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Genetic Association and Linkage Studies in Osteoarthritis

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1. Introduction

Text Osteoarthritis (OA) is the most common musculoskeletal disease in developed countries. It is characterized by progressive degradation of articular cartilage that leads to joint space narrowing, subchondral sclerosis, osteophyte and cyst formation, and eventually loss of joint function. While OA can be secondary to various factors, the majority of cases are considered primary. Certain OA forms have long been known to have a genetic component. Based on twin studies the heritability of OA has been estimated to be around 50 %. Since the disease is complex, with environmental and genetic factors acting together, the knowledge of the etiology and development of preventive medication have been a challenge. A better understanding of the predisposing genes and biological mechanisms behind OA are essential for future drug development.

The current estimate of the number of genes in the human genome is 23 500 (Patterson 2011). Almost the entire genome of 3.2 x 10^9 base pairs is identical between any two individuals, excluding the 0.1 % that varies. A large fraction of the variation is common in the general population, i.e. the variant allele is seen as often or almost as often as the wild-type allele. However, some of the variation is rare, seen only in less than 1% of individuals or possibly even unique to one person. The early genetic studies were performed by selecting biologically interesting candidate genes and searching for sequence variants segregating with the disease in families with multiple affected individuals or variants identified from a small number of affected cases. Many of these studies concentrated on genes coding for the structural components of cartilage, like the collagens (for reviews, see (Kuivaniemi et al. 1997; Loughlin 2001)).

Next, genome-wide studies were launched to search for chromosomal regions co-segregating with a disease in families or in sibling pairs. The genome-wide linkage analyses utilized a set of variants throughout the genome without prior knowledge or hypothesis of the function of the genes. Initially a few hundred microsatellite markers, which were located on average 10 million base pairs apart, were selected throughout the human genome. The chromosomal regions identified by the linkage analysis were usually

very large, containing hundreds of genes, and needed fine mapping with additional genetic markers to better locate the genome region of interest. The genome-wide linkage study approach has been very successful in locating disease-causing genes for monogenic diseases (for example (Kestilä et al. 1994; Mäkelä-Bengs et al. 1998; Nousiainen et al. 2008)). Genes causing rare, familial forms of OA have been identified by genetic linkage studies, which have also revealed novel insight on OA etiology, even though the identified variants have not been significant in predisposing to common forms of OA at the population level (Palotie et al. 1989; Ala-Kokko et al. 1990; Vikkula et al. 1993; Prockop et al. 1997; Jakkula et al. 2005).

In recent years, the knowledge of the human genome has grown substantially. The linkage disequilibrium (LD) structure of the human genome was studied in the international HapMap project, gaining understanding of genetic tag markers that are informative and can cover surrounding regions of the genome (Gibbs et al. 2003). That and the technological improvements in genotyping methods have decreased the cost of genotyping and thus enabled high throughput gene mapping studies with large numbers of informative variants in a large number samples (Craddock et al. 2010; Lango Allen et al. 2010). Genome-wide association studies use hundreds of thousands of tag markers throughout the genome and require no priori hypothesis on the disease etiology. The association is measured by a statistical test of the co-occurrence of an allele with a phenotype. The basic research frame in an association study is a case-control sample set of unrelated individuals. Genome-wide association analysis (GWAS) is usually performed with common single nucleotide polymorphism (SNP) markers. GWAS aiming to identify predisposing variants for common, multifactorial diseases require large sample sizes because the effect of a single variant is typically small. So far, GWAS studies of OA phenotypes have revealed few confirmed variants.

Many of the initial genetic associations have not been replicated in the follow-up studies. This may be due to many different factors such as a false positive original finding, a small sample size in the replication study, which does not have the power to detect a true association with a small effect size, or a difference in phenotypes between studies. An accurately defined phenotype should be reliably measurable and represent the biological phenomenon as closely as possible. Sometimes the optimal phenotyping method for a genetic study does not correspond with the diagnostic criteria used in patient care. For example, pain is an important symptom in evaluating the need for treatment in OA, but it is typically a poor phenotype for genetic studies since it can be caused by several factors and it is difficult to measure reliably.

Our aim is to review the studies aiming to identify disease-predisposing variants for different OA phenotypes. We will summarize different genome-wide linkage (GWL) and some of the earlier candidate gene studies performed in OA. Additionally we will present the novel findings in recent genome-wide association studies and discuss the challenges confronted in gene mapping studies of complex disease.

2. Heritability

Heritability is defined as the proportion of the total phenotypic variation that is caused by genetic factors. The heritability can vary between 1 - 100 % and it is dependent on the studied population. For example, the heritability of height is roughly 80 % (Silventoinen et al. 2003). Traditionally, twins have been used as study subjects for heritability estimates;

monozygotic twins share 100 % of their genome and dizygotic twins share on average 50 % of their genome. Since twins share their prenatal environment and often most of the environmental factors later in life, the higher concordance in the phenotype between monozygotic twins than between dizygotic twins is considered to be caused by genetic factors (Kempthorne et al. 1961).

In OA the heritability estimates have also varied between the study populations and different OA types, but can roughly be estimated to be between 50-60 %. Based on a twin study by Page et al. (2003), the heritability of hip OA was approximately more than half in males in the USA; the genetic effect on self-reported hip replacement surgery was 53 % and the effect for radiologically verified primary hip OA was 61%. Similar results were observed in a study by MacGregor et al. (2000) with a UK population-based cohort of women: Heritability of 58% was observed for radiographic hip OA and 64% for radiographic joint space narrowing. High heritability estimates were reported for radiological knee OA of medial osteophytes (69 %) and for joint space narrowing (80%) in a population-based study with twins from the UK (Zhai et al. 2007). The heritability of radiographic hand OA has been shown to vary between 47.6 % and 67.4 % in an UK population-based study sample of females. The lower value was for DIP OA based on joint space narrowing and osteophytes, and the upper value the total Kellgren and Lawrence value for all 30 hand joints (Livshits et al. 2007).

3. Genome-wide linkage studies

Similarly as in other complex diseases the early genetic studies in OA focused on rare families and genes known to have a biological role in the development and structure of cartilage (Palotie et al. 1989; Ala-Kokko et al. 1990; Vikkula et al. 1993; Jakkula et al. 2005). In the 1990s, the introduction of panels of highly informative microsatellite markers evenly covering the genome allowed hypothesis-free screening with no prior knowledge of the gene functions (Petrukhin et al. 1993; Straub et al. 1993).

The first genome-wide linkage studies in OA families were published over ten years ago (Leppävuori et al. 1999; Loughlin et al. 1999). They were followed by a number of twin, sib pair, and family-based studies and their meta-analysis, which together have identified at least fifteen OA loci with a genome-wide significant logarithm of odds score (LOD $\geq$ 3.3) (Leppävuori et al. 1999; Loughlin et al. 1999; Ingvarsson et al. 2001; Demissie et al. 2002; Loughlin et al. 2002b; Stefansson et al. 2003; Forster et al. 2004b; Hunter et al. 2004; Loughlin et al. 2004; Southam et al. 2004; Greig et al. 2006; Lee et al. 2006; Mabuchi et al. 2006; Meulenbelt et al. 2006; Livshits et al. 2007; Min et al. 2007; Meulenbelt et al. 2008). Of these, loci in 2p23-p24, 2q31-q33, 4q31-q32, 7q34-q36, and 19q13 have been implicated also in other independent studies. Table 1 lists loci identified with genome-wide significant evidence for linkage at least in one study and also additional studies showing suggestive evidence for linkage for these loci. However, since the identified linkage peaks have typically been wide and the marker maps quite sparse, it is challenging to evaluate the true overlap between the studies.

Although the linkage screens and their follow-up fine mapping studies have revealed several interesting OA candidate loci, very few, if any, OA predisposing variants that would explain the observed linkage have been identified within these loci. Loci with genome-wide significant evidence for linkage supported by at least one independent study, as well as some of the candidate genes within these regions, are shortly described below.

Chr	LOD	Phenotype	Country	n (individuals in screening/finemapping) n (families or sibpairs)**	Ref.
2p23.3–24.1	**4.4**	DIP/CMC1	Iceland	1143 cases + 939 relatives / 2162 cases + 873 controls 329 families (≥2 aff/fam)	(Stefansson et al. 2003)
2p23.3	2.2	JSN, hand	USA	1477 / - 296 families	(Demissie et al. 2002)
2p13.2–2p14 and **2p12–13.3**	2.9 and **4.0**	DIP and Tot-KL, hand	UK	1028 / - DZ twins	(Livshits et al. 2007)
2q12-2q21	2.3	DIP	Finland	54 27 sib pairs	(Leppävuori et al. 1999)
2q31.1	1.6	Thumb IP	USA	1214 / - 267 families	(Hunter et al. 2004)
2q24.3–31.1	1.6	Hip	UK	Finemapping > 962 / > 756 481 families (≥2 aff sib pair /fam) / 378 families (≥2 aff sib pair/fam)	(Loughlin et al. 2000) (Loughlin et al. 2002b)
2q32.1-2q34	p=0.03 meta	Knee, hip, hand	European + USA	3000 893 families	(Lee et al. 2006)
2q23	2.2	CMC1	Iceland	558 204 families	(Stefansson et al. 2003)
2q33.3	**6.1**	GOA	Netherlands	38 / 52+X 4/7 families 1228 assoc	(Meulenbelt et al. 2006)
4q12–21.2	3.1	Hip (women)	UK	178 female hip OA 85 families	(Loughlin et al. 1999)
4q13.1	2.7	PIIANP biomarker	Afr.Am/ Nat.Am.	350 1 extended family	(Chen et al. 2010) *
4q13.3	3.1	Hip (women)	UK	> 436 218 families (of which 146 THR)	(Forster et al. 2004b)
4q	2.3	DIP	Finland	54 27 sibpairs	(Leppävuori et al. 1999)
4q31.3	**3.3**	DIP	Iceland	1143 cases + 939 relatives / 2162 cases + 873 controls 329 families (≥2 aff/fam)	(Stefansson et al. 2003)
4q32.3	**3.8**	Tot-KL, hand	UK	1028 / - DZ twins	(Livshits et al. 2007)
6p21.1–q22.1	2.1	Hip	UK	416 194 families	(Loughlin et al. 1999)
6p21.1-q15	p=0.02 meta	Knee, hip, hand	European + USA	3000 893 families	(Lee et al. 2006) E

Chr	LOD	Phenotype	Country	n (individuals in screening/finemapping) n (families or sibpairs)**	Ref.
6p11.1	**4.8**	Hip (women)	UK	Finemapping > 292 146 families	(Southam et al. 2004)
6p12	**4.6**	THR, hip	UK	> 756 378 families (≥2 aff sib pair/fam)	(Loughlin et al. 2002c)
6q11.2–12	3.1	Tot-KL, hand	UK	1028 / - DZ twins	(Livshits et al. 2007)
7q34-36	p=0.004 meta	Knee, hip, hand	European + USA	3000 893 families	(Lee et al. 2006)
7q32	1.1	Knee, hip	UK	641 481 families	(Chapman et al. 1999)
7q35	3.1	DIP	USA	1214 / - 267 families	(Hunter et al. 2004)
8p23.2	**4.3**	PIIANP biomarker	Afr.Am/ Nat.Am..	350 1 extended family	(Chen et al. 2010)*
8p12	2.6	JSN, hand	UK	354 128 families	Greig et al. 2006
8q11	3.2	COMP biomarker	Afr.Am/ Nat.Am	350 1 extended family	(Chen et al. 2010)*
8q12–21	2.1	DIP	USA	1214 / - 267 families	(Hunter et al. 2004)
8q24.2	2.5	COMP	Afr.Am/ Nat.Am	350 1 extended family	(Chen et al. 2010)*
9q21.2	2.3	JSN, hand	USA	1477 / - 296 families	(Demissie et al. 2002)
9q34.2–34.3	**4.5**	DIP	UK	1028 / - DZ twins	(Livshits et al. 2007)
11p12–11q13.4	p=0.02 meta	Knee, hip, hand	European + USA	3000 893 families	(Lee et al. 2006)
11p11	1.32	Female knee, hip	UK	594 / 392 females 294 families / 192 pairs	(Chapman et al. 1999)
12q21.3–22	**3.9**	DIP	UK	1028 / - DZ twins	(Livshits et al. 2007)
12q24.3	1.7	JSN, hand	USA	1477 / - 296 families	(Demissie et al. 2002)
12q24.3	1.8	DIP	USA	1214 / - 267 families	(Hunter et al. 2004)
13q	2.3	First CMC	USA	1214 / - 267 families	(Hunter et al. 2004)

Chr	LOD	Phenotype	Country	n (individuals in screening/finemapping) n (families or sibpairs)**	Ref.
13q22.1	**3.6**	Hip associated with acetabular dysplasia	Japan	8 aff + 8 unaff 1 family	(Mabuchi et al. 2006)*
14q23-31	2.23	COMP, HA biomarkers	Afr.Am / Nat. Am	350 1 extended family	(Chen et al. 2010) *
14q32.11	3.0	GOA	Netherlands UK Japan	370 179 aff. siblings + 4 trios	(Meulenbelt et al. 2008)
15q21.3-15q26.1	p=0.04 meta	Knee, hip, hand	European + USA	3000 893 families	(Lee et al. 2006)
15q25.3	**6.3**	First CMC	USA	1214 / - 267 families	(Hunter et al. 2004)
19q13.2 and 19q13.4	**4.3** and 4.0	Tot-KL, hand and DIP	UK	1028 / - DZ twins	(Livshits et al. 2007)
19q13.3	1.8	Tot-KL, hand	USA	1477 / - 296 families	(Demissie et al. 2002)
20p13	**3.7**	DIP (women)	USA	1214 / - 267 families	(Hunter et al. 2004)

*Only one family; DIP = distal interphalangeal; GOA = generalized OA; OST = osteophyte; PIP = proximal interphalangeal; JSN = joint space narrowing; Tot-KL = Kellgren Lawrence score sum for both hands; CMC1 = carpometacarpal; TIP = thumb interphalangeal; European background including the USA; In the study by Chen et al. (2010), the phenotype correlates with visually graded hand OA (Chen et al. 2008). Overlapping studies: Lee et al. (2006) meta-analysis includes Chapman et al. 1999, Stefansson et al. 2003, Hunter et al. 2004; Demissie et al. 2002, Hunter et al. 2004; Loughlin et al. 1999, Loughlin et al. 2000, Loughlin et al. 2002b, Chapman et al. 1999, Forster et al. 2004, Southam et al. 2004; Meulenbelt et al. 2006, Meulenbelt et al. 2008.

** the amount of individuals in screening / finemapping, and the amount of families or sibpairs used in the study;

Table 1. Results from OA linkage studies. Modified from Kämäräinen (2009).

The 2p23.3–24.1 region harboring the matrilin (*MATN3*) gene was shown to be significantly linked with hand OA (LOD = 4.4) in a study utilizing 1143 affected individuals and 939 relatives in 329 families (Stefansson et al. 2003). The same region had been previously implicated by Demissie et al. (2002) in 296 families, but without genome-wide significance (LOD=2.2). A possible disease-causing variant was pinpointed in the *MATN3* gene in the same study using 1312 cases and 873 controls, but the mutation was rare and did not fully explain the observed linkage.

A wide locus on 2q12-q34 has provided some evidence for linkage in four independent linkage studies: for DIP OA (Leppävuori et al. 1999), HIP OA (Loughlin et al. 2002a; Loughlin et al. 2002b), thumb IP (Hunter et al. 2004), and generalized OA (Meulenbelt et al. 2006). Only evidence for generalized OA peaking at 2q33.3 was statistically significant and was also supported by a meta-analysis combining three previously published screens (Chapman et al. 1999; Stefansson et al. 2003; Hunter et al. 2004; Lee et al. 2006). It is, however, unlikely that these linkage signals represent the same variant and none of the variants within this locus have yet provided convincing evidence for association, though several candidate genes with suggestive association have been reported: the neuropilin 2 gene (*NRP2*), p = 0.02; the "isocitrate dehydrogenase 1 (NADP+), soluble" gene (*IDH1*), p = 0.03 (Min et al. 2007); FRZB (Loughlin et al. 2004); and IL1R1 (Näkki et al. 2010).

The 6p12-p11 region has shown significant evidence for linkage with hip OA in two overlapping UK screens conducted in 375 (Loughlin et al. 2002c) and 146 families (Southam et al. 2004). No significant OA-associated variants have been identified, but interestingly a variant (rs987237, *TFAP2B*) previously shown to associate with BMI ($p = 2.90 \times 10^{-20}$, n = 195,776) maps within the linked region (Speliotes et al. 2010) - overweight being one of the known predisposing factors for OA.

The loci on 7q35 and 15q25 were identified in a linkage screen for hand OA (n = 1216 study subjects in a DIP OA study) (Hunter et al. 2004) and were further replicated in a meta-analysis extended with independent knee and hip OA families (in total n = 3000 knee, hip, and hand OA study subjects) (Chapman et al. 1999; Stefansson et al. 2003; Hunter et al. 2004; Lee et al. 2006). No OA predisposing variants have been identified.

A region on 4q31-q32 has provided significant evidence for linkage with DIP (Stefansson et al. 2003) and hand OA (Livshits et al. 2007). Further, the locus on 19q13 has shown significant evidence for linkage with hand and DIP OA (19q13.2 and 19q13.4, respectively, (Livshits et al. 2007) and this locus was also supported by a family based earlier linkage screen (Demissie et al. 2002). However to our knowledge, no significant OA predisposing variants have been identified within these loci.

4. Candidate gene studies

OA predisposing genes have been searched for through candidate gene studies, selecting genes based on their biological relevance or following a promising linkage study. Many of these genes participate in the cartilage extracellular matrix (ECM) composition/homeostasis by encoding structural proteins, matrix degrading enzymes, and different inflammatory mediator genes, as well as regulating signaling pathway genes. To date only a few of the putative positive findings in candidate gene association studies have been successfully replicated in an independent population, and the associated variants lack solid evidence for causality and functional differences between susceptibility alleles. For a review, see (Ikegawa 2007). In Table 2 we summarize those candidate genes that have shown the most suggestive evidence for association to OA. Replication of the initial finding in an independent study sample was used as a selection criterion. In addition, we will shortly describe genes with putative biological relevance to OA. They have shown suggestive association with OA in different candidate gene studies (for more details, see reviews by (Loughlin 2005; Bos et al. 2008; Ryder et al. 2008)), but have mostly not been confirmed.

Gene	Locus	Variation	OA*	Cases (n) / Controls (n)	OR	p-value	Population	Reference
ACAN	15q26	VNTR	Ha	43 / 50	3.23 (1.24-8.41)	<0.05	US	(Horton et al. 1998)
		VNTR/A27	Ha	112 / 153	0.46 (0.27-0.78)	0.012	Finnish	(Kämäräinen et al. 2006)
		VNTR/A27	Ha	tot. 134	na	0.04	Australian	(Kirk et al. 2003)
ASPN	9q22.31	Allele D14	K	137 / 234	2.63 (1.5–4.7)	0.00084	Japanese	(Kizawa et al. 2005)
		Allele D14	H	593 / 374	1.70 (1.1–2.5)	0.0078	Japanese	(Kizawa et al. 2005)
		Allele D14	H	364 / 356	1.48 (1.09-2.01)	0.016	British	(Mustafa et al. 2005)
		Allele D14	K	218 / 454	2.04 (1.32-3.15)	0.0013	Chinese	(Jiang et al. 2006)
		Allele D14	K	354 / -	na	0.004	Chinese	(Shi et al. 2007)
COL2A1	12q13.1	HT of HaeIII, HindIII	GOA	123 / 697	5.3 (2.2-12.7)	0.9983	Caucasian	(Meulenbelt et al. 1999)
		VNTR	K	183 / 668p	2.06 (1.27-3.34)	na	Caucasian	(Uitterlinden et al. 2000)
		HT of SNPs in exons 5, 32 and 51	K/H	417 / 280	1.30 (1.04-1.63)	0.024	Japanese	(Ikeda et al. 2002)
		rs2276455	H	160 / 383	1.58 (1.05-2.36)	0.005	Finnish	(Hämäläinen et al. 2009)
ESR1	6q25.1	PvuII, XbaI	GOA	65 / 318	1.86 (1.03-3.24)	0.039	Japanese	(Ushiyama et al. 1998)
		HT of PvuII, XbaI	K	316 / 1122p	1.3 (0.9-1.7)	<0.01	Caucasian	(Bergink et al. 2003)
FRZB	2q32.1	Arg324Gly	H	378 / 760	1.50 (1.1–2.1)	0.04	British	(Loughlin et al. 2004)
		Arg200Trp and Arg 324Gly	H	558 / 760	4.10 (1.6–10.7)	0.007	British	(Loughlin et al. 2004)
		Arg324Gly	G	545 / 1362	1.60 (1.1-2.3)	0.02	Dutch	(Min et al. 2005)
		Arg200Trp and Arg 324Gly	H	570 / 1317	1.90 (1.22–2.96)	0.1	US	(Lane et al. 2006)
		Arg200Trp and Arg 324Gly	K	603 / 599	2.87 (0.92–8.95)	0.04	UK	(Valdes et al. 2007)
GDF5	20q11.22	rs143383	K	718 / 861	1.30 (1.10–1.53)	0.0021	Japanese	(Miyamoto et al. 2007)
		rs143383	H	1000 / 981	1.79 (1.53–2.09)	$1.8x10^{-13}$	Japanese	(Miyamoto et al. 2007)
		rs143383	K	313 / 485	1.54 (1.22–1.95)	0.00028	Chinese	(Miyamoto et al. 2007)
		rs143383	K/H	2487 / 2018	1.28 (1.08–1.51)	0.004	Spanish UK	(Southam et al. 2007)
		rs143383	K/H	1842 / 1166	1.29 (1.14-1.47)	$8x10^{-5}$	UK	(Valdes et al. 2009b)
		rs143383	Ha	604 / 1102	0.68 (0.54-0.85)	$8x10^{-6}$	Dutch	(Vaes et al. 2009)
		rs143383	K	494 / 1174	0.68 (0.53-0.88)	0.003	Dutch	(Vaes et al. 2009)

Gene	Locus	Variation	OA*	Cases (n) / Controls (n)	OR	p-value	Population	Reference
		rs143383	H	5,789 / 7,850	1.16 (1.03–1.31)	0.016	Caucasian Japanese (8 cohorts)	(Evangelou et al. 2009) ***
		rs143383	K	5,085 / 8,135	1.15 (1.09–1.22)	$9.4x\ 10^{-7}$	Caucasian Japanese (10 cohorts)	(Evangelou et al. 2009) ***
		rs143383	Ha	4,040 / 4,792	1.08 (0.96-1.22)	0.19	Caucasian Japanese (6 cohorts)	(Evangelou et al. 2009) ***
IGF-1	12q22-24	CA-repeat	Ha/H K/S	615 /135p	1.9 (1.2-3.1)	0.02	Caucasian	(Meulenbelt et al. 1998)
		CA-repeat	Ha/H K/S	1355/191p	1.4 (1.0-1.8)	0.03	Caucasian	(Zhai et al. 2004)
IL1B	2q12-13	+3954C>T/TaqI	K/H	61 / 254	2.59 (1.4-4.7)	0.0096	Caucasian	(Moos et al. 2000)
		-511C>T/AvaI	H	70 / 816p	1.5 (0.8-2.9)	0.004	Caucasian	(Meulenbelt et al. 2004)
		+3954C>T/TaqI	H	70 / 816p	0.6 (0.4-1.2)	0.003	Caucasian	(Meulenbelt et al. 2004)
		5819G>A	Ha	68 / 51	3.82 (na)	0.021	US	(Stern et al. 2003)
		rs1143634	Ha	165 / 377p	1.6 (1.08-2.26)	0.001	Finnish	(Solovieva et al. 2009)
MATN3	2p24.1	Thr303Met	Ha	2162 / 873	2.12 (0.92-4.86)	na	Iceland	(Stefansson et al. 2003)
		Thr303Met	Ha	50 / 356	4.28 (1.18-14.8)	0.007	German	(Pullig et al. 2007)
ANP32A	15q23	rs7164503	H	1,288 / 1,741	0.67 (0.53–0.84)	$3.8x10^{-4}$	Caucasian (4 cohorts)	(Valdes et al. 2009a).
SMAD3	15q22	rs12901499	H	1,288 / 1,741	1.22 (1.12-1.34)	$7.5x10^{-6}$	Caucasian (5 cohorts)	(Valdes et al. 2010b)
		rs12901499	K	1,888 / 1,741	1.22 (1.09-1.36)	$4.0x10^{-4}$	Caucasian (5 cohorts)	(Valdes et al. 2010b)
DIO2	14q31	rs225014	H	1839 / 2687	1.79 (1.37-2.34)	$2.02x10^{-5}$	Caucasian Japanese (4 cohorts)	(Meulenbelt et al. 2008)
DIO3	14q32	rs945006	G	3,252 / 2,132	0.81 (0.70-0.93)	0.04**	Caucasian (4 cohorts)	(Meulenbelt et al. 2011)
VDR	12q12-14	I365I, TaqI	K	82 / 269p	2.60 (1.01-6.71)	<0.05	Caucasian	(Keen et al. 1997)
		HT of BsmI, ApaI, TaqI	K	179 / 667p	2.31 (1.48-3.59)	0.005	Caucasian	(Uitterlinden et al. 1997; Uitterlinden et al. 2000)

[a]Association for early onset OA; 3 Association for joint involvement and disease severity; *G = generalized; Ha = hand; K = knee; H = hip; na = not available; population based study; HT=haplotype, A27=27 repeats;** = permutation based; *** = including Vaes et al. 2008, Valdes et al. 2008, Southam et al. 2007, Miyamoto et al. 2007; bold font indicates region with linkage finding

Table 2. Candidate gene studies

The first structural genes analyzed were genes coding for major cartilage collagens II, IX, and XI, where mutations causing Stickler syndrome, a mild chondrodysplasia associated with OA, have been identified (for a review, see Robin et al. (2010)). Earlier reports suggested linkage between *COL2A1* and OA in two large families (Palotie et al. 1989; Vikkula et al. 1993), and a causal Arg519Cys mutation in the α1(II) chain was identified in OA families (Ala-Kokko et al. 1990; Fertala et al. 1997). In addition rare sequence variants in the genes for collagens II and XI have been associated with hip/knee OA (Jakkula et al. 2005). Several mutations have been identified in the collagen IX genes in patients with MED, a mild chondrodysplasia characterized by early-onset OA (Paassilta et al. 1999; Czarny-Ratajczak et al. 2001; Briggs et al. 2002). The roles of these genes are indisputable in mild chodrodysplasias, but so far only suggestive evidence for different common variants predisposing to OA have been reported (Ikeda et al. 2002; Hämäläinen et al. 2008; Näkki et al. 2011), none of which have yet been confirmed. Interestingly, mutations causing MED have also been identified in the vWF domain of the *MATN-3* gene (Chapman et al. 2001), which has been suggestively associated with OA later in a linkage and association study. The chromosomal region of 2p23.3–24.1 harboring the *MATN3* gene was shown to be significantly linked with hand OA (LOD = 4.4) in a study utilizing 1143 affected individuals and 939 relatives (Stefansson et al. 2003). A possible disease-causing variant was pinpointed in *MATN3*. Matrilins are ECM proteins expressed in the developing skeletal system. MATN3 is mostly restricted to developing cartilage, especially the epiphyseal cartilage (Stefansson et al. 2003). The expression of *MATN3* has been shown to be enhanced in OA cartilage of humans (Pullig et al. 2002).

Aggrecan (*AGC1, ACAN*) is the most abundant proteoglycan in cartilage and is an essential molecule for its osmotic properties (Roughley et al. 1994). Aggrecan gene transcription was shown to be elevated in early osteoarthritis in STR/ort mice (Gaffen et al. 1997). It contains a large polymorphic *VNTR* region that has been a target for several association studies, as it provides the attachment sites for numerous glycosaminoglycan side chains. Some level of association between *ACAN* and OA has been shown, but the results have been inconsistent (Horton et al. 1998; Kirk et al. 2003; Kämäräinen et al. 2006).

The transforming growth factor-β (TGF-β) signaling pathway has provided interesting candidate genes for OA, such as asporin (*ASPN*), which binds to TGF-β and suppresses the expression of both *ACAN* and *COL2A1* and reduces proteoglycan accumulation (Kizawa et al. 2005). Asporin is expressed in human osteoarthritic cartilage at high levels, but is barely detectable in cartilage of healthy individuals (Kizawa et al. 2005). The association between *ASPN* and knee/hip OA was first found in a Japanese population by Kizawa et al. (2005) and then replicated for knee OA by Nakamura et al. (2007) in a meta-analysis combining Europeans and Asians ($p = 0.003$, summary OR 1.46 with significant heterogeneity ($p=0.047$)). After stratification, association of the *ASPN* D14 allele with knee OA was seen only in the Asian populations. It is difficult to prove whether there is a true ethnical difference seen in the study, since there were also differences in the patient selection criteria between different ethnic populations.

Another member of the TGF-β superfamily is GDF5, growth and differentiation factor 5, which is closely related to the subfamily of bone- and cartilage-inducing molecules called the bone morphogenetic proteins (BMPs). GDF5 seems to induce cartilage and bone formation and stimulate de novo synthesis of proteoglycan ACAN (Erlacher et al. 1998). Mutations in this gene cause skeletal alterations both in humans (Thomas et al. 1996) and in

mice (Storm et al. 1994). *GDF5* was first associated with hip and knee OA in Asian populations (1000 hip OA cases, 984 controls, $p = 1.8 \times 10^{-13}$) (Miyamoto et al. 2007), and the knee OA finding was replicated in a large meta-analysis (5085 knee OA cases and 8135 controls; OR 1.15, 95% CI 1.09-1.22, $p = 9.4 \times 10^{-7}$, Table 4) (Evangelou et al. 2009).

Participation of the TGF-β pathway was suggested also by a recent meta-analysis where the rs12901499 SNP in the *SMAD3* gene showed association with hip OA in a study utilizing five OA cohorts (1288 hip OA cases, 1741 controls; OR = 1.22, 95% CI 1.12-1.34, $p < 7.5 \times 10^{-6}$) and a similar trend was seen in knee OA (1888 knee OA cases, 3057 controls; OR = 1.22, 95% CI 1.09-1.36, $p < 4.0 \times 10^{-4}$) (Valdes et al. 2010b). SMAD3 has been suggested to act as an effector of the TGF-beta response (Zhang et al. 1996). *SMAD3* is located in chromosomal area 15q22.33 previously linked with OA: 15q21.3-15q26.1 with a p-value of 0.04 (Lee et al. 2006) and 15q25.3 with a LOD score of 6.3 (Hunter et al. 2004). In the same chromosomal region, *ANP32A* has been suggestively associated with hip OA in a study utilizing four patient cohorts (meta-analysis $p = 3.8 \times 10^{-4}$) and it was suggested to play a role in increased chondrocyte apoptosis (Valdes et al. 2009a). In mice, the over-expression of the Smurf2 gene seems to lead to dephosphorylation of Smad3 and cause the spontaneous OA phenotype (Wu et al. 2008).

The Wnt (wingless) signaling pathway that is involved in skeletal and joint patterning in embryogenesis has also raised interest in OA genetic studies. Previously, James et al. (2000) suggested that a member of this family, FrzB-2, may play a role in apoptosis and that the expression of this protein may be important in the pathogenesis of human OA. FRZB is a soluble antagonist of Wnt signalling and the gene showed some association with hip OA in a study by Loughlin et al. (2004) among others. However, the association could not be confirmed in a meta-analysis by Kerkhof et al. (2008) or in a large-scale association analysis of 5789 cases and 7859 controls with two *FRZB* variants (Evangelou et al. 2009), as the latter study revealed only a borderline association for hip OA ($p = 0.0199$).

The inflammatory cascade in OA cartilage is a widely studied topic in OA genetics. Interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α) have been shown to inhibit collagen II production in chondrocytes by activating signaling pathways c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38 MAPK), and nuclear factor kappa B (NF-κB) (Robbins et al. 2000; Seguin et al. 2003). Mechanical stress can also activate these pathways. The interleukin-1 gene family cluster is located on chromosome 2q12-13, and several association studies have shown a possible role for these genes in hip, knee, or hand OA (Moos et al. 2000; Loughlin et al. 2002a; Meulenbelt et al. 2004; Solovieva et al. 2009; Näkki et al. 2010). Individual associations have not been replicated, however. Kerkhof et al. (2011a) performed a meta-analysis to clarify the role of the common variants in the *IL1B* and *IL1RN* genes on the risk of knee and hip OA. No evidence of association was seen for individual variants ($p > 0.05$), but a suggestive association with reduced severity of knee OA was seen for a CTA-haplotype (rs419598, rs315952, and rs9005; OR 0.71, 95 % CI 0.56-0.91, $p = 0.006$).

Interleukin 6 (IL-6) is a pleiotropic proinflammatory cytokine that is markedly up-regulated in tissue inflammation. There is plenty of biological evidence of its role in OA pathogenesis. A significant rise in the level of IL-6 mRNA has been detected in OA-affected cartilage, and IL-6 levels in the serum and synovial fluid have been reported to be elevated among OA patients (Kaneko et al. 2000). Additionally, *IL-6* knockout mice develop more severe OA than wild-type animals (de Hooge et al. 2005). Genetic analyses

have not been able to show compelling evidence for any of the common variants in *IL-6* with OA, however. *IL-6* promoter variant rs1800795 has been found to correlate for example with pain sensation in rheumatoid arthritis (p = 0.014) (Oen et al. 2005), and there is initial evidence for its association in a small set of symptomatic hand OA cases (OR 1.52, 95% CI 1.5-9.0, p = 0.004) (Kämäräinen et al. 2008). A recent meta-analysis of this SNP, however, (1101 hip OA patients, 1904 knee OA patients, and 2511 controls) showed no evidence for association with the risk of hip and knee osteoarthritis (p = 0.95 and p = 0.30, respectively) (Valdes et al. 2010a), although the study sample had 80 % power to observe association with the OR 1.12 for hip and OR 1.10 for knee OA with p < 0.05. IL-6 has been reported to contribute to the disease symptoms in rheumatoid arthritis and in OA ((Kaneko et al. 2000; Cronstein 2007), respectively), and as Valdes et al. (2010a) point out, confirming the lack of genetic association does not imply a lack of involvement in disease. In addition, IL4R has a known role in cartilage homeostasis by affecting inflammation due to mechanical stress. Common variants in this gene have shown suggestive evidence for association with OA (OR 2.1, 95 % CI 1.3-3.5, p = 0.004) (Forster et al. 2004a), but the associations have not been confirmed.

In OA, the degradation of cartilage ECM exceeds its synthesis and the primary cause has been suggested to be an increase in proteolytic enzyme activity, since aggrecan cleavage products accumulate in the synovial fluid of OA patients (Sandy et al. 1992). Two aggrecanases, *ADAMTS4* and *ADAMTS5*, are expressed in human OA cartilage and localize in the areas of aggrecan depletion, and have the highest specific activity for aggrecan cleavage *in vitro* (Tortorella et al. 2002). Suppression of both enzymes by siRNA reduces aggrecan degradation (Song et al. 2007). Tetlow et al. (2001) showed that several matrix metalloproteinases (MMPs 1, 3, 8, and 13), IL-1β, and TNF-α are present in the superficial zone of OA cartilage, where the chondrocyte clusters are located and where degenerative matrix changes appear. Matrix metalloproteinases break down collagens and MMP-13 is specialized in breaking the type II collagen.

In a study by Meulenbelt et al. (2008), a suggestive association between hip OA and variant rs225014 (Thr92Ala) in the iodothyronine-deiodinase enzyme type II gene (*DIO2*) was detected in 1839 hip OA cases and 2687 controls from Asia and Europe. The variant was located in close proximity to the linkage region on 14q32.11 (LOD 3.03). Some association was observed in four independent OA study samples of females with Caucasian and Asian background, and an OR = 1.79 (95% CI 1.37–2.34; $p = 2.02 \times 10^{-5}$) was obtained for rs225014 and rs12885300 haplotypes. The authors hypothesized that the link between this gene and OA is the role of *DIO2* in one of the following: endochondral ossification, OA progression, or inflammatory pathways including NFκB. The gene product of *DIO2* participates in the regulation of intracellular levels of active thyroid hormone (T3) in target tissues such as the growth plate. A meta-analysis of genes modulating intracellular T3 bioavailability has shown a role for another gene, deiodinase iodothyronine type III (*DIO3*), in OA (Meulenbelt et al. 2011). A total of 3252 hip/hand/knee cases and 2132 controls were studied and the suggestive association was seen with variant rs945006 for knee and/or hip OA (OR 0.81, 95 % CI 0.70-0.93, p = 0.004, permutation-based corrected p = 0.039).

Several studies have investigated the role of the vitamin D receptor gene (*VDR*) in OA. Restriction enzyme polymorphisms have been suggestively associated with knee and hand OA in limited sample sets (Keen et al. 1997; Uitterlinden et al. 1997; Uitterlinden et al. 2000;

Solovieva et al. 2006). However, a meta-analysis of ten studies on VDR polymorphisms and OA provided no evidence of association (Lee et al. 2009). The studies used in the meta-analysis differed in respect to the site of OA involvement, and heterogeneity in clinical features such as age and sex, which both affect the development of OA, and was recognized by the authors.

The role of variants in the estrogen receptor genes (*ESR1*, *ESR2*) has also been studied in OA. The role of estrogen may be important in OA since estrogen has been shown to be chondrodestructive via a receptor-mediated mechanism, and estrogen receptors are found in canine, rabbit, and human articular cartilage (Tsai et al. 1992). Suggestive association of restriction polymorphisms in *ESR1* has been detected in three studies (Ushiyama et al. 1998; Bergink et al. 2003; Jin et al. 2004). A meta-analysis of 2364 hip, 1983 knee, and 1431 hand OA cases and 6773, 4706, and 3883 controls, respectively, was performed for variants in *ESR2*. Variant rs1256031 showed some evidence for association with increased risk for hip OA in women (OR 1.36, 95 % CI 1.08-1.70, p = 0.009), but the combined analysis with knee and hand OA data did not show evidence for this variant (OR 1.06, 95 % CI 0.99-1.15, p = 0.10). The study had 80 % power to detect an OR of at least 1.14 for hip OA (α=0.05).

5. Genome-wide association studies

Single nucleotide variants (SNPs) and information on the linkage disequilibrium (LD) structure between them identified by the HapMap and 1000 Genomes projects (Gibbs et al. 2003; Frazer et al. 2007; Durbin et al. 2011; Patterson 2011), as well as significant advancements in commercially available genotyping methods, have enabled development of genome-wide SNP arrays capable of genotyping a few hundred thousands to up to millions of evenly distributed variants within the genome at a reasonable cost in large amounts of samples. Genome-wide association studies (GWAS) have the advantage of not requiring knowledge and hypotheses on the gene functions beforehand, since the whole genome is under investigation in a systematic manner. GWAS analyses have proven a highly effective approach for identifying disease predisposing variants for common familial diseases (Wellcome Trust Case Control Consortium 2007).

The increased number of SNPs on arrays in recent years has improved the coverage of the common and especially the non-frequent variants; however, all common variations are still not fully covered. The increase in the number of SNPs represented on the arrays has also significantly increased the amount of association tests conducted in a project, thus making multiple testing correction and utilization of strict thresholds for statistically significant association very critical to avoid a multitude of false positive findings. The statistical significance threshold for the p-value suggested by the Wellcome Trust Case Control Consortium in 2007 was $p < 5x10^{-7}$ (2007), while the current broadly accepted threshold for genome-wide significance is $p < 5x10^{-8}$. The high quality genotype data produced from the commercially available arrays has also enabled the collection of sufficiently large data sets, which is a prerequisite for reliably identifying predisposing variants with low Odds Ratios (OR 1.1-1.5) typically seen in common, multi-factorial diseases (Manolio et al. 2009). Altogether four high density GWAS and one meta-analysis of GWAS have been conducted for OA phenotypes and the GWAS approach has proven to be a useful tool also in OA (Table 3). Three of the four genome-wide significant or highly probable OA predisposing variants have been identified by GWAS (Table 4).

Phenotype	Screening cases / controls, screening (population)*	Replication cases / controls, replication (population)**	Platform in screening phase	Ref
Hip: Radiological + clinical	93 / 631 (Japanese)	426 / 1006 (Japanese)	71,880 SNPs	(Mototani et al. 2005)
Knee: radiological, clinical	94 / 658 (Japanese)	1,399 / 2,141 (Japanese, Chinese)	99,295 SNPs The multiplex PCR–based Invader assay28 (Third Wave Technologies)	(Miyamoto et al. 2008)
Hand: radiological	1804 in total (UK, Dutch)	3266 in total (UK, Dutch, Caucasian from Russian Federation autonomous regions)	Illumina HumanHap 317 k Illumina HumanHap 550 k	(Zhai et al. 2009)
Hip: radiological or TJR Knee: radiological or TJR Hand: The American College of Rheumatology	hip + knee + hand: 248 + 515 + 578 / 1,411 + 1,047 + 1,038 (European ancestry: Dutch)	5,720 + 4,066 + 3,811/ 39,000 controls (European ancestry)	Illumina HumanHap 550v3 k Infinium HumanHap 300 k Affymetrix GeneChip Human Mapping	(Kerkhof et al. 2010)
Knee: radiological, clinical	906 / 3,396 (Japanese)	1,879 / 4,814 (Japanese, European ancestry)	Illumina HumanHap 550 k	(Nakajima et al. 2010)
Hip and knee: radiological, clinical	3177 / 4894 (UK)	~60.000 (European)	Illumina Human610 platform Illumina 1.2M Duo platform	(Panoutsopoulou et al. 2011)
Knee: radiological, clinical	2,371 / 35,909 (European ancestry: Icelandic, Dutch, UK, USA)	6,709 / 44.439 (European ancestry)	Illumina HumanHap 550v3 k Infinium HumanHap 300 k Affymetrix GeneChip Human Mapping	(Evangelou et al. 2011)

* In the screening phase, the nationality of the studied population is specified.
** Including the screening sample

Table 3. GWA studies performed in OA

Mototani and coworkers (2005) conducted a low density genome wide analysis by testing over 70,000 gene-based SNP markers for association with hip OA. The initial screening phase revealed a variant in the calmodulin 1 *CALM1* gene (rs3213718, IVS3 - 293C > T) on 14q24–q31 that showed some association in the small Japanese case-control set (OR=2.51, 95 % CI 1.40–4.50; p=0.0015). A replication in 334 individuals with hip OA and 375 control subjects provided a p-value of p=0.00065, (OR=2.40, 95 % CI 1.43–4.02) but when the reported genotype count data is combined into a meta-analysis, there is no genome wide significance (OR=1.35, 95 % CI 1.12-1.62; p = 0.0015, The Plink program (Purcell et al. 2007)).

The s3213718 SNP did not associate with knee OA in two low-powered Caucasian cohorts (298 male cases/300 male controls and 305 female cases, 299 female controls) (Valdes et al. 2007). Another SNP initially associating with hip OA in the Japanese study (rs12885713: 303 cases, 375 controls; OR = 2.56, 95 % CI 1.50–4.36, p = 0.00036) did not replicate in a study of 920 Caucasian hip OA cases and 752 controls, which had 97 % power to detect the original association (Loughlin et al. 2006). This might be due to a false positive original finding or due to substantial differences in the phenotypes, 40 % of the Japanese cases suffering from acetabular dysplasia (Hoaglund 2007).

Two GWA studies utilizing pooled knee OA and control DNA samples have been conducted. First, a low density genome-wide analysis of 25 494 SNPs located within gene regions utilizing pooled DNA samples of 335 female knee OA cases and 335 female controls was performed (Spector et al. 2006). The most significant SNPs were individually genotyped in the same samples and those with the most consistent difference were also genotyped in two replication sets of 1124 cases and 902 controls. One variant (rs912428a) in the *LRCH1* gene on chromosome 13 showed the most consistent difference in the replication samples, but the association was not significant after correcting for multiple testing (OR of 1.45, and a p-value < 5×10^{-4} in the analysis combining the screening and the replication sets).

A high-density GWAS was also conducted utilizing pooled samples. A three-phase study used a chip containing over 500 000 genome-wide variants to screen pools of 357 female knee OA cases and 285 female controls, replicated the most significant 28 variants in 871 knee OA cases and 1788 controls, and further validated seven variants in an additional 306 cases and 584 controls (Valdes et al. 2008). None of SNPs reached genome-wide significance in the screening phase, but one variant (rs4140564) located in an LD block containing the PTGS2 and PLA2G4A genes, which are involved in the prostaglandin E2 synthesis pathway, provided quite convincing evidence for association in the combined analysis of the screening and the replication samples (OR 1.55 (95% CI 1.30–1.85), p = 6.9×10^{-7}).

A second low density genome-wide analysis utilizing individually genotyped cases and controls was conducted in a limited sample of 94 knee OA cases and 658 controls of Japanese origin using approximately 100 000 SNPs (Miyamoto et al. 2008). Fine-mapping of the initially identified susceptibility locus and further validation in independent OA cohorts revealed variants with genome-wide significant association to knee OA (a combined p-value of 7.3×10^{-11} with an OR of 1.43 (95% CI 1.28–1.59 for rs7639618). Re-sequencing of the novel *DVWA* gene identified three putatively functional SNPs: two missense SNPs, rs11718863 (encoding Y169N) and rs7639618 (encoding C260Y), and rs9864422 located in intron 1. The two coding variants were in almost complete LD and one of the four observed haplotypes (Tyr169-Cys260) was significantly overrepresented in osteoarthritis and was found to bind β-tubulin weaker than the other three isoforms in a *in vitro* functional assay. Later, Wagener and co-workers (Wagener et al. 2009) suggested that the *DVWA* might actually represent the COL6A4 gene, but according to current RefSeq annotation it is a transcribed pseudogene and represents the 5' end of a presumed ortholog to a mouse gene encoding a collagen VI alpha 4 chain protein (UCSC Genome Browser, GRCh37/hg19; http://genome.ucsc.edu/). Association of the variants in the *DVWA* gene was not replicated in a follow-up analysis of 1120 European knee OA cases and 2147 controls, which had approximately 96 % power to observe an association with an effect size (OR= 1.43) reported in the combined Japanese and Chinese population and an allele frequency of 0.14 in cases) (Meulenbelt et al. 2009). Whether the lack of association is due to a limited sample size and overestimation of the effect size in the original publication,

difference in the phenotypes, heterogeneity in different populations, or a false positive initial finding, requires further analysis in a significantly large sample cohort.

A larger GWAS in a Japanese population genotyped over 500 000 SNPs in 906 knee OA cases and 3396 controls (Nakajima et al. 2010). Replication of the 15 SNPs with a p-value smaller than $1x10^{-5}$ in the initial screen in an independent Japanese cohort identified two SNPs (rs7775228 and rs10947262) showing genome-wide significant evidence for association in a combined analysis ($p = 2.43x10^{-8}$, OR= 1.34; 95% CI = 1.21–1.49 and $p = 6.73x10^{-8}$; OR= 1.32; 95% CI = 1.19–1.46, respectively). The two SNPs were in high LD with each other and were located within a 340-kb region within the HLA locus, including *BTNL2*, *HLA-DRA*, *HLA-DRB5*, *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1*. Most of the genes within the associated region belong to the HLA class II molecules, which are expressed in antigen presenting cells and play a central role in the immune system by presenting peptides derived from extracellular proteins. The *BTNL2* gene encodes butyrophilin-like 2, which negatively regulates T-cell activation. The variant rs10947262 in the *BTNL2* gene showed nominal evidence for association also in a European cohort and provided a p-value of $5.10x10^{-9}$ in a meta-analysis combining the Japanese and European data. The authors did not report whether the previously identified variants in the *DVWA* gene (Miyamoto et al. 2008) were tagged by the SNPs in the array and showed no evidence for association in the screen.

Over 300 000 genome-wide variants were analyzed for association to hand OA in the TwinsUK cohort, which had radiographs of both hands available for 799 subjects (Zhai et al. 2009). None of the SNPs achieved significant evidence for association in the first screening phase, and the top 100 SNPs were selected for further analysis in a part of the Rotterdam cohort with both genotype and hand OA data available. Of the five SNPs nominally replicated in the second cohort, none were significantly associated with hand OA in the meta-analysis combining the two screening and four additional replication cohorts. The strongest evidence for association was observed with an SNP rs716508 located in the intron of the *A2BP1* gene ($p = 4.75 x10^{-5}$), but did not reach genome-wide significance.

A high density GWAS of over 500 000 SNPs was aimed at identifying variants associated with a generalized OA (Kerkhof et al. 2010). In total, 1341 Dutch OA cases and 3496 Dutch controls were utilized in the screen, and SNPs associated with at least two OA phenotypes were analyzed in 12 additional cohorts including 14 938 independent OA cases and 39 000 controls in total. Of the twelve top hits analyzed in the replication cohorts, one variant (rs3815148) located in *COG5* on chromosome 7 was significantly associated with hand and/or knee OA in the meta-analysis combining screening and replication cohorts ($p = 8x10^{-8}$, OR 1.14, 95% CI 1.09-1.19). Variants in the previously identified *GDF5* gene (Miyamoto et al. 2007) showed evidence for association to hand OA in the screening phase ($p = 1x10^{-5}$), but the variant (rs6088813) provided only a p-value of 0.01 in the replication, although there were 8970 hand and/or knee of cases and almost 40 000 controls included in the analysis. None of the other previously identified OA variants were included in the replication effort. Although the authors monitored for their association in the screening cohort, it had only a limited power to observe the association. Variants rs225014 and 12885300 in the DIO2 gene were reported not to associate with hip OA in the Rotterdam Study, but they showed a trend towards the same direction observed in the original publication (Meulenbelt et al. 2008). The SNPs rs4140564 in *PTGS2* (Valdes et al. 2008) and rs7639618 in *DVWA* (Miyamoto et al. 2008) showed no evidence for association with knee OA in the to some extent undersized Rotterdam cohort.

Panoutsopoulou and co-workers (2011) conducted a GWAS of knee and hip OA with over 500 000 SNPs in 3,177 cases and 4,894 controls in the screening phase and almost 60,000 study subjects in the replication phase. Variant rs4512391 near the *TRIB1* gene showed the strongest association with combined hip and knee OA (OR=1.17, 95% CI 1.10-1.25; $p=1.8\times10^{-6}$) and with knee OA (OR = 1.23, 95% CI 1.13-1.33; $p = 1.1\times10^{-6}$) and rs4977469 in *FAM154A* with hip OA (OR = 1.30, 95% CI 1.17- 1.45; $p = 1.2\times10^{-6}$) in the initial screen. However, none of the SNPs included in the replication ($p<10^{-4}$) reached genome-wide significance in the analysis combining the screening and the replication data. The screening cohort had limited power to detect association with common variants with low Odds Ratios, thus the previously identified OA variants were not systematically followed-up. Yet, a few variants in biologically interesting genes providing suggestive evidence for association in the combined analysis (p-values between 1.2×10^{-6} and $7.59\text{x}10^{-5}$) were brought up in the discussion (rs13026243 in *NRP2,* rs7626795 in *IL1RAP,* rs2819358 in *ELF3,* rs2280465 in *ACAN,* rs2615977 in *COL11A1).*

The meta-analysis of GWAS for knee OA combined the data of the four previously published GWAS including in total 2371 knee OA cases and 35 909 controls of Caucasian origin in the screening phase (Evangelou et al. 2011). Altogether 11 SNPs (p-value < $5\text{x}10^{-5}$) in 10 different loci were replicated in 3326 cases and 7691 controls from eight European populations. Only two SNPs (rs4730250 and rs10953541), which are located in the previously identified 500 kb LD block on chromosome 7q22 containing six genes, replicated nominally in the combined analysis of the follow-up samples and showed genome-wide significant evidence for association with OA in the analysis combining the meta-analysis GWAS data and 10 replication cohorts of European origin ($p = 9.2\text{x}10^{-9}$, OR 1.17, 95% CI 1.11-1.24) for rs4730250. No evidence for either heterogeneity in the effect size between populations or gender-specific effects was observed. The association was not significantly replicated in an East-Asian cohort of 1183 knee OA cases and 1245 controls, which, however, had a limited power to observe an association of the effect size seen in the European populations (power of 6% when assuming MAF of 0.15 in controls based on HapMap). The meta-analysis combining the European and Asian samples yielded a global summary effect of 1.15 and showed no evidence of heterogeneity. The most significant variant rs4730250 is in high LD with rs10953541 (r2=0.63, D'=1 in HapMap-CEU) and with the previously identified variant rs3815148 (r2=0.77, D'=1 in HapMap CEU), and thus all three are likely to represent the same underlying association signal. None of the other previously confirmed OA variants yielded a p-value < $5\text{x}10^{-5}$, and were not followed up. This likely reflects the limited power of the meta-analysis, but may also indicate heterogeneity between the phenotypes or between European and Asian populations in at least some of the OA susceptibility variants.

As for the other confirmed OA loci, the predisposing gene/variant within the 7q22 locus remains yet to be defined. The associated 500 kb LD block contains six genes: *DUS4L, COG5, GPR22, BCAP29, PRKAR2B*, and *HPB1. DUS4L* encodes for a tRNA-dihydrouridine synthase 4-like. The protein encoded by *COG5* is one of eight proteins which form a Golgi-localized complex required for normal Golgi morphology and function (Ungar et al. 2002). Mutations in *COG5* have been shown to result in congenital disorder of glycosylation type 2I (Paesold-Burda et al. 2009). GPR22 encodes for a G protein-coupled receptor 22, which belongs to a family of the G-protein coupled receptors (O'Dowd et al. 1997). *BCAP29* encodes for a B-cell receptor-associated protein 29. The Bap29/31 complex has been shown to influence the intracellular traffic of MHC class I molecules (Paquet et al. 2004). *PRKAR2B* encodes for a

cAMP-dependent protein kinase, which is a signaling molecule important for a variety of cellular functions. *HPB1* encodes for a HMG-box transcription factor 1, which is a transcriptional repressor regulating the cell cycle and of the Wnt pathway (Sampson et al. 2001).

Chr.	Variant	Putative gene	Predispo-sing allele /Freq	p	OR (95 % CI)	Study population: cases/controls	Ref
3p24	rs7639618	DVWA/ COL6A4P1 CAPN7	C / 0.64	$7.3x10^{-11}$	1.43 (1.28–1.60)	1,399 knee / 2,141 Asian	(Miyamoto et al. 2008)
6p21	rs10947262 (rs7775228)	BTNL2 HLA-DQB1 HLA-DRA HLA-DRB5 HLA-DRB1 HLA-DQA1 HLA-DQB1 HLA-DRB3 HLA-DRB4	C / 0.58	$5.1x10^{-9}$	1.31 (1.20–1.44)	1,879 knee / 4,814 Asian & European	(Nakajima et al. 2010)
7q22	rs4730250 (rs3815148) (rs10953541)	DUS4L COG5 GPR22 BCAP29 PRKAR2B HPB1	G / 0.17	$9.2x10^{-9}$	1.17 (1.11-1.24)	6,709 knee / 44.439 European	(Evangelou et al. 2011) (Kerkhof et al. 2010)
20q11	rs143383	GDF5 UQCC CEP250	T / 0.26	$1.8x10^{-13}$	1.79 (1.53–2.09)	998 hip / 983 Asian	(Miyamoto et al. 2007)

Chr = chromosome; variant= rs number of the most significant reported variant (other reported variants shown in the parenthesis), p-value = combined p-value of screening and replication; OR = odds ratio; Study population= number of cases/controls utilized in the analysis providing the most significant p-value, OA= generalized OA, knee= knee OA, hip= hip OA, All findings were identified by a GWAS approach, except rs143383 in GDF5, which was identified by a candidate gene study.

Table 4. Loci with genome-wide significant evidence for association ($p < 5x10^{-8}$) with OA.

6. Other approaches

There have not been sufficiently large, systematic genome-wide expression studies on human cartilage samples to undoubtedly confirm or exclude any expression patterns in OA cartilage. Some examples of alternative approaches are shortly described below.

Genome-wide expression profiling by Karlsson et al. (2010) of healthy (n = 5) and osteoarthritic cartilage (n = 5) revealed several genes up- or downregulated in OA cartilage. The study analyzing over 47 000 transcripts suggested changes for several gene families: cytokines, such as the tumor necrosis factors (TNF), chemokines like interleukin 8 (IL8), enzymes like matrix metalloproteinase (MMP), growth factors like insulin growth factor (IGF), matrix components like collagen I (COL1), and others such as HLA-DQA1.

In the first serum-based metabolomic study of osteoarthritis in humans, the ratio of two branched-chain amino acids, valine and combination of leusine and isoleucine, to histidine was significantly associated with the disease. The study was conducted in 123 + 76 knee OA cases and 299 + 100 controls by analyzing 163 serum metabolites (Zhai et al. 2010).

In a candidate biomarker study using blood samples (n = 287), hyaluronan (HA), cartilage oligomeric matrix protein (COMP) and collagen IIA N-propeptide (PIIANP), high sensitive C-reactive protein (hs-CRP), and glycated serum protein (GSP) showed an association ($p < 0.05$) with clinical phenotypes of hand OA or hand symptoms, of which PIIANP (0.57), HA (0.49), and COMP (0.43) showed some level of heritability (Chen et al. 2008). PIIANP is a marker of a fetal form of collagen II recapitulated in OA (Chen et al. 2008). The COMP molecule binds to the collagenous structure in cartilage and can initiate the alternative complement pathway (Happonen et al. 2010). HA has a role in cartilage structure as well.

7. Conclusions

Earlier studies have shown the importance of some structural genes in familial OA, but their role in predisposition to common forms of OA remains unclear. It is possible that there are rare mutations with high risk for OA affecting single families (or individuals), and perhaps there are more common alleles with smaller effects functioning at the population level. In population-based genome wide association studies utilizing common variants a handful of genes have been confirmed to affect OA (Table 4), however these studies have not revealed additional evidence that common variants in the earlier candidate genes associate with OA.

The few confirmed genome-wide significant gene variants in OA (Table 4) locate in or near genes that have a role in cell signaling and immunity. For practically all the recognized variants, the functional gene and the predisposing variant is still unknown due to the LD structure of the pinpointed area, thus the mechanism how these loci increase OA susceptibility is yet unknown. The causative gene might not be located in close proximity to the observed variant, but the variant might also affect the gene expression of genes further away in the genome.

As presented in the current review, false positive findings and limited power are issues in many genetic studies of common diseases. In general the power to detect predisposing variants depends on the effect size of the single variant to the disease. The smaller the effect of one variant to the disease the larger the study sample that is needed to observe the effect. Usually in complex diseases the effect size of any single variant is very small thus small effect variants will be missed and negative findings do not exclude the role of a variant to the studied trait (Purcell et al. 2003). A positive finding from an association study could mean that a disease-causing or predisposing variant has been found or a variant in high LD with the true disease-causing or predisposing variant has been identified. However, many aspects in gene mapping need to be taken into account when interpreting the results.

One of the challenges in genetic studies is population stratification, which occurs when the studied population contains genetically different subsets. Significant association might be

due to the genetic difference between the case and control groups, which is unrelated to a given trait. In family-based analysis this is not an issue since the studied individuals share their genetic background, and in the GWAS studies it is possible to better control for the substructure by utilizing the genetic profiles of all the GWAS variants.

Type 1 error is unfortunately a common cause of positive findings. It arises from the fact that the more tests that are performed, the more positive findings that are seen by chance. Bonferroni correction and methods taking into account the LD structure of the genome are used to correct for multiple testing (Nyholt 2004; Li et al. 2005). To exclude the possibility of type 1 error, adequately stringent limit for p-value significance and replication of findings in independent study cohorts are needed. Many of the earlier suggestive candidate gene associations have not been followed-up in the recent GWAS projects leaving the significance of the many earlier findings still unconvincing. The lack of replication in the follow-up cohort may indicate false positive initial association, but might also be due to a limited size of the replication cohort not having enough statistical power to detect an association with a small effect size.

Differences in the phenotype definition may also be a cause for a seeming lack of replication (Kerkhof et al. 2011b). Very diverse diagnostic criteria have been used in different cohorts, which may have potentially enriched for specific subtypes of OA. However, in last few years there has also been successful attempts to harmonize the phenotype designation between cohorts (Evangelou et al. 2011). Further, the clinically used diagnostic criteria for OA are not always the optimal phenotypes in genetic studies. The clinical diagnosis has usually evolved historically on the basis of symptoms rather than the etiology of the disease (Plomin et al. 2009). Pain and disability caused by OA are likely affected by even a greater variety of genetic and environmental factors than the radiological findings of the joints, although they are naturally significant determinants in patient care.

According to current understanding OA is a multi-factorial disease, and several genetic and environmental factors are expected to affect the susceptibility. Although a few genetic predisposing variants have been identified, most of the disease heritability remains unsolved. It has been suggested that OA is a polygenic disease with hundreds or even thousands of predisposing variants, each having very small effect on the disease susceptibility (Evangelou et al. 2011). The challenge of missing heritability has been brought up in search for genes for other complex diseases, where significantly larger international collaborative efforts have already been made, and tens of confirmed and well-replicated disease variants have been identified (International Multiple Sclerosis Genetics Consortium and Wellcome Trust Case Control Consortium 2, 2011; De Jager et al. 2009; Lango Allen et al. 2010). In such cases GWAS conducted by large consortia have been able to identify disease variants that explain approximately 10-20% of the heritable component. Although recent international collaborative efforts have identified a few confirmed variants for OA, significantly larger efforts are needed to tackle the yet unidentified OA predisposing variants.

The methods in molecular genetics are developing rapidly, making it soon possible to sequence the entire human genome in a very reasonable time and cost, opening novel opportunities for genetic studies. Today we have plenty of suggestive evidence of the genes possibly involved in the etiology of OA, but what do we know for sure? We have rare mutations or variants in familial forms of OA, and a handful of confirmed genetic associations of common variants to continue in future studies on their biological function and role in the disease pathology. Significantly larger study cohorts with accurately defined

phenotypes, as well as studies on transcriptomics, proteomics, and lipidomics are needed for complete understanding of the disease.

8. List of abbreviations

Osteoarthritis: OA; linkage disequilibrium: LD; logarithm of odds: LOD; Genome-wide association analysis: GWAS; single nucleotide polymorphism: SNP; genome-wide linkage: GWL; distal interphalangeal: DIP; generalized OA: GOA; osteophyte: OST; proximal interphalangeal: PIP; joint space narrowing JSN; Kellgren Lawrence score KL; carpometacarpal CMC1; thumb interphalangeal: TIP, thumb IP; matrilin: MATN3; interphalangeal: IP; neuropilin 2: NRP2; isocitrate dehydrogenase 1 (NADP+) soluble: IDH1; frizzled-related protein: FRZB; interleukin 1 receptor 1: IL1R1; transcription factor AP-2 beta (activating enhancer binding protein 2 beta): TFAP2B; body mass index: BMI; Aggrecan: AGC1, ACAN: Aspirin: ASPN; collagen, type II, alpha 1: COL2A1; estrogen receptor 1: ESR1; growth differentiation factor 5: GDF5; odds ratio: OR; confidence interval: CI; insulin-like growth factor 1: IGF-1; interleukin 1 beta: IL1B; matrilin 3: MATN3; acidic (leucine-rich) nuclear phosphoprotein 32 family, member A: ANP32A; SMAD family member 3: SMAD3; deiodinase, iodothyronine, type II: DIO2; deiodinase, iodothyronine, type III: DIO3; vitamin D (1,25- dihydroxyvitamin D3) receptor: VDR; multiple epiphyseal dysplasia: MED; arginine: Arg; cysteine: Cys; bone morphogenetic protein: BMP; SMAD specific E3 ubiquitin protein ligase 2: Smurf2; Wingless: Wnt; Interleukin: 1 IL-1; tumor necrosis factor α: TNF-α; c-Jun N-terminal kinase: JNK; p38 mitogen-activated protein kinase: p38 MAPK; nuclear factor kappa B: NF-κB; interleukin 1 receptor antagonist IL1RN; interleukin 6: IL-6; interleukin 4 receptor: IL4R; messenger RNA: mRNA; extracellular matrix: ECM; ADAM metallopeptidase with thrombospondin type 1 motif, 4: ADAMTS4; ADAM metallopeptidase with thrombospondin type 1 motif, 5: ADAMTS5; small interfering: siRNA; matrix metalloproteinase: MMP; interleukin 1 beta: IL-1β; estrogen receptor 2: ESR2; total joint replacement: TJR; calmodulin 1: CALM1; leucine-rich repeats and calponin homology (CH) domain containing 1: LRCH1; prostaglandin-endoperoxide synthase 2: PTGS2; phospholipase A2, group IVA (cytosolic, calcium-dependent): PLA2G4A; collagen, type VI, alpha 4 pseudogene 1: DVWA, COL6A4P1; butyrophilin-like 2 (MHC class II associated): BTNL2; major histocompatibility complex, class II, DR alpha: HLA-DRA; major histocompatibility complex, class II, DR beta 5: HLA-DRB5; major histocompatibility complex, class II, DR beta 1: HLA-DRB1; major histocompatibility complex, class II, DQ alpha 1: HLA-DQA1; major histocompatibility complex, class II, DQ beta 1: HLA-DQB1; RNA binding protein, fox-1 homolog (C. elegans) 1: A2BP1, RBFOX1; component of oligomeric golgi complex 5: COG5; tribbles homolog 1 (Drosophila): TRIB1; interleukin 1 receptor accessory protein: IL1RAP; E74-like factor 3 (ets domain transcription factor, epithelial-specific): ELF3; collagen, type XI, alpha 1: COL11A1; minor allele frequency: MAF; Utah residents with Northern and Western European ancestry from the CEPH collection: CEU; dihydrouridine synthase 4-like (S. cerevisiae): DUS4L; component of oligomeric golgi complex 5: COG5; G protein-coupled receptor 22: GPR22; B-cell receptor-associated protein 29: BCAP29; protein kinase, cAMP-dependent, regulatory, type II, beta: PRKAR2B; PBRM1 polybromo 1: HPB1, PBRM1; calpain 7: CAPN7; ubiquinol-cytochrome c reductase complex chaperone: UQCC; centrosomal protein 250kDa: CEP250; hyaluronan: HA; cartilage oligomeric matrix protein: COMP; collagen IIA N-propeptide: PIIANP; high sensitive C-reactive protein: hs-CRP; glycated serum protein: GSP.

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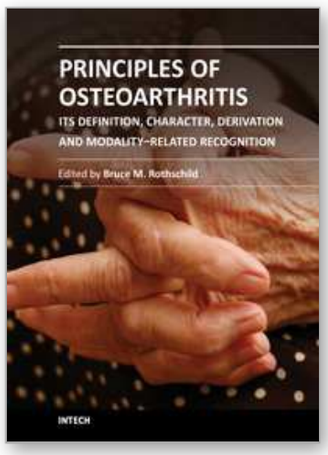

Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition

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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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