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Review

Osteoarthritis year in review 2016: genetics, genomics and epigenetics

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SUMMARY

The purpose of this narrative review is to provide an overview of last year's publications in the field of genetics, genomics and epigenetics in the osteoarthritis (OA) field. Major themes arising from a Pubmed search on (epi)genetics in OA were identified. In addition, general developments in the fast evolving field of (epi)genetics are reviewed and relevance for the OA field is summarized.

In the last 5 years, a number of genome-wide association studies have identified a modest number of genetic loci associated to OA. Continued functional research into these DNA variants is showing putative biological mechanisms underlying these associations. Over the last year, no additional large genome-wide association studies were published, but there clearly remains much to be discovered in the OA genetic field.

A lot of research has been done into the epigenetics of OA over the last year. Several genome-wide screens examining the methylome of osteoarthritic cartilage were done. Pathway analysis confirmed deregulation of developmental and extracellular pathways in OA cartilage. Over the last year many microRNAs (miRNAs) have been identified that potentially play important roles in cartilage homeostasis and/or OA process. Continued research will learn whether these identified miRNAs are truly causal and can be used in clinical applications. Many of the epigenetic findings need further confirmation, but they highlight potential novel pathways involved in cartilage biology and OA.

Introduction

Understanding the genetic basis of complex diseases, such as osteoarthritis (OA) has been the focus of many researchers over the last decade. Recent technological advances have expanded the amount "omic" data to multiple molecular levels, from detailed sequencing of the genome, to epigenetic markers, such as DNA-methylation and microRNAs (miRNAs), transcriptomics and metabolomics. Each of these molecular layers are now examined for its relation with OA to get more insight into disease mechanisms underlying OA, and to identify disease drivers. In addition, a key goal is to identify biomarkers that predict disease onset and course.

In this review, a summary is given of the progress of genetics and epigenetics of OA over the last year. This review focuses only on studies that use human material and highlights especially studies that use genome-wide "high throughput" techniques for discovering novel markers and mechanisms of disease. The overall results of OA-(epi)genetics is compared to that of other complex diseases and recommendations for exploiting the (epi)genetic basis of OA are given.

Genetics of OA

Evidence for a genetic component in OA comes from family and twin studies, who estimate the genetic component of OA to be between 40 and 80%, which is similar to many other complex traits. Over the whole spectrum of OA as a disease, a minority of cases are early-onset forms of OA characterized by a strong familial representation of disease (Fig. 1). These early-onset forms of OA represent Mendelian diseases, which are caused by a single mutation that have large effects on the function of the genes/proteins. In contrast, the common form of OA is caused by a combination of genetics and environment. In common age-related OA, many DNA-variants, each with small effects, together result in an increased risk for OA (Fig. 1). Over the last year, no new large genome-wide association studies have been published, and consequently discovery of novel genetic loci for common age-related OA was limited.

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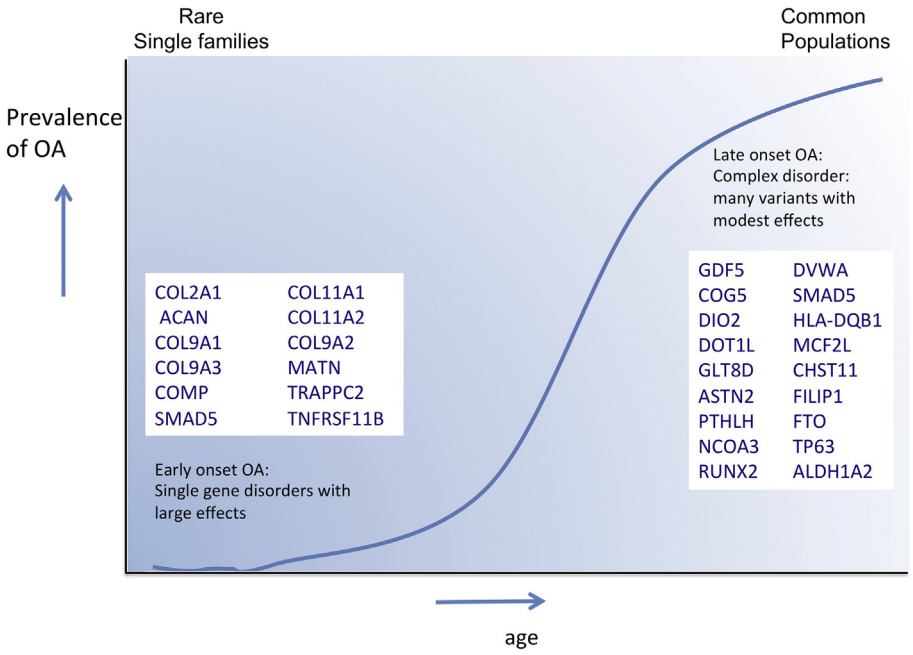

Fig. 1. Genetics of OA. Rare mutations in monogenetic disorders (single causal gene) are in general found in a single family and have a large effect size, resulting in early-onset OA. By contrast, late onset OA is a complex trait and is caused by a large number of common DNA variants together with environmental factors. The effect size of these common variants are in general small, and can vary between individuals in the population.

We can gain novel insights into biological mechanisms underlying OA from both rare Mendelian forms as well as the common forms of OA, by understanding the genetic basis of these diseases.

Rare early-onset forms of OA very often coincide with other clinical features, making it difficult to disentangle the causative role of the mutated gene in OA, since OA can develop as a secondary feature. There are only a few cases where early onset OA is the single feature of a disease[1]. Recently, a gain-of-function mutation in TNFRSF11B (Osteoprotegerin, OPG) was identified to cause familial early-onset OA in several joints[2]. This study identified a heterozygous read-through mutation (p.Stop402Leu) in an extended family by sequencing two distant family members. In addition, they showed enhanced capacity to inhibit osteoclastogenesis and bone resorption *in vitro*. Since drugs are already on the market targeting the OPG-RANKL-RANK pathway, this finding opens new possibilities for OA-treatment[3]. In addition, a linkage study on 33 families with early onset OA identified a region on chromosome 2q21. Targeted resequencing in six family members suggested a known insertion-deletion variant (rs11446594) as a potential functional variant underling the linkage signal[4].

The genetics of the common OA has been studied over the last decade using genomewide association studies, similar as for other complex diseases. Results from these studies have been reviewed extensively[5]. Over the last few years, major advances were made in elucidating the genetic background underlying complex traits. Particularly, for a number of phenotypes for which it was thought to be difficult to disentangle their genetic background, due to the large heterogeneity, such as Schizophrenia[6] and educational Attainment[7], large genomewide association screens (GWAS) have now yielded many loci. Despite considerable heterogeneity in phenotype definition, sample size seems to be a very important factor determining the success of GWAS. For OA, results from GWAS studies have lagged behind, yielding a combined total number of 17 loci for hip, knee and hand OA unto now[8–18]. It seems that many of the identified loci are joint-site specific and possibly even gender specific [Fig. 2(a), Table I], although this observation can still be the result of limited power of the published GWAS studies unto now. Compared to other complex traits, sample size of the largest GWAS upto now ($n = 7000$ discovery cases) is modest. It is expected that if case-numbers increase to tens of thousands of samples, many more loci will be discovered [Fig. 2(b)].

Genetics of OA endophenotypes

Another way to increase power in GWAS is to study intermediate phenotypes underlying the clinical endpoint. In OA, these are for example cartilage thickness, joint shape and other structural traits. Lindner *et al.*[19] studied joint shape in relation to known OA-susceptibility loci and observed that 3 of the 41 studied candidate SNPs showed association with hip joint shape in a cohort with moderate sample size ($n = 929$). During the OARSI2016 meeting, Yau *et al.* presented some preliminary data on a GWAS of bone marrow lesions, one of the major risk factors for knee pain[20]. It was shown that some of the previously identified genetic loci for BMD, also showed nominal association with bone marrow lesions. Continued work on these intermediate phenotypes is expected to yield more genetic loci and ethiological insight into the biological mechanism underlying the relationship between genetic variation and OA.

Is there a need for more genetic studies of OA?

Some voices have postulated that more genetic studies of complex traits might not be needed, and investment of money into genetics might not pay off[21]. There are several reason to keep on studying genetics of OA, especially now. As indicated in Fig. 2(b), it is expected that many loci remain to be discovered. And although the separate effect-sizes of these genetic loci will probably be small in the overall population, the importance of the gene for OA could be large. In contrast to epigenetic and transcriptomic markers, which are dynamic and sensitive to confounding and reverse causation, association between genetic variants and OA is proof for