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REVIEW ARTICLE

Epidemiology and Genetics of Osteoarthritis

Donald M Salter[1], Sui-Lung Su[2], Herng-Sheng Lee[3]

[1]Centre for Genomics and Experimental Medicine, MRC IGMM, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, United Kingdom, [2]School of Public Health, National Defense Medical Center, [3]Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China

Osteoarthritis (OA) is becoming a significant problem worldwide. Pain and loss of joint function have a major impact on an individual's quality of life and through loss of time at work and increasing health care costs has a significant economic burden on society. OA is a complex disease with a number of known risk factors. There is variable involvement of the synovial joints in populations as a result of both environmental and genetic factors. Recent candidate gene studies and genome-wide association studies are beginning to identify known and previously unsuspected genes to be associated with the development of OA. These studies raise the exciting prospect of future stratification of patients into genetically identified sub-groups that may have specific targetable pathways for disease management.

Key words: Epidemiology, genetics, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a disorder of diarthrodial or synovial joints. Although once thought of as a degenerative disease of articular cartilage, OA is now believed to be a disease of the diarthrodial joint as an organ. Pathological changes are seen in all joint and associated tissues including cartilage, synovium, periarticular bone, menisci (where present), ligaments and fibrous capsule. OA may develop in any of the synovial joints, but is most commonly seen in the weight-bearing joints such as the hip and knee or in the first metacarpal phalangeal joint of the hand and the distal interphalangeal joints of the fingers. OA is a relatively common disease with the lifetime risk of developing OA in one or more joints being in the region of 40-50%. Globally the number of individuals with OA is expected to rise considerably as a consequence of increasing longevity and prevalence of obesity, one of the major risk factors for the condition. Although patients with hip and knee joint OA may show an increase in all-cause mortality and serious CVD events[1] its major clinical effects are through a combination of pain and reduced physical activity. As such the disorder is a significant burden on the individual through loss of quality of life and society through an increasing economic burden as a result of increased health care costs and loss of time at work.

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Corresponding Author: Prof. Donald M Salter, Centre for Genomics and Experimental Medicine, MRC IGMM, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, United Kingdom. Tel: 44-31-242-7125; Fax: 44-31-242-7169.
E-mail: donald.salter@ed.ac.uk

DIAGNOSIS OF OSTEOARTHRITIS

The diagnosis of OA is suspected on clinical features but is frequently based on radiographic criteria, especially for epidemiological studies. The most common symptom of OA is pain related to the joint that gets worse on activity and weight bearing. OA is also associated with joint stiffness in the morning or after a period of inactivity. Some patients may complain of locking and instability of joints. The combination of pain, loss of movement and function significantly curtails an individual's day-to-day activities. Clinical examination demonstrates a range of findings including pain on movement, limitation of joint movement, effusion, crepitus on movement, joint line tenderness and palpable or observed deformities such as Heberden and Bouchard nodes in fingers. There may be regional muscle atrophy as a consequence of decreased joint use.

Radiological and other imaging investigation is not necessary to make a diagnosis of OA but can be useful in excluding other causes of joint disease or for assessing the severity and progression of underlying OA. A variety of diagnostic imaging modalities including CT, MRI and ultrasound are increasingly being used to monitor joint

disease but are less used in the standard clinical setting.[2] As such standard plain radiography is the imaging investigation of choice and the radiological features of OA seen on plain X-rays are well documented. The Kellgren–Lawrence criteria[3] for assessment of OA is widely used and allows OA to be identified and separated into five grades from 0 – normal to 4 – severe. These are based upon the identification of joint space narrowing, formation of osteophytes, periarticular bone sclerosis and bone deformity. Symptomatic OA is defined as pain or other symptoms such as aching in a joint with radiological OA. The underlying pathological changes associated with the clinical and radiological features are well recognized. Histologically identified articular cartilage loss and an increase in subchondral bone thickness are reflected in joint space narrowing and periarticular bone sclerosis radiologically. Peripheral joint osteophytes are noted clinically as palpable and visible lumps such as Heberden and Bouchard nodes.

CLASSIFICATION OF OSTEOARTHRITIS

Osteoarthritis has traditionally been subdivided by etiology into either primary, also known as idiopathic or secondary forms.[4] In the idiopathic form OA typically arises without an obvious initiating cause or event. In contrast, in secondary OA the disorder arises on the background of specific conditions that directly cause or enhance the risk of developing OA. In this classification idiopathic OA can be further categorized into localized or generalized forms with patients with generalized idiopathic OA having OA in three or more sites, typically the hands, feet, knee, hip or spine.

The concept that all cases of OA are essentially secondary to a known, or as yet not identified, cause or underlying condition has raised into question the validity of the idiopathic/secondary classification system. As more knowledge accumulates on how other risk factors associated with development of OA including ageing, obesity, hormonal balance and genetics contribute to disease onset and progression all cases of OA will probably be identified as being secondary in nature. Indeed increasing knowledge of the understanding of the pathology of OA has led to the promotion of an etiopathogenic classification of primary OA.[5] The authors proposed classifying primary OA into 3 distinct although interrelated subsets: type I OA, genetically determined; Type II OA, estrogen hormone-dependent; and Type III OA, aging related. Although this system has merits, it fails to recognize the importance of biomechanical factors in the development of OA and its relevance has been brought into question.[6] Indeed it is generally accepted that OA arises in a synovial joint secondary to abnormal biomechanical factors and intra-articular stresses. OA can develop when a normal synovial joint is exposed to mechanical loads over and above that which are normally encountered within the physiological range. In circumstances where there has been previous joint damage or where the intrinsic tissue of the joint are weak physiological loading and stresses can be over and beyond that which the joint can withstand and as a consequence appear as pathological within that joint. As such if the concept that the application of biomechanical forces inappropriate to a joint will lead to joint failure the all OA can be thought of as being secondary. Defining the causes of the biomechanical and biological mis-match becomes paramount to understanding the likely pathological processes that have led to disease development and therefore classification.

Osteoarthritis has also been classified by the presence or absence of specific features identified clinically or radiologically. These include inflammatory/erosive OA, atrophic or hypertrophic OA and OA with chondrocalcinosis. Erosive or inflammatory OA is a subset of primary OA with a predilection for the hands, in particular distal interphalangeal joints, proximal interphalangeal joints and the first carpometacarpal joint. It typically presents with abrupt onset and the presence of signs of inflammation.[7] Characteristic radiological features include diffuse cartilage space loss, central subchondral erosions producing a classic "gull wing" appearance and joint ankylosis.[8] Classification of OA as atrophic or hypertrophic relates to responses of the periarticular bone in the OA joint[9] and is likely to be a result of different pathological processes within the joint such as the level of bone morphogenetic protein-2 (BMP-2) production.[10]

EPIDEMIOLOGY

In general hand, OA is the most common form of OA and was identified in around 80% of the elderly in the North American Framingham Study.[11] The knee and hip joints are the next most common sites of involvement. The incidence of hand, hip, and knee OA increases with age. Women have higher rates of OA than men, especially after the age of 50. The prevalence of OA in a given population differs however depending on the nature of the epidemiological study, and the precise definition of OA used. Hospital based and population based studies produce different results for prevalence of knee and hip joint OA but not for hand.[12] Despite symptomatic OA being most important clinically, the majority of epidemiological studies define OA radiologically using conventional radiographs. In these studies, OA is normally defined as a Kellgren-Lawrence grade of >2. Importantly the radiological presence of OA may not be reflected in clinical OA scores. Most information on OA prevalence is however from population-based radiographic surveys.[4] A systematic review was recently undertaken in an

attempt to identify the effect of OA definition on prevalence and incidence estimates.[12] The authors concluded that radiographic case definition of OA presents the highest prevalence with self-reported and symptomatic OA definitions appearing to present similar estimates. In this study, the prevalence of knee OA in men/women identified radiologically or symptomatically was 45.1/33.4% and 15.7/8.8% respectively. Symptomatic OA prevalence estimates are likely to be lower since it requires the presence of radiographic OA with clinical symptoms including pain, aching or stiffness in the joint.

The different prevalence of OA in different geographical regions is probably the result of both genetic and non-genetic factors including socio-economic conditions, health-care access or other lifestyle or environmental factors. Nevertheless major differences in prevalence of hip OA between Caucasian and Asian populations are likely to be a result of genetic predisposition. However, in some instances, differences in behavior, such as prolonged squatting can account for a substantial proportion of the difference in knee OA prevalence between Chinese subjects in Beijing and Caucasians. Local differences in OA such are seen in rural and urban populations within the same country are nevertheless more likely to be the result of environmental, occupational or socio-economic factors.

JOINT SPECIFIC OSTEOARTHRITIS

Hand osteoarthritis

Radiographic hand OA is common, ranging in prevalence from 29% to 76%.[13,14] In contrast symptomatic hand OA is lower, albeit remaining more common in females (26%) than males (13%). OA of the hand appears to be less common in Chinese and Japanese population in comparison to Caucasians.[11]

Knee joint osteoarthritis

Knee OA is the most common type of large joint OA. Severe radiographic OA ranges from 1% of people between 25 and 34 years to nearly 50% in those over 74 years.[15] As with other joints symptomatic knee OA is more common in females than males. Interestingly OA appears to be more common in the right knee than the left knee in men but not in women.[16] There also appears to be significant racial differences in prevalence of knee OA. In the NHANES study knee OA prevalence was greatest in African Americans (52%) in comparison to Hispanics (40%) and Caucasians (36%).[17] Studies on Chinese populations indicate that knee OA might be as much as 2-3 times higher in Chinese cohorts compared with Americans.[18] Differences in disease prevalence within populations such as rural and urban Chinese and Indians may relate to environmental and occupational factors.[18,19]

Hip joint osteoarthritis

Hip OA is less common than knee OA and relatively rare in Asian populations.[20,21] The prevalence of hip OA without an obvious predisposing cause such as slipped femoral epiphyses, osteonecrosis, trauma, sepsis, Paget disease, rheumatoid arthritis, and childhood hip diseases such as developmental dysplasia of the hip and slipped capital femoral epiphysis ranges from 1% to 27% depending on the population. Initial studies suggested that hip OA was more common in Caucasian Americans in contrast to African Americans, but more recent studies have questioned these earlier observations.[22]

Facet joint osteoarthritis

The facet or zygapophyseal joint is the only true synovial joint of the spine. OA of the facet joint is linked to degenerative disc disease and is associated with both neck and lower back pain. Imaging of facet joint OA shows the typical radiological appearances of OA as seen in other diarthrodial joints. Facet joint OA is most common in the L4-L5 and L5-S1 joints in the lower back and the C3-C5 mid cervical vertebral joints but rarely occurs in the thoracic spine.[23] As with other forms of OA the prevalence of facet joint OA increases with age being identified in the cervical spine in around 19% of the 45-64 age group increasing to 51% in those over age of 65 in a community-based US population.[24] CT imaging identifies features of lumbar facet joint OA in 67% of adults aged 45-64 years and 89% of that age 65 years and older. Obesity is a minor risk factor for cervical facet joint OA. In contrast being, overweight is associated with lumbar facet joint OA.

Ankle joint osteoarthritis

The ankle joint is rarely affected by OA. Epidemiological studies show a 1% prevalence. Most cases of ankle OA appear to have a history of previous trauma in comparison to only 9.8% of patients with knee OA and 1.6% of patients with hip OA.[25] In a North American tertiary orthopedic center 70% of the patients with ankle OA had a history of prior trauma, whereas 7% had no identifiable predisposing cause and 12% of cases were in patients with RA.[26]

GENETICS AND OSTEOARTHRITIS

The heritable component of OA is estimated to be around 40-65%. Twin studies have reported heritability for radiographic hand, and knee OA to be between 39% and 65%[27] and around 60% for radiographic hip OA.[28,29] OA is not inherited as a Mendelian trait. The genetic susceptibility to OA is complex with hundreds of genes likely involved, the majority contributing small effects and a very few having large effects. Early-onset OA may represent monogenic disease sub-

types while the more late-onset OA is likely to be polygenic. As such a number of different approaches have been followed to identify susceptibility genes that are associated with the development and progression of OA. These include linkage, candidate gene and association studies.

An important issue needing considered in all genetic studies of OA susceptibility is the definition of the disease group and relevant controls. OA is a heterogeneous disease. As noted above, OA in different joints shows different prevalence in populations. Significantly, mutations in some genes, including COL2A1, COMP, MATN3, and the genes encoding Type IX and Type XI collagen produce different gene effects specific to particular skeletal sites[30] indicating the possibility of OA associated mutations resulting in joint specific disease. Phenotypic differences which relate to the presence of non-genetic risk factors including gender, obesity, trauma and age also need to be taken into consideration. In many studies, OA is defined radiographically by a Kellgren-Lawrence score of >2 while in other studies surgical joint replacement may define the disease group. The latter will consist of a heterogeneous population with variably advanced OA whose major clinical complaint is likely to be a pain. As such there is an increasing debate on how to best select groups of patients for genetic-based studies. As such, it may be useful to examine endophenotypes, measurable intermediate phenotypes that can be more specific or closer to the action of the gene product than the disease status. Such populations would be expected to exhibit higher genetic signal-to-noise ratios and provide greater power to localize disease-related quantitative trait loci than disease status alone.[31] Endophenotypes useful in OA could include cartilage characteristics, joint shape, presence of osteophytes and pain among others.

As association studies identify susceptibility loci that may not be a true risk variant, but simply be in linkage disequilibrium with the causative variant, it is necessary to undertake functional studies to help support causality. Such studies often involve the use of genetically modified mice in which the gene of interest is either overexpressed or knocked-down either in the whole animal or in specific tissues such as cartilage. In these studies, the influence of gene knock-out or overexpression on spontaneous development of OA with age can be assessed. In addition, many investigators use a particular OA model/induction method to induce joint instability, for instance by intra-articular collagenase injection, or through a particular surgical intervention such as medial meniscectomy to alter joint biomechanics. As completely opposite effects may be seen depending on the OA model used[32] it appears that some genetic influences relate to the subtype of OA in the mouse model, which will presumably be reflected in patient populations.

Candidate gene studies

Candidate gene studies remain useful in identifying associations of genetic polymorphisms with OA susceptibility although subsequent large-scale studies and meta-analyses have often failed to support the initial observations. For instance in early studies ASPN, COMP, FRZB, COL2A1, GDF5 and IL4Ralpha were all shown to be associated with OA but subsequently only GDF5 and ASPN continue to be of interest. More recently polymorphisms in toll-like receptors (TLRs), including a functional single-nucleotide polymorphism (SNP) in TLR-3, have been shown to be associated with knee OA in a Chinese Han population.[33,34]

The association of GDF5 with OA was first reported in a Japanese population where a large-scale candidate gene association study showed that a SNP in the 5' untranslated region of GDF5 (+104T/C; rs143383) was significantly associated with hip OA.[35] This association was subsequently replicated in Japanese, Chinese and European Caucasian populations with OA of a variety of joints.[36,37] The finding that an SNP in GDF5 has wide-ranging influence on the development of OA in multiple populations and joints underlines the importance of candidate gene studies especially when the work is based on a strong hypothesis. GDF5 is closely related to the BMP family. It is known to have important roles in skeletal and joint development and mutations in the gene caused a range of skeletal abnormalities.[38] Subsequent studies have shown that the OA associated rs143383 SNP results in reduced GDF5 transcription in all joint tissues with *in vivo* studies also supporting a role for decreased expression of GDF5 being associated with OA developmen.[39,40]

The ASPN gene encodes a 382 amino-acid protein, asporin. Asporin is a member of the sub family of small leucine-rich proteoglycans that also includes decorin and biglycan. The asporin gene contains a triplet repeat within exon 2, coding for a polymorphic stretch of aspartic acid (D) residues in the N-terminal region of the protein.[41] This consecutive aspartic acid residue (D-repeat) has 10 alleles encoding 10-19 residues, with the D13 allele being most common. Functional analysis supports the idea that asporin polymorphisms might have a role in OA. In normal cartilage ASPN is expressed at low levels but expression is significantly increased in OA cartilage.[42] Asporin binds to transforming growth factor-beta (TGF-β), preventing its binding to the TGF-β Type II receptor and inhibiting TGF-β-induced expression of anabolic cartilage molecules including aggrecan and Type II collagen.[43] he inhibitory effect of asporin on TGF-β signaling is influenced by the number of D-repeats.[44,45] Subsequent studies have indicated that asporin expression is increased by inflammatory cytokines including IL1b.[46] Biologically, inhibition of TGF-β activity is greater in the presence of the D14 allele than other alleles suggesting

functional roles which correlate with disease association.[44] A case-control association study of ASPN in Japanese individuals with knee OA identified the D14 allele of ASPN as being over-represented relative to the common D13 allele.[44] A replication study in a Greek population in 2006 however could only partially support these findings.[47] A protective role of the D13 allele in knee OA was confirmed but the association of the D14 allele with knee OA was not replicated. A further allele, D15, however was associated with the disease. Since then multiple studies have failed to show consistent results. A recent meta-analysis, using nine studies from eight articles involving 4417 OA patients and 3403 controls which examined the association between the ASPN D14, D13, and D15 alleles and OA of the knee and hip in Asian and European populations concluded that there was no association between development of knee and hip OA in either ethnic group.[48] However this study, whilst supporting the lack of an association of ASPN polymorphisms and Caucasian populations did identify high heterogeneity of ASPN polymorphisms in different Asian populations which may account for the failure to show consistent associations with OA in the Asian populations. The D13 and D14 repeat polymorphisms of ASPN appear to be associated with development dysplasia of the hip in the Han Chinese[49] raising the possibility that variation in the etiology of the OA in studies may be a significant confounder and more detailed studies in which OA phenotypes are better characterized may be needed. Interestingly a recent candidate gene study in Caucasian sibling pairs found that the SNP rs13301537 in ASPN was associated with radiographic progression of hand OA over a 6 year period[50] highlighting the importance of focusing on particular OA subtypes.

GENOME WIDE ASSOCIATION STUDIES

Genome-wide association scans of OA provide the opportunity for discovery of unsuspected and unknown genes that are associated with OA. As such several genome-wide association studies (GWAS) have now been reported which have identified a number of OA susceptibility loci with genome-wide significance levels. Common variants of the double von Willebrand factor Type A domain gene on chromosome 3p24.3 are significantly associated with knee OA in Japanese and Chinese cohorts,[51] but not in European populations.[52] An association with knee OA susceptibility in a Japanese population and a region of chromosome six containing HLA class II/III genes (HLA-DQA2 and HLA-DQB1) and BTNL2 (Nakajima *et al*., 2010) was not subsequently replicated in European or Chinese studies.[52,53]

An OA susceptibility locus at 7q22 associated with hand and/or knee OA was first identified in Europeans by Kerkhof *et al*.[54] In an additional meta-analysis study the locus was confirmed to be associated with knee OA.[55] The locus stretches over 500 kb and contains at least six genes - PRKAR2B, HPB1, COG5, GPR22, DUS4 L and BCAP29. Despite none of these genes being obvious OA candidates, their expression at the RNA level was confirmed in joint tissues.[55]

The Arthritis Research UK OA Genetics (arcOGEN) consortium has investigated the genetics of hip and knee OA in a large two-stage GWAS in Europeans. All primary OA cases displayed radiographic evidence of advanced disease, and approximately 80% had also undergone total joint replacement.[56,57] These studies identified several new susceptibility loci that exceeded genome-wide significance. The strongest signal associated with total joint replacement is tagged by two SNPs at locus 3p21.1. These SNPs, rs6976 and rs11177, lie in the 3'UTR of glycosyltransferase 8 domain containing 1 (GLT8D1) and in the coding region of guanine nucleotide binding protein-like 3 (GNL3 or nucleostemin), respectively.[57] GNL3 is expressed in mesenchymal stem cells and articular chondrocytes. In cultured chondrocytes from patients with OA GNL3 mRNA, but not protein values, are substantially higher than normal controls, suggesting that this gene may be functionally important in the pathogenesis of OA. The susceptibility locus with the greatest effect size was that on chromosome 9q33.1 which was associated with hip OA in females. This locus is delimited by two recombination hot-spots, and it contains only four genes, ASTN2, pregnancy-associated plasma protein A (PAPPA), TRIM32, and the recently identified LOC100128505. The ASTN2 gene encodes a protein that is highly expressed in developing neurons, but is of unknown function in joints. PAPPA and TRIM32 may have stronger biological relevance to the development of OA. The PAPPA gene encodes the PAPPA that is a zinc-binding metalloproteinase with IGFBP4 as its substrate through which it may regulate effects of insulin-like growth factors on cartilage during development and post-natal growth. TRIM32 is ubiquitously expressed and encodes a protein with E3 ubiquitin ligase activity[58] responsible for attaching ubiquitin molecules to lysine residues of target proteins prior to proteosome degradation. It may also be involved in activating miRNAs.[59] Mutations in TRIM32 have been identified in limb-girdle muscular dystrophy type2H. It is possible that the association of TRIM32 and OA may be through the neuromuscular system[60,61] rather than directly on joint tissues. MCF2 L, which codes for the Rho-specific guanine nucleotide exchange factor Dbs that catalyzes guanine nucleotide exchange on RHOA and CDC42 and interacts specifically with the GTP-bound form of RAC1 has been shown to be associated with knee and hip OA.[62] A polymorphism in the DOT1 L gene has been demonstrated to be associated hip OA in men.[63]

A subsequent assessment of OA candidate genes in a meta-analysis of nine GWAS has identified a further two candidate genes, COL11A1 and VEGF, associated with hip OA.[64] In contrast 197 other candidate genes, selected through the Phenopedia tool of the human genome epidemiology navigator, that have been studied for their possible association with OA, did not show any association. Severe OA of the hand has been recently shown to associate with common variants within the ALDH1A2 gene and with rare variants at 1p31 in Northern European Caucasians.[65]

CONCLUSION

Osteoarthritis is a complex and heterogeneous disease of synovial joints. That there is a hereditable component is clear but understanding how genetics impact on disease susceptibility, onset and progression is not yet clear. Candidate gene studies have shown only limited success in identifying associations of mutations in genes and proteins believed to be important in joint function and OA. Indeed only GDF5 appears to be consistently important in this regard. GWAS has the value of identifying novel genes associated with OA, but the populations being studied need to be better-defined to overcome problems associated with the intrinsic heterogeneity of the disease. Some polymorphisms will be associated with specific joint disease and gender. It will also be necessary to separate groups of patients with differing clinical symptoms and signs. Pain and radiological changes in OA are not always synonymous and using end-stage joint replacement as an OA phenotype will without doubt result in a markedly heterogeneous group of patients whose disease is likely to have developed along a number of different pathways. The study of less heterogeneous, narrower OA endophenotypes may lead to the identification of more common and low frequency/rare variants. Understanding how functional differences in genetic variants contribute to OA development through appropriate experimental studies should lead to novel routes by which early diagnosis and precision treatment of defined OA subtypes can be instituted.

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