Osteoarthritis and Cartilage 22 (2014) 2017–2024

Osteoarthritis and Cartilage

Review

Osteoarthritis Year in Review 2014: genetics and genomics

A. Tsezou*

University of Thessaly, Faculty of Medicine, Dept. Biology, 41110 Larissa, Greece

ARTICLE INFO

Article history:
Received 8 May 2014
Accepted 29 July 2014

Keywords:
Osteoarthritis
Genetics
Functional genomics
Transcriptomics
Epigenetics
microRNAs

SUMMARY

Recent developments in genetics/genomics of osteoarthritis (OA) are discussed to improve our understanding of OA pathophysiology. The discovery of a novel variant near the *NCOA3* (nuclear receptor coactivator 3) gene associated with hip OA and the regulation of *GDF5* gene by four transcription factors via the OA susceptibility locus rs143383 are among important findings in OA genetics. Several microarray-based gene expression studies were published for different tissues of the joint. In OA synovium elevation of collagens and cross-linking enzymes (COL1A1, COL5A1, PLOD2, LOX and TIMP1) responsive to TGF-β was found as well as differential expression pattern between different areas of the osteoarthritic synovial membrane. In OA peripheral blood the role of apoptotic genes was highlighted, while whole genome expression profiling in OA subchondral bone and cartilage revealed common genes in cartilage and bone to be involved in OA development. In epigenetics, several microRNAs (miRNAs) were found to regulate genes' expression in chondrocytes, among which miR-125, miR-127b miR-21, miR-148a and their use as potential drug targets was highlighted. Future studies must focus on the integration of genetics, genomics and epigenetics for the identification of signaling pathways and regulatory networks responsible for OA development.

Introduction

The goal of this review is to present highlights from the published literature related to genetics, functional genomics and epigenetics of human osteoarthritis (OA). A summary of studies published in PUBMED between April 2013 and May 2014, as well as data presented during the 2014 OARSI meeting were selected by the author and are included in the review.

OA is the most common degenerative joint disease and is predicted to be the single greatest cause of disability in the general population by 2030[1]. It has been estimated that 35% of persons suffering from OA are active and therefore its negative impact on work is liable to grow in view of the aging of the population and the longer working lives in developed countries[2]. Despite its high prevalence and substantial public health impact, disease etiology is not fully understood. OA is a multifactorial disease with strong genetic component and heritability estimates ranging from 40% to 65% depending on the joint site[3–5]. The identification of genes associated with OA will help reveal the underlying molecular mechanisms and pathways and may lead to development of OA' gene targeted therapies.

Genetics of OA

Numerous candidate gene association studies aiming to identify disease susceptibility genes have been published in recent years, although few positive results have been firmly replicated across multiple populations. As with other complex diseases, Genome Wide Association Studies (GWAS) have tested the association between thousands of single nucleotide polymorphisms (SNPs) in the whole genome and OA. To date GWAS have identified 15 common variants associated with knee or hip OA in European and Asian populations that have surpassed or reached the genome wide significance level ($P < 5 \times 10^{-8}$)[6,7]. However, the identified individual risk alleles have been found to exert only moderate to small effects to the overall susceptibility to OA development[7]. Among them loci on chromosome 13q34 near the *MCF2L*[8] gene, on chromosome 7q22[9,10], rs143383 polymorphism in *GDF5* gene[11–13], *DVWA*, (HLA) class II/III and *BTNL2* genes[14,15], 9q33 (*ASTN2*), 6q14 (*FILIP1*/*SENP6*), 12p11 (*KLHDC5*/*PTHLH*) and 12q23 (*CHST11*)[16] were strongly associated with hip or knee OA susceptibility. In addition, rs12982744 on 19q13 in *DOT1L* gene was associated with hip OA and cartilage thickness[17,18] and with lower height[19,20]. Growing evidence implicates a functional polymorphism in the *DIO2* gene as an OA risk factor with a current meta-analysis *P* value for the association of this gene with OA of 2.02×10^{-5}[21].

* Tel: 30-241350-2557; Fax: 30-241350-2558.

http://dx.doi.org/10.1016/j.joca.2014.07.024

Recently, a large GWAS meta-analysis from the TREAT-OA consortium consisting of 11,277 cases with radiographic and symptomatic hip OA and 67,473 controls, identified a novel variant rs6094710 at 20q13 near the nuclear receptor coactivator 3 gene (*NCOA3)* associated with hip OA[6]. The SNP is a G/A transition, conferring to A allele carriers about 30% greater risk to develop hip OA and this association reached genome wide significance level with *P* value 7.9×10^{-9} and odds ratio 1.28. Castano-Betancourt *et al.* in a GWAS of 13,013 participants tested for associations between minimal joint space width (mJSW) genetic risk score and mJSW/hip OA. They identified 5 novel loci, there of which, *TGF-a, RUNX-2, FGFR3, FGF3* were significantly associated with cartilage thickness and hip OA with *P* value $<10^{-4}$, suggesting that the identified loci for mJAW may be used to risk-stratify individuals for hip OA[22].

In addition, several meta-analyses of candidate gene association studies have been conducted with positive and negative association for OA susceptibility. In a recent meta-analysis several BMD-identified SNPs were nominally associated with knee OA risk. The strongest signal mapped to 12q3, which contains a gene coding for *SP 7* with odds ratio 1.22 and a *P* value of 9×10^{-4}. Additional loci map to 7p14.1 (*TXNDC3*), 11q13.2 (*LRP5*) and 11p14.1 (*LIN7C*). For all four loci the allele associated with higher BMD was associated with higher odds of OA supporting the hypothesis that BMD may be a risk factor contributing to OA development[23].

An assessment of OA candidate gene approach in a meta-analysis of 9 GWAS in Europeans including 5,636 knee OA patients and 16,972 controls and 4,349 hip OA and 17,836 controls found that SNPs at only two genes, *COL11A1* and *VEGF,* of the 199 analyzed OA candidate genes were associated with hip OA[24]. *COL11A1* showed two independent associations, rs4907986 with odds ratio 1.12, 95 % CI 1.06–1.17 and a *P* value of 1.29×10^{-5} and rs1241164 with OR 0.82, CI 0.74–0.89 and a *P* value of 1.47×10^{-5}, while *VEGF* was associated in a male-specific analysis (rs833058, odds ratio 0.85, CI 0.79–0.91 and a *P* value of 1.35×10^{-5}), pointing to the lack of reproducibility of OA candidate gene studies[24]. No association was found between knee and hip OA and the D13, D14 and D15 repeats of asporin gene (*ASPN*) in Caucasian and Asian populations in a meta-analysis including 4,417 OA patients and 3,403 controls[25] and between *VDR* BsmI, TaqI and ApaI polymorphisms and OA in a meta-analysis including 1,626 knee, hip, hand and lumbar spine OA cases and 2,024 controls[26,27]. Another meta-analysis including 5,409 knee OA patients, 4,355 hip OA patients and 5,362 healthy controls showed there is no direct implication of the *FTO* gene with OA susceptibility and that the effect of the *FTO* variant rs8044769 on OA is solely due to its effect on BMI[28].

Furthermore, in the period covered in this review, several OA candidate gene association studies have been published. However, only studies with large numbers of participants and/or functional studies will be mentioned. The polymorphism rs11564299 in the N-cadherin (*CDH2*) promoter region was associated with OA risk in 312 OA patients and 259 controls, with odds ratio 1.14, 95% CI 0.49–2.62 and a *P* value of 1.5×10^{-3}, with carriers of the minor allele of rs11564299 displaying increased N-cadherin levels in synovial fluid[29]. In silico analysis showed that the minor allele generated a novel transcription factor binding site and hnRNPK was found to be involved in the regulation of elevated N-cadherin expression in OA patients carrying the minor allele of rs11564299[29]. The functional exon 3 deleted growth hormone receptor gene polymorphism *(d3-GHR)* was associated with symptomatic hip OA independently of age and BMI in a combined analysis consisting of 2,175 female cases and 2,623 controls with pooled odds ratio 1.17, 95% CI 1.04–1.32 and a *P* value of 8×10^{-3}[30]. Vidal-Bralo *et al.* identified a new functional microsatellite in macrophage migration inhibitory factor (*MIF*) gene associated with hip OA in a case-control study including 1,775 knee OA patients, 1,782 hip OA patients and 1,878 controls from three European cohorts with *P* of the Mantel–Haenszel analysis 1.8×10^{-2} in women and 2.9×10^{-2} in men[31]. For all above candidate gene association studies, replication studies in different ethnic populations, as well as functional studies for the identification of the mechanisms that confer increased OA risk are needed.

Until now, all identified OA-associated variants explain only a small fraction of less than 10% of the genetic component. Large-scale studies with whole-genome sequencing focusing on variants with low minor allele frequency (MAF 1–5%) and rare variants (MAF <1%) have already starting to emerge[7]. Complete sequence of large OA cohorts will undoubtedly result in novel DNA-variants contributing to disease susceptibility. A recent GWAS identified through whole-genome sequencing of 2,230 individuals, two genome-wide significant loci, rs4238326(C/T) with odds ratio1.44, 95% CI 1.29–1.60 and a *P* value of 8.6×10^{-11} and rs3204689(C/G) with odds ratio 1.46, CI 1.31–1.63 and a *P* value of 1.1×10^{-11} at 15q22 in the *ALDH1A2* gene and a rare variant at 1p31 with odds ratio 47.7 and a *P* value of 1.53×10^{-9}[32]. The variants within the *ALDH1A2* gene were confirmed in replication sets from the Netherlands and the UK yielding an overall association with odds ratio 1.46 and a *P* value of 1.1×10^{-11}[32]. Allelic imbalance analysis for rs3204689 showed that the transcript with the risk-conferring C allele was expressed at a lower level in cartilage and adipose tissue compared to the non-risk allele, suggesting that *ALDH1A2* mediates the effect of the OA risk variants in the associated locus[32]. It is interesting that carriers of the rare variant at 1p31 belonged to an Icelandic family, in several members of which, the risk allele segregated with hand and generalized OA[32]. An exome-sequencing study conducted in 199 hip OA cases and 1,337 controls and in a group of hip OA and mJSW candidate genes (*ASTN2, DIO2, DOT1L, FGFR3, FILIP1, GLT8D1, GNL3, MCF2L, NCOA3, PIK3R1, PTHLH, RUNX2, SENP6, TGF-*α) identified 761 variants in these genes associated with hip OA and mJSW[33]. The strongest signal for mJSW was a rare variant in the *FGF3* gene with a *P* value of 8.6×10^{-5}, which however was not associated to the GWAS signal identified before by the same group[22]. *FGFR3* has previously been shown to be involved in endochondral bone formation and mutations in *FGFR3* result in achondroplasia[33]. Functional assessment of the identified variant is awaited.

Functional studies in OA loci

So far there are limited functional studies that provide possible mechanisms by which genetic variation at OA susceptibility genes confer increased OA risk. Genetic variation at the type II deiodinase (D2) gene *(DIO2)* has been identified as OA risk factor. Bos *et al.* showed that in OA cartilage, ligaments and subchondral bone there is differential allelic expression of *DIO2* mRNA, with the OA-associated 'C' allele of rs225014 in the *DIO2* gene being more abundant in heterozygous carriers (1.3-fold higher presence) than the wild type allele, suggesting that genetic variation at *DIO2* might confer to OA risk[34]. The same group recently identified a possible molecular mechanism of *DIO2* susceptibility in symptomatic OA[35]. It was shown that OA-related changes in methylation at CpG-2031, upstream of *DIO2,* caused significant upregulation of its expression, with β 4.96 and a *P* value of 1.6×10^{-3}, despite the conventional inverse relation between CpG methylation and gene expression, and this effect appeared to be driven by the *DIO2* rs225014 risk allele, with β 5.58 and a *P* value of 6×10^{-4}[35]. Using an *in vitro* chondrogenesis model with genetically modified hBMSC it was shown that up-regulation of *DIO2* induced *EPAS1* and *RUNX2* mediated up-regulation of cartilage degrading enzymes *(MMP-13* and *ADAMTS5*) and markers of mineralization (*ALPL*)[35]. However, as