META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES OF OSTEOARTHRITIS


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Purpose: Osteoarthritis (OA) is the most prevalent articular disorder and accounts for substantial morbidity and disability, particularly among the elderly, with a considerable health care burden in the developed countries. A large body of evidence, including familial aggregation and classical twin studies, indicates that primary OA has a strong hereditary component that is likely polygenic in nature. Genome wide association studies have been shown to be able to detect novel variants associated with other human diseases. The aim of this study is to identify novel genes involved in OA using data from four different genome-wide association (GWA) studies from Europe and the US.

Methods: In the setting of the Translational Research in Europe Applied Research in Osteoarthrits (TREAT-OA) four teams contributed data for knee hip and hand OA. The GWA studies were performed in the Rotterdam Study, deCODE, the Framingham Study (only for knee OA) and TwinsUK. Imputation of SNPs was performed in order to increase the coverage. More than 2.3 million Single Nucleotide Polymorphisms (SNP), both genotyped and imputed, were available for the analysis after passing different quality control assessments. Meta-analytical techniques were applied for the combination of the available data. The advantage of a meta-analysis approach is that it increases power and hence decreases the probability of false positive findings which is a common scenario in genetic association studies. Fixed effect model analyses were performed unadjusted and adjusted for age. We used phenotype definitions based on joint replacement or radiographic criteria. For radiographic criteria, we preferred the Kellgren-Lawrence classification system. A cut-off of 2 was used to classify OA (in 2 out of 3 hand joint groups for hand OA).

Results: The total number of cases/controls in our sample sets was 2371/35834, 2116/35683 and 3724/35666 for knee, hip and hand OA, respectively. Several SNPs in a region on chromosome 7q were associated with knee OA with p-value < 1 × 10^{-6} using fixed effects analysis. SNPs mapping on chromosomes 5, 18 and 21 were associated with hip OA with p-values < 1 × 10^{-6}. For hand OA most associations were found for SNPs in chromosome 18 (p-value < 1 × 10^{-9}). All these findings were based on fixed effects models.

Conclusions: We identified common variants in a new locus on chromosome 7 that may be involved in risk of knee osteoarthritis. In silico and de novo replications is ongoing for validation of the aforementioned signals.

EXERCISE OR NOT TO EXERCISE: A GENOME WIDE ANALYSIS OF EFFECTS OF EXERCISE ON EARLY AND LATE OA

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Purpose: Osteoarthritis (OA) is inflammatory and progressively degenerative disease with multifactorial etiology. While physical therapies have frequently shown to retard progression of cartilage damage, the success of these treatments remains variable. To identify exercise-induced genes that are regulated by exercise and how they affect cartilage at various stages of OA, we carried out a genome wide association study between extent of cartilage damage and effects of exercise.

Methods: Osteoarthritis was induced in Sprague Dowley rats (12 to 16 wks old females, n=10/gr) via intraarticular injection of mono-iodoacetate (MIA, 2 mg/50.l saline). The OA progression was allowed for 5, 10, 15 or 21 days. Alternatively, rats were subjected to exercise on treadmills (12 ft/min) following onset of OA for 1, 5, 10, or 15 days. All rats were sacrificed on day 21, and joints, and blood harvested. The knees were quick frozen for microarray analysis. Femoral cartilage was then chipped, disrupted, and extracted with Trizol (Invitrogen), labeled and analyzed by Affymetrix Rat GeneChip 1.0 ST Arrays. Partek and Ingenuity software were used to analyze the gene expression. Alternatively, femurs were fixed in formalin for magnetic resonance imaging (MRI) and micro CT for the assessment of cartilage/bone damage, or phase contrast angiography (PCA), followed by histological analysis.

Results: MIA induced a time dependent progression of cartilage/bone damage in femur, meniscus and tibia. The maximal damage was approximately 60% cartilage loss on femurs on day 21. The rats subjected to exercise on day 1 or day 5 following MIA injection and examined on day 21, rescued cartilage from MIA induced damage, as shown by microCT, MRI, PCA, and histological analysis (Fig 1). Rats subjected to exercise 10 days after OA induction exhibited some damage, but it was 15 to 20% of the OA afflicted knees. Contrarily, rats subjected to exercise 15 days post OA induction exhibited cartilage damage that was greater than the untreated control OA afflicted knees. Femurs from knees 5, 10, 15, and 21 days post OA induction and from knees of rats subjected to exercise post 1, 5, 10, or 15 days post OA induction were analyzed by microarray analysis. Four main groups of genes were analyzed, inflammatory genes, growth factor associated genes, matrix associated genes and transcription factors. Gene expression analysis by Partek followed by Ingenuity software demonstrated that proinflammatory genes and chemokines and reparative (growth factors and matrix associated) genes were expressed during the progression of OA on day 1, 5 and 10. However expression of reparative genes progressively decreased as OA advanced. However, in knees subjected to exercise on day 1 and day 5 after OA induction, the major proinflammatory and chemokine genes either not expressed or expressed at lower concentrations. The major genes expressed were IL-6, Tissue factor inhibitor, LIF, BMP-2, VEGF, prostaglandin synthase 1, and transcription factors such as Atf3, ETS1 and 2. Strikingly, the rats subjected to exercise, 15 days post OA induction showed more proinflammatory gene induction and very little growth factor associated genes.

Conclusions: In early OA, proinflammatory genes, chemokines, growth factors and matrix associated genes were among the highly