LARGE-SCALE GENOME-WIDE META-ANALYSES PROVIDE INSIGHTS FOR THE DEVELOPMENT OF NEW DISEASE MODIFYING TARGETS FOR OSTEOARTHRITIS.

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Purpose:
Osteoarthritis is the most prevalent musculoskeletal disease with 250 million people affected worldwide. The heritable component of osteoarthritis is ~50% and previous genetic studies have identified 86 risk loci in total. Here, we conduct the largest genome-wide association studies (GWAS) meta-analysis for osteoarthritis to date to better understand the genetic determinants of the disease and provide new targets for discovery and translation into therapies.
Methods:
We performed a genome-wide meta-analysis for osteoarthritis across 20 international cohorts in up to 830,743 individuals (179,305 osteoarthritis patients), across 11 osteoarthritis phenotypes. To identify putative effector genes and causal pathways, we integrated results from a series of post-GWAS analyses, including single nucleotide polymorphism (SNP) heritability, pathway analyses, genome-wide linkage disequilibrium (LD) score regression, phenome-wide association studies (PheWAS), statistical fine-mapping, expression and protein quantitative trait loci (eQTL and pQTL) colocalization, two-sample Mendelian randomization (MR) and examination of quantitative proteomics and RNA sequencing data for all genes within 1Mb of the osteoarthritis-associated variants.
Results:
We identified 100 statistically independent genome-wide significant variants ($P \leq 1.3 \times 10^{-8}$) associated with osteoarthritis, 52 of which are novel at 50 loci, thus increasing the number of established loci from 86 to 136. Five of these variants are rare (minor allele frequency≤0.001) with large effect sizes (OR: 3.62-9.52). The majority of variants are significantly associated with multiple osteoarthritis phenotypes, although some variants demonstrate a joint specific effect within the power constraints of the study. Fine-mapping analysis shows that in 7 of the 52 novel variants, a single variant can be postulated as causal. We found *TNC*, *SLC44A2* and *FKBP11* show both differential abundance and differential gene expression between paired intact and degraded cartilage from osteoarthritis patients that had undergone total joint replacement surgery. We observed colocalization with 5 genes in 4 different tissues from Genotype-Tissue Expression (GTEx) database. Causal inference analysis identified ART4 to play an important role in osteoarthritis of the finger and hand. Gene-set enrichment analyses identified bone-, cartilage- and nerve- developmental pathways to be significantly associated (false discovery rate<0.05) with osteoarthritis. LD score regression analysis unveiled significant correlations (FDR<0.05) between osteoarthritis and traits within the obesity, cognition, smoking, bone mineral density and pain trait categories. Similar traits were also identified by PheWAS. The estimates of SNP heritability range between 11% and 57% among the 11 osteoarthritis phenotypes.
Conclusions:
In this study, we have identified 52 novel risk variants for osteoarthritis, including novel loci associated with spine, finger and thumb osteoarthritis. We have found evidence for a role of rare variation of large effect in osteoarthritis susceptibility. We have integrated results from several strands of investigation to better understand the genetic architecture of the disease and identify putative genes and pathways of osteoarthritis pathogenesis, which represent attractive targets for drug discovery.