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Prevalence and inheritance of hip osteoarthritis in Iceland

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THESIS

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List of Papers

I. Ingvarsson T, Hägglund G and Lohmander LS. Prevalence of hip osteoarthritis in Iceland. Ann Rheum Dis 1999; 58: 201-207.

II. Ingvarsson T, Hägglund G, Lindberg H, Lohmander LS. Assessment of primary hip osteoarthritis: A comparison of two radiographic methods using colon radiographs. Ann Rheum Dis 2000; 59: 650-653.

III. Ingvarsson T, Hägglund G, Jónsson H, Lohmander LS. Incidence of hip replacement in Iceland 1982–1996. Acta Orthop Scand 1999; 70: 229-233.

IV. Ingvarsson T, Stefánsson SE, Hallgrímsdóttir IB, Jónsson jr H, Gulcher J, Jónsson H, Ragnarsson JI, Lohmander LS, Stefánsson K. The inheritance of hip osteoarthritis in Iceland. Arthritis Rheum 2000; in press.

V. Ingvarsson T, Stefánsson SE, Gulcher J, Jónsson HH, Frigge M, Lohmander LS, Stefánsson K. A large Icelandic family with osteoarthritis of the hip associated with a susceptibility locus on chromosome 16p. Manuscript, submitted.

Definitions and abbreviations

Allele One of two or more alternative forms of a gene.

Candidate gene A gene whose protein product can reasonably be assumed to influence the heritable trait being studied.

cM Centimorgan, a unit of genetic distance, 1/100th of a Morgan, which is the distance over which we would expect to see one recombination per meiosis. Approximates 1 million DNA base pairs, 1 megabase (mB).

CMC I First carpometacarpal joint.

DIP Distal interphalangeal joint.

Familial cluster Individuals who are related to each other at a given meiotic distance.

JS Joint space.

K&L Kellgren and Lawrence.

KC Kinship coefficient.

Locus, loci Part(s) of a chromosome that most likely include a gene at least partly responsible for a disease.

LOD score Logarithm-of-odds: the likelihood ratio [log(base 10) (Likelihood (theta)/likelihood (null hypothesis))].

MFT Minimal Founder Test.

MJS Minimal joint space.

OA Osteoarthritis.

PCR Polymerase Chain Reaction.

PIP Proximal interphalangeal joint

Primary osteoarthritis Osteoarthritis without known cause.

Qualitative measurement Measurement with a ordinal, subjective scale such as K&L grading of radiological OA.

Quantitative measurement Measurement with quantitative scale such as mm.

RR Relative Risk

Secondary osteoarthritis Osteoarthritis with known cause such as Legg-Calvé-Perthes' disease, injury, etc.

SNP Single Nucleotide Polymorphism.

THR Total hip replacement.

TKR Total knee replacement.

Introduction

Osteoarthritis (OA, synonyms osteoarthrosis, arthrosis) is the most frequent cause of musculoskeletal disability in developed countries. It is regarded as a final common pathway of a disease with multifactorial and unknown etiology affecting various joints (Dieppe 1984, 1991). OA represents a major disease burden to the individual and society (Murray and Lopez 1996, Consensus Document Bone and Joint Decade 1998). For example, in a British survey of a population aged 16 years and older, 5 percent of the subjects reported unspecified arthritis, believed to be mainly OA, in conjunction with disability (Badley et al. 1993). Among subjects 75 years and older, 20 percent had OA with disability. The authors concluded that OA was one of the most common causes of dependence and incapacitating pain in the population. The hands, spine, knees and hips are commonly affected by OA. Increasing age or higher physical demands will increase the impact of OA.

The joint cartilage together with synovial lining tissue, capsule and subchondral bone constitute a functional unit that dissipates the forces of weight bearing on joints. Muscle function influences coordination and stability of the joint. During development of OA, the gliding surfaces deteriorate, leading to loss of joint integrity, pain and disability. By the time that OA is radiographically visible as "joint space narrowing", cartilage damage may be irreversible. It is generally agreed that successful therapy should be initiated before the disease has progressed to this stage.

A significant problem in dealing with OA in research and in the clinic is the lack of sensitive and specific methods for diagnosing and monitoring the disease before permanent changes have developed. This is illustrated by the discrepancy between accepted clinical markers such as pain and stiffness on the one hand, and radiographic OA changes or even arthroscopic cartilage pathology (Felson 1988, Brandt et al. 1991). To facilitate the development of new treatments we must improve the methods for diagnosing OA and our understanding of the pathogenetic mechanisms that initiate and lead to progress of the disease.

As a junior orthopedic surgeon in Iceland I saw many patients with the common feature of being relatively young and in good health but having hip OA. Many of them had OA also in other joints. They came from different parts of Iceland and from various working classes. When I asked them if they knew anyone else in their family who had this disease, many of them told me that they had parents or aunts or even sisters or brothers with this disease. In 1987 one of these patients came to Akureyri Central Hospital for a THR and told me that she was one of 17 siblings and that at least 12 of them had the disease, in addition to her mother and the brother of her mother. I was by then convinced that this family had an inherited form of hip OA and determined to investigate this further.

Anatomy of the hip joint

The hip is a ball and socket joint and by its design has both an intrinsic stability and a wide range of motion. The cartilage of the acetabular surface is thickest at the periphery whereas cartilage of the femoral head is thickest on the medial-central surface. The femoral neck has two angles important for transmission of forces, the neck-shaft angle in the coronal plane, and the anteversion angle in the transverse plane. The neck-shaft angle is about 135 degrees and the anteversion angle about 10–15 degrees in a grown individual. Motion takes place in three planes: the sagittal with a range of motion from 140 degrees in flexion to 15 degrees in extension, the frontal with 45–50 degrees of abduction and 20–30 degrees adduction and the transverse plane with an internal rotation of 35 degrees and external of 45 degrees with the hip joint flexed. In everyday activities, full flexion is needed for such simple things as tying a shoe or picking up a small object.

Definitions of hip OA for epidemiological studies

Osteoarthritis (OA) is a common disorder of synovial joints characterized by destruction of hyaline articular cartilage and reactive bone changes (Pritzker 1998). The disorder is associated with joint pain and stiffness and radiological signs in the form of decreased joint space, marginal osteophyte formation and changes in subchondral bone density (Flores et al. 1998).

Most individuals with OA have no identifiable cause for the disorder. An underlying etiology is suggested, however, when OA develops at young age and involves multiple synovial joint groups and joints not usually affected in primary (idiopathic) OA (Pritzker 1998). Numerous acquired and inherited disorders are associated with secondary OA, such as Legg-Calvé-Perthes' disease, slipped epiphysis and congenital dislocation of the hip, trauma, microcrystalline disease, hemochromatosis, and chondrodysplasia (Felson 1998).

Different specialties may not concur in their definitions of hip OA (McAlindon & Dieppe 1989) and different definitions are used for different purposes. In epidemiological surveys definitions may be based on symptoms, clinical signs, radiological signs, or any combination thereof. In orthopedic and rheumatology practice, OA is often defined as combination of joint pain, stiffness and radiographic changes such as loss of joint space, osteophytes, cysts and sclerosis. The associations between these clinical and radiological features of OA are inconstant.

The correlation between pain and degree of structural OA change is best at the hip, then the knee, and is worst for hand and spinal apophyseal joints (O'Reilly et al. 1998). At any site, however, joints with severe radiographic change are more likely to be painful than those with mild or no change (O'Reilly et al. 1998). Patients requiring hip replacement for OA show a strong association between symptoms and radiological changes (Fox et al. 1996) and in those with radiological evidence of moderate hip OA the radiological changes correlate with reduction of hip movement (Theiler et al. 1996).

Symptoms, signs and diagnosis of hip OA

The first symptom from hip OA is pain which is typically felt deep in the groin, but may be referred over a wide area including the lateral thigh and buttock, anterior thigh and knee, and as far down as the ankle. Pain is initially felt on walking, but later occurs at rest and subsequently at night. Stiffness is common and patients may have particular difficulty with bending to put on socks and shoes, walking, etc. The principal finding at clinical examination is painful restriction of both active and passive movements of the hip. Anterior groin tenderness lateral to the femoral pulsation is common, while pain and tenderness over the greater trochanter, worse when lying on that side, implies secondary bursitis; an antalgic gait is common. In advanced cases wasting of the gluteal and anterior thigh muscles may be apparent, with Trendelenburg gait due to abductor weakness. A fixed flexion, external rotation deformity is the most usual end stage result. Ipsilateral leg shortening follows severe joint attrition and superior femoral migration.

The clinical diagnosis of hip OA is usually made on the basis of the patient history combined with clinical examination and radiograph of the hip. The plain radiograph remains a key tool in the orthopedic clinical management of hip OA.

Radiographic features of hip OA

The four main radiographic features of OA are joint space narrowing, subchondral sclerosis, subchondral cyst formation and osteophytosis. These radiological features of OA are most easily understood in terms of the underlying pathology (Resnick 1995). The simplest concept involves initiation of OA within cartilage and bone at points of high stress. Focal cartilage degeneration results, with associated attrition of underlying subchondral bone. Elsewhere in the joint, stress shielding occurs and a reparative process characterized by new cartilage and bone formation ensues. The disease is thus characterized by the simultaneous occurrence of destructive changes and attempts at repair. However, differences in radiological patterns between different patients

suggest that these two processes are not always linked.

Joint space – Loss of cartilage is a cardinal feature of OA. It is usually focal and tends to predominate at sites of maximum load-bearing within individual joints. The focal thinning of cartilage is an important observation that allows differentiation of OA from other arthropathies, such as rheumatoid arthritis, which commonly cause generalized cartilage loss (Jewell et al. 1998). The normal mean hip joint space is reported to be 4 mm (Köhler 1956, Fredensborg et al. 1978, Buckland-Wright 1998).

Subchondral sclerosis – Changes in the thickness and mechanical properties of hyaline cartilage during the evolution of OA lead to increased transmission of forces to the subchondral bone (Jewell et al. 1998). The bone responds with increased local blood flow and deposition on existing trabeculae. Trabecular microfractures, and then macroscopic bony collapse, may also occur. These events are identified on plain radiographs by development of subchondral sclerosis at the sites of maximal stress. In general, subchondral sclerosis is not observed on plain radiographs until the cartilage thinning is recognizable.

Subchondral cyst formation — They are typical features of OA but are also seen in other arthropathies. The term "cyst" is most commonly used but is erroneous because these cavities are not lined by epithelium. They occur within areas of bony sclerosis at sites of increased pressure transmission. Radiographically, the cysts occur in areas of increased joint stress and are associated with bony sclerosis and joint space narrowing.

Osteophyte formation – Osteophytes are cartilage-bone outgrowths that occur most commonly at the margins of OA joints, by a process of enchondral ossification at the junction of hyaline cartilage and synovium/periosteum. The stimulus causing metaplasia of synovium into cartilage and subsequent osteophyte growth is unknown, but may be related to changed stress transmission consequent to changes elsewhere in the joint (Thompson et al. 1970).

OA of the hip exhibits all the cardinal signs mentioned here. The variations in the pattern of radiographic abnormalities suggests that the patients with OA of the hip form a heterogeneous group with different precipitating factors and reaction patterns (Jewell et al. 1998).

The hemispherical head of the femur articulates with the cup-shaped acetabulum in a ball and socket configuration. However, the articular cartilage of the acetabulum is horseshoe-shaped, rather than hemispherical, because of the presence of the acetabular notch. Combined with the presence of acetabular anteversion, this means that hyaline cartilage is distributed predominantly superolaterally and posteriomedially.

The pattern of JS narrowing in hip OA may thus vary depending on the precise location of focal cartilage loss. Such patterns are more easily appreciated early in the development of OA and may be more difficult to observe in established OA. The most common site of joint space narrowing is in the superior weight-bearing portion of the joint. Superior-lateral migration of the femoral head is thus the most common pattern in both sexes and is often unilateral (Ledingham et al. 1992). It incorporates superior JS narrowing and lateral migration of the femoral head, with accompanying widening of the posteromedial joint space. Superomedial and posteromedial migration is more commonly seen in women and is often bilateral (Ledingham et al. 1992). The posteromedial JS narrowing is associated with preservation or widening of the lateral joint space. Axial migration of the femoral head includes features of the previously described patterns and results in concentric loss of hyaline cartilage. This is less common than the other patterns. These radiographic patterns of hip OA are often referred to as superolateral, superomedial or mixed, respectively. When the hip OA is severe, it is often impossible to classify.

For epidemiological studies standard radiographs have many advantages and remain the most important source of information for classification of hip OA in community and population based studies (Nevitt 1996). Radiographs are practical in most study settings, they provide a permanent and objective record, and the imaging technique and classification procedures can be standardized and reproduced (Buckland-Wright 1994, Nevitt 1996).

Methods of radiographic assessment of hip OA

The global radiographic grading system of Kellgren and Lawrence (Kellgren & Lawrence 1957, Kellgren et al. 1963) with its accompanying atlas has been used to grade OA in different joints in epidemiological studies for almost four decades. Although essentially a global scale, the system relies heavily on the presence of osteophytes, with subsequent increases in grading being related to concomitant loss of JS, subchondral sclerosis and cyst formation (Table 1). Most epidemiological studies define hip OA as K&L grade 2 or higher.

Table 1. The Kellgren and Lawrence classification of osteoarthritis (Kellgren 1963)

Grade	
0	Normal
1	Doubtful narrowing of JS, possible osteophytes
2	Definite osteophytes, slight sclerosis definite narrowing of JS
3	Moderate osteophytes, marked narrowing of JS, some sclerosis and possible cysts, possible deformity
4	Large osteophytes, gross loss of JS, severe sclerosis, cysts and definite deformity

However, epidemiological studies support the concept that radiographic grading systems should be joint specific. Several reports have thus suggested that the K&L grading scale is inconsistent in its interpretation (Croft et al. 1990, Spector et al. 1993, Nevitt 1996). This can result in poor reproducibility between different investigating centers, due to low inter- and intra-observer reproducibility (Spector et al. 1993). Limitations of the use of the K&L grading system for the hip have long been apparent. Discrepancies between the original atlas photos and legends (Kellgren et al. 1963) which place greater emphasis on joint space narrowing and subchondral bone changes, and later revisions (Lawrence 1977) have created confusion (Spector et al. 1993, Nevitt 1996). For example, the original atlas defines grade 2 hip OA as "definite osteophytes, slight sclerosis and definite joint space narrowing" (Kellgren et al. 1963) while a later version describes it by "definite osteophytes, joint space unimpaired" (Lawrence 1977).

Emphasis on osteophytes as the initial defining feature of disease, and the implicit assumption of an invariant developmental sequence of bone and cartilage changes, were questioned early on by those who suggested that hip osteophytes without other changes are part of normal aging (Danielson 1964) and more recently for failing to accommodate atrophic OA with little or no marginal bone reaction (Solomon et al. 1976, Ledingham et al. 1992).

Inconsistencies in the definitions of OA contribute significantly to the poor between-observer reproducibility reported for the K&L system (Spector et al. 1993). It is not known if it is the system itself that is responsible for this poor between- and intra observer reproducibility or if it is the confusion between atlases. There are still uncertainties about how to define OA for epidemiological studies using individual radiographic features.

Alternative radiographic methods — Several alternatives to the K&L radiographic criteria have been proposed for the hip with assessment of joint space narrowing playing a central role (Danielson 1964, Lequèsne 1982, Croft et al. 1990, Altman et al. 1991, Lane et al. 1993).

The Danielsson method — In his thesis in 1964 Danielsson proposed that the classification of hip OA should be based on JS narrowing, since the presence of osteophytes alone did not satisfy the radiographic criteria of hip OA. He suggested a criterion of radiological hip OA based on the presence of a JS less than 4 mm in those younger than 70, or less than 3 mm in those 70 or older (Danielsson 1966). The presence of structural changes such as osteophytes, sclerosis and cysts in the absence of JS narrowing was not sufficient for the diagnosis of radiological hip OA. Finally, the JS was interpreted as abnormally decreased if it was more the 1 mm less than the JS on the contralateral side. This proposal challenged the K&L system.

Measuring minimal joint space – A single measurement of minimal joint space (shortest distance between femoral head margin and acetabulum) was more recently suggested to represent the best assessment on which to base the diagnosis of radiographic hip OA in epidemiological studies (Croft et al. 1990). The proposal was based on

four considerations: (1) The selected criterion correlated with symptoms, (2) It was related to other accepted radiologic features of the disease, (3) The measurements were repeatable within and between observers, and (4) The method was easy to use. The single measurement of hip JS was superior in these aspects when compared with other radiographic measurements and the K&L grading. The relationship between hip JS on the one hand and symptoms and other radiologic indices of OA on the other hand suggested that JS values of 2.5 mm or less on an intravenous urogram or similar projection was associated with an increased prevalence of hip OA, and that JS values of 1.5 mm or less were highly predictive.

Other qualitative scales – Subsequent to the Kellgren and Lawrence atlas of radiographic changes, more recent atlases have been published to aid in the radiographic assessment of OA (Burnett et al. 1994, Altman et al. 1995).

Epidemiology of hip OA

The variable criteria used for case definition in studies of hip OA epidemiology confound the interpretation of the results. Thus, the use of clinical, radiological or combined methods for defining hip OA cases have been described (Lequèsne 1982, Danielson et al. 1984, Croft et al. 1990, Altman et al. 1991).

The prevalence of OA in all joints is strikingly correlated with age, with an almost exponential increase in prevalence with increasing age over 50. Regardless of how OA is defined, it is uncommon under age of 40 but prevalent above age 60. OA commonly affects certain joints, yet spares others. For example, in the hands the DIP and PIP joints and the CMC joint of the thumb are frequently involved. Other joints commonly affected are the cervical spine, lumbosacral spine, hip, knee and MTP joints. Notably, the ankle, wrist, elbow and shoulder are often spared.

Reports on the relationship between hip OA and other forms of OA are inconsistent. Thus, several studies failed to show a high prevalence of multiple joint involvement in patients with hip OA (Kellgren 1961, Yazici et al. 1975). In contrast, several other investigations have reported a significant association between hip OA and hand OA, where between 25 and 65 percent of patients with hip OA also have hand OA (Roh et al. 1973, Croft et al. 1992, Ledingham et al. 1992, Hochberg et al. 1995, Felson 1998).

In a recent study of 420 patients with hip OA and 389 patients with knee OA scheduled for joint replacement, the patients underwent radiography both of the ipsilateral and contralateral hip or knee joints and both hands. Hand OA was defined as radiographic changes of two joint groups of the hands, and hip or knee OA as K&L grade 2 or higher. Generalized OA was defined as OA in two different joint regions in addition to OA of at least one large peripheral joint (Günther et al. 1998). By this definition hand OA was associated with hip OA in 24 percent of the hip patients and in 28 percent of knee patients after adjusting for age and sex.

The prevalence rates of OA differ between races. Thus, the prevalence of hip OA is much lower in Asians than in Caucasians, while the prevalence of hand OA is similar (Hoaglund et al. 1973).

Many population based radiographic prevalence surveys for hip OA have been performed, beginning with those of Kellgren and Lawrence (Kellgren 1961, Lawrence et al. 1966). In their northern England surveys they observed that radiological hip OA increased with age, with 16 percent of men and 6 percent of women affected in the age group between 55 and 74 (Kellgren 1961, Lawrence et al. 1966). A survey of a farming community in Switzerland corroborated these rates (Zinn 1970). Subsequent Swedish studies have noted prevalence rates of hip OA of between 1.6 and 2.0 percent in subjects older than 55 years (Danielsson 1966). A Danish study reported a prevalence rate of 4.7 percent, but the age group studied was not stated (Jörring 1980). Examination of other Caucasian populations have reported equal rates of hip OA for older men and women, but in general lower rates than those found in England, Table 2.

The reasons for the apparent variations in OA prevalence found in these investigations may be related to the variable definitions used for hip OA, whether based on symptoms, clinical examination and history, or radiographic signs. This makes the comparison of prevalence rates of hip OA between different populations, based on published data, difficult or even impossible. Moreover, un-

Table 2. Published studies on prevalence of hip OA (in alphabetical order of first author)

First author	Publication year	Ethnic group	Country	Size of population examined	Age	OA definition	Prevalence %		
							Men	Women	Total
Croft	1990	Caucasian	England	1315	60–75	MJS [d]	14.4	-	-
Cvijetic	2000	Caucasian	Croatia	304	45+	K&L[1]	27.1	-	-
Danielsson	1966	Caucasian	Sweden/Malmö	3903	55+	JS [b]	3.8	3.4	3.4
Danielsson	1984	Caucasian	Sweden/Malmö	4027	40+	JS [b]	2.0	2.2	2.0
Danielsson	1997	Caucasian	Sweden/Malmö	4121	40+	JS [b]	1.6	2.0	2.1
Forsberg	1992	Caucasian	Sweden/Gotland	5420	45+	JS [c]	5.0	4.1	4.7
Hoaglund	1973	Asian	Hong Kong	294	55–64	K&L[2]	1.2	0.8	1.0
Ingvarsson	1999	Caucasian	Iceland	1530	35+	JS [d]	11.8	10.1	10.8
Jörring	1980	Caucasian	Denmark	6321	?25+	MJS [a]	-	-	4.7
Lawrence	1954[3]	Caucasian	England	501	55–64	K&L[1]	25.0	15.0	-
Lawrence	1958[3]	Caucasian	England	251	55+	K&L[1]	22.0	16.0	-
Lawrence	1960[3]	Caucasian	Germany	119	55+	K&L[1]	16.0	10.0	-
Lawrence	1961[3]	Caucasian	England	77	55+	K&L[1]	12.0	7.0	-
Lawrence	1961[3]	Indian	USA	242	55+	K&L[1]	8.0	11.0	-
Lawrence	1962[3]	Indian	Canada	36	55+	K&L[1]	7.0	-	-
Lawrence	1962[3]	Caucasian	Czechoslovakia	376	55+	K&L[1]	17.0	10.0	-
Lawrence	1963[3]	Indian	USA	267	55+	K&L[1]	12.0	5.0	-
Lawrence	1964[3]	Black	Jamaica	178	55–64	K&L[1]	1.0	-	-
Lawrence	1970[3]	Caucasian	Switzerland	223	55+	K&L[1]	17.0	7.0	-
Lindberg	1993	Caucasian	Sweden/Malmö	572	?	JS [b]	2.8	-	-
Muller	1970	Black	Nigeria	122	55+	K&L[1]	3.0	2.0	-
Nevitt	1998	Caucasian	USA	4450	65+	MJS [d]	-	20.8	-
Odding	1998	Caucasian	Netherlands	2895	55+	K&L[1]	14.1	15.9	-
Odding	1998	Caucasian	Netherlands	2895	55+	Clinical	8.3	16.6	-
Ota	1965	Asian	Japan	165	55–64	K&L[1]	4.6	-	-
Petersen	1941	Caucasian	Iceland	220	40+	-	-	-	9.1
Pogrund	1982	Jewish	Israel/Jerusalem	641	45+	K&L[1]	43.9	4.2	4.1
Solomon	1976	Black	South Africa	199	55+	K&L[1]	3.0	3.0	-
Steffensen	1941	Caucasian	Iceland	-	25+	-	-	-	25
Tepper	1971	Black	USA	2358	55-74	K&L[1]	3.2	3.0	-

[a] Definition of OA was minimum hip joint space of 3 mm or less.
[b] Definition of hip OA according to Danielson (Danielson 1964, 1966): the hip joint space was regarded as abnormally decreased when found to be < 4 mm in patients younger than 70 or < 3 mm in patients 70 years of age and older, or a reduction >1 mm compared to contralateral hip.
[c] Definition of hip OA was narrowing of the hip joint space to < 2 mm, or obvious asymmetry in unilateral cases.
[d] Definition of hip OA was minimum hip joint space ≤ 2.5 mm.
[1] Definition of hip OA according to Kellgren and Lawrence class 2 or higher.
[2] Definition of hip OA according to Kellgren and Lawrence class 3 or higher.
[3] See Lawrence 1980.

derlying but unreported differences in population structure may further confound attempts to compare prevalence rates of OA between different populations. Additional reasons for the variable prevalence rates noted in these surveys undoubtedly exist, such as hereditary factors (Williams et al. 1993, Hoaglund et al. 1995, Cicuttini et al. 1996, Hopper 1996, Spector et al. 1996, Chitnavis et al. 1997, Meulenbelt et al. 1997), but their contribution to population-related differences in rates of hip OA is difficult to determine, for the reasons given.

Risk factors for hip OA

As noted, the prevalence of hip OA increases sharply with age after 50. The prevalence among men and women is similar. This is in contrast to other forms of OA, for which there is a female dominance, at least after menopause. Age, sex, developmental abnormalities, inheritance and possibly bone mass may be characterized as endogenous risk factors. Obesity, joint injury and overuse in work and sports may be regarded as exogenous risk factors.

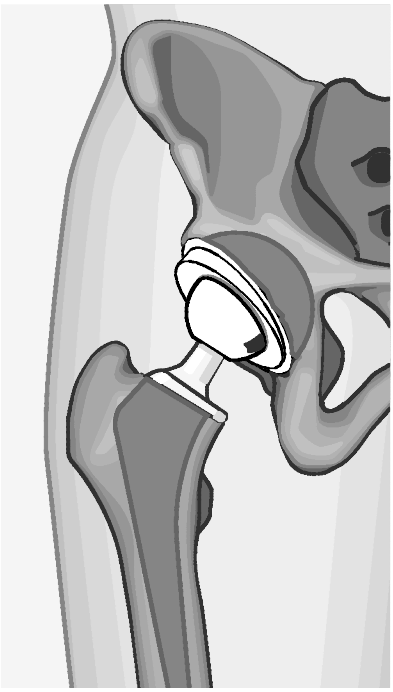

Figure 1. Conventional hip prostheses have a cobalt chromium stem fixed with bone cement to the femoral shaft. The head is modular and fixed to the neck with a taper lock. The polyethylene cup is fixed with bone cement in the acetabular cavity. Reproduced with permission of Oxford University Press.

Interest in the relationship between OA and osteoporosis first arose when surgeons in the 1960s noticed the general absence of OA changes in the femoral head excised in the treatment of osteoporotic fractures of the femoral neck (Foss et al. 1972). The weight of the evidence favors an inverse relationship between the two common disorders of OA and osteoporosis. Recent studies have suggested that local change in joint bone mineral density could be a component of the disease process in hip OA and that the higher bone mineral density could be an inherited trait (Antoniades et al. 2000).

Obesity appears to increase the risk for hip OA, although the association of body weight with hip OA is not as strong as for knee OA (Felson 1998). Surprisingly, obesity also appears to increase the risk for hand OA (Felson 1998), suggesting a systemic risk factor for OA associated with obesity.

With respect to joint overuse, studies have focused on occupational and athletic activities. Standing, bending, walking long distances over rough ground, lifting, moving heavy objects, and tractor driving all appear to pose an increased risk for hip OA, putting farmers at higher risk (Vingård et al. 1991, Croft et al. 1992). The increased risk for hip OA in some other occupational groups has also been shown, with the highest risk in men and women with heavy physical work. A Swedish study (Vingård et al. 1991), showed that farmers, firefighters, mill workers, butchers, dockers and to a lesser degree, manual workers, fishermen and miners all had a higher than average risk for THR for hip OA. In contrast to this another Swedish survey found no difference in hip OA prevalence between shipyard laborers and white-collar workers (Lindberg et al. 1984).

An increased risk for hip OA has been described in former soccer players and track and field athletes (Lindberg et al. 1993), while the influence of long distance running on the risk for hip OA is controversial (Puranen et al. 1972, Maarti et al. 1989, Vingård et al. 1993).

Treatment

The main problem for the patient with hip OA is pain and functional impairment. The consequences of pain and impairment on the individual varies greatly, depending on factors such as personality, occupation and coexistent diseases and disability. Concomitant OA in other joints plays an important role.

The principal objectives of management of hip OA are to educate the patient, control pain, optimize function and reduce handicap. The rule is to try first interventions such as weight loss, analgesics and NSAIDs, possibly including aids and physical therapy. When pain and disability cannot be controlled by these interventions, surgical treatment is indicated. The standard surgical treatment for the hip OA patient is THR (Figure 1). THR for OA results in improvement in function and pain (Bellamy et al. 1988), and is a safe and cost-effective treatment (Garellick 1998, Birrell et al. 1999).

Table 3. Published studies on incidence of total hip replacement (in alphabetical order of first author)

First author	Year	Years studied	Country	Incidence per 100,000 per year	All causes for primary THR included	Age standardized	Register based
Birrell	1999	1995–1996	England	87	Yes	No	No
Ingvarsson	1999	1992–1996	Iceland	77	Only OA	No	Yes
Ingvarsson	1999	1992–1996 [a]	Iceland	319	Only OA	Yes	Yes
		1992–1996 [a]	Sweden	209	Only OA	Yes	Yes
Havelin	2000	1987–1997	Norway	120	Yes	No	Yes
Havelin	1993	1987–1991	Norway	140	Yes	No	Yes
Hoaglund	1995	1984–1988	USA	75	Only OA	Yes	No
Johnsson	1987	1981–1982	Southern Sweden	92	No	No	No
Malchau	2000	1979–1998	Sweden	100	Yes	No	Yes
Malchau	1993	1990	Sweden	130	Yes	No	Yes
Melton	1982	1969–1980	USA Olmsted County	45	Yes	Yes	No
Overgaard	1991	1981–1990	Denmark	82	Yes	No	No
Paavolainen	1996	1980–1994	Finland	77	Yes	No	Yes

[a] Age > 49

Incidence of THR for OA

The reported incidence of THR varies considerably between regions and countries. Several factors undoubtedly contribute to the varying reported rates, in addition to possible underlying differences in the prevalence of hip OA and social structure supporting the use of THR. Firstly, there is no generally accepted and standardized indication of THR for OA, although guidelines for prioritization have been published for countries such as Sweden, USA and New Zealand (Lidgren & Lohmander 1995, Total hip replacement – NIH consensus 1995, Hardon & Holmes 1997). Secondly, the quality of the data reported may vary due to the handling of confounding factors such as the inclusion/exclusion of other causes for THR than primary hip OA such as femoral neck fracture and rheumatoid arthritis. Thirdly, the population structure ("the shape of the population pyramid") differs significantly between different countries, and unless the THR incidence data are reported in relation to age and sex, together with data on the underlying population structure, useful comparisons between different populations is impossible. Comparisons of the incidence of THR for OA between regions and countries are therefore often more complex than first appreciated, because of differences in demographics and reporting, and changes in incidence with time.

Accordingly, most studies on the incidence of total hip replacements have reported overall incidence, often without precisely specifying how the overall incidence was calculated, and not accounting for differences in age distribution between the patients and the population, and without specifying the underlying diagnosis when making comparisons with other reports. Thus, the overall incidence of THR varies in different reports between 45 and 140/100 000/year (Table 3). For Sweden, the overall annual incidence per 100 000 was reported to be 130 in 1990, with an average of 100 for the time period between 1979 and 1998 (Malchau et al. 1993, Herberts et al. 2000). For Norway, the corresponding average rate was reported to be 140 between the years 1987 and 1991 (Havelin et al. 1993) and 120 between 1987 and 1997 (http://info.haukeland.no/nrl). The overall incidence rates reported are difficult to compare, even if done for the same time periods, because of differences in population structure between the different countries. In order to make useful comparisons of 'true' rates of total hip replacements we need to correct for differences in the population structures.

Very few surveys report on the specific incidence of THR for primary hip OA. A Swedish study from 1981–1982 is an exception from this, where an incidence of 92/100 000 for primary hip OA is reported for Southern Sweden (Johnsson 1987). However, a population-based study from

San Francisco identified extreme variations in racial rates of THR for primary hip OA, with rates in Chinese being but a fraction of those for Caucasians (Hoaglund et al. 1995). Similar discrepancies were noted between Caucasian and Asian population groups in Hawaii (Oishi et al. 1998). Projection of age- and sex-specific hip replacement needs was done in a UK study, taking into account projected demographic changes and with extrapolation of arthroplasty rates from Sweden. The authors concluded that there will be a sharp rise in the number of THR procedures to satisfy needs in the UK during the next 30 years (Birrell et al. 1999).

Inheritance of OA

The concept of hereditary OA was probably first described by Stecher in 1941, who investigated the families of 64 patients with Heberden's nodes, and found the condition to be twice as frequent in the mothers and three times as frequent in the sisters of affected women (Stecher et al. 1941). It was suggested that the nodes were inherited as a Mendelian dominant trait in women and recessively in men (Stecher et al. 1941, Stecher et al. 1954).

In the early 1960s, studies of individuals with generalized OA suggested that first-degree relatives were twice as likely to have radiographic generalized OA as the general population (Kellgren et al. 1963). In a study of 391 cases of OA, 120 patients, largely middle aged women, were identified having polyarthritis. 20 percent of these patients reported a family history of similar joint disease (Kellgren et al. 1963). This and other studies suggested a polygenic form of inheritance rather than a single gene defect (Allison et al. 1958, Buchanan & Park 1983). Additional studies provided further evidence for the familial occurrence of Heberden's and Bouchard's nodes and degenerative arthritis involving multiple joints (Allison et al. 1958, Hirsch et al. 1996, Hirsch et al. 1998). A report on the Framingham cohort supported a significant genetic contribution to OA, with evidence for a major recessive gene and additional multifactorial components, representing either polygenic or environmental factors (Felson et al. 1998).

A clear genetic influence on OA was also suggested by the findings of a study of 500 unselected female twins aged 45 to 70 years who were screened for radiological OA of the hands and knees (Spector et al. 1996). The concordance of OA disease status was consistently twofold higher in the 130 pairs of identical compared with the 120 non-identical twin pairs. The influence of genetic factors was estimated to be between 35 and 65 percent, independent of known environmental or demographic confounders (Spector et al. 1996). From these observations it seems clear that hereditary factors are involved in the pathogenesis of hand, knee, and generalized OA, and that subsets of OA have different hereditary patterns (Stecher et al. 1941, Stecher et al. 1954, Kellgren et al. 1963, Spector et al. 1996).

Inheritance of hip OA

The association of a hereditary factor with hip OA was suggested by results showing that the prevalence of primary hip OA in siblings of patients with primary hip OA was 8 percent, compared with 3.8 percent in controls (Lindberg 1986). This proposal was supported by the findings of a prospective survey of 402 patients who had been operated on with THR and TKR for primary OA in England and which compared the prevalence of THR and TKR for primary OA in their 1171 siblings and 376 spouses. Using spouses as controls, the RR for THR in siblings was 1.86 (95% CI 0.93, 3.69). The RR for TKR in siblings versus spouses was 4.8 (95% CI 0.64, 36.4). These findings were consistent with genetic influences being important in end-stage OA of both the hip and knee (Chitnavis et al. 1997).

A strong genetic component of OA of the hip was further supported in a study of families of patients who had undergone THR for primary hip OA (Lanyon et al. 1999). In this study, 604 siblings from 391 THR families were age- and sex-matched to controls that had undergone an intravenous urography. The mean age of both groups was 65 years. Hip OA was defined as MJS $\leq$ 2.5 mm (definite OA) and $\leq$ 1.5 mm (severe OA). The siblings had much higher risk of having definite radiological hip OA than the controls. For definite hip OA, the RR in men was 6.5 and in women 4.7.

For severe hip OA, the RR was 11.3 for men and 4.9 for women. Even after adjusting for other risk factors (BMI, nodal status, occupational lifting, smoking) the relative risks for OA were high in the siblings. The authors concluded that there was a strong genetic component to "common" hip OA in men and women, which existed even after adjusting for other known risk factors (Lanyon et al. 1999). The same authors noted that there was a significantly greater genetic influence in siblings of parents in which the hip OA showed "no bone response" (little or no osteophytes). This suggests the existence of more than one radiographic phenotype of hip OA, associating with different heredity.

A population-based twin study examined women in monozygotic or dizygotic twin pairs with a mean age of 53 years (Antoniades et al. 2000) with plain radiographs of the pelvis. Hip OA was defined as MJS ≤ 2.5 mm, with an overall prevalence of hip OA of 8 percent. A direct relationship was found between hip OA and bone mineral density of the femoral neck of the affected side. A higher femoral neck bone density was particularly associated with the presence and severity of osteophytes in the affected hip joint. The authors suggested that their findings provide further support for investigations to search for genes common to OA and bone formation.

Inherited specific forms of OA and mutations associated with OA

Although the multifactorial nature of OA is well recognized (Marks et al. 1979), the role of genetic factors in the development of OA has recently received considerably increased attention with the development of molecular biology techniques.

Evidence for the existence of a genetic predisposition to OA is given by a number of rare subtypes of OA including familial calcium pyrophosphate deposition disease, Stickler syndrome and some chondrodysplasias that have a genetic basis and are associated with OA (Jimenez et al. 1998). The spectrum of these particular hereditary forms of OA is quite varied encompassing mild disorders, which do not become clinically apparent until late adult life, to very severe forms that manifest during childhood. Many of these disorders have been classified as secondary OA (Schumacher 1972). They all have the common characteristic of being associated with mutations in genes encoding macromolecules predominantly expressed in cartilage. Genes that may be involved in these diseases include those encoding cartilage-specific collagens (types II, IX, X, and XI), proteoglycan core protein and link proteins, noncollagenous components of the cartilage matrix, growth factors involved in cartilage differentiation or in the regulation of chondrocyte proliferation and specific gene expression, and genes encoding enzymes involved in various cartilage-specific metabolic pathways. Thus, these disorders may be seen to represent a distinct subgroup of OA that can be separated from secondary OA (Jimenez et al. 1998).

After the initial descriptions of genetic linkage between the phenotype of precocious OA and the type II procollagen gene COL2A1 on chromosome 12 (Palotie et al. 1989), a large number of mutations in the genes encoding structural and functional components of cartilage have been identified in various hereditary diseases affecting this tissue (Ala-Kokko et al. 1990, Williams et al. 1993, Vikkula et al. 1994). Progress on the elucidation of gene mutations in hereditary OA has been most substantial for COL2A1, the gene encoding for type II collagen, the most abundant collagen in articular cartilage. Accordingly, the term "type II collagenopathies" has been used to describe hereditary cartilage diseases in which their primary defect are mutation in COL2A1 (Spranger et al. 1994). Over 40 mutations are known in the COL2A1 gene associated with different forms of hereditary cartilage aberrations and OA.

Primary generalized OA – This is thought to be the most common form of inherited OA. It is characterized by the familial trait of hand OA (Heberden's and Bouchard's nodes) and premature alterations of cartilage in multiple joints (Kellgren et al. 1963). Typically, the clinical and radiological features have a precocious onset and an accelerated progression. Generally, the loss of articular cartilage is concentric in the knees and hips. The radiographic appearance is indistinguishable from that of non-hereditary OA, except for the premature occurrence, increased severity

and rapid progression (Jimenez et al. 1998). In the hand the DIP, PIP and CMC I joints are involved. The hip is affected in early adult life.

Mutations in COL2A1 genes have been identified in affected members of several families with generalized OA with premature onset and rapid progression. However, all these families also display evidence of mild spondyloepiphysesal dysplasia (SED) (Jimenez et al. 1998). Conversely, however, a recent study analyzing COL2A1 for mutations in 47 families with early onset generalized OA without SED, identified a possible COL2A1 mutation in only one of the cases (Ritvaniemi et al. 1995). Other reports suggest that COL2A1 is not the disease locus in families with premature generalized OA without evidence of SED (Loughlin et al. 1994).

A genetic predisposition in primary generalized OA has also been suggested to be associated with HLA-A1B8 and HLA-B8 haplotypes (Pattrick et al. 1989) and with alfa-1-antitrypsin isoform patterns, while other studies have failed to confirm this association (Cicuttini et al. 1996).

Familial calcium pyrophosphate deposition – This condition is also known as familial chondrocalcinosis. Following an initial description of the disease in 5 Czech families (Zitnan et al. 1963), multiple ethnic series have been reported (Jimenez et al. 1998). The condition appears to be inherited in an autosomal dominant manner with precocious onset and severe clinical expression. Radiographs show chondrocalcinosis most frequently in the knees, symphysis pubis and the wrist. These changes may precede OA changes in the joint. No linkage to the COL2A1 gene on chromosome 12 has been proven, but susceptibility loci have been described on chromosome 5 and 8 (Baldwin et al. 1995, Hughes et al. 1995, Rojas et al. 1999).

Familial hydroxyapatite deposition disease – Another form of inherited crystal deposition disease is due to deposition of hydroxyapatite crystals in articular cartilage. The mode of inheritance is that of an autosomal dominant pattern with full penetrance. This disorder results in periarticular disease in the form of tendinitis or bursitis and less frequently, true articular disease. The most common locations are the shoulders, wrist and hips. A recent study of a family from Argentina with this condition and mild SED excluded several candidate genes including type II and X collagen (Marcos et al. 1995).

Chondrodysplasias – These disorders represent a group of clinically heterogeneous hereditary disorders characterized by abnormalities in the growth and development of articular and growth plate cartilages. The classifications are based on clinical and radiographic features of the affected individuals. Several of them are associated with the development of premature OA. Linkage to COL2A1 has been demonstrated in some cases and excluded in others (Jimenez et al. 1998). These disorders include spondylo-epiphyseal dysplasias, Stickler syndrome, Kniest dysplasia, multiple epiphyseal dysplasia, and metaphyseal chondrodysplasias.

Spondylo-epiphyseal dysplasias (SED) – This is a heterogeneous group of autosomal dominant disorders characterized by abnormal development of the axial skeleton and severe alterations of the epiphysis of long bones, often resulting in dwarfism with marked shortening of the trunk and to a lesser extent of the extremities (Jimenez et al. 1998). The phenotype of SED is quite varied, ranging from severe forms that are clinically apparent at birth to milder forms which manifest in childhood or early adolescence. In the late onset form, early degenerative changes are seen in multiple joints, often as generalized OA. Hip OA may develop in adolescence, worsening in early adulthood. There may be mild epiphyseal abnormality in the peripheral joints, for example in the MCP joints. The most constant features in peripheral joints are the flattening of the articular surfaces of the ankles and knees and shallowness of femoral intercondylar notches. In adult classic cases, platyspondyly may be severe, accompanied by severe coxa vara and small and irregular femoral epiphyses. In milder cases the features of SED are not clinically obvious and many patients initially present with severe OA affecting multiple joints (Jimenez et al. 1998). Many different mutations have been described in families with SED. Several supposedly unrelated families have demonstrated co-inheritance of primary generalized OA with mild SED with specific alleles of the gene for type II procollagen on chromosome 12 (Bleasel et al. 1995, 1996, 1998). This allele has now been

cloned and found to contain a single base mutation at position 519 of the alpha 1(II) chain (Bleasel et al. 1996). It was speculated that 3 of the known families with OA and mild SED and which share this COL2A1 gene defect may be related through an early founder (Bleasel et al. 1998). In SED tarda a different mutation was recently described on chromosome Xp22 (Gedeon et al. 2000).

Stickler syndrome – A form of inherited OA characterized by ocular involvement associated with severe premature OA. Patients have myopia, hearing loss and epiphyseal dysplasia and even mandibular dysplasia. Linkage analysis of several Stickler's syndrome kindreds has demonstrated that this disease is linked to COL2A1 in some 25-50 percent of the families and mutations have been shown (Francomano et al. 1987). Linkage to collagen XI on chromosome 6 and a mutation in the gene encoding the alfa2 XI collagen chain was demonstrated in one family (Brunner et al. 1994, Sirko-Osadsa 1998).

Kniest dysplasia – A disorder characterized by an autosomal dominant pattern of inheritance displaying shortening of the trunk and limbs, flattening of the face and severe joint abnormalities. The majority of affected individuals develop severe premature OA, most prominent in the hips and knee. Mutations in COL2A1 have been identified in Kniest dysplasia (Jimenez et al. 1998).

Multiple epiphyseal dysplasia (MED) – A heterogeneous disorder characterized by alterations in epiphyseal growth that cause irregularity and fragmentation of the epiphyses of multiple long bones. Spinal alteration is absent or slight. The condition results in premature OA of both weight bearing and non-weight bearing joints, often in childhood or early adulthood. Early studies of MED failed to identify an association with the genes for collagen types II and VI, chondroitin sulfate, proteoglycan core protein and cartilage link protein. Subsequent studies identified mutations in the gene encoding the cartilage oligomeric matrix protein (COMP) (Briggs et al. 1995, Hecht et al. 1995). Linkage has also been described in MED to a region of chromosome 1 where the COL9A2 gene for the alfa2 chain of type IX collagen is located (Briggs et al. 1994, Muragaki et al. 1996). It is likely that additional and different loci will be identified, since other families with this phenotype have been shown to lack genetic linkage with either COMP or COL9A2 (Deere et al. 1995).

Metaphyseal chondrodysplasias – More than 150 different types are known. The clinical features of affected individuals include short stature with short limbs, bowed legs and a waddling gait. Mutations have been shown in the COL2A1 gene (Jimenez et al. 1998).

OA linked to the genes for the vitamin D receptor and the type II collagen alpha I chain – A vitamin D-receptor (VDR) haplotype was shown to be associated with higher risk for knee OA in both women and men (Uitterlinden et al. 1997). The authors concluded that the 2.3-fold risk increase associated with this haplotype was due to increased osteophytosis rather than joint space narrowing, suggesting that radiologic changes indicative of cartilage degeneration were not associated with this haplotype. In further support of an association of the VDR with OA, a British survey showed that women with a specific VDR haplotype had a 3-fold increase of knee OA (Keen et al. 1997).

It is interesting to note, however, that the VDR gene locus is located in close proximity (within 100 000 base pairs) of the type II collagen gene (COL2A1) on chromosome 12q. Accordingly, it was speculated that the vitamin D-receptor is not the causative locus, but that it may be in linkage disequilibrium with a neighboring disease-causing gene (Holderbaum et al. 1999).

Adding further complexity, a recent study suggested that the COL2A1 gene and the VDR gene are associated with separate features of radiographic OA of the knee. The investigators concluded that both genes are involved in knee OA, but with separate features of radiographic knee OA: the COL2A1 phenotype is associated with JS narrowing, while the VDR phenotype is associated with osteophytes (Uitterlinden et al. 2000).

Genome wide screening for chromosomal loci associated with OA

As summarized above, a number of candidate genes have been proposed to be associated with primary OA, but the results from studies published so far are somewhat conflicting. This may

be a reflection of the complexity of the disease and/or be related to the limited power of some of these studies. The pathophysiology of OA is complex and the 'a priori' choice of candidate genes is increasingly difficult and prone to bias. Association studies may provide support for the role of specific candidate genes in an inherited disease, but population heterogeneity provides a limitation to this study design.

Systematic genome wide screening for linkage of markers to phenotypes of interest, using large numbers of randomly distributed anonymous polymorphic microsatellite markers together with DNA samples from large families or large numbers of sibling pairs with OA may be used to identify yet other, unknown, predisposing chromosomal loci for OA. However, depending on the density and location of microsatellite markers used in the genome wide scan, the chromosomal region implicated may sometimes contain a large number of genes. Often, 300–900 microsatellite markers are used. The LOD score is used as a measure of support for linkage versus absence of linkage (Lander et al. 1995, Ott 1999), where a LOD score above 2.0 is sometimes referred to as 'suggestive', and a LOD score above 3.0 as 'significant' linkage. These are, however, arbitrary LOD score cut-off levels and may need to be changed depending on the particular experimental design and statistical analysis performed.

Genome wide scans are often followed by further scans of the chromosomal region of interest with higher density marker panels, to narrow down the chromosomal region (and number of genes) associating with the phenotype of interest. However, assuming that a gene can eventually be identified through this search strategy, the challenge remains to identify sequence variants that influence the function of the protein and result in the phenotype.

In a study using 481 families with at least two siblings each of whom had undergone one or more of THR or TKR, or both, for primary OA, Heberden's nodes were noted in 39 percent of the affected individuals. Using a genome-wide scan, a locus associating with OA in women was identified on chromosome 11q with a LOD score between 2 and 3. The authors suggested that a female-specific susceptibility gene for primary OA was present on chromosome 11q (Chapman et al. 1999). Further reports on genome-wide scans have indicated the existence of multiple susceptibility loci for OA by stratifying the same material by gender and joint. Thus, linkage to loci on chromosomes 2, 4, 6 and 16 was proposed (Loughlin et al. 1999, Loughlin et al. 2000).

For chromosome 2 suggestion of linkage was based on a LOD score of 1.22 which increased to 2.19 in hip patients and it was stated that this suggestive linkage was greater for male hip patients. The proposed region 2q31 is at a similar location described in nodal OA (Wright et al. 1996) and near a locus which were described for DIP OA (Leppävouri et al. 1999). It appears possible that chromosome 2q contains at least one susceptibility locus for OA.

For chromosome 4 the suggestion of linkage was based on a LOD score of 3.9 and centered on the chromosomal region 4q12-21.2, based on female sibling pairs with hip OA (Roby et al. 1999). A separate study of a Dutch family with hip OA proposed linkage to a region of chromosome 4 more than 50 cM distal from the locus at 4q12-21.2. These authors concluded that it was unlikely that the two linkages had detected the same locus (Loughlin et al. 1999).

The chromosome 6 linkage for hip OA was based on a LOD score of 2.9 and centered on a strong candidate gene for OA, COL9A1 at 6q12-613 (Loughlin et al. 1999). This locus was further confirmed in an additional report by the same group, suggesting that the COL9A1 gene was associated with susceptibility for hip OA in females (Mustafa et al. 2000).

A chromosome 16 linkage showed a LOD score of 2.1, but no candidate genes for OA were associated with this locus. Again, the material was stratified for hip OA in women (Loughlin et al. 1999).

The authors concluded that their analysis highlighted the potential utility of genome-wide screens and that stratification of the material revealed additional chromosomal regions that may harbor susceptibility loci for OA (Loughlin et al. 1999).

Aims

- To assess the prevalence of radiological primary hip OA in Iceland
- To compare the prevalence of radiological primary hip OA in Iceland with published rates of radiological primary hip OA for related Scandinavian populations
- To assess the age-related incidence of THR for OA in Iceland for the years between 1982 and 1996
- To compare the incidence of THR in Iceland with published rates of THR in other Nordic countries
- To estimate the future demands in Iceland for THR
- To compare the reliability of a quantitative measurement of minimum hip joint space with a qualitative global assessment of radiological features for estimating the prevalence of primary OA of the hip from colon radiographs
- To assess in a population-wide study in Iceland the hereditary contribution to hip OA leading to THR
- To perform a genome wide scan to identify genetic loci associated with THR for hip OA in a large Icelandic family

Patients and methods

Iceland: geography and history of settlement and population

Iceland is an island in the North Atlantic between Europe and North America, with a size of 103 000 km^2. Settlement in Iceland begun in AD 870 and was considered completed in the year of 930, at which time there were some 10 – 20 000 inhabitants on the island (Steffensen 1975). The names and land claims of the 435 Norwegian Viking chiefs listed as Icelandic settlers in this period are known. The chiefs brought slaves into the country, mostly from Ireland, during the same period. Thereafter the population is believed to have increased rapidly to some 70 000 by the end of the 12^{th} century, after which it went in to a gradual decline, reaching 40 000 at the end of the 18^{th} century. This period of decline was accentuated by a number of abrupt and catastrophic reductions in population size. The most severe of these demographic bottlenecks occurred during the years 1402-1404, when 45 percent of the population was eliminated by an outbreak of the pneumonic plague. Other significant decreases in population size include a 35 percent reduction in 1708, due to a particularly severe smallpox epidemic (leading to an all-time post-settlement minimum of 33 000) and a 20 percent reduction in 1784–1785 due to widespread famine following large volcanic eruptions. From the 19^{th} century onward, the population grew rapidly to its present size of 275 000.

This demographic history is likely to have reduced the genetic diversity introduced by the original settlers. Moreover, since the natural barrier of the North Atlantic has tended to limit post-settlement immigration to the island, there would have been no mechanism to replenish genetic diversity (Helgason et al. 2000). Immigration has continued to be low since the time of settlement. Until very recently, much of the population lived in small isolated fishing and farming communities along the coastline. The Icelandic population thus fulfills several conditions for an enrichment and identification of inherited diseases.

Written and oral records maintain a detailed family history for the Icelandic population since the time of settlement more than a thousand years ago. An Icelandic nation-wide computerized genealogy database was recently developed which uses, as its raw data, the extensive genealogical information collected over the last 10 centuries by the government-supported churches, together with other historical records. It includes all 275 000 living Icelanders, in addition to most of their ancestors since the time of the settlement in the 9^{th} century. Over 600 000 individuals are currently registered in the database (http://decode.is). It is estimated that fewer that 800 000 Icelanders have lived since the country was settled. It was pointed out that Icelanders are an ideal nation for genetic studies because it is an isolated population with extensive genealogical records spanning 11 centuries of its history (Gulcher et al. 1998).

Overview of patient/subject allocation

Papers I and II

1530 patients who had undergone a colon radiography (double contrast, barium enema) during the years between 1990 and 1996. This represents 40 percent of all Icelandic colon radiographs for this time period.

Paper III

All patients who where operated in Iceland with total hip replacement during the years 1982 to 1986. A total of 3403 hips were identified, out of which 2399 were operated on because of primary hip OA.

Paper IV

THR patients: All patients who had been operated on in Iceland with total hip replacement between the years 1972 and 1996. A total of 3887 patients were identified, out of which 2713 were operated

on because of primary hip OA.

The Icelandic genealogy database: All available Icelandic genealogy records with a total of approximately 600 000 individuals, including the entire current population of 275 000.

Control subjects: 1000 matched control groups, each of the same size as the THR patient list of 2713 individuals.

Paper V

One family with a high incidence of hip OA, including a total of 129 individuals in four generations.

Patient identification

The use of a social security number for all inhabitants available through a national census register is unique to the Nordic countries, including Iceland. The number includes information of the date of birth and gender and is used by everyone in their contact with authorities, hospitals and most private companies when identification is needed. It is readily available, is printed on ID cards and passports, and permits life-long tracing of patients including date of death. This is in contrast to the situation in most countries, where such tracing is an immense if not impossible task.

The Icelandic health care system

The health service in Iceland is primarily financed by the central government. Financing is based on taxes to 85 percent and a 15 percent fee for service.

The country is divided into health care regions, each with their own primary health care centers, some of which are run jointly with the local community hospital. The primary health care centers have the responsibility for general treatment and care, examination, home nursing as well as preventive measures such as family planning, maternity care and child health care and school health care.

Hospitals in Iceland are ranked into specialized teaching hospitals, general hospitals and community hospitals. Hospitalization is free of charge. The specialized hospitals perform most operations and procedures in all specialist medical fields.

The Icelandic health service is highly computerized and every patient is identified for all procedures by his or her social security number. All Icelandic hospitals use the ICD-10 (ICD-9) coding system.

Population examined

Patients undergoing colon radiography – All colon radiographs (double-contrast, barium enema) taken at three different radiographic departments in Iceland during the years 1990–1996 were examined. In total, radiographs from 1530 patients (877 females) were analyzed. The patients were referred for radiography at these radiographic departments from four different hospitals (community and academic), as well as from the primary health care system. Patients were from both rural and urban areas. National radiology data show that approximately 3800 colon radiographs were performed in the country during 1990–1996, and the radiograms examined in this study thus represent approximately 40 percent of all colon radiographs taken in Iceland during this 7-year period. Only radiographs from patients 35 years of age or older at the time of the colon examination were used. All patients were Icelanders.

Total hip replacement – We performed a computer-aided search of hospital records from all 6 orthopedic clinics in Iceland. This generated information on all patients who had been operated on with THR for primary OA of the hip from the time that this procedure was generally introduced in Iceland in 1972, and until and including 1996. Information on identity, sex, age at operation, diagnosis and type of prosthesis was registered. 3887 patients operated on with THR were identified. 2500 of 3887 cases were verified against the original patient records. The proportion of errors in the computer database diagnosis was less than 2 percent. Diagnoses such as fracture, rheumatoid arthritis, etc. were excluded from further analysis, and 2713 patients (1383 females) operated on with THR for hip OA were used for further analysis. A National Registry of all THR done in Iceland from the beginning of these operations in 1972 and until 1996 was thus generated. This database now serves as a starting base for the prospective registering of all THR in Iceland.

The family with hip OA – The study was initiated by the admission to hospital of a woman aged 50 with OA of the hip and scheduled for THR. At admission, she divulged that she had a strong familial history of hip OA and that, in fact, she was 1 of 17 siblings and that 11 of them had been operated on because of hip OA (Ingvarsson 1991, Ingvarsson and Lohmander 1996). Information was obtained from living members of the family of 4 generations, including any information suggesting the presence of clinical OA in these generations. Clinical and radiological evaluations, as well as blood samples were obtained from all the 17 siblings and their mother and from all family members older than 18 years. From each individual, 50 mL of venous blood was collected into EDTA-containing tubes, and DNA was extracted by conventional techniques. By using the genealogical database this family was connected to other Icelandic families with hip OA.

The Icelandic genealogical database – deCode Genetics has entered Icelandic genealogy records for the last 11 centuries into a computerized database. Approximately 600 000 of these individuals (out of the fewer than 800 000 that ever lived on Iceland) are now included in the genealogy database, including the entire current population of 275 000 and most of their ancestors back to the 9th century. Each individual is given a unique personal identifier number (PN, different from the social security number), and is in the database connected to the corresponding PNs of the father and the mother. Maternal connections in the genealogy database have been estimated to be 99.3 percent accurate by examining mitochondrial DNA sequences of maternally related individuals (Gudmundsson et al. 2000). By examining the genotypes of more than 20 000 Icelanders it has been estimated that the sum of laboratory error rate and the non-paternity rate is less than 1.5 percent.

Controls – In order to assess whether the observed differences in familial clustering of THR patients was significantly different than could be expected within the population of Iceland, we generated 1000 independently drawn, matched control sets using the national genealogy database. These control sets were used for the Minimum Founder Test and also in producing p-values and confidence intervals for the kinship coefficients and relative risks for THR patients. Each THR patient has a matched control in every control set. Thus each control set is the same size as the patient list. The matched control for each patient was drawn so that the control had the same year of birth as the patient which avoids biases due to different clustering patterns in different birth cohorts. We also made sure that the matched control had the same number of ancestors going back 5 generations in the national genealogy as did the patient. This ensures that the control lists are as 'connected' to the genealogy as the patient list.

Radiographic techniques

The most common routine examination of the hip joint consists of two standard projections, taken with the patient supine. The hip is straight for the anteroposterior (AP) projection, and then semiflexed and rotated outwards for the "frog" position view.

The double-contrast (barium enema) colon radiographs included at least two AP and several oblique exposures of the hip joint. The hip joints were assessed from an AP control colon radiograph, which is taken with the same tube-to-film distance of 100 cm that is used in a standard anteroposterior view of the pelvis. The measurements of hip joint space were done on the AP film. To be included in the investigation both hips had to be clearly visualized on an AP film. The oblique exposures were used to assess osteophytes, sclerosis, cysts and any signs of secondary OA.

Radiological classification systems

Quantitative – Minimum hip joint space (MJS) was measured on the AP film with a ruler divided in mm (Croft et al. 1990). A minimum joint space of 2.5 mm or less was used as a definition of hip OA (Croft et al. 1990, Ingvarsson et al. 1999).

Qualitative – Global joint assessment was done according to Kellgren and Lawrence as described in Atlas of standard radiographs of arthritis (Kellgren et al. 1963). Hips classified as grade 2 (definite narrowing in presence of definite osteophytes) or higher were defined as having OA.

Observer reliability

Interobserver and intraobserver reliability in assessing hip radiographs for OA was estimated by using the Kappa statistic for categorical variables and the intraclass correlation coefficent for continous variables.

Ascertainment of diagnosis of hip OA

For patients who underwent colon radiography – Hip OA was diagnosed if MJS was 2.5 mm or less, or Kellgren and Lawrence grade 2 or higher. The localization of radiographic changes was classified as lateral, medial or mixed. Hips with signs of secondary OA such as congenital dislocation or dysplasia, Perthes' disease or slipped epiphysis, were excluded. All hips with THR because of primary OA were recorded as hips with joint space of 0 mm in paper I, but excluded from analysis in paper II.

For the THR patients - The diagnosis of primary hip OA was made primarily by the operating surgeon. The diagnosis as recorded in hospital files was verified by reviewing patients records in 3 of 6 hospitals. Thus 2500 of 3887 cases were verified against the original patient records. The proportion of incorrect diagnosis was less than 2 percent. A total of 2713 cases were used for further analysis in paper IV and 2399 in paper III.

For the family with hip OA – The probands and family members answered a questionnaire about their familial and medical history and symptoms and signs of OA in hips and other joints. They were also examined by one of the authors (TI). Their height and weight was recorded. OA of the hip was classified as: (a) absent, (b) symptoms (presence of symptoms consistent with hip OA, such as hip or groin pain when moving or at night, etc.), (c) radiological (see below), or (d) total hip replacement (THR) associated with hip OA (based on clinical and radiological signs of OA leading to THR) (paper V).

Radiographs of hips, knees, hands and spine of family members were analyzed. Diagnosis of hip OA was made if MJS was ≤ 2.5 mm. Diagnosis of OA in other joints was made by Kellgren and Lawrence classification with grade 2 or higher regarded as OA.

Assessment of inheritance – statistical methods

Familial clustering of THR for OA – Familial clusters were generated by combining information in the genealogy database with the patient list of 2713 patients with THR for OA, and the control lists, respectively. Familial clusters at several different meiotic distances (see Figure 4) were thus constructed both for the THR patient list and the control lists. A cluster at a given meiotic distance, e.g. four, was constructed as follows. One individual was selected at random from the list. All individuals that were on the list and were related to this individual at a meiotic distance of four or less were then added to the cluster. The process was repeated for all individuals thus added to the cluster by identifying all individuals in the list that were related to them at a meiotic distance of four or less and they were added to the same cluster. When no more individuals were found in the genealogy database that connected at four meioses, the cluster was closed and the next cluster created by picking at random an individual that was not in the first cluster and reiterating the process. Finally, the size of the clusters obtained for the patient list were compared to the mean size of the clusters obtained for the control lists.

Minimum Founder Test – The Minimum Founder Test (MFT) was constructed at deCode to make a use of the genealogical database for inheritance tests (Gudmundsson et al. 2000). In the present study the MFT was used to test whether the individuals on the list of patients with THR for OA were more closely related than the individuals on the control lists, which would indicate a heritable component of THR for OA (Gudmundsson et al. 2000). The extensive genealogical information in the database was used to find all ancestors of the individuals on the patient and control lists. Reaching a given number of generations back we identified the minimum set of ancestors (founders) such that everybody on the list was a descendant of one of these founders. The more related the people on a list were, the fewer founders were needed to account for all individuals on the list. To generate complete data for a given list of individuals, the genealogy database was used to go back to a certain year and find the minimum

number of founders, born in that year or later, for the relevant list. This was done for a number of years, both for the patient list and the control lists.

Kinship coefficient – The kinship coefficient (KC) is a measure of the relationship of two relatives. It is defined as the probability that a randomly selected allele from each of a pair of individuals is inherited from a common ancestor, i.e. that the alleles are identical by descent (IBD) (Lange 1997). For any pair of relatives the KC is approximately one half of the expected proportion of their genome shared due to common ancestry. In the case of no consanguinity the KC is 1/4 for first degree relatives, 1/8 for second degree relatives, 1/16 for third degree relatives, etc. For the present study, the pairwise KC distribution for the patient list was calculated by calculating the KC of every possible pair of patients and generating the average THR for OA patient KC (Gudmundsson et al. 2000). The result was compared to the distribution of the average pairwise KC for the 1000 matched control lists.

Relative risk – The relative risk for siblings of affected individuals is equal to the risk of THR for OA in siblings, divided by the risk of THR for OA in the general population. Relative risk can be calculated for different types of relatives, e.g. siblings, cousins or spouses. Since THR for OA is not common among young people we restricted our calculations to individuals born in the period between 1900 and 1935 both when calculating the population risk and the risk in the relatives. We did not need to rely on a control group to estimate the population risk since we used a population based list of THR OA patients and know the total number of individuals in the population born in the period.

Gender difference – To assess the presence of a possible gender difference in the inheritance of OA associated with THR the patient list was divided according to sex. For both lists 1000 matched control lists were generated, matched for gender as well as for age and ancestral connections in the genealogy database. The average pairwise KC was calculated and the MFT applied on both lists.

Population statistics

Population statistics were obtained from Statistics Iceland (http://www.hagstofan.is) and Statistics Sweden (http://www.scb.se), respectively.

Genome-wide scan

Genotyping – DNA was extracted from pelleted nuclei of peripheral blood and purified using organic extractions. The DNA samples were genotyped using approximately 900 fluorescent labeled primers. We have developed a microsatellite screening set based in part on the ABI Linkage Marker (v2) screening set and the ABI Linkage Marker (v2) intercalating set in combination with 500 custom made markers. All markers were extensively tested for robustness, ease of scoring, and efficiency in 4X multiplex PCR reactions. In our framework marker set the average spacing between markers was approximately 4 cM with no gaps larger than 10 cM. PCR amplifications were set up, run and pooled on Perkin Elmer/Applied Biosystems 877 Integrated Catalyst Thermocyclers with a similar protocol for each marker. The reaction volume used was 5 mL and for each PCR reaction 20 ng of genomic DNA was amplified in the presence of 2 pmol of each primer, 0.25 U AmpliTaq Gold, 0.2 mM dNTPs and 2.5 mM $MgCl_2$ (buffer was supplied by manufacturer). The PCR conditions used were 95 °C for 10 minutes, then 37 cycles of 15 s at 94 °C, 30s at 55 °C and 1 min at 72 °C. The PCR products were supplemented with the internal size standard and the pools were separated and detected on Applied Biosystems model 377 Sequencer using Genescan v3.0 peak calling software. Alleles were called automatically with the TrueAllele program (Cybergenetics, Pittsburg, PA (http://www.cybgen.com)), and the program, DecodeGT, was used to fractionate according to quality and edit the called genotypes (Palsson et al. 1999). This process results in greater than 99.5% accuracy. 180 Icelandic controls were genotyped to derive allelic frequencies. The marker orders were originally obtained from the publicly available genetic map at the Marshfield Medical Clinic web site (http://www.marshmed.org).

Linkage analysis – All analyses presented were

performed using the program Allegro (Gudbjartsson et al. 2000), a linkage program developed at deCode Genetics and available free for non-commercial use by sending e-mail to allegro@decode.is. Allegro is faster than the program Genehunter (Kruglyak et al. 1996). All allele sharing LOD scores presented are multipoint and are computed using the exponential model (Kong et al. 1997). The reported P values associated with the LOD scores are computed by comparing the observed lod scores to their complete data distributions. The complete data distribution of a LOD score is computed under the assumptions of no linkage and that the sharing information is complete.

Ethics

All studies were approved by the Bioethics Committee of the Icelandic Health Ministry and the Data Protection Commission of Iceland. All patients in family who participated in the DNA research had signed a written informed consent as requested of the Bioethics Committee of the Icelandic Health Ministry and the Data Protection Commission of Iceland.

Data encryption and protection of the individual

All patient lists used at deCode Genetics are encrypted by the Data Protection Commission of Iceland, before arriving at the laboratory (for details, see website at http://www.decode.is/ppt/protection/index.htm). Encrypted versions of the databases were used to examine the familial relationships in this study.

Summary of papers I-V

Paper I: Prevalence of hip osteoarthritis in Iceland

Objectives – To assess the prevalence of primary hip OA in Iceland and to compare with published rates of primary hip OA for related Scandinavian populations.

Methods – Radiograms were examined of 1530 Icelandic individuals 35 years or older subjected to colon radiography during the years 1990–1996, representing approximately 40 percent of all colon radiographs taken in Iceland during this period. After exclusion of non-primary hip OA cases, the minimum hip joint space was measured with a mm ruler. Presence of hip OA was defined as a minimum joint space of 2.5 mm or less on an AP radiograph. Intra-class correlation coefficients for inter- and intra-observer variability of assessment of mm joint space were 0.91 and 0.95, respectively.

Results – Of the 1517 individuals included, 227 hips in 165 patients (88 women) were diagnosed as having radiologic primary hip OA. The mean age at colon examination for these patients was 68 (35–89) years. The overall prevalence of hip OA among all examined individuals 35 years and older was 10.8 percent (12 percent for men, 10 percent for women), rising from 2 percent at 35–39 years to 35.4 percent for those 85 years or older. If the population structure (age and sex distribution) for those older than 35 years in Iceland was used to standardize prevalence for both Iceland and South Sweden (using previously published data for South Sweden), the age- and sex-standardized prevalence of hip OA for those older than 35 years in Iceland was 8 percent, compared to 1.2 percent for South Sweden.

Conclusions – The prevalence of radiologic primary hip OA is high in Iceland, and in excess of 5-fold higher than the prevalence found by using similar techniques in studies on related populations in Southern Scandinavia. The rate difference is particularly notable for those younger than 70 years.

Paper II: Assessment of primary hip osteoarthritis. A comparison of radiographic methods using colon radiographs

Objective – In paper I a large difference was found in the prevalence of hip OA between the Icelandic and Swedish populations. The objective of paper II was to determine the influence of different methods of assessing colon radiographs on the prevalence rates of hip OA.

Methods – All colon radiographs from patients 35 years of age or older, taken at three different radiographic departments in Iceland during the years 1990–1996 were examined. 3002 hips in 638 males and 863 females were analyzed. Intra- and interobserver reliability was assessed by measuring 147 randomly selected radiographs (294 hips) twice by the same observer, and 87 and 98 (174 and 196 hips) randomly selected radiographs by two additional independent observers. Minimum hip joint space was measured with a mm ruler, and global assessment of radiological features by a published atlas (Kellgren et al. 1963).

Results – With a minimum joint space of 2.5 mm or less as definition for OA, 212 hips were defined as having OA. Using the global Kellgren and Lawrence assessment with grade 2 (definite narrowing in the presence of definite osteophytes) or higher as definition for OA, 202 hips were found to have OA. However, only 166 hips were diagnosed as having OA by both systems. With 2.0 or 3.0 mm minimum joint space as cut-off, the difference between the two methods increased. Both intra- and interrater reliability was significantly higher with joint space measurement than with global assessment.

Conclusions – Overall prevalence of radiological OA was similar with the two methods. However, the quantitative measurement of minimum hip joint space had a better within- and between observer reliability than qualitative global assessment of radiographic features of hip OA. We thus suggest that minimum joint space measurement is

a preferable method in epidemiological studies of radiological hip OA.

Paper III: Incidence of total hip replacement for primary osteoarthrosis in Iceland 1982–1996

Objective – To assess the incidence of THR in different age groups in Iceland for the years 1982 - 1996, to compare the Icelandic incidence with the incidence in the other Nordic countries and to estimate future demand for this procedure in Iceland.

Methods – Through a computer-aided search of hospital records we obtained information from all 6 orthopedic clinics in Iceland that performed THR during the period 1982 to 1996. Population data from Statistics Iceland and Statistics Sweden were used to age standardize the data and to calculate the future demand for THR in Iceland by taking in to account the expected changes in the population.

Results – During this time period 2399 total hip replacements were done because of primary OA. The annual number of procedures increased from 77 hips in 1982 to 221 hips in 1996. For the years 1992–1996 the overall incidence of THR in Iceland was 77/100 000/year due to primary OA. During the same time period the corresponding incidence in Sweden was 80/100 000. Thus, based on overall incidence rates, not adjusted for age, there would appear to be no difference between Sweden and Iceland. However, the incidence of THR for Sweden in 1992–1996 in the population over 49 years of age was 209/100 000, while the corresponding incidence in Iceland for the same age group and time period was 319/100 000. For the population over 59 years of age the THR incidence for primary OA in Sweden was 287/100 000, and for Iceland 488/100 000 in this time period. This illustrated the importance of using age adjusted incidence rates when making comparisons between populations. In order to make useful comparisons of 'true' rates of THR, we need to correct for differences in the population structure.

Conclusion – By using age standardized data and correction for differences in population structures between Iceland and Sweden we find that the incidence of total hip replacement for primary OA of the hip is at least 50 percent higher in Iceland than in Sweden. This difference is consistent with an observed higher prevalence for hip OA in Iceland, compared to Sweden. The future demand for THR for primary OA in Iceland was estimated to rise from 221 in 1996 to 300 in the year 2015.

Paper IV: The inheritance of hip osteoarthritis in Iceland

Objective – To assess, in a population-wide study in Iceland, the genetic contribution to hip OA leading to THR.

Materials and methods – Information from two population-based databases in Iceland were combined: A national registry of THR between 1972 and 1996, and a genealogy database containing information from all available Icelandic genealogy records for the last 11 centuries. Genetic contribution to THR for OA was assessed by: (a) identifying familial clusters of THR for OA patients, (b) calculating an average pairwise kinship coefficient (KC) for the patient list and 1000 control lists, (c) estimating the relative risk (RR) for relatives of patients with THR for OA and comparing with control lists, (d) applying the Minimum Founder Test (MFT) to estimate the minimum number of ancestors to account for all 2713 patients with THR for OA, compared to the average number of founders for control lists. 1000 matched control lists were created using the genealogy database. Each was of the same size as the patient list.

Results – A large number of familial clusters of patients with THR for OA were identified. MFT showed that OA patients descended from fewer founders than the control groups ($p < 0.001$). The average pairwise KC among patients with OA was greater than in the population ($p < 0.001$). RR for siblings of OA patients was 3.05 (2.52, 3.10).

Conclusions – This population-based study shows that Icelandic patients with hip replacement for OA are significantly more related to each other than are matched controls drawn from the Icelandic population. These findings support a significant genetic contribution to a common form of OA and encourages the search for genes conferring an increased susceptibility to OA.

Paper V: A large Icelandic family with osteoarthritis of the hip associated with a susceptibility locus on chromosome 16p

Objective – To describe a large kinship with inherited hip OA and the identification of a susceptibility locus for hip OA leading to THR.

Patients and methods – Four generations of a kinship (129 individuals) with heritability for hip OA were identified and characterized by family history and clinical, radiographic and histopathological examination. For the genome-wide search of a susceptibility locus, OA cases were defined as having had THR with the clinical and radiological diagnosis of hip OA. A genome wide scan was performed on woman 489 and her affected descendants using framework map of microsatellite markers with an average spacing of 4 cM between markers. The data were analyzed using affecteds only, multipoint non-parametric/allele sharing methods. The computations were performed using Allegro.

Results – 20 individuals from the family had a THR or osteotomy because of hip OA at an average age of 53 (42–67). OA of hands, spine and knee were not uncommon, although not leading to disability. The hip OA of this family was indistinguishable from that of idiopathic, non-familial hip OA. There was no apparent evidence of spondyloepiphyseal or other dysplasias usually associated with mutations in collagen genes. The genome-wide scan identified a susceptibility locus for hip OA leading to THR on chromosome 16p with the lodscore 2.58 (p-value of 1.6×10^{-4}).

Conclusions – We have identified the largest kinship with heritable hip OA described so far. This appears to be the first instance where two groups independently have identified a similar or identical locus related to a common form of OA in different populations.

Discussion

The prevalence of hip OA and THR is high in Iceland

Hip OA prevalence – The prevalence of hip OA as assessed by colon radiographs is high in Iceland compared with Southern Sweden and Denmark (Paper I) (Figure 2).

Overall OA prevalence rates published from Southern Scandinavia and Denmark have not been corrected for differences in distribution of age or sex between the groups studied and the populations from which these groups were drawn. If we are to make relevant comparisons between different populations, such differences between populations must be accounted for. If we thus use the population statistics (age and sex distribution) for Iceland in the relevant time period to standardize *both* the Icelandic and the Swedish prevalence, we find a more than 5-fold higher age- and sex-standardized prevalence rate of hip OA for those older than 35 years in Iceland, compared to the rate in Malmö, Sweden (Figure 2). This illustrates the importance of using detailed age- and sex-related prevalence data, as well as the importance of taking differences in population structure into consideration when comparing prevalence rates between different countries.

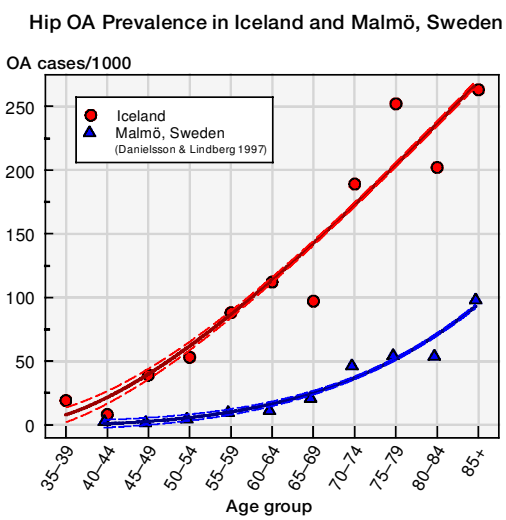

Figure 2. Hip OA prevalence in relation to age in Iceland (●) and Malmö, Sweden (▲), assessed from colon radiographs. Data points represent observed values, lines represent predicted curve fits with r^2 greater than 0.9, broken lines represent 95 % confidence intervals for predicted curves. Data for Malmö, Sweden from Danielsson et al. 1997. Reproduced with permission from Annals of the Rheumatic Diseases.

We defined radiologic hip OA as a joint space of 2.5 mm or less, in agreement with previous suggestions that a measurement of the MJS with a ruler is a simple, reproducible way to estimate prevalence of radiological OA of the hip well suited for epidemiological studies (Croft et al. 1990, Nevitt 1996).

The criteria for hip OA used in the studies of the related Scandinavian populations in both Southern Sweden and Denmark, while also using colon radiographs, were less stringent than those used in the present study of the Icelandic population. Had we used the same joint space width as used for the studies in Southern Sweden (or Denmark), the estimated overall prevalence of hip OA in Iceland would be considerably higher, 25.7 percent (23 percent) instead of 10.8 percent for those 35 years and older. Had we, similar to the Malmö investigations, included those cases where there was a difference of 1 mm or more in joint space between the two hips, the number of cases in our material classified as having hip OA would have increased from 165 to 300 (or from 227 hips to 362 hips). Detailed comparisons with the published South Scandinavian data are, however, handicapped by the absence of information on JS distribution or how many patients were diagnosed with hip OA based on a more than 1 mm difference in JS.

The prevalence rates for radiologic hip OA for English males aged 65–70 as reported by Croft and coworkers are, in contrast to the South Scandinavian rates, comparable to the rates for Iceland (Croft et al. 1990). Further investigations using population statistics and standardized criteria for ascertainment of radiological hip OA will be

needed to confirm whether the English and Icelandic rates are similarly high or not, in comparison with Southern Scandinavia. It is in this context of interest to take note of recent suggestions, based on the analysis of mitochondrial DNA, that Scandinavian and British populations could have contributed the majority of the Icelandic mtDNA (i.e. female) lineages (Helgason et al. 2000).

The use of varying criteria for defining hip OA in epidemiological studies generates considerable and further uncertainty when attempting to compare studies and populations. Undoubtedly, the use of patient symptom reports, clinical examination by a health professional, and radiological examination will yield different outcomes when used singly or in different combinations. A golden standard that could be used in large population-based studies remains to be agreed upon.

Several population-based studies, including the present one in paper I, have been based on the use of the assessment of colon radiographs or intravenous urograms where the hip is visualized.

The risk factors associated with primary hip OA are not well defined (Felson 1998). Some investigations have associated an increased risk of hip OA with heavy labor such as farm work (Axmacher et al. 1993), and with sports (Lindberg et al. 1993). It is notable that the higher rate of hip OA observed for the Swedish island of Gotland, as compared to that for Malmö city, Sweden, was entirely due to a higher prevalence among the rural, farming, population on the island (Forsberg et al. 1992). A higher risk for primary hip OA associated with farming was, however, only observed for males, not for females (Lindberg et al. 1988). For Iceland, we found a greatly increased prevalence of primary hip OA in both Icelandic men and women. This would perhaps suggest that physical work load is not the main reason for the high Icelandic prevalence, unless there was, in the relevant time period, a significant difference in this risk factor between rural women in Iceland and Southern Scandinavia, which seems unlikely since only some 4 percent of the Icelandic population are farmers (Statistics Iceland). The Icelandic population studied was both rural and urban. The observation that the 'excess' of cases in Iceland was greater at younger than at older age, would perhaps also speak against a heavier physical work load being a major causative factor.

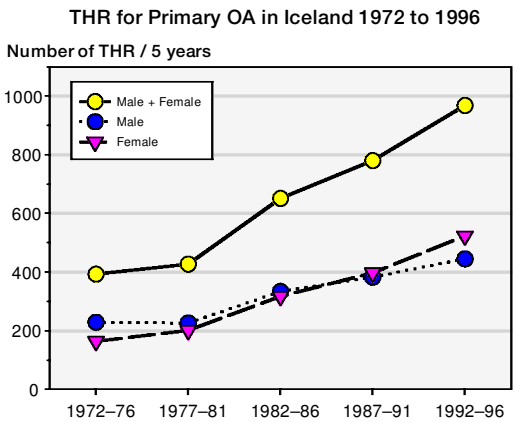

Figure 3. Icelandic incidence of THR by five year periods in Iceland from 1972-1996.

In the apparent absence of obvious differences in other risk factors between the populations compared here, these results suggest that it may be of interest to screen the Icelandic population for hereditary factors which could be associated with the development of hip OA.

Incidence of THR – The clinical end point of hip OA is destructive and wasting for the patient because of pain and disability. When the noninvasive treatment fails the only treatment option is operation and a total hip replacement. THR was introduced in Iceland in 1967, and during the first years only one surgeon performed this type of surgery. The first orthopedic ward opened in 1972. The annual number of THR has been rising steadily and demand does not yet appear to be met (Figure 3). The majority of the interventions are done in the age class between 70 and 79 years old (Figure 4).

In Paper III the incidence of THR in Iceland was assessed for the years 1982–1996 and compared to Nordic countries. Such comparisons between regions and countries are often more complex than first appreciated, because of differences in demographics and reporting, and changes with time. Most studies on the incidence of total hip replacements have reported overall incidence, often without precisely specifying how the overall incidence was calculated, and not accounting for dif-

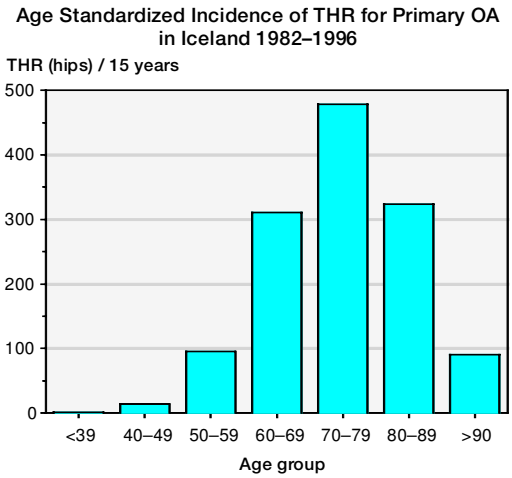

Figure 4. Incidence for THR in Iceland by age classes 1982–1996.

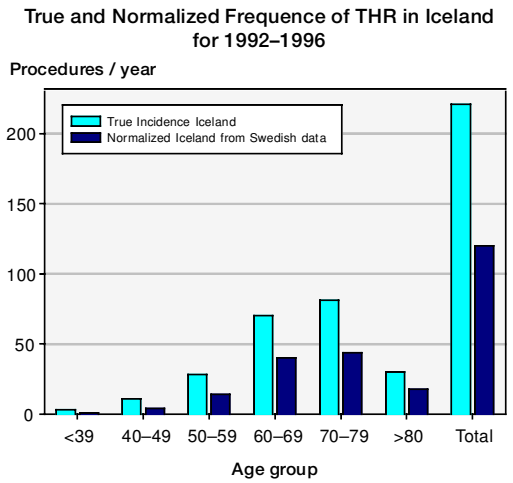

Figure 6. Age standardized frequencies of THR for primary hip OA in Iceland 1992–1996, compared with Icelandic rates normalized to the Swedish population structure. Reproduced with permission from Acta Orthopaedica Scandinavica.

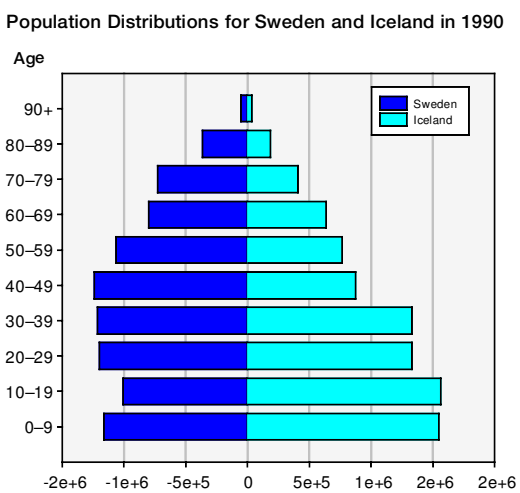

Figure 5. Population distributions for Iceland and Sweden in 1990. The Icelandic population is younger than the Swedish.

ferences in age distribution between the patients and the population, and without specifying the underlying diagnosis, when making comparisons with other reports. The incidence rates of THR for primary hip OA have been reported to differ between different populations and ethnic groups. Thus, the overall incidence of total hip replacements varies in different reports between 45 and 140/100 000/year (Table 3).

The comparison between Iceland and South Sweden revealed that after correction for the differences in population structure (Figure 5), the THR for OA incidence was at least 50 percent higher in Iceland (Figure 6).

The reasons for this difference in THR rates are not obvious. Indications for THR should be similar in Iceland compared to Sweden and Norway since almost all Icelandic orthopedic surgeons are trained there and the health system are highly similar. The waiting lists are suggested to be similar during this time period (3–6 months at local hospitals, 6–18 months at academic centers) (Goldie 1991). However, the prevalence of hip OA is known to be much higher in Iceland than in other Nordic countries, which could explain at least part of the difference in THR incidence.

The future demand for THR for primary OA in Iceland can be estimated from the age standardized figures (Figure 6), taking into account the expected increase in the Icelandic population (Statistics Iceland). The estimated calculated annual need of THR procedures for primary OA will thus rise from 221 in 1996, to 250 in the year 2005, and to 300 in the year 2015. The need for revision surgery may also be expected to rise, but since no implant survival data are available for THR in Iceland, no precise estimates can be made. Since these estimates do not take into account a possible

further increase in incidence of THR in Iceland (Figure 3), they should be regarded as minimum estimates.

The choice of radiologic definition of hip OA makes a difference

Epidemiological studies of hip OA using radiological criteria have rarely agreed on the case definition, making it difficult to assess differences among studies of different populations, or to understand the contribution of different risk factors to those variations. Several studies have used (or discussed) minimum joint space width as the single variable for definition of hip OA, with a cut-off for case definition varying between 1.5 and 4 mm (Danielsson 1966, Jörring 1980, Danielsson et al. 1984, Forsberg et al. 1992, Lindberg et al. 1993, Nevitt 1996, Danielsson et al. 1997). Some investigators have arbitrarily defined hip joint space narrowing (hip OA) as a joint space less than 4 mm in persons aged 70 years or less, or less than 3 mm in persons older than 70 years and/or the presence of structural changes such as subchondral bone sclerosis or cyst formation (Danielsson 1966, Danielsson et al. 1984, Lindberg et al. 1993, Danielsson et al. 1997). In addition, a side-to-side difference of more than 1 mm was classified as hip OA by these investigators. Other Scandinavian investigators have used cut-off values, independent of age, of 2 mm or less (Forsberg et al. 1992), or 3 mm or less (Jörring 1980).

Previous studies have reported a normal joint space between 3 and 5 mm (Köhler 1956, Armbuster et al. 1978, Fredensborg et al. 1978, Buckland-Wright 1994, Buckland-Wright 1998). The mean minimal joint space in the present material was 4.0 mm (SD 0.68 mm), similar to other studies. It decreased slightly with age, and was 0.3 mm less in women than in men in all age groups. We chose to use the same joint space width cut-off as OA criterion for all age groups and both sexes. Hip radiographs used in OA epidemiology studies have regularly been non-weight bearing (whether using hip or colon radiograms), although recent investigations have suggested that weight-bearing radiographs might be preferable in examination of hip OA (Conrozier et al. 1997, Buckland-Wright 1998).

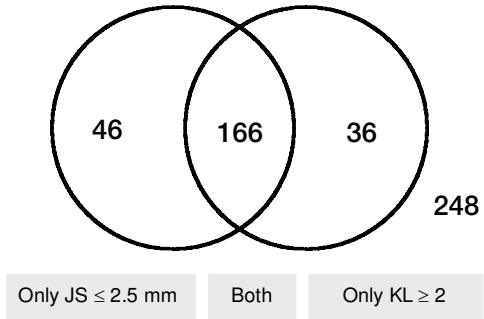

Figure 7. Agreement between two methods for assessment of radiological hip OA. Definition for radiological hip OA: joint space 2.5 mm or less. *Left circle*: number of hips graded as having OA *only* with quantitative measurement of joint space. *Right circle*: number of hips graded as having OA *only* with qualitative assessment of radiological features by atlas (definite joint space narrowing in the presence of definite osteophytes). *Overlapping circles*: number of hips graded as having OA by *both* methods. *Number outside circles*: sum of number of hips assessed as having OA by *any* of the two methods. Reproduced with permission from Annals of the Rheumatic Diseases.

Several reasons contributed to the choice of minimal joint space as the feature by which to define OA in our study: (1) the MJS was previously shown to be reproducible and easy to use, and (2) the method was previously used in studies of hip OA in related populations providing the opportunity for comparisons. The present study (Paper II) confirmed the better within- and between-investigator reproducibility of joint space measurement as compared to the K&L global grading. The two methods yielded an almost equal prevalence of OA, but only 166 of 248 hips were defined as having OA by both methods (Figure 7). A change of JS cut-off for OA further decreased the level of agreement between the two methods (Table 4).

It would thus appear possible that these methods of assessment primarily recognize two separate phenotypes of hip OA, one mainly characterized by decreasing joint space, and another by osteophytes. Interestingly, several reports have suggested that VDR gene polymorphisms are associated with 'osteophytic' knee OA (Uitterlinden et al. 1997, Keen et al. 1997). It was subsequently proposed that both the COL2A1 gene and the adjacent VDR gene on chromosome 12 are associated with radiological knee OA. However, the VDR genotype was associated specifically with

Table 4. A comparison of findings (number of hips) using quantitative measurement of minimum joint space and the Kellgren and Lawrence qualitative global assessment. The horizontal and vertical lines the denote cut-off for definition of hip OA in the two assessment systems

Minimum joint space (mm)	Kellgren and Lawrence grade					Total number of hips
	0	I	II	III	IV	
0	0	0	8	30	17	55
0.5	0	0	0	3	0	3
1	0	0	11	16	1	28
1.5	0	1	11	2	0	14
2	1	8	31	12	0	52
2.5	7	29	21	3	0	60
3	323	127	16	2	0	468
3.5	252	22	2	0	0	276
4	1275	91	12	1	0	1379
4.5	134	10	0	0	0	144
5	486	9	2	0	0	497
5.5	3	0	0	0	0	3
6	17	1	1	0	0	19
7	4	0	0	0	0	4
Total	2502	298	115	69	18	3002

osteophytes, while the COL2A1 genotype was associated with joint space narrowing (Uitterlinden et al. 2000).

Choosing the population

Colon radiographs were chosen to estimate the population prevalence of hip OA in Iceland. The AP pelvic view has been used in several previous epidemiological surveys of hip OA (Danielson 1966, Jörring 1980, Danielsson et al. 1984, Forsberg et al. 1992, Lindberg et al. 1993, Danielsson & Lindberg 1997). The similarities of the health care systems and specialty training (http://www.stjr) in Sweden and Iceland would suggest that the indications for colon radiography are similar in the two countries. The colon examinations used in paper II were undertaken during the years 1990–1996, in which period the population of Iceland was about 250 000, comparable in size to the population of Malmö city, Sweden, that has provided the basis for a series of studies on hip OA prevalence, using a technique similar to that used in the present investigation.

The colon radiographs examined represent approximately 40 percent of those performed in the country of Iceland during this time period. Subjects were recruited from both rural and urban areas, and from both academic centers and primary care. There was no difference in the prevalence of hip OA between the three different radiological departments studied. Age and sex data for some 3000 (out of a total of 3800) of all individuals examined by colon radiography in this time period was available, and the age and sex distribution for the 3000 individuals was similar to that of the 1517 individuals examined in this study. This suggests that the subjects studied here are representative for the Icelandic population 'at risk' in this time period.

Hip OA is an inherited disease

Until recently, most reports on inherited OA focused on rarities, such as small families with precocious OA. The exception was generalized OA, described for almost 40 years ago (Kellgren et al. 1963). Although the inheritance of hip OA has not been well recognized in the medical community, the common Icelandic patient has been well aware this disease is inherited. The common statement "it is in the family" describes this well. Many of the patients can even recount this disease in three or more generations of their family. Our Icelandic sagas and genealogy records are rich in history and description of diseases, including descriptions of people who most likely have suffered from secondary OA such as Perthes', acetabular dysplasia, etc. The names such as "limping Jón" or "Sigurd the crooked" are suggestive of such conditions. The long-standing knowledge of the Icelandic hip OA patient is now increasingly being corroborated by recent investigators showing evidence on the inheritance of hip OA both as a isolated disease and in combination with OA in other joints (Chitnavis et al 1997, Loughlin et al 1999).

The availability of a genealogical database comprising the entire Icelandic population and dating back to the settlement, combined with a national registry for THR, provided us with the opportunity to study the genetic contribution of hip OA associated with THR (Paper IV). The use of a complete population-based patient registry eliminated possible bias in the data collection such as

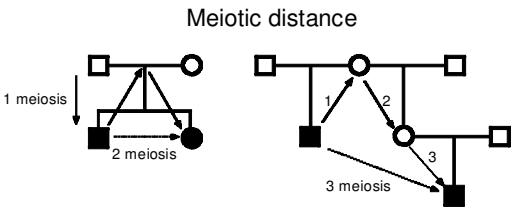

Figure 8. Schematic representation of meiotic distances in pedigrees.

oversampling of familial material as opposed to sporadic cases and problems in proband identification. The universal access health care system provided in Iceland further minimized possible phenotypic differences associated with differences in socioeconomic status. Indications for THR for OA is similar in all orthopedic centers in Iceland and the radiological characteristics of the hip OA leading to THR and studied here is similar to that reported in other investigations (Danielsson et al. 1984, Ledingham et al. 1992).

A broad range of algorithms was applied to make the best use of these databases, including algorithms that allowed us to identify, for each person on a list, all relatives of a specific type, e.g. siblings or cousins. Recursive pedigree algorithms were also used which identified, for each person on a list, all ancestors within a given number of generations back. Having identified the ancestors we were then able to search for ancestors common to any two or more members of the THR patients list and thereby create clusters of related individuals and ancestral pedigrees of individuals related to the same founder. It should be noted that the clusters can also grow laterally through marriage.

This combined use of the databases enabled the identification of the largest family clusters of patients with total joint replacement for hip OA described to date. The largest cluster was a family of 190 patients with THR at meiotic distance of 5. At 5 meioses distance (Figure 8), only 1 out of 1000 control lists had more individuals in clusters than the patient list. The clustering of patients in pedigrees which extend beyond the nuclear family suggests that the pathogenesis of OA has a familial component. Our results extend previous reports that THR due to OA is influenced by genetic or hereditary factors (Chitnavis et al. 1997).

The methods used here represent an entirely new approach to (1) identify families belonging to a specific phenotype, and (2) demonstrate the familial clustering of hip OA. The familial clustering of hip OA is a marker of the heritability of the disease. In the future it will be possible through this approach to study how other forms of OA run in families. The cluster function is based on the genealogical database and with time better and better information will be added. An example of a pedigree identified through this computerized search in the combined national THR and genealogy databases is shown in Figure 9.

A significant genetic component in hip OA leading to THR was further supported by the examination of familial relationships by application of three different statistical methods.

The newly developed minimum founder test (MFT) provided a way to examine the relationship among THR patients by calculating the minimum number of ancestors needed to account for all individuals with THR. As the calculations go back

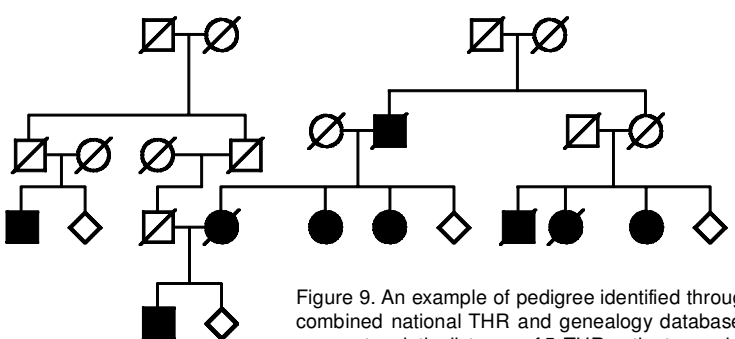

Figure 9. An example of pedigree identified through the computerized search in the combined national THR and genealogy databases. This pedigree contains 9 THR cases at meiotic distance of 5. THR patients are denoted by the filled symbols, males with square symbols, females with round symbols. Symbols with diagonal slash for deceased. Diamond symbol for unknowns.

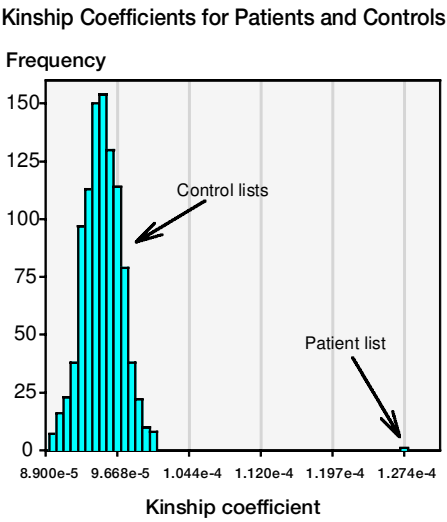

Figure 10. Kinship coefficient distribution for the 1000 control lists (histogram in left part of graph) compared with the kinship coefficient value for the complete 1972–1996 list of 2713 patients with THR due to OA (small bar at far right).

in time more and more connections are found among the individuals and the number of ancestors (founders) decreases. A comparison was made with 1000 matched control lists. The greatest difference between THR patients and controls was seen in the year 1860 where the number of founders for the THR patient lists diverged 11.7 standard deviation units from the mean of the control lists, providing further support for hip OA being an inherited disease.

Calculation of the kinship coefficient (KC) was done to compare the degree of IBD (identity by descent) sharing within the patient and control lists, respectively, and again showed a significantly greater familial element for THR for OA patients than for controls (Figure 10).

Lastly, a more conventional measure of relatedness was used by calculating the overall risk of having a THR operation for OA. The time interval between 1900 and 1935 was chosen because it is representative for patients who have been operated on with THR, and the overall risk was 2.7 percent. For individuals born between 1915–1920 it was even higher, or 4 percent. Siblings of affected individuals had a RR of 3.05 for THR for OA, considerably higher than a previously reported RR of 1.86 (Chitnavis et al. 1997). It remains to be shown if this difference is due to hip OA being more strongly inherited in Iceland than in England or if it is due to the power of a population based study with a genealogical data base.

To determine genetic factors in multifactorial disease, controls used in sibling studies should ideally resemble siblings with respect to environmental risk factors but differ from them in regard to possible genetic determinants. Furthermore, they should be representative of the general population in terms of their susceptibility to disease. Spouses of patients fulfill both these criteria by their longstanding proximity to the patient and have previously been used as controls in family studies (Chitnavis et al. 1997). In the present study, cousins of affected showed a modest but significant increase of the risk of THR, while spouses did not show a significant risk increase. This would argue against a marked influence of shared environment, although the contribution of 'family-related' environmental factors was not specifically addressed in this study.

Genes and OA

The studies of family resemblance in hip OA have relied on number of phenotypes for OA, including include rarities as SED, Stickler syndrome, etc. At least 40 mutations at different sites are known in the COL2A1 gene, leading to very different phenotypes, from hip OA to crippling disease with short stature and OA in multiple joints. These mutations are of considerable scientific interest, but there is yet little evidence that common forms of OA are due to mutations in type II collagen. The OA families so far identified are extremely rare and commonly associated with mild chondrodysplasia. Further screenings of families with generalized OA showed that only some 2 percent of them had a mutation in the COL2A1 gene, suggesting that only a small proportion of OA can be explained by this genetic variation. The nature of the genetic influence in OA thus remains speculative.

Is hip OA subject to major gene effects?

Given that genetic factors may play a major role in the etiology of hip OA, the question arises whether these influences are exerted by one or a few

"major genes" each with a relatively large effect, such as the COL2A1 gene, or by a large number of "polygenes", each with a relatively minor effect. Presumably, in the monogenic form of OA the genes would be easier to identify and could have greater relevance to public health. Complex segregation analysis can be used to study the mode of inheritance of a trait and in particular to infer whether the distribution of the trait within pedigrees is compatible with the action of a major gene. This was done by Felson and co-workers in 1998, concluding that in generalized OA (in this study hand and knee OA) there was evidence to support a significant genetic contribution, with evidence for a major recessive gene and a multifactorial component, representing either polygenic or environmental factors. However, the evidence is not yet conclusive that "common OA such as hip OA" is influenced by major genes (Loughlin et al. 1999). On the contrary, several susceptible loci for hip OA have been suggested and each and one of them are thought to include a possible gene for hip OA. This could support the notion that the inherited hip OA is a polygenic disease.

Defining the phenotype for genetic studies of hip OA

Because the statistical power of a genetic study depends in part on the number of relative pairs analyzed it is important to correctly define the phenotype. In both the inheritance study (Paper IV) and the linkage study (Paper V) THR for OA was defined as the phenotype. THR for OA represents end-stage OA disease and may be regarded as a surrogate for the diagnosis of hip OA by other means. The use of the THR for OA phenotype importantly made it possible to generate a population-based patient list. However, it is clear that this phenotype criterion encompasses only a fraction of all patients with hip OA (by whatever criterion). The relationship between the THR for OA phenotype and other hip OA phenotypes is not well established. A further restriction induced by the use of the THR for OA phenotype is that the average THR patient is about 70 years old at surgery. This limits the number of parents of THR patients available for sampling, and also the potential number of children of THR patients who also fulfill the case definition of having THR for OA, thus decreasing the possibility to build pairs and multigenerational relationships of affecteds.

It remains to be seen whether the enhanced statistical power obtained by using surrogate phenotypes that can be more rapidly applied to relatively large samples outweighs the loss of information resulting from their less than perfect correlation with more definitive phenotypes. Alternative, definitive, phenotype definitions are greatly needed for future studies.

The hip OA family

We identified a large family with an inherited disease of the hip that is indistinguishable from nonfamilial primary hip OA by symptoms, radiographs and by histopathological examination of the joint (Paper V). Extensive radiographic examination of many family members failed to show any evidence for epiphyseal dysplasia (SED or MED). The disease spans at least 5 generations. One branch of the family consists of 17 siblings, out of which 11 have hip OA treated with THR. The onset of symptoms often occurs between ages 25 and 35, and the members of the family are operated on with THR at an age that, on average, is younger than the average hip OA patient in Iceland. This family appears to be the largest described with familial OA.

The study of candidate genes for OA

A candidate gene is defined as a gene whose protein product, based on its biological activity, can plausibly be assumed to influence the disease (phenotype) under consideration. The candidate gene can be directly screened for mutations in the affected family or individuals. The main problem with this approach is that the number of these proteins is already large and as more is learned about cartilage and bone biology the list of potential candidate genes keeps growing. The chances of a "lucky hit" would seem to be remote and indeed studies of candidate genes have been disappointing, with the exception of some of the chondrodysplasia families. A list of some potential candidate genes in OA is shown in Table V.

Table 5. Examples of candidate genes, their chromosomal location and the respective protein

Gene/locus	Chromosome	Protein
Alfa1AT	14q32.1	Alfa-1-antitrypsin
COL11A1	1p21	Alfa-1-chain type XI collagen
COL11A2	6p21.3	Alfa-2-chain type XI collagen
COL2A1	12q13-q14	Alfa-1-chain type II collagen
COL9A1	6q12-q13	Alfa-1-chain type IX collagen
COL9A2	1p32	Alfa-2-chain type IX collagen
COMP	19p13.1	cartilage oligomeric matrix protein
CRTL1	5q13-14.1	cartilage link protein
DTDST	5q31-q34	diastrophic dysplasia sulfate transporter
VDR	12q13-q14	Vitamin D receptor

Association and linkage studies

Before investing major resources in the detailed study of a potential candidate gene, it would seem that a stronger prior hypothesis implicating the proposed candidate gene is needed, rather than just a general sense based on its biology. Such information can be gained in association studies which can be done on both related and unrelated individuals. In this case one or several markers are selected for study which are located within or adjacent to the candidate gene and the association of these and other markers with the phenotype is investigated. Population stratification with the existence of more than one ancestral source of population gene pool represents a major limitation of this study design. If, as likely, the various ancestral sources differ both in their susceptibility to various diseases and in the frequency of various genetic markers, false associations may be observed between genetic markers and phenotypes. It is likely that population stratification is at least partly responsible for some of the associations between candidate gene polymorphisms and diseases that have later proven to be nonreplicable.

Genome wide scanning for linkage to OA phenotypes

With the increasing availability of large numbers of highly informative genetic markers, particularly microsatellite markers that now span the entire genome, the strategy of whole–genome scanning for linkage to phenotypes of interest has become feasible. Such scans are now done with hundreds of markers spaced at regular intervals throughout the genome, at a distance of e.g. 10 cM.

A candidate gene located in a chromosomal region that has been linked to a phenotype of interest such as hip OA is referred to as a "positional" candidate. Sometimes a gene whose protein product might not otherwise strongly recommend itself as a candidate by virtue of its biological activity may be considered a plausible candidate because of its presence in a linked region. Caution should be exercised, however, since linkage detected in whole-genome scans with microsatellite markers typically implicate relatively large chromosomal regions extending over perhaps 20–30 cM (approximately 20–30 megabases). Such regions may include hundreds of genes. If a genetic variant in a positional candidate gene is later found to be associated with a phenotype, the prior evidence of linkage provides at least some degree of reassurance that the associations were not an artifact of population stratification. It should be noted that just as the presence of detectable linkage does not anoint a positional candidate gene, neither does the absence of linkage exclude a candidate's possible significance.

In our study (Paper V) the results of the genome wide scan suggested a susceptibility locus of hip OA on chromosome 16p with a LOD score of 2.58, ($p = 1.6 \times 10^{-4}$). A susceptibility locus with a LOD score of 2.1 associated with hip OA in 297 families was previously described on chromosome 16p (Loughlin et al. 1999). This locus appears to be in close proximity to the one identified in the present study. This would represent the first instance in which a susceptibility locus for hip OA has been independently identified in more than one population. However, plausible candidate genes have yet to be revealed in this region. The results of our present investigation were obtained through the use of the single, originally identified family. With the use of the Icelandic genealogical database, this family can now be significantly extended and together with additional families provide the basis for more detailed genome wide scans of these and other regions of the genome for linkage to different OA phenotypes.

Challenges in the search for OA genes

The recent publication of a first draft of the human genomic sequence will facilitate the search for OA genes but the obstacles remain significant. For example, the identification of positional candidates still depends on uncovering evidence of linkage between a chromosomal region and an OA phenotype. Once a chromosomal region has been found to link to OA it will be necessary to find a gene in the linked region and for this it will in many cases be necessary to narrow the region down, by applying additional marker sets, to a more manageable size for DNA sequencing or other mutation detection techniques. However, it is not sufficient merely to show an association between a variant in a candidate gene and a phenotype, since such an association may merely reflect linkage disequilibrium. The variant, such as a missense mutation, must also be shown to alter the biological function of a protein in animal models or a tissue such as cartilage that relates to OA. For putative mutations in regulatory regions this chain of evidence becomes even more crucial. Current developments in molecular biology such as microarray chips now allows the simultaneous large-scale identification of thousands of genes with differential expression in disease. This will enhance our ability to identify candidate molecules and processes that are relevant to OA pathology.

Multiple pathogenetic mechanisms are implicated in the development of OA. Continued studies of the kind outlined here will clarify the complex genetic background of OA and identify genetic variation associated with the disease. In addition to improving our understanding of the pathogenesis of OA and identifying new molecular targets for treatment, this knowledge will also allow a better insight into the interactions between the genetic background and the environmental factors that initiate and drive OA.

Conclusions

- The prevalence of radiological hip osteoarthritis in Iceland is higher than in the other Nordic countries.
- The incidence of total hip replacement for osteoarthritis in Iceland is higher than in the other Nordic countries.
- The assessment of hip osteoarthritis on radiographs by the quantitative measurement of minimal joint space is more reliable than a qualitative global assessment of radiological features.
- Icelandic patients with total hip replacement for osteoarthritis are significantly more related to each other than are matched controls from the Icelandic population, supporting a substantial genetic contribution to a common form of osteoarthritis.
- A genome wide scan for susceptibility loci for hip osteoarthritis, using the largest described kinship with familial hip osteoarthritis, identified a suggestive linkage on chromosome 16p.
- The results of this work encourages more detailed genome wide scans of the human genome to search for genetic variations associated with different phenotypes of osteoarthritis.

Summary

The purpose of this study was to: (I) assess the prevalence of hip osteoarthritis (OA) in Iceland and compare it with that in Southern Scandinavia, (II) determine the incidence of total hip replacement (THR) for primary OA in Iceland, (III) compare two different methods for defining radiographic hip OA, (IV) assess in a population-wide study in Iceland the genetic contribution to hip OA leading to THR, and (V) perform a genome-wide scan of a large Icelandic family to identify a chromosomal susceptibility locus for hip OA leading to THR.

Many Icelandic patients with hip OA have been well aware that this disease "goes in the family". By examining a large proportion of all Icelandic colon radiographs taken 1990–1996 the prevalence of radiographic hip OA in Iceland was found to be at least five-fold higher compared to Swedish and Danish studies that have used the same methods. A comparison of two methods for estimating hip OA from colon radiographs showed that a simple quantitative method of measuring joint space was more reliable than a qualitative method. The age-standardized incidence of THR for primary hip OA in Iceland between 1982 and 1996 was estimated and found to be about 50 percent higher than for Sweden. The higher Icelandic prevalence of hip OA may explain most of this difference.

To investigate the contribution of heritability to hip OA leading to THR, information from two population-wide databases in Iceland was combined: A national registry of THR between 1972 and 1996, and a genealogy database of all Icelandic genealogy records for the last 11 centuries made available by deCode Genetics. The genetic contribution to THR for OA was assessed by (a) identifying familial clusters of THR for OA, (b) applying the minimum founder test (MFT) to estimate the minimum number of ancestors to account for all patients with THR for OA, compared to the average number of founders for control lists, (c) calculating an average pairwise kinship coefficient (KC) for the patient and control lists, (d) estimating the relative risk (RR) for relatives of patients with THR for OA. A large number of familial clusters of patients with THR for OA were identified. MFT showed that OA patients descended from fewer founders than the control groups. The average pairwise KC among patients with OA was greater than in the population. RR for siblings of THR for OA patients was 3.05 (2.52, 3.10). Icelandic patients with THR for OA are thus significantly more related to each other than are matched controls. These findings support a significant genetic contribution to a common form of OA and encourages the search for genes conferring an increased susceptibility to OA.

New techniques now make it possible to search the whole human genome for chromosomal susceptibility loci associating with OA. A genome wide scan was done to identify susceptibility loci for hip OA leading to THR, using DNA from a large Icelandic family with a very high prevalence of primary hip OA. A genome locus with a lod score of 2.58 was identified on chromosome 16p. A similar locus has been reported on from England. This is the first instance where what may be the same susceptibility locus for OA is independently described in two different populations with hip OA. We have identified other families with hip OA which link to the studied family and are continuing an expanded genome-wide scan.

Continued studies of the kind outlined here will clarify the complex genetic background of OA and identify genetic variation associated with the disease. In addition to improving our understanding of the pathogenesis of OA and identifying new molecular targets for treatment, this will allow a better insight into the interactions between genetic background and environmental factors that initiate and drive OA.

Sammanfattning på svenska

Syftet med denna studie var att: (I) undersöka förekomsten av höftartros på Island i jämförelse med södra Skandinavien, (II) utreda frekvensen av operation med total höftledsplastik (THP) för artros på Island, (III) jämföra två olika metoder för bedömning av höftartros med röntgenbilder, (IV) i en populationsbaserad studie påvisa förekomsten av ärftlighet för höftartros på Island, (V) genomföra en undersökning av genomet hos en stor Isländsk familj med höftartros för att identifiera områden på kromosomer som har samband med ärftlig höftartros som leder till THP.

Vid granskning av en stor andel av de röntgenundersökningar av tjocktarmen som utfördes på Island under 1990-1996 kunde höftlederna bedömas med avseende på artros. Vi visade att förekomsten av röntgenfynd som vid artros i höften var åtminstone fem gånger vanligare på Island än Malmö, där liknande undersökningar tidigare utförts med samma metod. Vår jämförelse av två metoder för att bedöma artrosförändringar på röntgenbilder visade att en enkel kvantitativ metod var överlägsen en tidigare använd kvalitativ metod.

En jämförelse av den ålderstandardiserade frekvensen av THP för artros under tiden 1982–1996 gav vid handen att frekvensen på Island var åtminstone 50 procent högre än den i södra Sverige under samma tidsperiod. Sannolikt bidrar den höga förekomsten av höftartros på Island till denna skillnad i operationsfrekvens.

Många isländska patienter med höftartros är medvetna om att höftartros ”går i släkten”. För att undersöka rollen av ”arvet” för uppkomst av höftartros som leder till THP samkörde vi två isländska, populationsbaserade databaser: ett nationellt register över alla THP som utförts 1972–1996 och en genealogisk databas med all tillgänglig släktinformation från de senaste 11 seklerna på Island. Den senare databasen har skapats och gjorts tillgänglig av deCode Genetics. Arvets avsevärda inverkan på risken för att få höftartros visade sig genom att vi fann (a) många stora familjer med höftartros, (b) att artrosfamiljerna härstammade från betydligt färre förfäder än islänningarna i allmänhet, (c) att patienterna i artrosfamiljerna uppvisade en högre grad av inbördes släktskap än islänningar i allmänhet, och (d) att den relativa risken för barn till en förälder med THP för höftartros var trefaldigt ökad att få samma sjukdom jämfört med ”medel-islänningen”. Våra fynd styrker arvets stora betydelse för uppkomst av höftartros och stödjer ett fortsatt sökande efter gener som har samband med artros.

Nya metoder gör det nu möjligt att genomsöka hela det mänskliga genomet för att finna genvariationer som har samband med uppkomst av artros och andra sjukdomar. Vi identifierade en stor isländsk släkt med mycket hög frekvens av höftartros. Med hjälp av DNA isolerat ur blodprov från dessa patienter påvisade vi hos denna familj ett område på kromosom 16p som har samband med förekomst av höftartros i denna släkt. Vi har med våra databaser hittat ett flertal andra släkter med höftartros och ett intensifierat sökande pågår nu med syfte att dels identifiera vilken eller vilka gener som finns inom området på kromosom 16p, dels söka efter andra kromosomlokus med betydelse för uppkomst av artros i höften och andra leder.

Vårt arbete kommer att leda till en bättre förståelse av de variationer i vår arvsmassa som har betydelse för uppkomsten av artros, och även göra det lättare att förstå samspelet mellan arv och miljö för uppkomsten av denna vanliga sjukdom.

Ágrip á íslensku

Markmiðið með þessari rannsókn var; (I) að kanna algengi frumslitgigtar í mjöðm á Íslandi og bera saman við niðurstöður frá suður-Svíþjóð og Danmörku, (II) að athuga tíðni gerviliðaaðgerða í mjöðmum Íslendinga vegna frumslitgigtar og framtíðarþörf fyrir slíkar aðgerðir, (III) að bera saman tvær myndgreiningaraðferðir sem notaðar eru til að greina slitgigt í mjöðmum, (IV) að ákvarða hvort slitgigt í mjöðmum erfist og (V) að framkvæma kembileit að erfðavísum eða meingenum stórrar íslenskrar fjölskyldu með arfgenga slitgigt í mjöðmum sem leiðir til gerviliðaaðgerða.

Íslendingar með slitgigt í mjöðmum hafa lengi gert sér grein fyrir að sjúkdómurinn erfist, samanber "þetta er í fjölskyldunni". Algengi slitgigtar í mjöðmum íslendinga var athugað með því að skoða ristilmyndir af um 1.500 íslendingum, en á ristilmyndum sjást mjaðmaliðir vel. Slitgigt í mjöðmum reyndist allt að fimm sinnum algengari á Íslandi en í suður-Svíþjóð og Danmörku þar sem sambærilegar rannsóknir hafa verið gerðar. Við samanburð tveggja myndgreiningaraðferða, sem notaðar eru til að greina slitgigt í mjöðmum, kom í ljós að einföld mæling með reglustiku var áreiðanlegri en flóknari eldri aðferðir byggðar á huglægu mati. Fjöldi gerviliðaaðgerða sem gerðar voru vegna frumslitgigtar í mjöðmum á árunum 1982-1996 var ákvarðaður og niðurstöður aldursstaðlaðar. Erlendur samanburður reyndist erfiður þar sem ekki er tekið tillit til mismunandi aldurssamsetningar þjóða við framsetningu þeirra niðurstaðna. Að teknu tilliti til hennar kemur í ljós að um 50% fleiri gerviliðaaðgerðir eru gerðar á Íslandi en í Svíþjóð vegna frum-slitgigtar í mjöðm. Há tíðni slitgigtar á Íslandi gæti skýrt þennan mun að einhverju leyti.

Til að kanna arfgengi slitgigtar í mjöðmum, voru upplýsingar úr tveimur gagnagrunnum samkeyrðar. Annars vegar upplýsingar um þá sem höfðu gengist undir gerviliðaaðgerð í mjöðm á árunum 1972-1996 og hinsvegar erfðafræðiupplýsingar í Íslendingabók Íslenskrar erfðagreiningar. Í ljós kom að arfgengi mjaðmarslitgigtar er mikil; (a) því fjöldi einstaklinga úr sömu fjölskyldu með gerviliði í mjöðm er mikill, (b) slitgigtarsjúklingarnir eiga miklu færri sameiginlega forfeður en samanburðarhópurinn, (c) slitgigtarfjölskyldurnar eru miklu meira skyldar innbyrðis en samanburðarhópur, (d) börn slitgigtarsjúklinga með gerviliði í mjöðmum er í þrefalt meiri hættu við að fá sjúkdóminn heldur en "meðal íslendingurinn". Þessar niðurstöður styrkja mjög þá skoðun að slitgigt í mjöðmum sé erfður sjúkdómur, a.m.k að hluta og hvetur til áframhaldandi leitar að meingenum slitgigtar.

Nýjar aðferðir gera það nú mögulegt að kemba allt erfðamengi mannsins í leit að erfðavísum og meingenum sem hafa áhrif á eða geta orsakað slitgigt og aðra sjúkdóma.

Gerð var kembileit í erfðamengi stórrar íslenskrar fjölskyldu með erfða slitgigt í mjöðmum. Í ljós kom erfðavísir á litningi 16 sem er talin innihalda meingen sem getur orsakað slitgigt í mjöðmum og stendur leit að meingeninu nú yfir. Fleiri skyldar fjölskyldur fundust með hjálp Íslendingabókar og er nú verið að undirbúa kembileit á erfðamengi þeirra með það fyrir augum að kanna hvort þessi erfðavísir eða aðrir finnast sem geta valdið slitgigt í mjöðmum og öðrum liðum.

Rannsókn þessi varpar ljósi á hlutverki erfða í slitgigt í mjöðmum og getur auðveldað skilning á samspili umhverfisþátta og erfða í framtíðinni og hvetur til áframhaldandi leitar að meingenum slitgigtar.

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