**Title:**

**A comprehensive transcriptional map of knee osteoarthritis**

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Osteoarthritis is a degenerative joint disease with huge public health burden and no curative therapy. Therefore, it is urgent to translate insights from genomics into disease mechanisms. We molecularly endotype joint tissues from 200 patients undergoing total knee replacement.

We generated RNA-seq data from patient knee tissues (primary chondrocytes from low-grade and high-grade cartilage, synoviocytes, and adipocytes) and genotype data from peripheral blood. We: (1) investigate gene expression differences between low and high-grade cartilage (2) examine alterations in chondrocyte population markers and (3) determine expression quantitative loci (eQTL) effects in all the aforementioned tissues.

Differential expression analysis identified 4,512 and 4,365 significantly upregulated and downregulated genes in high-grade cartilage respectively. Strong effects were observed for genes associated with osteoarthritis pathology including *CRLF1* (P= 1.54e-86, LFC > 2) and *CHRDL2*, (P= 9.19e-64, LFC < -2). Functional analyses pointed significantly enriched terms including skeletal system development (P = 3.49e-06), ossification (P = 1.48e-05) and activation of ECM-receptor interaction pathway (P = 4.14e-06). We detected significant downregulation in the expression of effector chondrocytes markers in high-grade cartilage, a chondrocyte population associated with high metabolic activity in early-stage osteoarthritis. The eQTL analysis revealed widespread significant associations between genetic variants and gene expression in all tissues.

We have identified large-scale transcriptional signatures of disease grade in key tissues of the knee joint in the largest osteoarthritis transcriptomic analysis to date. The identified genes and eQTL forward the understanding of molecular mechanisms in osteoarthritis. The impacted pathways serve as potential targets for novel therapeutics.