

## Description of Additional Supplementary Files

Supplementary Data 1. Detailed list of differential eQTLs, i.e. variants with high posterior probability for presence of eQTL effect in high-grade cartilage ( $m > 0.9$ ) and low for presence in low-grade cartilage ( $m < 0.1$ ), or vice versa.

Supplementary Data 2. Genes with significant cross-omics differences between high-grade and low-grade cartilage.

Supplementary Data 3. Pathways and gene sets associated with significant RNA-level and/or protein-level differences between high-grade and low-grade cartilage.

Supplementary Data 4. Replication of molecular differences between high-grade and low-grade cartilage, based on an independent RNA sequencing dataset of 35 patients.

Supplementary Data 5. Genes with significantly different expression profiles between high-and low-grade cartilage that were also found to be associated with genetic risk of osteoarthritis in a recent GWAS (multiple-testing corrected significance threshold of  $P < 1.02 \times 10^{-6}$ ).

Supplementary Data 6. Comparison of perturbations by compounds, gene knockdown or overexpression, to differences between high-grade and low-grade cartilage. The comparison was based on data from ConnectivityMap and genes with higher expression in high-grade than in low-grade cartilage on both RNA- and protein-level, see Methods.

Supplementary Data 7. List of all assayed patient tissue samples with detailed information including cohort, batch, and quality control exclusions.