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The clinical relevance of genetic susceptibility to osteoarthritis

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Osteoarthritis is a major musculoskeletal cause of disability in the elderly, but current therapeutic approaches are insufficient to prevent initiation and progression of the disease. Genetic studies in humans have identified molecules involved in signalling cascades that are important for the pathology of the joint components. These include the bone morphogenetic protein (BMP) signalling, the wingless-type signalling and the thyroid pathway as well as apoptotic-related molecules. There is emerging evidence indicating that inflammatory molecules related to cytokine production, prostaglandin and arachidonic acid metabolism are also involved in susceptibility to osteoarthritis. All of these pathways are likely targets for pharmacological intervention. Genetic variation also affects pain due to osteoarthritis highlighting molecular mechanisms for pain relief. Moreover, combinations of genetic markers can be used to identify individuals at high risk of osteoarthritis and risk of total joint arthroplasty failure, which should facilitate the application of preventive and disease management strategies.

Osteoarthritis (OA) is the most common joint disorder and the leading cause of disability in the elderly in the US and Europe [1]. Physician-diagnosed arthritis occurs in more than 50% of adults older than age 65 years and in more than 30% of adults aged 45–64 years [1].

The loss of articular cartilage is the hallmark of OA [2], but all the joint components, including the ligaments, tendons, capsule, synovial lining and periarticular bone, undergo structural and functional

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alterations during the course of OA progression [3]. Although the pathogenesis of osteoarthritis is not fully understood, it is strongly age related, being rare before 40 years, and rising in frequency with age, such that a large proportion of people over the age of 70 have radiographic evidence of osteoarthritis in some joints [4]. OA is a multifactorial disease with genetic and environmental determinants. All cases are probably affected by both genetics and environment, with a continuous distribution between the extremes of predominantly genetic or predominantly environmental causes [4]. For example, the risk of post-traumatic OA after a meniscal injury of the knee is strongly affected by a family history of osteoarthritis, by the presence of nodal osteoarthritis of the hand (the classical marker of generalised osteoarthritis), by obesity and by sex [4].

How do we know that genetics is important in OA?

Evidence for a genetic predisposition to osteoarthritis was reported as early as the 1940s [5]. The clustering of OA in families has been measured by using the risk ratio for a relative of an affected individual compared with the population prevalence [6]. For affected sib pairs, this sib recurrence risk is termed the lambda sib (λs). Large values of λs indicate that a gene involved in traits should be easier to map than if λs is low [6,7]. Thus, it is possible to identify subjects with clinical disease with severe enough symptoms to lead to total joint replacement (TJR) and to compare the prevalence of OA in their siblings (who have a genetic exposure) with that in controls who are matched as closely as possible to the siblings.

A study in Nottingham [8] assessed the prevalence of hip OA in siblings of individuals undergoing total hip replacement (THR) to the prevalence of radiographic hip OA in subjects undergoing intravenous urograms for investigation of a renal problem (i.e., controls). A similar study was carried out using total knee replacement (TKR) as the selection criterion [9]. Similar data, but using self-reported total joint arthroplasty in a smaller data set were found by a study in Oxford [10]. The data shown in Table 1 indicate a strong familial aggregation, although lower than autoimmune arthropathies, not much lower than rheumatoid arthritis and much higher than metabolic disorders such as Type 2 diabetes.

An alternative method to assess the actual genetic contribution to a condition is the use of classical twin studies, which enable investigators to quantify the environmental and genetic factors that contribute to a trait or disease. Comparing the resemblance of identical twins for a trait or disease with the resemblance of non-identical twins offers the first estimate of the extent to which genetic variation determines variation of that trait or heritability. The heritability of OA has been calculated in twin sets after adjustment of the data for other known risk factors such as age, sex and body mass index (BMI). Such findings show that the influence of genetic factors in radiographic OA of the hand, hip and knee in women is between 39% and 65%, independent of known environmental or demographic confounding factors. Classical twin studies and familial aggregation studies have also investigated the genetic contribution to cartilage volume and progression of disease (see MacGregor *et al.* [16]).

Table 1
Familial aggregation of osteoarthritis and of other disorders.

Type of disorder	Condition	Ascertained via	Sibling recurrence risk λ_S	Data from reference:
Autoimmune arthropathies	Rheumatoid arthritis	Sibs with condition	5.0–8.0	[11,12]
	Juvenile arthritis	"	15	[13]
	Systemic lupus erythematosus	"	30	[12]
Metabolic osteoarthritis	Type 2 diabetes	"	1.2–1.6	[14]
	Knee OA (TF and/or PF)	"	2.08	[9]
	TKR	"	4.81	[10]
	Anteromedial OA	Sibs with UKR	3.21	[15]
	Hip osteophytes grade 3	Sibs with THR	4.27	[8]
	THR	"	1.87–8.53	[8,10]
	Hip KL grade $>=3$	"	4.99	[8]
	Hip JSW $<=1.5$ mm	"	5.07	[8]

TKR = total knee replacement, THR = total hip replacement, UKR = unicompartmental knee replacement, KL = Kellgren – Lawrence grade, JSW = joint space width, PF = patellofemoral TF = tibiofemoral.