Review
Genetic markers of osteoarticular disorders: facts and hopes
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Abstract
Osteoarthritis and osteoporosis are the two most common age-related chronic disorders of articular joints and skeleton, representing a major public health problem in most developed countries. Apart from being influenced by environmental factors, both disorders have a strong genetic component, and there is now considerable evidence from large population studies that these two disorders are inversely related. Thus, an accurate analysis of the genetic component of one of these two multifactorial diseases may provide data of interest for the other. However, the existence of confounding factors must always be borne in mind in interpreting the genetic analysis. In addition, each patient must be given an accurate clinical evaluation, including family history, history of drug treatments, lifestyle, and environment, in order to reduce the background bias. Here, we review the impact of recent work in molecular genetics suggesting that powerful molecular biology techniques will soon make possible both a rapid accumulation of data on the genetics of both disorders and the development of novel diagnostic, prognostic, and therapeutic approaches.

Keywords: candidate genes, genetics, multifactorial diseases, osteoporosis, osteoarthritis

Background
Osteoarthritis (OA) and osteoporosis (OP) are two common age-related chronic disorders of the skeleton with a complex, multifactorial pathogenesis. They are both associated with considerable morbidity and mortality. Apart from being influenced by environmental factors, OA and OP have a strong genetic component, as has been shown by twin and family studies [1–4]. Although in clinical practice, a combination of OP and OA may be coincidentally encountered, particularly in the very elderly, there is now considerable evidence from large population studies that these two disorders are inversely related [5–8]. While low bone mineral density (BMD) is an essential feature of OP, an increased BMD has been often shown in subjects with OA. Moreover, if OA patients develop osteoporotic fractures, they do so in very old age, suggesting that OA, or related factors, might have a protective effect on the progression of OP [7]. Patients with primary OP and those with OA also appear to represent anthropometrically different populations. The typical patient with OA tends to be a mesomorph, to be fatter, and to have greater muscular strength, whereas the typical OP patient tends to be an ectomorph [8]. Because of the contrasting levels of BMD in OA and OP, studies on the
first-degree relatives of PGOA probands were twice as likely to have radiographically visible generalized disease as were population controls [15]. Recently, a twin study of 120 nonidentical and 130 identical female twins, examined for radiological evidence of OA, showed a striking genetic influence on the development of PGOA, with a score of 40 to 70% for an effect of hereditability [2]. This result has been recently confirmed by evidence that osteoarthritis of the hand, knee, and hip, and disc degeneration of the spine, is statistically more frequent in sibling studies [16].

The cluster of familial chondrodysplasias, which are inherited as an autosomal Mendelian trait, is characterized by induction of precocious cartilage destruction with consequent OA. Several mutations in genes encoding the components of cartilaginous extracellular matrix have been described [13]. Conversely, the multifactorial nature of PGOA and the heterogeneity that characterizes the syndrome greatly complicate the choice of putative candidate genes. Moreover, there is now substantial evidence from epidemiological, twin, and segregation studies that the genetic contribution to osteoarthritis is gender- and joint-related [17–21]. In PGOA, identification of genes that could lead to development of the disease is still under investigation.

Studies of collagen genes
Mutations of the COL2A1 gene have been identified in familial chondrodysplasias [13,22]. This gene also seems to be involved both in early-onset PGOA [23–25] and in families with crystal deposition disorder [26]. However, linkage analysis of 14 candidate genes in OA kindreds resulted in the exclusion of 10 important genes, including COL2A1 [27]. Moreover, both PGOA and familial crystal deposition disease have been related to a region of chromosome 8q [28], while nodal OA appeared significantly associated with loci on chromosome 2q23–35, where the gene encoding the α3-chain of collagen type VI is located [29]. Recently, various other chromosomal loci have reported to be associated with OA [30–35], as summarized in Table 2.

Studies of estrogen receptor genes
Evidence that PGOA is becoming apparent in postmenopausal women [36,37] prompted investigations on the role of genes encoding for estrogen receptors (ERs). In a Japanese study, a restriction-fragment-length polymorphism at the ERα gene locus appeared to associate significantly with PGOA [38], although studies in other populations failed to confirm this association [39].

Studies of the gene for vitamin D receptor
The association of polymorphism of the gene for vitamin D receptor (VDR) with BMD [40] was followed by investigations of this gene’s possible association with OA. VDR
gene polymorphisms segregated significantly (showing a 2.27-fold increased relative risk) with the presence of osteophytes in knee OA [41,42] and in the spine [43]. The genetic association is substantial: subjects with the VDR allelic variant TT have a 50–60% lower risk of spinal osteophytosis and disc narrowing than the opposite (tt) genotype [43]. To date, results do not allow us to distinguish the associations between VDR and osteophytes or between VDR and disc narrowing. Polymorphisms of this receptor might directly affect the pathophysiology of OA by promoting either osteophytosis or disc narrowing. VDR is expressed in both osteoblasts and chondrocytes, both of which are found in osteophytes, suggesting a role for the vitamin D/VDR complex in the formation or progression of osteophytes, or both. It has also been hypothesized that polymorphisms in COL2A1, one of the major candidate genes for familial OA, are in linkage disequilibrium with VDR gene polymorphisms [41].

Studies of other candidate genes
In recent years, new polymorphisms in other candidate genes, such as IGF1 [44], COL1A1 [39], COL2A1 [45–47], TGFβ1 [48], and the gene for aggrecan proteoglycan [49], have been identified and found to be correlated with OA in some studies, although agreement is not universal [39,50,51]. An updated list of candidate genetic polymorphisms associated with osteoarthritis is reported in Table 3.

### Table 2

| Reference | QTL | Region affected | Phenotype |
|-----------|-----|-----------------|-----------|
| [28]      | 8q  | GOA             | Early-onset OA-CPDD (1 family) |
| [29]      | 2q23–35 | Hand           | Nodal OA |
| [30]      | 11q | Hip, knee       | Female OA |
| [31]      | 2q  | Hip, knee       | OA of the hip |
|           | 4q  | Female OA of the hip | |
|           | 6p/6q | OA of the hip | |
|           | 11q | Female OA      | |
|           | 16p/16q | Female OA of the hip | |
| [32]      | 2q12–13 | Hand           | Distal interphalangeal joint OA |
|           | 4q26–27 | Distal interphalangeal joint OA | |
|           | 7p15–21 | Distal interphalangeal joint OA | |
|           | X-cen | Distal interphalangeal joint OA | |
| [33]      | 4q35 | Hip             | Premature degenerative OA of the hip |
| [34]      | 6q12–13 | Hip, knee     | Female OA of the hip |
|           | 6p21.3 | Female OA of the hip | |
| [35]      | 2q31 | Hip, knee       | Familial OA of the hip |

CPDD = calcium pyrophosphate deposition disease; GOA = generalized osteoarthritis; OA = osteoarthritis.

### Table 3

| Genetic polymorphism | Phenotype | Association found? | Reference |
|----------------------|-----------|---------------------|-----------|
| VDR                  | Female knee OA | Yes | [42] |
|                      | Knee OA (osteoophytosis) | Yes | [41] |
|                      | Female OA (hip replacement) | No | [50] |
|                      | Hand, hip, knee OA | No | [51] |
|                      | Idiopathic OA | No | [39] |
| COL2A1               | PGOA/chondrodysplasia | Yes | [140] |
|                      | Nodal GOA | No | [141] |
|                      | GOA, finger joints OA | No | [24] |
|                      | GOA | Yes | [45] |
|                      | Female OA (hip replacement) | No | [50] |
|                      | GOA | Yes | [46] |
|                      | Knee OA (joint space narrowing) | Yes | [47] |
| COL1A1               | Female OA (hip replacement) | No | [50] |
|                      | Idiopathic female OA | Yes | [39] |
| ERα                  | GOA | Yes | [38] |
|                      | Idiopathic OA | No | [39] |
| TGFβ1                | Spine OA (osteoophytosis) | Yes | [48] |
| IGF-I                | GOA | Yes | [44] |
|                      | Aggrecan proteoglycan | Male bilateral hand OA | Yes | [49] |

OA = osteoarthritis; COL = collagen; ER = estrogen receptor; GOA = generalized osteoarthritis; IGF = insulin-like growth factor; PGOA = primary generalized osteoarthritis; TGF = transforming growth factor.

### Gene–environment interaction
Finally, a strong interaction between genes and environment plays an important role, because increasing age and body mass index are known to be associated with increased prevalence and severity of spinal degenerative disease, as are smoking and quadriceps strength for osteophytosis. Moreover, joint degeneration in the early stages of OA may be reflected in changes in structural and material properties of the articular cartilage. A recent study showed that for a given loading condition, the contact areas are higher and peak stresses are lower in a diseased joint than in a normal one [52]. Thus, loading stress conditions may play a critical role in the selection of 'genetically' susceptible joints.

OA has wide variability, both clinically and radiologically. The identification of gene(s) linked to PGOA might make it possible to construct a new OA classification based on...
genetic causes, independent of clinical or radiological features, to develop molecular tests for definition of OA risk, and to design a preventive therapeutic strategy based on gene therapy [53], as has already been done successfully by gene transfer of interleukin-1 receptor antagonist in the animal model [54].

Animal model
Very recently, an elegant study in mice demonstrated that mutation at the progressive ankylosis (ank) locus, mapped to proximal mouse chromosome 15, causes a generalized progressive form of arthritis with mineral deposition, formation of bony outgrowths, and joint destruction. Interestingly, the human orthologue of the ank gene, ANK, is nearly identical to the mouse gene and maps to chromosome 5p in a region showed to be linked in several human pedigrees with arthritis and chondrocalcinosis [55,56].

Genetic markers in osteoporosis
Osteoporosis is a systemic multifactorial disease characterized by decreased BMD and microarchitectural deterioration of bone structure, leading to a higher susceptibility to fractures [57]. Although there are several environmental influences on BMD, such as diet and amount of physical exercise, a genetic contribution to the pathogenesis of OP accounting for 50% to 70% of the interindividual variability in bone mass has been recognized [3,4]. Given the complex biology of the skeleton, it is likely that bone mass is under the control of a large number of genes, many of which exert relatively small effects on BMD and a few of which contribute substantially to the variation in this trait. It is also likely that complex gene–environment interactions exist. Many candidate genes have been implicated in the determination of BMD and in the pathogenesis of OP, including those encoding cytokines, calcitropic hormones and their receptors, and matrix bone proteins (see Table 1).

To date, among the genetic strategies commonly employed for the dissection of complex traits, the analysis of the genetic determinants of BMD has largely relied on association studies, in which a polymorphism in a candidate gene is analyzed in unrelated affected and unaffected individuals from a given population. However, there are some pitfalls for such an approach in late-onset disorders such as OP, mainly due to inappropriate choice of the control group, to population admixture, and to competing risk leading to selection bias [58]. Moreover, a positive association can arise for any of three reasons: a given allele might in effect be a cause of the disease; or it might not cause the trait but be in linkage disequilibrium with the actual cause; or the apparent association might be an artifact of population admixture.

Studies of vitamin D receptor gene
Among the several candidate genes, that encoding VDR was the first to be proposed as a major locus for the genetic effect on bone mass. The VDR gene possesses several polymorphic sites, of which that detected by the restriction endonuclease BsmI at intron 8 was associated with BMD in the Australian population [40]. Since that original report, conflicting data have been published on the association of the diallelic BsmI restriction-fragment-length polymorphism (RFLP) with the VDR gene and BMD in both premenopausal [59–62] and postmenopausal [63–68] women. Similarly, studies examining the relation of this polymorphism with skeletal growth [69–72], bone turnover markers [59,63,73,74], rates of bone loss [63,74–76], intestinal calcium absorption [74,77–80], and osteoporotic fractures [81–83] yielded conflicting results. A meta-analytical approach incorporating the results from 16 studies revealed a weak contribution of the allelic variant at the 3′ end of the gene to the variation of BMD values [84], while a more recent meta-analysis concluded that BMD is associated with VDR polymorphism at high confidence levels and that both genetic and nongenetic factors can interfere with the unmasking of the effects of VDR variants on bone phenotype [85].

There are several possible explanations for the discrepancies among these studies. First, interactions of environmental factors such as dietary calcium intake appeared to represent an important confounding factor [72,78,79,86–88]. Moreover, linkage disequilibrium with other bone-metabolism-related genes on chromosome 12 (i.e. collagen type 1 and retinoic acid receptor genes) cannot be excluded. Finally, the limited sizes of samples, differences in genotype distribution among different ethnic groups, and interactions with other genes all have to be considered as potential confounders. Other polymorphic genes, such as the one encoding ERα, have been shown to modulate the effect of the VDR gene in the determination of BMD, confirming the existence of gene–gene interaction [87,89]. Taken together, these findings may help to explain contrasting data among published studies, suggesting the possibility of modifying genetically determined BMD through appropriate lifestyle changes. However, polymorphisms at the 3′ end of the VDR gene are anonymous polymorphisms, as they do not code for different amino acids in the VDR protein. Therefore, a major question is how these allelic differences may be related to functional differences. Current evidence suggests that these VDR restriction-fragment-length polymorphisms do not affect the abundance of VDR mRNA [90–92]. Recently, a new diallelic (ATG/ACG) polymorphic VDR variant has been described in exon 2 of the gene, detectable with the restriction endonuclease FokI [93]. This polymorphism is responsible for a three-amino-acid difference in VDR length between FF and ff individuals and the short form of the VDR gene (FF) gave an approximately 1.7-fold increase in transcription activation in transfected HeLa cells [94]. Mexican–American postmenopausal women with the ff genotype showed lower lumbar BMD than
those with the FF genotype [93]. This relation, also found in Japanese [94], North American [95], and Italian [96] populations, was not found in French [97] and Swiss [98] women, although a significant association of this genotype with differences in urinary type I collagen cross-linked n-telopeptide was observed in the French population [97].

**Studies of estrogen receptor genes**

The importance of the ER genes in the determination of BMD is supported by several observations. Firstly, osteoblasts, osteoclasts, and bone marrow stromal cells bear ERs and are modulated by estrogen [99,100]. In addition, a homozygotic inactivating mutation of the ERα gene caused OP in a male patient [101]. Finally, ERα knockout mice exhibit a low BMD [102]. It is possible that common allelic variants of the ERα gene cause milder estrogen resistance, which becomes evident with aging or with menopausal hypogonadism, leading to clinical disorders such as OP. Both intrinsic polymorphisms (recognized by the restriction endonucleases PvuII and Xbal) and polymorphic variable numbers of (TA)n repeats upstream of the ERx have been associated with BMD in Japanese populations [103,104]. Similar studies in other populations yielded conflicting results [67,89,105–107]. Recently, we investigated the role of these polymorphisms at the ERα gene locus in a large sample of postmenopausal Italian women [108]. We found a strong linkage disequilibrium between intron 1 (PvuII and Xbal) polymorphic sites and also between these sites and the microsatellite (TA)n dinucleotide repeat polymorphism, with a high degree of coincidence of the short TA alleles and the presence of PvuII and Xbal restriction sites. Interestingly, a statistically significant correlation between the (TA)n repeat allelic variants and osteoporosis was observed, with subjects with a low number of repeats (TA<15) showing the lowest BMD values and the highest risk of vertebral fracture. Two studies, in American and Danish populations, recently confirmed this observation [109,110]. However, in another study in a Scottish population, no overall association between the TA repeat number and BMD was observed [111]. All the positive studies are concordant and demonstrate a significant association between reduced BMD values and the presence of a low number of TA repeats. Conversely, in the Scottish study, the small group of subjects with the highest number of TA repeats (having at least one allele TA≥26) appeared to have lower BMD values at the spine than those with fewer TA repeats [111]. The molecular mechanism underlying how bone mineralization is affected by the variation in the number of dinucleotide repeats is still unclear. However, because of the TA repeats position, between promoters A and B of the ERα gene and next to a regulatory region, it is possible that allelic variation due to different (TA)n dinucleotide repeat lengths might have physiological relevance by affecting promoter usage and/or mRNA transcription.

**Studies of collagen genes**

Collagen type I is the major constituent of bone matrix proteins and, therefore, collagen type I genes (COL1A1 and COL1A2) have been proposed as candidates for the determination of bone mass. Indeed, the osteoporotic phenotype of osteogenesis imperfecta is due to mutations that affect the coding regions of collagen type I genes [112]. Recently, Grant and colleagues showed that a G/T polymorphism in the first intron of COL1A1 strongly segregated with BMD and osteoporotic fractures [113]. Additional data in larger samples of different populations support these findings [114–116]. A recent cross-section large-scale study indicates that the unfavorable COL1A1 allele (the T variant, arbitrarily called the ‘s’ allele) acts as a marker for accelerated age-related bone loss rather than a marker for lower peak bone mass [117]. However, a small study in a Finnish population [118] showed no significant association of COL1A1 Sp1 polymorphism with bone mass or fracture, nor did another study in twins in the USA [119]. Sp1 is a transcription factor. To date, the molecular mechanisms by which the described COL1A1 Sp1 diallelic polymorphism associates with bone mass are currently unclear. Preliminary data have recently supported evidence of allele-specific differences in binding of the Sp1 protein to the polymorphic recognition site, in collagen protein production and in bone strength in samples derived from patients with different genotypes [120].

**Other studies of candidate genes and linkage analysis**

Polymorphisms of other candidate genes such as those for interleukin-6 [121], transforming growth factor-β [122], apolipoprotein E [123], calcitonin receptor [124,125], androgen receptor [109], and osteocalcin [109] have been related to BMD in some isolated studies. These observations have not yet been confirmed by other independent studies; certainly other genes, with as great or even greater effects both on BMD and bone metabolism, have yet to be mapped and identified. An updated overview of candidate genes related to BMD and osteoporotic risk is depicted in Fig. 1.

The absence of a clear Mendelian pattern of inheritance (at least for a subset of cases) makes it extremely difficult, if not impossible, to determine a priori the number of involved genes and their effects on the trait of interest (i.e. peak bone mass, BMD, rates of bone loss) [72]. A study in 22 French families unraveled an autosomal dominant pattern of transmission for BMD [126]. However, in the French study and in general, the term ‘familial osteoporosis’ is lacking a clinical definition, because of the difficulty of separating genetic from environmental factors. Criteria for definition and selection of osteoporotic kindreds are therefore essential. One possibility could be to focus on subsets of kindreds showing a clear family history of low BMD/OP and of characteristics that make the pedigree ‘interesting’. Some families with apparently transmissible
osteoporosis also exhibit clinical evidence of connective tissue dysplasia, with no clinical or biochemical evidence of osteogenesis imperfecta or Ehlers-Danlos syndrome [127]. This sign can itself become a hallmark for definition of the 'patients' within the kindred. The a priori chance of success for linkage studies in a family is increased by the analysis of multiple generations (a minimum of three generations could be the cut-off) exhibiting a pattern of inheri-
tance with high penetrance. The need for at least four affected (i.e. having low BMD and osteoporosis) members in multiple generations, including males, will help to narrow the definition of an ‘interesting’ pedigree as a pedigree that constitutes a rare subset of a common phenotype. Linkage studies in man and experimental animals suggested the existence of multiple loci regulating bone mass, but the genes that account for such effects remain to be defined. Linkage analysis for chromosome 11q12–13 polymorphic loci indicated the possible existence of a candidate gene or genes in this region that may play an important role in the variation of BMD in a normal population [128]. Linkage studies in sib-pairs were able to define other loci controlling the BMD on different human chromosomes in different populations [129–131]. To date, traditional linkage analysis has been successfully used to find major contributory genes but has limited power to detect genes with only a modest effect. In the latter case, different approaches, such as nonparametric allele-sharing methods (i.e. affected sib-pair analysis, linkage disequilibrium, and transmission/disequilibrium testing) have far greater power [132,133]. In this respect, recent observations have revealed a few chromosomal regions containing genes (quantitative trait loci) modulating the BMD [128–130,134,135], as shown in Table 4. Recruitment of a large number of sib-pairs would be valuable for doing linkage studies of haplotype sharing and transmission/disequilibrium tests in humans [136]. Affected relatives should show excess allele sharing even in the presence of incomplete penetrance, phenocopy, genetic heterogeneity, and a high frequency of disease alleles [132]. Nonparametric linkage approaches testing multiple candidate genes in large pedigrees could also provide interesting information. Preliminary data from such a study showed a suggestive linkage of the parathyroid hormone receptor type 1 to osteoporosis [131]. A limiting factor in linkage analysis of multiple candidate genes is the lack of accurate statistical software to clearly define the threshold of significance.

Information derived from cross-sectional association studies could offer potential starting points, although a complete genomic screening with high-resolution linkage maps and regional follow-up by additional markers could not be excluded.

Animal models
Comparative genetics could add information about potentially interesting genes in humans once quantitative trait loci in animal models (i.e. rodents, primates) are identified [137]. Very recently, an autosomal recessive mutation at locus sfx, mapped to central chromosome 14, was found to segregate with stage-specific bone growth failure and fracture in a new mouse model, designated spontaneous fracture (sfx) [138]. Fine mapping of this chromosomal region could define the role of this gene in the pathophysiology of the skeleton and could provide evidence of other genes co-localizing with sfx.

Together, these efforts will make it possible to map unknown OP-related genes to defined chromosomal regions, to clone them, and to identify their function.

Conclusions
OP and OA affects hundreds of millions of people throughout the world, causing pain and disability and having a great impact on individuals and on society as whole. There is evidence that the two disorders are often inversely correlated and that they have a complex genetic component. The identification of the genetic pathways involved is difficult and represents a great challenge in the near future. As in other multifactorial diseases (such as hypertension and diabetes), in both OA and OP, the initiation, progression, and severity of the disease may be influenced by multiple environmental factors with multiple genes in a given individual. The authors of some association studies have suggested the possibility that a given allelic variant in a candidate gene (i.e. VDR) may increase the risk for OP and be protective for OA, and vice versa [40–43,47,60,61,67]. However, this intriguing hypothesis remains to be confirmed in larger samples, in different populations, and by other genetic approaches. Moreover, we must take into account that the inverse correlation between OP and OA observed in several epidemiological reports may have other, nongenetic, components. Indeed, it is known that increased physical loading due to enhanced weight-bearing activity is protective for OP but

### Table 4

| Reference | QTL | Genetic analysis | Phenotype |
|-----------|-----|-----------------|-----------|
| [135]     | 11q12-13 | Linkage       | High BMD  |
| [129]     | 1p36  | Linkage        | Low BMD   |
|           | 2p23-24 | Linkage       | Low BMD   |
|           | 4qter | Sib-pairs     | Femoral neck BMD |
| [128]     | 11q12-13 | Sib-pairs   | Femoral neck BMD |
| [130]     | 2p   | Sib-pairs     | Proximal and distal forearm BMD |
| [134]     | 1q21-23 | Sib-pairs | Lumbar or femoral BMD |
|           | 5q33-35 | Linkage       | Lumbar or femoral BMD |
|           | 6p11-12 | Linkage       | Lumbar or femoral BMD |
|           | 11q12-13 | Linkage       | Lumbar or femoral BMD |

BMD = bone mineral density.
seems to confer a higher risk of developing OA in the elicited joint structures.

Several large-scale investigations now under way, involving thousands of patients and genome-wide screening, may make it possible to identify multiple gene variations associated with an increased risk for OA and/or OP. However, the importance of genetic heterogeneity, including ethnicity, as well as of environmental, hormonal, and constitutional confounders (e.g., skeletal and body size) will need to be taken into serious account in future genetic studies. Gene–gene and gene–environment interactions and interactions between pharmaceuticals and the genome in humans and animal models will be critical targets for future research. Further developments in molecular genetics, such as microarray chips, will allow simultaneous large-scale differential identification of thousands of genetic polymorphisms segregating with OA or OP or both [139]. All these efforts will improve our understanding of the pathogenesis of these two disabling disorders, making possible earlier preventive strategies as well as the development of more appropriate and effective treatment options.

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