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Review

Genomics of pain in osteoarthritis

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SUMMARY

Osteoarthritis (OA) accounts for the majority of the disease burden for musculoskeletal disorders and is one of the leading causes of disability worldwide. This disability is the result not of the cartilage loss that defines OA radiographically, but of the chronic pain whose presence defines symptomatic OA. It is becoming clear that many genes, each with a small effect size, contribute to the risk of developing OA. However, the genetics of OA pain are only just starting to be explored. This review will describe the first genes to have been identified in genomic studies of OA pain, as well as the possible dual roles of genes previously identified in genomic studies of OA in the context of pain. Difficulties associated with attempting to characterise the genetics of OA pain will be discussed and promising future avenues of research into genetic and epigenetic factors affecting OA pain described.

Introduction

Recent years have seen substantial advances in the understanding of the genetic architecture of osteoarthritis (OA). Unbiased genetic screens of large OA cohorts such as those included in the arcOGEN and TREAT-OA consortia have had sufficient power to reveal a wide range of relatively common susceptibility loci[1]. These studies have defined OA according to a composite definition, with cases either having structural damage to the joint, evaluated using radiographic criteria such as the Kellgren Lawrence score, or having previously undergone joint replacement.

However, the presence of radiographic evidence of OA does not always correlate with the main clinical presentation of OA, which is joint pain. Patients consistently describe the most distressing aspect of living with OA as the fatigue, disability and reduced quality of life produced by chronic joint pain[2]. A disease-modifying drug that restored cartilage without any reduction in pain would have little clinical utility[3]. Currently available analgesics have limited efficacy, high numbers needed to treat and high incidences of adverse events when taken chronically to combat joint pain[4]. Therefore, a greater focus on symptoms as well as aetiology of cartilage loss is critical if OA research is to produce clinically relevant therapies. Some recent genomic studies have acknowledged this by including a large proportion of patients who had previously undergone joint replacement[1]. Joint pain is likely to be the main factor prompting the decision to replace joints in these patients. But despite this fact, there have been very few studies which set out to specifically examine the genomic factors underpinning OA pain, in contrast to the relatively well characterised genomics of broadly-defined OA risk and cartilage loss.

This review will describe the genes identified in current OA genomic studies which focussed on joint pain, as well as the possible dual roles of genes identified in broader genomic studies of the disease. The difficulties and limitations of genetic and epigenetic studies will also be discussed.

Which genes are currently known to associate with OA pain?

The gold standard for genetic association studies are unbiased Genome-Wide Association Studies (GWAS). These are well suited to the identification of common gene variants with small or large effects, but require large cohorts of patients to provide sufficient statistical power, and hence are costly to perform. An example is the £2.2 million arcOGEN study, which in its first phase compared 7410 patients with severe OA with 11,009 unrelated controls in a UK cohort, and went on to replicate the most promising signals from this cohort in a wider European cohort of 7473 cases and 42,923 controls[1].

Although 80% of patients included had undergone joint replacement, the arcOGEN study did not set out to identify genetic influences on pain in OA *per se*, but used a focus on severe OA as a

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means of increasing the power of the analysis by ensuring greater homogeneity of their OA cohort. As the decision to perform joint replacement in these patients would have been informed principally by the degree of pain and disability the patients were experiencing, the presence of joint replacement can arguably function as a valid proxy for explicit measures of joint pain.

As part of its analysis, the study did look for loci that had stronger association in a joint replacement only subset of patients (i.e., those who had experienced pain associated with OA) vs the broader composite-defined cohort (which included the patients who only had radiographic changes). Four such loci were found, corresponding to chromosome regions close to the genes *GLT8D1*, *ASTN2*, *CHST11* and *TP63*, none of which are presently represented in the pain literature. Investigations of the role of these genes in preclinical models of OA pain will reveal if they can be manipulated to affect pain outcomes.

A study guided by a novel imputation strategy in the arcOGEN cohort genotyped an single nucleotide polymorphism (SNP) in *MCF2L* as a risk locus for OA[5]. *MCF2L* codes for the Rho-specific Guanine nucleotide exchange factor DBS. DBS is phosphorylated by TrkC, a receptor of the Nerve Growth Factor (NGF)-family member neurotrophin NT-3, and enhances Schwann cell migration when activated[6]. Growth factors are potent regulators of pain-sensing fibre function[7]. Antibody therapies neutralising NGF are the single most promising putative analgesics currently being assessed for OA pain[8]. *MCF2L* regulation of Schwann cell–neuronal interaction could conceivably play a role in the dysregulated articular innervation observed in osteoarthritic cartilage[9]. However, NT-3 is expressed at very low levels in synovial fluid of individuals with RA and OA compared to expression of the other neurotrophic factors NGF and brain derived neurotrophic factor (BDNF)[10]. Also, the SNP was equally frequently found in the radiographically- and symptomatically-defined cohorts used in the study. This makes it less likely that this SNP has a specific role in OA pain over cartilage loss.

To date, the only adequately powered GWAS to be carried out in the pain field was for chronic widespread pain[11]. This may reflect the difficulties in undertaking time-consuming and potentially expensive standardised quantitative phenotyping of this subjective phenomenon across a large cohort of individuals of diverse ethnic and cultural backgrounds. Accordingly, candidate gene association studies, which can be adequately powered with much smaller cohorts, are more common in the pain field. However, as these smaller studies are hypothesis-led, they tend to have a narrow focus on genes already known to be involved with pain sensitivity, and are thus more likely to produce false positive results.

One reason for the relatively small body of detailed data on pain genomics in OA is that the cohorts used for radiographic OA GWAS tend to be community-based, while symptomatic criteria tend to be better reported and assessed in clinical settings. Additionally, radiographic reporting criteria are more standardised than symptomatic reporting criteria, which frustrates the formation of large subgroups of patients with similar symptomatic profiles[12]. However, from the existing studies, there are five genes claimed to associate with OA pain.

The *SCN9A* gene encodes the alpha subunit of voltage gated sodium channel $Na_v1.7$. This is selectively expressed by nociceptors and known to be essential for transmission of pain-related signals. Rare mutations in the channel confer a congenital insensitivity to pain. In contrast, gain of function is seen in primary erythromelalgia, fibromyalgia and idiopathic small fibre neuropathy[13–15]. These mutations have Mendellian characteristics. In addition, however, a SNP conferring an Arg-1150-Trp substitution in this channel was found to associate with higher pain reports in four clinical trial cohorts of 578 OA patients, as well as in a variety of other painful conditions and healthy controls. The SNP in question is present in 10% of people and was thought to account for around 0.8 points on the 20 point Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale[16]. Unfortunately this SNP has failed to replicate in a larger independent cohort[17]. The authors of the latter study conclude that their result may be consistent with a weak effect of the Arg-1550-Trp substitution on overall pain sensitivity, rather than a specific effect in OA, as the SNP was also present more often in individuals with poorly localised multiple regional pains.

TRPV1 is a ligand-gated ion channel enriched on thermosensitive peripheral nerve fibres. TRPV1 is expressed on articular chondrocytes[18], as well as intraarticular nerve fibre terminals[19,20]. Ile-585-val TRPV1 variants are reported to confer reduced sensitivity to cold pain[21,22]. The Ile–Ile variant is associated with lower risk of symptomatic vs asymptomatic knee OA (odds ratio (OR) = 0.74) in a cohort of 3270 symptomatic vs 1098 asymptomatic cases[23]. This association was specific to symptomatic OA, and was not seen in patients with radiographic changes but no pain. There are many other SNPs in *TRPV1* which are already known to affect pain reporting[24]. It will be interesting to assess whether these other variations also have any association with symptomatic OA over asymptomatic OA.

Paired amino acid converting enzyme 4 (PACE4, coded by the *Pcsk6* gene) is an enzyme in cartilage that activates the cartilage degrading aggrecanases ADAMTS-4 and -5[25]. In a candidate gene study in 674 patients with radiographic knee OA with pain vs 2068 radiographic knee OA/no-pain patients, a SNP in *Pcsk6* was strongly associated with protection against pain when radiographic OA was present, with an OR of 1.33. While there was no further investigation to determine whether this specific SNP conferred a loss or gain of function, the group also performed a number of pain tests in *Pcsk6* null transgenic mice. These mice had, on the whole, a normal pain phenotype, with the exception of a mild reduction in mechanical sensitivity as well as substance P- and acetic acid-evoked pain behaviours[26]. Unfortunately, the phenotype of these mice in experimental OA models is not yet known.

P2X7 is a purinergic channel expressed on cells of myeloid lineage such as macrophages. A SNP in this gene determines the ability of the channel to form a pore that allows high molecular weight material to pass through the membrane. P2X7 is highly polymorphic in humans[27]. Individuals with radiographic OA (numbering 743 cases) possessing the hypofunctional variant of the channel were significantly less likely to have clinically relevant OA pain when compared with 586 unaffected controls (defined quite liberally at a WOMAC score >3 in this study – 6 is more often used as the cutoff). This study also showed that SNPs in P2X7 associated with pain intensity in a post-masectomy pain cohort. P2X7-selective antagonists are currently being evaluated as analgesics in both inflammatory and neuropathic pain states[28], though there are currently no studies of the role of this gene in experimental OA.

Finally, the common Val-158-Met polymorphism reduces the activity of the catecholamine degrading enzyme catechol-O-methyltransferase (COMT). This SNP was shown to increase the risk of hip pain amongst 171 female, but not 288 male individuals with confirmed radiographic OA, with an OR of 4.9[29]. COMT polymorphism is also known to associate with maladaptive coping and pain catastrophising in fibromyalgia and shoulder pain[30,31], as well as influencing acute experimental pain reports in healthy controls[32].

When assessing these studies, it is important to note the relatively small cohorts used. With one of the genes linked to OA pain already shown not to replicate in a larger cohort, it remains to be seen whether the contribution of the other genes will be confirmed or refuted by further studies. The genes linked to pain in OA are summarised in Table I.