11

The Genetics of Osteoarthritis

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1. Introduction

Complex or common diseases are those which are common in the population-at-large, are responsible for the majority of morbidity and mortality, and substantially affect individuals and society health-care costs. As such, they are responsible for the greatest burden to society and to the population. It is widely accepted that all complex diseases possess a genetic component that, in addition, plays a role in their pathogenesis. Therefore, clarification of their genetic determinants will lead to a better understanding of the causes and it will be possible to develop tools to identify persons who are at risk in families and in the population in general (Schork, 1997).

Osteoarthritis (OA) is a complex disease with multiple environmental and genetic factors contributing to its pathogenesis (Felson, 2004; Peach et al., 2005). It is strongly age-related, rare prior to the age of 40 years, but importantly increasing in frequency later; in fact, it is estimated that approximately up to 80% of people aged > 65 years exhibit radiographic evidence of OA (Oddis, 1996). OA has been classified into two classes: primary OA, which is the late-onset form and that has no obvious causes, and secondary OA, which has a clearly identifiable cause comprising a developmental abnormality or a major environmental effect (Altman, 1995). It has long been suggested that OA is inherited. The clinical studies by Stecher (1941) on Heberden's nodes, a common manifestation of OA and by Kellgren et al. (1963) on generalized OA suggested that specific forms of common OA clusters in families.

Due to its nature, primary OA is the target of studies on the genetic factors associated with its development and, as in other complex diseases, different strategies have been employed to investigate this genetic contribution. This chapter will be centered on familial aggregation studies, twin studies, and association studies on candidate genes. Other strategies, such as linkage analysis and Genome-wide association studies (GWAS), will be contemplated elsewhere.

2. Familial aggregation

2.1 Sibling risk studies

A genetic component for a disease may be suspected if there is clustering in families. Sibling risk studies may be useful to clarify this search if the frequency of disease in the siblings of affected probands is higher than that in general population; if so, the disease probably has a genetic component and the susceptibility genes probably are segregated in the proband's family. Nevertheless, the disease may afflict several family members because several

predisposing environmental factors also share a greater frequency in the proband's family and this could also result in higher disease concordance. To limit this possibility, researchers are required to match population controls to proband siblings as closely as possible. From sibling risk studies, a risk of recurrence to a relative of an affected individual, given that these share a particular allele compared with the general population, can be calculated through a measurement termed lambda sib (λs) (Guo, 2002; Rich & Sellers, 2002).

In OA, sibling studies have been conducted that principally identify subjects who have undergone total joint replacement due to primary OA. In a study in the U.K., the prevalence of OA in siblings of probands who had undergone primary OA-related Total hip (THR) or Total knee replacement (TKR) surgery was compared with the prevalence in a control group consisting of siblings' spouses; the latter were selected because they share a common environment to sibling group but they differ from these regarding possible genetic determinants and are representative of general population in terms of their disease susceptibility. The frequency of OA in siblings was higher compared with controls; hence, an increased risk to siblings to undergo THR (λs = 1.8), TKR (λs = 4.8), or both (combined λs = 1.98) for idiopathic end-stage OA was determined (Chitnavis et al., 1997). A similar study also carried out in the U.K. recruited probands who had experienced THR, compared the frequency of hip OA between their siblings to that of unrelated matched controls who had undergone intravenous urography and in whom a pelvic x-ray was obtained to document OA. As in the previous study, the frequency of hip OA was greater in siblings, indicating an increased risk for developing definite and severe hip OA (λs = 5.0 and 9.8, respectively). When stratification by gender was performed, the increased risk was maintained; however, this was greater for THR in males than in females (λs 14.4 and 7.7, respectively) (Lanyon et al., 2000). Another sibling study, conducted by the same research group, analized the genetic contribution to knee OA including siblings of probands with TKR. Siblings were assessed for radiographic knee OA of all knee compartments and were compared with subjects from the general population, finding an increasing risk for tibiofemoral and patellofemoral OA (λs = 2.9 and 1.7, respectively), which was maintained after stratification by gender (Neame et al., 2004).

As mentioned previously, sibling studies require a control group whose participants reflect as possible general population in order to compare disease frequencies and to deduce a Relative risk through λs. Another related design, denominated sib pair study, does not employ a control group and only siblings of probands are recruited and compared among themselves to determine whether siblings or other close relatives tend to express the same disease phenotype or similar values of a quantitative trait. From these studies, it is possible to estimate a risk calculated by means of Odds ratios (ORs), and heritability (h^2), which is the proportion of the population variance in the trait that is attributable to the segregation of a gene or genes and whose values are between 0 and 1; the greater the h^2, the more significant the genetic component. However, due to their methodological differences with those of sibling risk studies and that measurement of familial aggregation as ORs does not yield the risk of recurrence, these results are not comparable with those of sibling risk studies. They do, however, contribute substantially to the study of genetic determinants in OA.

The GARP study (Genetics, Arthrosis, and Progression) was conducted in The Netherlands and was designed to identify determinants of OA susceptibility and progression. For this, the study recruited Caucasian probands and their siblings of Dutch ancestry with

symptomatic OA at multiple sites. To analyze whether there is some familial aggregation of OA at specific joint sites, such as hands, knees, and hips, and at combination of joint sites, the control population comprised probands and their siblings with OA but not at the specific disease site. ORs were calculated to estimate possible risks. After adjustment of ORs for age, gender, and Body mass index (BMI), siblings were affected in an increased manner at the same joint sites as the proband in OA of the hand (OR 4.4) and hip (OR 3.9); OA of the knee showed no increased risk (OR 1.0). When different joint-site combinations were analyzed, hand-hip demonstrated the most increased risk (OR 4.7) (Riyazi et al., 2008). Later, the same group analyzed familial aggregation of radiologic progression of OA at multiple joint sites in a longitudinal study from the GARP cohort. To assess radiologic progression, x-rays were graded on a scale of 0 - 3 for Joint space narrowing (JSN) and osteophytes including all hand, hip, and knee joints to obtain a total score. Radiologic progression of OA was defined as a 1-point score increase in total scores of JSN or osteophytes on x-rays obtained at baseline and after 2 years. ORs adjusted for age, gender, and the BMI, of a sibling having radiologic progression if the proband had progression were 3.0 for JSN progression and 1.5 for osteophyte progression. A dose-response relationship was found between the amount of increase in JSN total scores among probands and the progression of JSN in siblings (Botha-Scheepers et al., 2007).

Some other studies have analyzed the genetic contribution in characteristics associated with OA development through a sib pair design. In a sib pair study designed to assess whether the h^2 of knee structural components is independent of radiologic OA, 115 siblings of patients who had had a TKR were recruited. Muscle strength of lower limbs was measured, x-rays of the knees were obtained to assess JSN and osteophytes, and Magnetic resonance imaging (MRI) of the knee to determine cartilage volume was carried out. Lower limb muscle strength showed a high h^2 (42%); nonetheless, this was higher for medial tibial, for lateral tibial, and for patellar cartilage volume (h^2 = 65, 77, and 84%, respectively). For radiographic OA, h^2 was 61% for presence and 61% for severity (Zhai et al., 2004). Later, to search for longitudinal changes, this same sib pair cohort was followed for 2.4 years. Successful follow-up was achieved in 95 sibling pairs, and a higher h^2 was observed for changes in medial and lateral cartilage (73 and 43%, respectively), muscular strength (64%), and for progression of medial and lateral chondral defects, (90 and 80%, respectively) (Zahi et al., 2005).

2.2 Population-based family studies

Designs that involve family- and population-based sampling allow for the investigation of both genes and environment, separately or together, and permit valid inference to the population. These designs can be utilized for determining familial risks and to understand the nature of the transmittal of the OA genetic component better.

In an interesting study developed in Iceland to assess the genetic contribution to hip OA leading to THR, a population-wide study was conducted. The researchers used information obtained from a national registry of patients who underwent THR, as well as data from an Icelandic genealogy data base that includes the entire current population and the majority of their ancestors back to the IX century. With these resources, numerous large family clusters from 2,713 patients with THR for OA were identified. In order to assess whether these familial clusters were significantly different from what could be expected, matched control sets were generated utilizing the national genealogy database; subsequently, the following

tests were performed to assess the genetic contribution: determination of the degree of familial clustering of OA in patients with THR; estimation of the minimum number of founders who could account for the genealogy of these patients and comparison of this with the average number of founders for their controls; determination of the overall degree of relatedness among Icelandic controls, and an estimate of RR. This analysis demonstrated that the cases were more related to each other than would be expected if no genetic component predisposing to OA were segregated in these, and supports the existence of a significant genetic component in familial aggregation of hip OA in Iceland. On the other hand, the siblings of these patients were found to be three times more likely to require THR than were controls. (Ingvarsson et al., 2000).

To evaluate whether OA is inherited and to investigate the most likely transmission pattern, a segregation analysis was performed taking data from the Framingham Study. This study was not designed to analyze OA, but rather to evaluate risk factors for heart disease; the study cohort was assembled in 1948 as a random sample of adults. Segregation analysis was performed in 337 families with radiographic OA on hand and knee and included both parents and at least one of their adult children. An OA count was generated, adding up the number of joints affected and creating standardized residuals that were used to obtain correlations in pairs drawn from each family. There was little correlation between pairs of spouses; however, correlations between parents and offspring (r = 0.115) or between siblings (r = 0.306) were higher. Remarkably, mother-daughter and mother-son correlations were 0.206 and 0.158, respectively, whereas father-daughter and father-son correlations were 0.084 and 0.007, respectively, suggesting that mothers are more likely to transmit OA to their offspring than are fathers. The analysis also revealed a significant genetic component of the disease and suggested that this component may involve a major recessive locus (Felson et al., 1998). These results showed a greater female h^2 for OA.

A cohort of families drawn from the Baltimore Longitudinal Study of Ageing was obtained to assess OA changes in order to determine the familial aggregation of OA; as in the previous study, this was not designed for analysis of OA. X-rays of hands and knees were obtained and identified 167 nuclear families with hand, 157 with knee, and 148 with hand and knee radiographic data. The outcome variable was OA defined as presence/absence of disease or as severity, taking into account the number of joints affected or the sum of all joints of a given site. When data were analyzed as presence or absence, no significant sib-sib correlations were observed; however, in terms of OA severity, significant correlations were found for Distal interphalangeal (DIP)- and Proximal phalangeal (PIP)-joint OA, and for OA affecting two or three hands sites (r = 0.81, 0.45, and 0.33, respectively). For OA of the knee, no significant correlation was found (r = 0.33); however, as the authors themselves stated, this finding could be due to underestimating of the number of cases of knee OA. The results from this cohort demonstrate familial aggregation of OA and suggest that genes could play a more significant role in severity than in occurrence (Hirsch et al., 1998). This, however, does not exclude a role for environmental influences because the authors did not look for putative environmental factors, as frequently occurs in large-scale studies in which control or ascertainment of all variables is difficult.

As part of the Rotterdam Study, which is a prospective population- based, follow-up study of the determinants and prognosis of chronic diseases in the elderly, a random sample of 1,583 individuals was calculated to estimate the genetic influence on the occurrence of

radiographic OA in knees, hips, and hands. From the random sample, 118 probands with multiple-affected joint sites and their 257 siblings were identified, and OA frequency between these and the remainder of study participants was compared. Hand OA was found to be more common in proband siblings, knee OA was no more common in probands, and hip OA was even less common than that in the random sample. The h^2 for a score that summed the number of joints affected was 78%. For individual joint sites, the h^2 of OA of the hand was 56%; however, OA of the knee was not significantly correlated (h^2 = 7%). These data suggest that there is a strong genetic effect for hand, but not for knee or hip OA (Bijkerk et al., 1999). These findings do not support the results of other studies in which a greater contribution for hip and knee OA was demonstrated.

3. Twin studies

Familial aggregation does not result exclusively from genetic factors and may reflect an environmental exposure shared by family members. An alternative method for assessing the actual genetic contribution to a condition, in this case OA, is the use of classic twin studies, which enable researchers to quantify the environmental and genetic factors that contribute to a trait or disease. In these studies each member of a twin pair are evaluated with respect to the presence or absence of a disease or trait and the disease concordance rates are compared in Monozygotic (MZ) and Dizygotic (DZ) twin pairs. While higher concordance in MZ than in DZ twin pairs suggests that a significant part of familial aggregation is due to genetic factors and to equal rates of concordance or to the presence of an MZ twin concordance, <100% emphasizes the importance of environmental factors. From these concordance rates, it is possible to estimate the h^2 of the trait (Hawkes, 1997; Risch & Sellers, 2002).

The first large-scale OA twin study was published in 1996 on 130 MZ and 120 DZ female twin pairs in whom radiographic examination of hand and knee were carried out. MZ twins exhibited a higher intra-class correlation compared with DZ twins for several clinical and radiographic features of OA. The concordance rate in MZ twins was 64% compared with 38% in DZ pairs, and the h^2 ranged between 39 and 65%. Incomplete concordance in MZ pairs clearly showed an environmental component of disease expression; however, these authors demonstrate an important genetic contribution to primary OA (Spector et al., 1996). The same research group performed another twin study, but on this occasion they focused on radiographic hip OA. Concordance for JSN was higher in MZ than in DZ twin pairs (43 and 21%, respectively), as well as for other radiographic characteristics, and h^2 was ~60% (MacGregor et al., 2000). Later, this research group searched for genetic influences, but at different skeletal sites. They observed a strong genetic correlation in OA of the hand (h^2 = 53–68%) but not of hip or knee. This suggests that OA is unlikely to be explained by a single, common genetic mechanism, and it is possible that the genetic factors that contribute to OA are specific to individual joint sites (MacGregor, et al., 2009).

Different from these previously mentioned studies, a twin study from Finland included both genders with a large proportion of male pairs. This was a questionnaire-based twin study, and OA at any joint group was employed as the disease criterion. Concordance was higher in female MZ twin pairs compared with that of DZ female twin pairs, and an h^2 of 44% was obtained. However, in male twin pairs, concordance in MZ was of 34% and in DZ, this was 38%; therefore, no genetic component in the disease in males was

detected. These results suggest that genes do not play a significant role in OA in males (Kaprio et al., 1996).

These twin studies have focused on hand, knee, and hip OA, each reporting a significant h^2 whose values vary among different joint groups; this could comprise evidence for differences in genetic susceptibilities at these sites; nevertheless, this remains unclear. On the other hand, it appears apparent that MZ twin concordance does not reach 100%, suggesting an important role for primary OA-associated environmental factors.

As in sibling studies, some twin studies have been employed to analyze disease progression and certain characteristics related with OA. To analyze genetic influences on OA progression, the T. Spector group designed a longitudinal twin study that included 114 MZ and 195 DZ female twin pairs in whom radiographic OA of the knees was documented during a 7.2-year follow-up time. Progression of osteophyte and JSN were assessed and the researchers observed that concordance for both radiographic characteristics were greater in MZ than in DZ pairs, with 69 and 38% for osteophyte, respectively, and 73 and 53% in JSN, respectively. The h^2 estimates were 69 and 80% for medial osteophyte and JSN, respectively, demonstrating a significant genetic influence in progression of OA of the knee (Zahi et al., 2007). To assess the genetic contribution of cartilage volume, 31 MZ and 37 DZ twin pairs, all females, were evaluated through MRI of the knees. Concordance was always higher in MZ than that of DZ twins, and estimated h^2 was 61 for femoral, 76 for tibial, for patella, 66, and total cartilage volume, 73% (Hunter et al., 2003). These results indicate the importance of genetic factors in determining cartilage volume.

4. Association studies

A case-control study is a useful method to determine whether there is an association between an exposure-of-interest, in this case, a candidate gene or a genetic marker, and a disease. Association tests determine whether a specific allele of a genetic marker is found with increased frequency in cases compared with the frequency of this marker in controls. If an association is found between the disease and the particular allele, this may suggest a causal relationship. Strength-of-association is quantified by the Odds ratio (OR); this signifies the odds of exposure to any given disease relative to the odds of exposure given to no disease. If a study yields an OR of 1.0, the odds of exposure are the same between cases and controls, implying no association. If the OR are >1, the event is more likely to happen than not, and if the OR is <1, the event is less likely to happen than not (Caporaso, 1999; Risch & Sellers, 2002).

The above mentioned segregation and twin pair studies have highlighted the fact that primary OA possesses a major genetic component. Association studies, through a case-control design, have been useful to investigate the relationship between candidate genes and OA. Even if, after a linkage analysis or a GWAS has encountered a probably relationship with a gene or a genetic marker, case-control studies are employed to replicate these findings. Several genes with different functions have been tested for an association, and Valdes & Spector (2009a) have categorized these genes in different molecular pathways or types of molecules as follows: inflammation; Extracellular matrix (ECM) molecules; Wnt signaling; Bone morphogenetic proteins (BMPs); proteases or their inhibitors, and genes related with modulation of osteocyte or chondrocyte differentiation (Table 1).

Gene	Name	Association Positive Trait	OR	Author	Negative Author
Inflammation					
CCL2	Chemokine (C-C motif) ligand 2	Knee	2,2	Park, 2007	
COX2 (PTGS2)	Cyclooxygenase 2 (Prostaglandin G/H Synthase2)	Knee	0,7	Valdes, 2004	Valdes, 2006
			1,5*	Valdes, 2006	
			1,5	Valdes, 2008	
			0,6	Schnider, 2010	
IL-1 gene cluster	Intrleukin 1-α, β, interleukin receptor antagonist (IL1RN)	Hand	1,6	Solovieva, 2009	Moxley, 2010
		Hip	2,4	Meulenbelt, 2004	Sezguin, 2007
			0,7	Jotanovic, 2011	
		Knee	0,1	Attur, 2010	
IL-6	Interleukin-6	Hand	4,7	Kämäräinen, 2008	Valdes, 2010
		Hip	0,4	Pola, 2005	
IL-10	Interleukin-10	Knee	4	Fytili, 2005a	Riyazi, 2005
HLA	Human leukocyte antigen system	Hand	2,4	Riyazi, 2003	Shi, 2010
		Knee	1,3	Nakajima, 2010	
		Knee/Hip	1,6	Moos, 2002	
Extracelular matrix molecules					
ASPN	Asporin	Knee/hip	2,4	Kizawa, 2005	Mustafa, 2005
			1,9	Jiang, 2006	Rodriguez-Lopez, 2006
			1,5	Nakamura, 2007	Kaliakatsos, 2006
COL2A1	Collagen type II α-1	Generalized	5,3	Meulenbelt, 1999	Baldwin, 2002
		Hand	1,6	Hämäläinen, 2008	Aersens, 1998
		Knee	2,1	Uitterlinden, 2000	
			4,1	Galves-Rosas, 2010	
		Knee/Hip	1,3	Ikeda, 2002	
COMP	Cartilage oligomeric matrix protein	Knee/Hip	1.5*	Valdes, 2007	Mabuchi, 2001
CILP	Cartilage intermediate layer protein	Knee	0.4*	Valdes, 2006	
MATN3	Matrilin-3	Hand	2,6	Steffanson, 2003	Pullig, 2007
			2	Min, 2006	
			4,3	Pullig, 2007	
Wnt signaling pathway					
CALM1	Calmodulin 1	Hip	2,4	Mototani, 2005	Shi, 2008b
				Mototani, 2010	Poulou, 2008
					Valdes, 2007
					Loughlin,2006
FRZB	Frizzled related protein 3	Generalized	1,4	Min, 2005	Kerkhof, 2008
		Knee	2,9	Valdes, 2007	Evangelou, 2009
			2	Ródriguez-López, 2007	
		Hip	4,1**	Loughlin, 2004	
			3,2	Lane, 2006	
LRP5	Low density lipoprotein receptor-related protein 5	Knee	1,6	Smith, 2005	Kerkhof, 2008

Gene	Name	Association Positive Trait	OR	Author	Negative Author
Bone morphogenetic proteins					
BMP2	Bone morphogenetic protein 2	Knee	1,7 1,3**	Valdes, 2004 Valdes 2006	
BMP5	Bone morphogenetic protein 5	Hip	0.007¤ 0.018	Southam, 2004 Wilkins, 2009	
GDF5	Growth differentiation factor 5	Hip Hip/Knee Knee Hand/Hip/Knee	1,8 1,3 1,2 1,3 1,1	Miyamoto, 2007 Southam, 2007 Chapman, 2008 Valdes, 2009b Evangelou, 2009	Tsezou, 2008
Protease/protease inhibitors					
AACT	Alpha-1-antichymotrypsin	Knee	0,7**	Valdes, 2006	
ADAM12	A desintegrin and metalloproteinase domain 12	Knee	7,1** 2,5* 1,9 3,5	Valdes, 2006 Valdes, 2004 Kerna, 2009	Limer, 2008 Rodriguez-Lopez 2009
ADAMTS14	ADAM with trombospondin motif	Knee	1,4**	Rodríguez-López 2009	
MMPs	Matrix metalloproteinase	Knee	0.001¤	Barlas, 2009	
TNA	Tetranectin	Knee	1,5** 1,4*	Valdes, 2006	
Modulation of osteocyte or chondrocyte differentiation					
ESR1	Estrogen receptor α	Knee Hip	1,4 1,03 3,6** 0,5 0,7 0,8** 1,3*	Jin, 2004 Fytili, 2005b Valdes, 2006 Borgonio-Cuadra, 2011 Lian, 2007 Riancho, 2010	Wise, 2009 Loughlin, 2000b
IL-4R	Interleukin -4 receptor	Hip	2,1	Forster, 2004	
OPG	Osteoprotegerin	Knee	0,5**	Valdes, 2006	
VDR	Vitamin D receptor	Hand Knee	1,9 2,3 2,8 1,9*	Solovieva, 2006 Uitterlinden, 1997 Ken, 1997 Valdes, 2006	Aerssens, 1998 Huang, 2000 Loughlin, 2000b Baldwin, 2002 Lee, 2009
Others					
CALCA	Calcitonin	Knee	0,4	Magaña, 2010	
DIO2	Iodothyronine deionidase enzyme type 2	Hip	1,8	Meulenbelt, 2008	

Gene	Name	Association Positive Trait	OR	Author	Negative Author
LRCH1	Leucine-rich repeats and calponin homology (CH) domain containing 1	Knee	1,5	Spector, 2006	Snelling, 2007
RHOB	Ras homolog gene family member B	Knee	0,3*	Shi, 2008a	Loughlin, 2007
TXNDC3	Thioredoxin domain containing 3	Knee	1,4	Shi, 2008a	Loughlin, 2007

* Males; ** Females; ¤ p value, OR not available.

Table 1. Association studies on candidate genes in osteoarthritis.

4.1 Inflammation

Classically, OA has been considered a degenerative joint disease; however, the role is currently recognized of an inflammatory process in its pathogenesis, which is reflected by several clinical signs and symptoms as swelling of affected joints and joint stiffness. Synovial membrane also exhibits inflammatory changes which in addition to cartilage damage could result in the release of antigenic determinants leading to the production of inflammatory cytokines, chemokines, and destructive enzymes, between other inflammatory components, increasing the inflammatory process and damage to the articular structure (Yuan et al., 2003). It is unclear if this is actually caused by OA or by associated/complicating crystalline (e.g., calcium pyrophosphate or hydroxapatite) arthritis.

Several kinds of interleukins have been associated with OA; however, the results have been inconclusive. Results concerning *IL1* are controversial because while some reports suggest an association, there are reports in which no association has been found (Jotanovic et al., 2011; Meulenbelt et al., 2004; Moxley et al., 2010; Sezguin, 2007; Solovieva et al., 2009). However, there is a report in which a very significant association of *IL1* with severity of OA of the knee was shown (p <0.0001) (Attur et al., 2010). *IL-6* has been reported to be associated with OA (Kämäräinen et al., 2008; Pola et al., 2005); however, in a large-scale meta-analysis, there was no reproducibility of the results (Valdes et al., 2010)

Prostaglandins are well known modulators of the activities of bone cells and inflammation. The COX2 protein is encoded by the *PTGS2* gene and is expressed in meniscus, synovial membrane, and osteophyte fibrocartilage, particularly during early OA (Hardy, 2002). *PTGS2* gene polymorphisms have been associated significantly with OA of the knee (Schnider et al., 2010; Valdes et al., 2004, 2006). Interestingly, during the replication stage of a GWA, this association was confirmed, and through an expression-analysis study, the transcripts of two genes related with the synthesis of *PGE2* were abundantly expressed in chondrocytes of patients with OA, underlying its importance in the pathogenesis of the disease (Valdes et al., 2008).

The association with Human leukocyte antigen (HLA) has also been shown (Moos et al., 2002; Nakajima et al., 2010; Riyazi et al., 2003), and in a GWA, two markers mapped to DQB1 and to the butyrophilin-like 2 protein (BTNL2), which regulates T-cell activation (Nguyen et al., 2006). These findings demonstrate the importance of the HLA system in risks for OA.

4.2 Extracellular matrix molecules

The alterations in osteoarthritic cartilage are numerous and involve morphologic and metabolic changes in chondrocytes, as well as biochemical and structural alterations in ECM macromolecules. A hallmark of OA is the degradation of ECM (Malemud et al., 1987; Martel-Pelletier et al., 2008); therefore, genes encoding its molecules have become strong candidates for association studies.

Of the structural genes, *COL2A1* has received the most attention because it encodes type II collagen, which is the most abundant protein of articular cartilage and because has been implicated in several osteochondrodysplasias that develop early OA. Several studies have demonstrated an association of *COL2A1* gene polymorphisms (Galves-Rosas et al., 2010; Hämäläinen et al., 2008; Ikeda et al., 2002; Meulenbelt et al., 1999; Uitterlinden et al., 2000); however, some other studies have not found such an association (Aersens et al., 1998; Baldwin et al., 2002).

One gene that exhibited interesting results is Asporin (*ASPN*). Asporin is an ECM protein member of the small leucine-rich proteoglycan subfamily of proteins that binds to Transforming growth factor-β (TGF-β), a key growth factor in cartilage metabolism, and to collagen and agrecan. The *ASPN* gene contains a polymorphic aspartic acid (D) repeat in its N-terminal region, and its mRNA is expressed abundantly in osteoarthritic articular cartilage (Henry et al., 2001; Lorenzo et al., 2001, Lorenzo, 2004). Kizawa et al. (2005) observed that *ASPN* containing 14 aspartic acid repeats (D14) was significantly associated with OA of the knee. Other length variants were identified, the most common being D13 repeats. The authors generated cell lines from a murine chondrogenesis model expressing different *ASPN* alleles, and they found that cells containing the D14 allele result in greater inhibition of AGC1 and COL2A1 than cells containing other alleles. Additionally, *in vitro* binding assays showed a direct interaction between *ASPN* and TGF-β, concluding that their findings demonstrate a functional link among ECM proteins, TGF-beta activity, and disease. These results were interesting; however, subsequent association studies in Caucasian populations did not support the association of D14 with OA (Kaliakatsos et al., 2006; Mustafa et al., 2005; Rodríguez-López et al., 2006). A meta-analysis including data on Asian and Caucasian individuals demonstrated that combined D14 is associated with OA (p = 0.0030; OR, 1.46); however, in the stratification analysis, a positive association between knee OA and the D14 allele (p = 0.0000013; summary OR, 1.95) was found only in Asians, suggesting that the association of *ASPN* and OA of the knee has global relevance, but that its effect possesses ethnic differences (Nakamura et al., 2007).

4.3 Wnt signaling pathway

Wnts comprise a family of glycoproteins involved in developmental processes such as embryogenesis, organogenesis, and tumor formation, as well as in cartilage and bone development and degeneration. The Wnt1 class activates the canonical Wnt signaling pathway, which involves the formation of a complex among Wnt proteins, frizzled, and LRP5/6 receptors, promoting the inhibition of β-catenin degradation and its subsequent accumulation in the nucleus, which was suggested to contribute to cartilage loss. This pathway also plays a role in the endochondral ossification that causes osteophytes (Yavropoulou & Yovos, 2007; Yuasa et al., 2008).

The association of *FRZB* with OA was analyzed after a genome-wide linkage scan mapped a hip OA susceptibility locus to 2q (Loughlin et al., 2000a). In the subsequent association

analysis, a Single nucleotide polymorphism (SNP) in *FRZB* resulting in an Arg324Gly substitution at the carboxyl terminus was associated with hip OA in female probands (p = 0.04), and this was confirmed in an independent cohort of cases involved female hip OA (p = 0.04). Additionally, haplotype coding for substitutions of two highly conserved arginine residues (Arg200Trp and Arg324Gly) in *FRZB* was a strong risk factor for primary hip OA, with an OR of 4.1 (p = 0.004) (Loughlin et al., 2004). Several replication studies (Min et al., 2005; Lane et al., 2006; Rodríguez-López et al., 2007; Valdes et al., 2007) confirmed the association; however, others that were sufficiently powered failed to find any association. In a large meta-analysis, a weak association in a SNP to hip OA was found (OR = 1.12; p <0.016), but not with other OA sites (Evangelou et al., 2009).
Another gene of the Wnt signaling pathway, *LRP5*, has also been associated with OA (Smith et al., 2005), although the results were unable to be replicated in a large population-based study (Kerkhof et al., 2008).

4.4 Modulation of osteocyte or chondrocyte differentiation

Bone mass and probably rate of change in bone density are controlled to a great extent by genetic factors, and a range of regulatory and structural genes has been proposed as being involved, including Collagen 1α1 (*COL1A1*), the Estrogen receptor (*ER*), and the Vitamin D receptor (*VDR).* These genes have been studied in OA, but *VDR* has received the most attention, and first reports have shown significant associations with an increased risk in the presence of different polymorphisms (Ken et al., 1997; Uitterlinden et al., 1997; Solovieva et al., 2006; Valdes et al., 2006); however, this has not always been confirmed (Aerssens et al., 1998; Baldwin et al., 2002; Huang et al., 2000; Loughlin et al., 2000b). A meta-analysis on the most frequently studied *VDR* polymorphisms (TaqI, BsmI, and ApaI) in OA analyzed a total of 10 studies of persons of Asian or European origin involving a total of 1,591 patients with OA and 1,781 controls. Nine studies were performed on *VDR* TaqI polymorphisms, six on *VDR* BsmI polymorphisms, and 5 on *VDR* ApaI polymorphisms. The results showed no association between OA and the *VDR* TaqI T allele among all study subjects (OR, 0.841; p = 0.15). Stratification by ethnicity yielded no association between the *VDR* TaqI T allele and OA in Europeans or Asians. Moreover, no association was found between OA and *VDR* TaqI polymorphisms by meta-analysis of recessive and dominant models, and contrasts of homozygotes. And finally, no association was found between OA and *VDR* polymorphisms with respect to BsmI and ApaI polymorphisms by meta-analysis. Therefore, the authors concluded that there is no association between *VDR* gene polymorphisms and OA (Lee et al., 2009)
Several studies have tested for an association between *ESR1* gene polymorphisms and the risk of OA. Some studies reported an association for either increased or decreased risk (Borgonio-Cuadra et al, 2011; Fytili et al., 2005b; Jin et al., 2004; Lian et al., 2007; Valdes et al., 2006). A large study exploring the association of two common polymorphisms within the *ESR1* and aromatase (*CYP19A1*) genes polymorphism with severe OA included 2,176 patients with hip OA, 971 patients with knee OA, and 2,381 controls who were recruited at three centers in Spain and one in the U.K. The rs2234693 (*ESR1*) and rs1062033 (*CYP19A1*) single nucleotide polymorphisms were genotyped, and in the global analysis, both were associated with OA, but there was significant gender interaction. The GG genotype at rs1062033 was associated with an increased risk of knee OA in women (OR, 1.23; p = 0.04). The CC genotype at rs2234693 tended to be associated with reduced OA risk in women (OR,

0.76; p = 0.028 for knee OA and OR, 0.84; p = 0.076 for hip OA), but with an increased risk of hip OA in men (OR, 1.28; p = 0.029). The rs1062033 genotype associated with higher OA risk was also associated with reduced expression of the aromatase gene in bone. These results are consistent with the hypothesis that estrogen activity may influence the development of large-joint OA (Riancho et al., 2010).

4.5 Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) are multi-functional growth factors that belong to the TGF-β superfamily and they were first identified by their ability to induce the formation of bone and cartilage. They function as regulators of bone induction, maintenance, and repair and are critical determinants of the embryological development of mammalian organisms (van der Kraan et al., 2010).

BMP2 has been associated with OA of the knee (p = 0.007), particularly with JSN (Valdes et al., 2004). BMP5 was detected after a linkage analysis study; the linkage encompassed two strong candidate genes: *BMP5*, and *COL9A1*. When each marker was tested for association with a marker within intron 1 of *BMP5* was associated (p <0.05) (Southam et al., 2004; Wilkins et al., 2009).

GDF5 is required for formation of bones and joints in the limbs, skull, and axial skeleton (Settle et al., 2003). This gene was shown to associate with hip OA in an Asian study, including Japanese and Chinese patients. An SNP, the rs143383, showed the strongest association ($p = 1.8 \times 10^{-13}$) (Miyamoto 2007). This SNP is located in the *GDF5* core promoter and exerts allelic differences on transcriptional activity in chondrogenic cells, with the susceptibility allele exhibiting reduced activity. These findings implicate *GDF5* as a susceptibility gene for OA and suggest that decreased *GDF5* expression is involved in its pathogenesis (Myamoto et al., 2007). This association was confirmed by other studies, and a meta-analysis employing a larger collection of European as well as Asian studies validated the association with OA. The combined association for both ethnic groups is highly significant for the allele frequency model (OR, 1.21; p = 0.0004). These findings represent the first highly significant evidence for a risk factor for the development of OA that affects two highly diverse ethnic groups (Chapman et al., 2008).

4.6 Proteases and their inhibitors

Increased proteolytic activity leads to degradation of ECM components such as agrecan and COL2A1, resulting in cartilage degradation. The Matrix metalloproteinases (MMPs) have been considered the main enzymes responsible for this degradation. Members of this MMP family include ADAM and ADAMTS (Nagase & Kashiwagi, 2002). A haplotype of the *ADAM12* gene polymorphism has been significantly associated with knee osteoarthritis demonstrating differences between genders, conferring a risk of up to 7-fold in women ($p < 1 \times 10^{-6}$) and 2-fold in men (p <0.014) (Valdes et al., 2006). On the other hand, an *ADAM12* gene polymorphism has been associated with progression in OA of the knee, particularly with changes in Kellgren-Lawrence and osteophyte grades (p <0.07 and 0.004, respectively) (Valdes et al., 2004).

4.7 Other genes

There are other genes that have shown susceptibility to OA. The *DIO2* gene encodes an intracellular enzyme in the thyroid pathway that converts thyroxin (T4) into an active thyroid hormone (T3), which in the growth plate specifically stimulates chondrocyte

differentiation and induces hypertrophy of the chondrocytes, initiating terminal differentiation and formation of bone. As in other OA susceptibility genes, *DIO2* was identified by a genome-wide linkage scan, and during replication in UK, Dutch, and Japanese, an association of a common *DIO2* haplotype, exclusively containing the minor allele of rs225014 and common allele of rs12885300, was observed with a combined recessive OR of 1.79 (p = 2.02 × 10^{-5}) in cases of females with advanced/symptomatic hip osteoarthritis, indicating *DIO2* as a new susceptibility gene that confers risk for osteoarthritis (Meulenbelt 2008).

5. Conclusions

The existence is clear of genetic determinants related with OA, as has been demonstrated in sibling studies, familial aggregation, and twin pair studies; however, it appears that there are differences in genetic susceptibility according to affected sites, gender, and disease stage. Association studies also show differences in site, gender, and ethnicity. To date, one of the most consistent associations is that of *GDF5*; however, it is clear that there are other genes implicated, not only with the disease prevalence, but also with disease progression. It is important to continue the search for genes implicated in development of OA in order to acquire a better understanding of its pathogenic mechanisms in order to plan prevention strategies in populations-at-risk and to design different therapeutic interventions.

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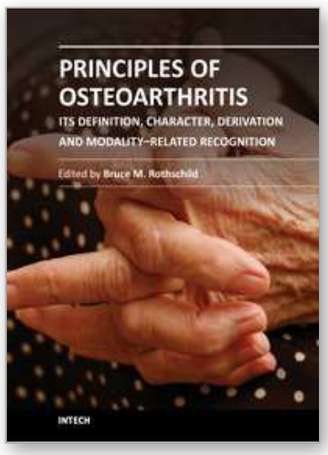

Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition

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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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