Osteoarthritis is a condition characterized by the destruction of articular cartilage, resulting in pain and dysfunction of the affected joint. Over time, articular cartilage degenerates with fibration, fissures, ulceration, and eventual full-thickness loss of the joint surface. Outgrowths of bone at the margin of the affected joints appear in later life, which cause joint pain and stiffness. It is now recognized that osteoarthritis is probably the result of a group of overlapping distinct diseases, which may have different etiologies but similar biological, morphologic, and clinical outcomes. Additionally, it should be appreciated that the disease processes can involve the entire joint, including the subchondral bone, ligaments, joint capsule, synovial membrane, and periarticular muscles.

At present, osteoarthritis is the most commonly observed nontraumatic orthopedic condition of dogs in the United Kingdom. More than 20% of dogs that are > 1 year of age are estimated to be affected by osteoarthritis.

Primary and secondary osteoarthritis in dogs—Osteoarthritis in dogs may develop secondary to an identifiable initiating cause (eg, secondary to hip laxity with hip dysplasia or secondary to FCP with elbow dysplasia) or as an idiopathic, primary event. The role of genetic susceptibility to osteoarthritis in dogs with elbow dysplasia is unknown. Differences in breed tolerance threshold of passive laxity for the development of osteoarthritis of the hip suggest that genetic differences are involved in the severity of osteoarthritis. Although the importance of primary versus secondary osteoarthritis in dogs is unresolved, osteoarthritis in dogs per se is likely to have a substantial genetic background.

Primary osteoarthritis in humans is recognized as developing with an earlier onset and with greater severity than naturally occurring damage caused by usage. In humans, primary osteoarthritis is the most prevalent form of the disease, although population studies of osteoarthritis are often defined purely on a radiologic basis and therefore may include secondary forms, such as hip dysplasia, that cannot necessarily be differentiated once osteoarthritis develops. Even with secondary osteoarthritis in humans, considerable genetic influences exist that affect the severity of the osteoarthritis that develops.

Hip dysplasia—Hip dysplasia in dogs was first recognized in 1935 and is now understood to be a developmental trait characterized by instability of the hip joint, which leads to hip subluxation. Hip dysplasia has a biphasic distribution within the canine population; young dogs are affected with the condition within the first year of life, with pain resulting from clinical subluxation of the hip, and older dogs have pain resulting from the development of osteoarthritis of the hip, presumably as a result of coxofemoral incongruity, laxity, and subluxation. The true prevalence of hip dysplasia within breeds is unknown, although estimations vary between 4.2% to 9.6% for clinical signs and between 10% and 73% for radiographic prevalence have been reported.

The development of hip dysplasia in dogs is affected by nutritional status, genetics, and hormonal factors. Breed variations exist in the relative risk of developing clinical signs of hip dysplasia, with a higher frequency of disease observed in large and giant breeds, such as German Shepherd Dogs and Labrador Retrievers. Hip joint laxity has been identified as an important risk factor in the development of degenerative joint disease of the hip joint. Breed differences in the tolerance threshold of passive laxity for the development of osteoarthritis of the canine hip joint imply that genetic differences exist among dogs for similar conditions that alter the phenotypic expression of osteoarthritis.

Estimates of heritability for hip dysplasia in dogs vary between 0.18 and 0.34. Initial investigations into the molecular genetic control of hip dysplasia in dogs have identified major QTL that influence the phenotypic expression of hip dysplasia. By use of a backcrossed canine pedigree of dysplastic and nondysplas-
tic dogs, the number of QTL associated with susceptibility traits for hip dysplasia has been estimated.\(^2\) The power of this pedigree sufficiently supported an initial genome wide scan for QTL by use of the minimal screening set 1 microsatellite markers\(^2\) with additional selected markers; on the basis of these findings, multiple QTL with high logarithm of the odds scores have been identified.\(^3\) To our knowledge, a candidate gene approach for the investigation of hip dysplasia has not been reported.

**Elbow dysplasia**—Elbow dysplasia in dogs encompasses a number of well-defined phenotypes of the cubital joint, such as FCP,\(^4\) osteochondrosis dissecans of the medial part of the humeral condyle,\(^5\) and ununited anconeal process.\(^6\) Each of these conditions results in the development of osteoarthritis of the affected joint. Heritability estimates for elbow dysplasia (0.25% and 0.77%)\(^2\)\(^6\)-\(^2\)\(^9\) and strong breed associations with each of the associated conditions\(^1\) indicate that a substantial genetic component to the condition exists. The radiographic prevalence of elbow dysplasia is between 2.9% and 17.8%,\(^1\)\(^0\)-\(^2\)\(^9\) and the clinical prevalence is approximately between 4% and 5% in Labrador Retrievers.\(^7\)

Salq et al\(^8\) analyzed a population of Labrador Retrievers by pedigree and sibling pair analysis and reported that FCP was controlled by a major gene, with variable expression (a male-to-female ratio of 75%:25%). Results of epidemiologic studies\(^8\)-\(^1\)\(^1\) of FCP support the finding that this condition has a 3:1 male-to-female sex bias.\(^8\)-\(^1\)\(^1\) COL1A1 (encodes \(\alpha\) chain of type I collagen), COL1A2 (encodes \(\alpha\) chain of type I collagen), COL2A1 (encodes \(\alpha\) chain of type II collagen), COL11A2 (encodes \(\alpha\) chain of type XI collagen), and VDR (encodes vitamin D \([1,25\text{-dihydroxyvitamin D}_3]\) receptor) were selected as candidate genes within the population of Labrador Retrievers studied on the basis of their involvement in the bone formation and skeletal disorders in humans. No significant deviation from 50% allele sharing between affected sibling pairs was observed by use of variable number tandem repeat markers near the candidate genes, indicating that none of these genes were associated with the development of FCP within the Labrador Retriever population studied. No estimations of statistical power were provided with the study, although only 34 sibling pairs were evaluated, which is a relatively small number, implying that these genes should not be completely discounted until further work confirms these findings.

**Application of population genomics to osteoarthritis in dogs**—Genomic investigation of developmental diseases within dog populations requires either a study by association or gene linkage approach (Figure 1). In either case, studies are compromised by the variability of the phenotypic presentation of the disease and the patients themselves (breeds). This certainly applies to studies examining hip or elbow dysplasia in dogs, where many different clinical, morphologic, and radiographic phenotypes exist for each diagnosis. The genetic heterogeneity that exists among and within breeds\(^8\) further compounds the difficulty of studying canine genomic diseases.

**Gene linkage**—Gene linkage maps are maps of known genetic loci across a genome at known genetic intervals. As the physical distance between loci decreases, it becomes less likely that genes causing a phenotypic trait will be subject to recombination during meiosis. Hence, it becomes more likely that alleles at specific loci will be transmitted with the causative gene or genes and the genetic trait. As such, the loci and gene are said to be in linkage. Each locus on a linkage map is genotyped in each individual within a known pedigree, for which phenotypic information is recorded for the trait being investigated. This allows a mathematic measurement of linkage to be made with the phenotype; thus, the loci in linkage with the phenotype can be identified.

Suitable canine gene linkage maps exist,\(^1\)\(^1\) and the use of a gene linkage approach with pedigree analysis allows the most accurate method for identification of genes involved with a phenotypic trait. However, the process is time and labor intensive, requiring the genotyping of a large number of loci and the recording of a large amount of phenotypic information. The likelihood of obtaining a positive association with such a study is dependent of the quality of the pedigree and phenotypic information and the strength (which reflects density or the number of loci investigated) of the linkage map used.

Polygenic disorders are difficult to elucidate by use of conventional linkage analysis, as the linkage maps

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Figure 1—Basic overview of genomic investigation within populations.
available are frequently not powerful enough to detect an association with the multiple genes involved. Additionally, results of these studies provide suggestive evidence of linkage to large chromosomal regions, and finer linkage maps with larger studies are required to pinpoint the genes responsible for a given disorder.\footnote{59}

Controlling genes may have small or moderate effects on a trait or disease, thus requiring large pedigree numbers to produce reliable results.\footnote{52} Obtaining suitable pedigree sizes and numbers with full phenotypic information in studies on canine diseases is time consuming.

Studies of association—Studies of association are applicable for canine polygenic disorders where pedigree information is inaccurate or unavailable. Genetic polymorphisms may be identified near or within genes of interest (candidate genes), and then matched populations with and without disease may be screened for polymorphisms and their associations tested by statistical means.\footnote{30,33} These studies have the advantage of not requiring pedigree information for completion, so they can be rapidly set up and screen fewer polymorphisms than linkage studies, allowing for time and cost savings. However, it should be mentioned that genes with positive polymorphisms identified by association are not confirmed as being linked to the phenotype until they have been tested by gene linkage.

The success of genetic association studies in humans to date has been limited with many successful association studies not being consistently repeatable.\footnote{36} It is usually assumed that association studies are less powerful than linkage studies, allowing for time and cost savings. However, it should be mentioned that genes with positive polymorphisms identified by association are not confirmed as being linked to the phenotype until they have been tested by gene linkage.

Clearly, the same would be expected to be true of studies on canine diseases. However, low haplotype diversity exists within dog breeds, with 80% of chromosomes in a breed carrying 2 to 4 haplotypes, and a large degree of haplotype sharing is observed among breeds,\footnote{36} suggesting that breed diversity may be less important, provided that disease-specific rather than breed-specific polymorphic loci are evaluated. Additionally, dog breeding has resulted in extensive linkage disequilibrium, which is up to 100 times as great as in humans.\footnote{36} Hence, a smaller number of markers should be required in canine gene association studies, and relatively small sample sizes should still produce strong associations, compared with human studies. Furthermore, the high linkage disequilibrium observed in dogs also implies that a small number of loci would be required in gene linkage maps to obtain strong linkage, compared with such studies in humans.

Labrador Retrievers have the lowest linkage disequilibrium, compared with Akitas, Bernese Mountain Dogs, and Pekingeses.\footnote{38} This is probably a result of their popularity and broader founder population, which will promote a greater degree of heterogeneity, although they still have a high degree of haplotype sharing. Clearly, the issue of breed specificity with regard to studies of canine diseases not specific to breeds, such as hip and elbow dysplasia, will remain unresolved until more information has been published on polymorphic allele frequencies within and among breeds.

Two further variables exist that need to be considered when investigating canine disease by use of polymorphism association studies. Firstly, sample sizes of affected dogs and control dogs must be large enough to ensure that positive associations are of reasonable power (ie, 80%),\footnote{39} which can be estimated from the allele frequencies in different populations. Secondly, the quality of the control population must be high enough (ie, they must be well phenotyped) to prevent the failure of association (false negatives) purely on the basis of a control background noise. Clearly, ethical issues exist regarding sampling and phenotyping control populations for genotyping studies, and ethical frameworks regarding these points need to be determined at the point of study design.

Polymorphic loci used in association studies and linkage studies include microsatellite markers, variable number tandem repeats, and SNPs. Microsatellite markers and variable number tandem repeats are short repeated lengths of sequence, which are polymorphic in the number of repeated elements that they contain. Such markers are usually identified adjacent to genes, although they may occasionally be intronic or exonic in location. Different lengths (numbers of elements) of these repeated sequences are different alleles. In contrast, SNPs are single nucleotide changes within the genome in which the most common allele occurs with <99% frequency in the population at large.\footnote{40} Within and around genes, SNPs are functionally important. In a coding region, SNPs may directly impact the protein structure and function; in an intronic region, they may alter splicing; and in the promoter region, they may influence gene expression.\footnote{47}

Multiple advantages exist in the study of SNPs for investigating genetic influences on disease. The large number of SNPs present within the genome may have distinctive patterns of linkage disequilibrium, which may be used in genetic linkage and direct association analyses. Allelic discrimination is straightforward, and multiple methods of high throughput genotyping exist.\footnote{44} The SNPs are less mutable than other types of polymorphism,\footnote{46} which should make them more reliable for assessing linkage disequilibrium, allelic associations, and cosegregation phenomena, as associations are unlikely to be confounded by mutation between generations.\footnote{49} Thus, SNP identification in genes potentially provides a rapid and straightforward method of evaluating gene association with disease in canine populations.

Methods for genomewide SNP identification have been developed in human research and are already being used to identify genes and SNPs associated with human diseases.\footnote{50,53} Population simulations estimate that roughly 500,000 SNPs will be required in humans to provide genomewide linkage,\footnote{47} but the more extensive linkage disequilibrium observed in dogs implies that far fewer SNPs would be required. Such technology is currently being developed for the canine genome, but at present, candidate gene studies by association are the most viable method for identifying those genes.
likely to have an influence on susceptibility or outcome of canine diseases.

Candidate gene selection—Candidate genes for a disease are genes for which evidence exists indicating that they may be related to that disease. Candidate gene selection is not an exact science. Valid criteria for the selection of candidate genes include the following: gene position within a particular region of the human genome with evidence of linkage to disease, gene involvement in a physiologic process relevant to disease, an increase or decrease in the level of gene expression in diseased tissue in vivo, the level of gene expression in tissue models of disease in vitro, or identification of gene polymorphism with a familial form of the disease. Once candidate genes have been identified, SNP identification provides a rapid and straightforward method of evaluating gene association with disease in canine populations. Although results of such studies in humans have frequently indicated associations with disease states, they are often not consistently repeatable.

Rationale for gene expression profiling to select candidate genes—The most successful disease association study of candidate genes in osteoarthritis of humans to date is that of Valdes et al, who reviewed the quantity of cDNA transcripts in 4 sequence libraries. By comparing mRNA expression in normal and osteoarthritis-affected synovium and normal and osteoarthritis-affected cartilage, they were able to identify genes with transcripts that appeared to be differentially expressed in osteoarthritic tissue, compared with normal tissue, and subsequently evaluated 22 genes for intragenic SNPs by use of public databases and information found in the literature (10 genes) or by screening them for polymorphisms (12 genes). Seven genes were significantly associated with the onset or progression of arthritis in the knee joints of females, whereas 8 genes appeared associated with osteoarthritis, but this association was not significant (P < 0.07). Additionally, significant associations were made between genes with susceptibility traits and 4 genes with progression traits. These results demonstrate the benefit of gene expression profiling to select candidate genes for disease association studies. On this basis, it is likely that whole-genome expression profiling should identify multiple candidate genes, which will ultimately be confirmed by whole-genome linkage screening.

If this approach is to be applied to the study of osteoarthritis in dogs, then gene expression profiling of diseased articular connective tissues (such as articular cartilage, synovium, and ligament) from dogs with the disorder needs to be performed. With the development of the quantitative (real-time) PCR assay and publication of the canine genome, it is now possible to quantify individual mRNA expression in osteoarthritic tissue specimens (cartilage, synovium, or synovial fluid) from clinically affected dogs, within explant cultures, or in osteoarthritic tissue specimens from dogs with experimentally induced osteoarthritic processes. Gene expression profiling is a genomewide assessment of mRNA (ie, an evaluation of which genes are expressed within an RNA sample). The development of cDNA-array technology has allowed the simultaneous evaluation mRNA expression of up to tens of thousands of genes within a single tissue specimen. Cartilage is particularly suited to the use of microarray techniques because it consists of a single cell population (chondrocytes); therefore, the level of gene expression can be attributed to this cell population alone.

Gene expression profiles of normal, early degenerative, and end-stage osteoarthritic cartilage have been evaluated by use of a human cancer array. Expression profiling was checked by use of a quantitative PCR assay for type I, II, and III collagen; aggrecan; β-actin; and glyceraldehyde phosphate dehydrogenase. Type II and III collagen expressions were upregulated in late disease, as assessed by microarray and quantitative PCR assay. Aggrecan expression was not changed when evaluated by either assessment method. Expression of β-actin was variable when measured by either method, and COL1A2 expression was upregulated in late osteoarthritic cartilage, as measured by microarray, but was not changed when measured by use of a quantitative PCR assay.

A total of 68 genes were upregulated or downregulated in osteoarthritic cartilage, compared with normal cartilage samples, in this landmark study. Genes involved with cartilage metabolism, anabolism, and catabolism were identified by this means. These may be regarded as candidate genes by association for studies of osteoarthritis in humans and include the following: COL1A2; COL2A1; COL3A1 (encodes α1 chain of type III collagen); COL6A1 (encodes α1 chain of type VI collagen); COL6 A3 (encodes α3 chain of type VI collagen); proteoncogenes, c-myc, c-jun, and c-fos; MAD (encodes MAX dimerization protein 1); biglycan gene, BMP3 (encodes BMP 3); α2-macroglobulin gene, FRZB (encodes frizzled-related protein); IL6R-α (encodes IL-6 receptor alpha); insulin-induced protein gene, MAD3 (encodes MAX dimerization protein 3); MMP-2, -3, and -1 genes; tissue inhibitor of MMP-4 gene; tenascin gene; tissue necrosis factor receptor 1 gene; and the ubiquitin gene. Interestingly, a number of these genes (COL2A1, FRZB, and COX2) have shown polymorphic associations with osteoarthritis in population studies. By use of a different microarray chip, Zhang et al identified 131 genes that were upregulated in severely osteoarthritic cartilage. Many of the genes that were upregulated were the same as those identified by Aigner et al, with a number of notable additions, such as IL1 (encodes IL-1), ILIRA (encodes IL-1 receptor antagonist), decorin gene, osteopontin gene, and the β2-macroglobulin gene.

Results of in vitro cell culture experiments evaluating chondrocyte expression by use of microarray technology have been published, however, doubt has been cast as to their importance, compared with in vitro assessment of tissue specimens. Comparisons of gene expression between cells in culture and in vitro assessment of tissue specimens have demonstrated upregulation of similar genes, although the level of gene expression can be widely different.
A valid argument exists for the evaluation of candidate genes expressed in tissues other than cartilage for association studies of secondary osteoarthritis in dogs with joint dysplasia. The role of laxity in the development of osteoarthritis implies that other tissues such as a joint capsule and the ligament of the head of the femur (ligamentum capitis femoris) should be evaluated. Likewise, the potential role of articular incongruency in the pathogenesis of some forms of elbow dysplasia indicates that genes involved in the regulation of physical growth should be evaluated.

Candidate genes for studies on osteoarthritis—A number of interlinked molecular pathways contributing to the degenerative process have been identified in osteoarthritic cartilage, such as those of cytokines, degradative enzyme production, and matrix synthesis.

Table 1—Summary of positive and negative candidate gene association in studies of osteoarthritis in humans:

<table>
<thead>
<tr>
<th>Genes</th>
<th>Positive association (reference No.)</th>
<th>No association (reference No.)</th>
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<tr>
<td>Collagens</td>
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<tr>
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<tr>
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</tr>
<tr>
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NR = Not reported.

Collagens

Collagen is the predominant ECM protein of articular cartilage representing over 50% of the dry weight of articular cartilage. At least 16 types of collagen exist, with 29 different chains, although all contain a characteristic triple-helical structure. Type II, V, VI, IX, XI, and XVI collagens are the most commonly identified isoforms in articular cartilage.

Type I collagen is present in small amounts in articular cartilage; thus, it has a limited role in the structure of the cartilage ECM. Type II collagen represents 90% to 95% of the total collagen in articular cartilage. Type IX collagen is present in small amounts in articular cartilage where it is found in association with the surface of type II collagen fibrils, although its exact function remains unknown. Type X collagen is a short-chain collagen expressed in hypertrophic cartilage but only to a limited degree in articular cartilage. Type XI collagen is a long-chain collagen that is present in the deep calcified zone of mature joints.

Other components of ECM

Other ECM protein genes have been assessed as candidate genes for osteoarthritis. A noncollagenous cartilage intermediate layer protein of undetermined function is synthesized by chondrocytes and is encoded by COMP. Synthesis of the noncollagenous protein is increased in early osteoarthritis. Cartilage oligomeric matrix protein, encoded by COMP, is a noncollagenous ECM protein that has a function that is not entirely determined. Cartilage oligomeric matrix proteins mediate the cell-matrix and matrix-matrix interactions and, possibly, chondrocyte attachment. Expression of cartilage oligomeric matrix protein is increased in the articular cartilage of mice with experimentally induced osteoarthritis, and synovial fluid concentrations are increased in osteoarthritic dogs. Mutations of COMP are the cause of other osteochondral dysplasias, such as pseudochondrodysplasia and multiple epiphyseal dysplasia, which are associated with the early development of osteoarthritis.

Matrilin (encoded by MATN1) is a noncollagenous protein expressed in developing cartilage, particularly epiphyseal cartilage. Aggrecan (encoded by AGR1) is the primary proteoglycan constituent of cartilage ECM. This molecule is important in the proper functioning of articular cartilage because it provides a hydrated gel structure (via its interaction with hyaluronan and link protein) that endows the cartilage with load-bearing properties and thus is an obvious candidate gene for genetic studies of osteoarthritis.

Asporin (encoded by ASPN) is an ECM protein identified as belonging to the small leucine-rich proteoglycan family, which also contains decorin and biglycan.
inhibited by osteoprotegerin.118 The ratio of osteoprotegerin to RANKL prevents interaction with its ligand. The RANK ligand, osteoprotegerin (encoded by TNFRSF11B) is a member of the TNF receptor superfamily (No. 11B), expressed on the osteoclasts and thus regulates osteoclastogenesis. Increased prostaglandin E2 synthesis from COX-2 in articular cartilage is a cellular response to activation by proinflammatory stimuli and an important component in the pathogenesis of arthritis. Osteoarthritic cartilage produces more prostaglandin E2 than nonarthritic cartilage,127 and the synovium produces COX-2 in osteoarthritic patients, although to a lesser degree than in immune-mediated arthritis.129 NCOR2 encodes nuclear receptor corepressor 2, which is a nuclear transcription factor that is under hormonal control; this factor acts as a silencing mediator for retinoid and thyroid hormone receptors.

Tetranectin (encoded by CLEC3B) is a phosphorylated glycoprotein postulated to regulate mineral deposition within bone.130 Although the role of tetranectin in the pathogenesis of osteoarthritis is currently unknown, it has been implicated in the impaired regulation of fibrinolysis associated with the inflammatory process in rheumatoid arthritis.131

α1-Antichymotrypsin is a serine protease inhibitor that helps regulate diverse physiologic processes such as coagulation, fibrinolysis, complement activation, angiogenesis, apoptosis, inflammation, and neoplasia and viral pathogenesis and thus potentially can prevent the degradation of connective tissue components. The α-induced protein of TNF is also referred to as TNF-secreted glycoprotein 6 and functions to modulate the interaction between hyaluronan and cell-surface receptor CD44. The α-induced protein of TNF is expressed in the synovium and cartilage of osteoarthritic and rheumatoid joints, further indicating that it may have a role in the pathogenesis of arthritic conditions.

Cytokines
Several cytokines are involved in cartilage metabolism and synthesized by synovial cells and cartilage chondrocytes. The interleukins are cytokines that have a primary role in the development and progression of osteoarthritis.62 Interleukin-1 is believed to be an important catabolic cytokine of the osteoarthritic joint and can stimulate synthesis of a number of proteases, which results in the breakdown of the ECM. Interleukin-1 receptor antagonist competes with IL-1 for binding to the IL-1 receptors and can act as an inhibitor of cartilage loss when the catabolic and anabolic activities of the cytokines are balanced, cartilage integrity is maintained. When an imbalance favoring catabolism exists, however, cartilage destruction can proceed, resulting in osteoarthritis. Hence, a proportion of the genetic susceptibility to osteoarthritis may be encoded for by variation in the activity of IL genes. Interleukin-4 is an active signaling molecule involved in the regulation of cartilage integrity by mechanical stimulation.117

Osteoprotegerin (encoded by TNFRSF11B) is a member of the TNF receptor superfamily (No. 11B), which is secreted without a transmembrane domain. Osteoprotegerin binds RANK, a member of the TNF receptor family, expressed on the osteoclasts and thus prevents interaction with its ligand. The RANK ligand, also known as osteoprotegerin ligand, is a cell membrane-anchored or soluble ligand for RANK expressed on the osteoblast-stromal cell surface; interaction with RANK stimulates osteoclastogenesis, which can be inhibited by osteoprotegerin.118 The ratio of osteoprotegerin and osteoprotegerin ligand correlates strongly with indices of bone remodeling (histomorphometric data) in normal human cancellous bone.119 Osteoprotegerin expression is increased in osteoarthritic cartilage and by IL-1 stimulation of chondrocytes in vitro.120

Growth factors
Growth factors are important in the homeostatic regulation of cartilage, controlling functions such as chondrocyte integrin expression.121 The BMPs are potent growth and differentiation factors, which belong to the TGF-β superfamily. Exogenous BMP-2 increases proteoglycan and collagen synthesis, maintains the adult chondrocytes response in vitro,122 and is identified in osteoarthritic chondrocytes and osteophyte tissue but not in chondrocytes from healthy cartilage.123 Growth factor IGF-1 plays an important role in cartilage homeostasis; IGF-1 stimulates chondrocytes proliferation and synthesis of proteoglycan and type II collagen and inhibits the endogenous catabolic activity of articular cartilage in vitro. Depending on experimental conditions, TGF-β may inhibit or stimulate articular cartilage matrix synthesis.24

Other genes associated with osteoarthritis
A number of other genes have been associated with the development of osteoarthritis. The ADAM metallopeptidase domain 12 gene, ADAM12, regulates the formation of macrophage-derived giant cells, possibly by mediating the effects of 1,25-dihydroxyvitamin D3 on cell-cell fusion. Blocking mRNA of ADAM12 in osteoclast precursor cells results in a 50% decrease in giant cell formation, which may explain the association of mutations of this gene with the presence and progression of osteopetrosis.

CD36 is a type I collagen-thrombospondin receptor, which is expressed primarily in midzone chondrocytes, and its expression is markedly increased in osteoarthritic cartilage, although whether this is a cause or effect of osteoarthritic changes is unclear. As a membrane-bound haem protein, COX is expressed in the synovium and chondrocytes of osteoarthritic cartilage. Increased prostaglandin E2 synthesis from COX-2 in articular cartilage is a cellular response to activation by proinflammatory stimuli and an important component in the pathogenesis of arthritis. Osteoarthritic cartilage produces more prostaglandin E2 than nonarthritic cartilage, and the synovium produces COX-2 in osteoarthritic patients, although to a lesser degree than in immune-mediated arthritis. NCO2 encodes nuclear receptor corepressor 2, which is a nuclear transcription factor that is under hormonal control; this factor acts as a silencing mediator for retinoid and thyroid hormone receptors.

α1-Antichymotrypsin is a serine protease inhibitor that helps regulate diverse physiologic processes such as coagulation, fibrinolysis, complement activation, angiogenesis, apoptosis, inflammation, and neoplasia and viral pathogenesis and thus potentially can prevent the degradation of connective tissue components. The α-induced protein of TNF is also referred to as TNF-secreted glycoprotein 6 and functions to modulate the interaction between hyaluronan and cell-surface receptor CD44. The α-induced protein of TNF is expressed in the synovium and cartilage of osteoarthritic and rheumatoid joints, further indicating that it may have a role in the pathogenesis of arthritic conditions.
An enzyme, ACE, is responsible for converting angiotensin I to angiotensin II, which is a potent vasoconstrictor of the renin-angiotensin system, and also inactivates bradykinin, a vasodilator of the kallikrein-kinin system. Kinin B2 receptors in synovium are upregulated in osteoarthritic patients, thus indicating that a potential link may exist between the features of osteoarthritis and ACE activity.

Secreted frizzled-related protein 3 is a glycoprotein that antagonizes the signaling of wingless ligands through the frizzled membrane-bound receptors, which control the primary activation of T-cell factor lymphoid-enhancing, factor-dependent transcriptional activation. Joint patterning in embryogenesis and bone formation are determined by the wingless normal cartilage. It has been hypothesized that the repeated class II alleles and the development of osteoarthritis: implications for research. Clin Orthop Relat Res 2004;427:56–513.

Calmodulin 1 is a ubiquitous, calcium-binding protein that regulates calcium signaling and may be involved in collagenases and proteoglycanase activity. Calmodulin 1 expression is increased in hip joint and knee joint osteoarthritic cartilage, compared with normal cartilage.

Osteoarthritis and MHC—Strong associations have been identified between MHC alleles and immune-mediated arthritis, which is unsurprising given the proposed pathogenesis of these diseases. Associations have also been identified between MHC class II alleles and the development of osteoarthriti.

It has been hypothesized that the repeated association of the DR2 allele with osteoarthritis indicates that DR2 may have a role in restricting immunologic responses to the low-grade inflammation characteristic of osteoarthritis; or may predispose to T-cell activation in other tissues, such as synovium or bone, involved in the pathogenesis of osteoarthritis.

Conclusions—On the basis of information provided in this review, a large number of genes are suitable for analysis in case control studies on secondary osteoarthritis in dogs with joint dysplasia. However, success and repeatability of such investigations depend on the quality of the phenotypic data provided and the quantity of samples available. Researchers active in the field of companion animal genomics will need to cooperate on a global scale to produce studies of sufficient magnitude that will allow these goals to be achieved. Ultimately, it is hoped that genomic research will provide information that will lead to new diagnostic and therapeutic strategies for the management of osteoarthritis in humans and dogs.

References


