. Interleukin-8 and -10 gene polymorphisms in irritable bowel syndrome. Mol Biol Rep 2012;39:8837-43.
36. Chen WS, Chang YS, Lin KC, et al. Association of serum interleukin-17 and interleukin-23 levels with disease activity in Chinese patients with ankylosing spondylitis. J Chin Med Assoc 2012;75:303-8.
37. Han L, Lee HS, Yoon JH, et al. Association of IL-17A and IL-17F single nucleotide polymorphisms with susceptibility to osteoarthritis in a Korean population. Gene 2014;533:119-22.
38. Peng R, Yue J, Han M, et al. The IL-17F sequence variant is associated with susceptibility to tuberculosis. Gene 2013;515:229-32.
39. Brzozowski T. Role of renin-angiotensin system and metabolites of angiotensin in the mechanism of gastric mucosal protection. Curr Opin Pharmacol 2014;19:90-8.
40. Qing Z, Ye J. Association between ACE polymorphisms and osteoarthritis susceptibility. Int J Clin Exp Pathol 2015;8:7391-6.
41. Poornima S, Subramanyam K, Khan IA, et al. The insertion and deletion (I28005D) polymorphism of the angiotensin I converting enzyme gene is a risk factor for osteoarthritis in an Asian Indian population. J Renin Angiotensin Aldosterone Syst 2015;16:1281-7.
42. Bijsterbosch J, Kloppenburg M, Reijnierse M, et al. Association study of candidate genes for the progression of hand osteoarthritis. Osteoarthritis Cartilage 2013;21:565-9.
43. Liang W, Gao B, Xu G, et al. Association between single nucleotide polymorphisms of asporin (ASPN) and BMP5 with the risk of knee osteoarthritis in a Chinese Han population. Cell Biochem Biophys 2014;70:1603-8.
44. Kaliakatsos M, Tzetis M, Kanavakis E, et al. Asporin and knee osteoarthritis in patients of Greek origin. Osteoarthritis Cartilage 2006;14:609-11.
45. Dai X, Wang C, Dai J, et al. Association of single nucleotide polymorphisms in estrogen receptor alpha gene with susceptibility to knee osteoarthritis: a case-control study in a Chinese Han population. Biomed Res Int 2014;2014:151457.
46. Ryder JJ, Garrison K, Song F, et al. Genetic associations in peripheral joint osteoarthritis and spinal degenerative disease: a systematic review. Ann Rheum Dis 2008;67:584-91.
47. Ushiyama T, Ueyama H, Inoue K, et al. Estrogen receptor gene polymorphism and generalized osteoarthritis. J Rheumatol 1998;25:134-7.
48. Bergink AP, van Meurs JB, Loughlin J, et al. Estrogen receptor alpha gene haplotype is associated with radiographic osteoarthritis of the knee in elderly men and women. Arthritis Rheum 2003;48:1913-22.
49. Jin SY, Hong SJ, Yang HI, et al. Estrogen receptor-alpha gene haplotype is associated with primary knee osteoarthritis in Korean population. Arthritis Res Ther 2004;6:R415-21.
50. Valdes AM, Van Oene M, Hart DJ, et al. Reproducible genetic associations between candidate genes and clinical knee osteoarthritis in men and women. Arthritis Rheum 2006;54:533-9.
51. Lian K, Lui L, Zmuda JM, et al. Estrogen receptor alpha genotype is associated with a reduced prevalence of radiographic hip osteoarthritis in elderly Caucasian women. Osteoarthritis Cartilage 2007;15:972-8.
52. Riancho JA, García-Ibarbia C, Gravani A, et al. Common variations in estrogen-related genes are associated with severe large-joint osteoarthritis: a multicenter genetic and functional study. Osteoarthritis Cartilage 2010;18:927-33.
53. Borgonio-Cuadra VM, González-Huerta C, Duarte-Salazár C, et al. Analysis of estrogen receptor alpha gene haplotype in Mexican mestizo patients with primary osteoarthritis of the knee. Rheumatol Int 2012;32:1425-30.
54. Loughlin J, Sinsheimer JS, Mustafa Z, et al. Association analysis of the vitamin D receptor gene, the type I collagen gene COL1A1, and the estrogen receptor gene in

idiopathic osteoarthritis. J Rheumatol 2000;27:779-84.
55. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol 2011;23:471-8.
56. Chen S, Zhou Y, Li J, et al. The effect of bradykinin B2 receptor polymorphisms on the susceptibility and severity of osteoarthritis in a Chinese cohort. J Biomed Biotechnol 2012;2012:597637.
57. Uede T. Osteopontin, intrinsic tissue regulator of intractable inflammatory diseases. Pathol Int 2011;61:265-80.
58. Honsawek S, Tanavalee A, Sakdinakiattikoon M, et al. Correlation of plasma and synovial fluid osteopontin with disease severity in knee osteoarthritis. Clin Biochem 2009;42:808-12.
59. Lv C, Li Y, Xu J, et al. Association of SPP1 promoter variants with hip osteoarthritis susceptibility in Chinese population. Gene 2015;564:9-13.
60. Sofat N. Analysing the role of endogenous matrix molecules in the development of osteoarthritis. Int J Exp Pathol 2009;90:463-79.
61. Yang HY, Su SL, Peng YJ, et al. An intron polymorphism of the fibronectin gene is associated with end-stage knee osteoarthritis in a Han Chinese population: two independent case-control studies. BMC Musculoskelet Disord 2014;15:173.
62. Yang HY, Chuang SY, Fang WH, et al. Effect of RAGE polymorphisms on susceptibility to and severity of osteoarthritis in a Han Chinese population: a case-control study. Genet Mol Res 2015;14:11362-70.

doi: 10.21037/aoj.2017.08.01
Cite this article as: Chen W, Wang Y, Zhao J, Bao N. The effect of single nucleotide polymorphism on susceptibility of osteoarthritis: recent progression and implications. Ann Joint 2017;2:52.