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Dissecting cellular function of fibronectin in osteoarthritic cartilage

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Citation

Hoolwerff, M. van. (2022, September 6). *Dissecting cellular function of fibronectin in osteoarthritic cartilage*. Retrieved from <https://hdl.handle.net/1887/3455075>

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

Chapter 2

Elucidating epigenetic regulation by identifying functional *cis*-acting long noncoding RNAs and their targets in osteoarthritic articular cartilage

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Abstract

Objective. To identify robustly differentially expressed long noncoding RNAs (lncRNAs) with osteoarthritis (OA) pathophysiology in cartilage and to explore potential target messenger RNAs (mRNAs) by establishing coexpression networks, followed by functional validation.

Methods. RNA sequencing was performed on macroscopically lesioned and preserved OA cartilage of patients who underwent joint replacement surgery due to OA (N=98). Differential expression analysis was performed on lncRNAs that were annotated in GENCODE and Ensembl databases. To identify potential interactions, correlations were calculated between the identified differentially expressed lncRNAs and previously reported differentially expressed protein-coding genes in the same samples. Modulation of chondrocyte lncRNA expression was achieved using locked nucleic acid GapmeRs.

Results. By applying our in-house pipeline we identified 5,053 lncRNAs to be robustly expressed, of which 191 were significantly differentially expressed (according to false discovery rate) between lesioned and preserved OA cartilage. Upon integrating mRNA sequencing data, we showed that intergenic and antisense differentially expressed lncRNAs demonstrate high, positive correlations with their respective flanking or sense genes. To functionally validate this observation, we selected *P3H2-AS1*, which was down-regulated in primary chondrocytes, resulting in down-regulation of *P3H2* gene expression levels. As such, we can confirm that *P3H2-AS1* regulates its sense gene *P3H2*.

Conclusion. By applying an improved detection strategy, robustly differentially expressed lncRNAs in OA cartilage were detected. Integration of these lncRNAs with differential mRNA expression levels in the same samples provided insight into their regulatory networks. Our data indicate that intergenic and antisense lncRNAs play an important role in regulating the pathophysiology of OA.

Introduction

Osteoarthritis (OA) is an age-related, heterogeneous, degenerative disease of the articular joints, characterized in part by cartilage degeneration and remodeling of subchondral bone, which results in stiff and painful joints and decreased mobility [1]. Despite the fact that OA is the most globally prevalent joint disease, no effective treatment is currently available [2]. It has been demonstrated that OA pathophysiology in cartilage is marked by altered gene expression regulation in chondrocytes [3, 4]. This alteration of gene expression regulation could be triggered by adaptation processes occurring due to aging, genetic predisposition, or environmental stimuli, and is in part caused by aberrant epigenetic mechanisms. These mechanisms include DNA methylation, histone modifications and expression of microRNAs (< 22 nucleotides) [4-6]. More recently, long noncoding RNAs (lncRNAs; > 200 nucleotides) have been shown to play an important role in the homeostasis of the extracellular matrix of cartilage [5, 7-10].

lncRNAs are defined as RNA transcripts with little or no protein-coding potential and are known to regulate transcription and translation by numerous mechanisms, such as chromatin remodeling, messenger RNA (mRNA) stabilization, microRNA modulation, and recruitment of scaffolding proteins. One classification type of lncRNAs is based on the genomic location with respect to protein-coding genes, so-called biotypes, including antisense RNAs, sense RNAs, pseudogenes, and long intergenic noncoding RNAs (lincRNAs). Another type of classification is based on the location at which the lncRNA functions relative to its transcription site, which can be in *trans* or *cis* [11-13]. *Cis*-acting lncRNAs comprise a considerable portion of known lncRNAs and can be positioned at various distances and orientations relative to their target genes, such as lincRNAs around transcription factor start sites, as well as sense and antisense lncRNAs that overlap with their sense gene [13, 14]. Potentially, lncRNAs could be candidate targets in OA treatment, since their expression can be highly tissue specific [9].

RNA sequencing (RNA-seq) has improved the ability to detect lncRNAs, but mapping and annotating lncRNAs remains challenging. These challenges arise from the fact that they are usually expressed at very low levels and their sequence-function relationship is still poorly understood. Moreover, recent findings from studies on ribosome profiling and bioinformatics suggested that a large proportion of transcripts has unknown coding potential [15]. Recent studies on OA have focused on intergenic lncRNAs, even though the proportion of genic and intergenic lncRNAs can be similar depending on the investigated tissue [15, 16]. To determine the complete lncRNA transcriptome, we used an in-house pipeline to robustly capture lncRNAs in a previously assessed RNA-seq dataset of lesioned and preserved OA cartilage samples [4]. Subsequently, lncRNAs associated with OA pathophysiology were identified, and potential interactions with OA-specific mRNAs were investigated.

Materials and Methods

Sample collection

Macroscopically lesioned and preserved articular cartilage samples were obtained from participants in the Research osteoArthritis and Articular Cartilage (RAAK) study described by Ramos *et al.* [3]. In the present study, a total of 98 samples was used (65 knees, 33 hips) (**Supplementary Table 1**). Ethical approval was obtained from the medical ethics committee of the Leiden University Medical Center (no. Po8.239/P19.013) and informed consent was obtained from all participants.

RNA sequencing

Total RNA from articular cartilage was isolated using a Qiagen RNeasy Mini Kit (Qiagen, GmbH, Hilden, Germany). Paired-end 2×100 bp RNA sequencing (Illumina TruSeq RNA Library Prep Kit, Illumina HiSeq2000 and Illumina HiSeq4000) was performed. Strand-specific RNA-seq libraries were generated, which yielded a mean of 20 million reads per sample. Quality control was performed as previously described [4], and reads were subsequently aligned to the GRCh38 reference genome with the RNA-seq aligner STAR (version 2.6.0) [17]. Thereafter, aligned reads were processed into individual transcripts using StringTie (version 1.3.4) [18]. LncRNAs were identified by mapping the transcripts to GENCODE (version 29) [11] and Ensembl (version 94) [19].

In order to filter transcripts with unknown protein-coding potential, we integrated two sources of evidence: (1) predictions from the alignment-free Coding Potential Assessment Tool (CPAT, version 1.2.2) [20], and (2) predictions from the LncFinder R package (version 1.1.3) [21]. CPAT is a machine learning-based method that analyzes the sequence features of transcript open-reading frames (ORFs) using a logistic regression model built from ORF size, Fickett TESTCODE statistic and hexamer usage bias. In CPAT, a transcript with a coding probability ≥ 0.364 was considered to be a coding sequence. LncFinder predicts lncRNAs using heterologous features and machine learning model [21]. Transcripts with protein-coding potential predicted by both tools were removed from the dataset.

Differential expression analysis and replication

Differential expression analysis was performed on 32 paired samples (25 knees and 7 hips) (**Supplementary Table 1A**) using the DESeq2 R package (version 1.24) [22]. A general linear model assuming a negative binomial distribution was applied, followed by a paired Wald's test comparing lesioned OA cartilage samples and preserved OA cartilage samples, with the preserved samples as the referent. P values less than 0.05 (after Benjamini-Hochberg correction) were considered significant and are reported as the false discovery rate (FDR). This analysis was repeated for knee and hip samples separately.

Furthermore, to validate the results, five significant differentially expressed lncRNAs were selected and measured by reverse transcription-quantitative polymerase chain

reaction (RT-qPCR) in ten paired cartilage samples overlapping with the RNA-seq samples (**Supplementary Table 1B**), and replication was performed in an independent cohort of ten paired cartilage samples (**Supplementary Table 1C**). Total RNA was isolated using an RNeasy Mini Kit, followed by complementary DNA (cDNA) synthesis using 100 ng RNA with a First Strand cDNA synthesis kit according to the instructions of the manufacturer (Roche Applied Science). Expression levels of *AC025370.1*, *AC090877.2*, *MEG3*, *P3H2-AS1*, *TBILA*, and *GAPDH* were determined using FastStart SYBR Green Master reaction mix (Roche Applied Science). Primer sequences are shown in **Supplementary Table 2**. Relative gene expression levels were calculated with the $2^{-\Delta\Delta C_t}$ method, using *GAPDH* as internal control. A paired t-test was performed on the $-\Delta C_t$ values, and P less than 0.05 were considered significant.

LncRNA-mRNA interactions

To identify potential interactions, correlations were calculated between the identified differentially expressed lncRNAs and previously reported differentially expressed protein-coding genes in the same samples. LncRNA expression data were normalized and variance stabilizing transformed using the DESeq2 R package (version 1.24) [22], and batch effect was removed using the limma R package (version 3.40.6) [23]. Our previously published mRNA data [4] were equally normalized and transformed, and batch effect was removed. Subsequently, Spearman's correlations were calculated between the significantly differentially expressed lncRNAs identified in the combined analysis of knee and hip samples and the differentially expressed protein-coding genes previously published [4], using the Hmisc R package (version 4.2.0) for OA cartilage samples (**Supplementary Table 1D**). Correlations with P values less than 0.05 were considered significant. Network visualization was performed using the RedeR package (version 3.10) [24].

In vitro down-regulation lncRNA using locked nucleic acid GapmeRs

Primary chondrocytes were isolated from three independent donors and passaged twice or thrice, as previously described [25]. Chondrocytes were transfected in duplo with antisense locked nucleic acid (LNA) GapmeR (Qiagen) targeting *P3H2-AS1* (TGAGCAACTAGGTGTA) or GapmeR negative control (AACACGTCTATACGC) at 10 nM final concentration using Lipofectamine RNAiMax Transfection Reagent according to instructions of the manufacturer (Invitrogen). Cells were lysed 30 hours posttransfection with TRIzol Reagent (Thermo Fisher Scientific) for RNA isolation, which was done using an RNeasy Mini Kit. Synthesis of cDNA was performed with 150 ng of total RNA using a First Strand cDNA Synthesis kit according to the instructions of the manufacturer. Expression levels of *P3H2-AS1*, *P3H2*, and *GAPDH* were determined using FastStart SYBR Green Master reaction mix. Primer sequences are shown in **Supplementary Table 2**. Relative gene expression levels were calculated with the $2^{-\Delta\Delta C_t}$ method, using *GAPDH* as internal control. A paired t-test was performed on the $-\Delta C_t$ values, P values less than 0.05 were considered significant.

Data availability

FASTQ files are available on ArrayExpress E-MTAB-7313.

Results

Characterization of lncRNAs in OA cartilage

To characterize lncRNAs in OA cartilage, we used our previously assessed RNA-seq data of 32 paired samples (25 knees, 7 hips) of lesioned and preserved OA cartilage [4] (**Supplementary Table 1A**). Our in-house pipeline was applied to capture lncRNAs from 2 databases (GENCODE and Ensembl). As shown in **Figure 1**, 30,354 lncRNAs were initially detected

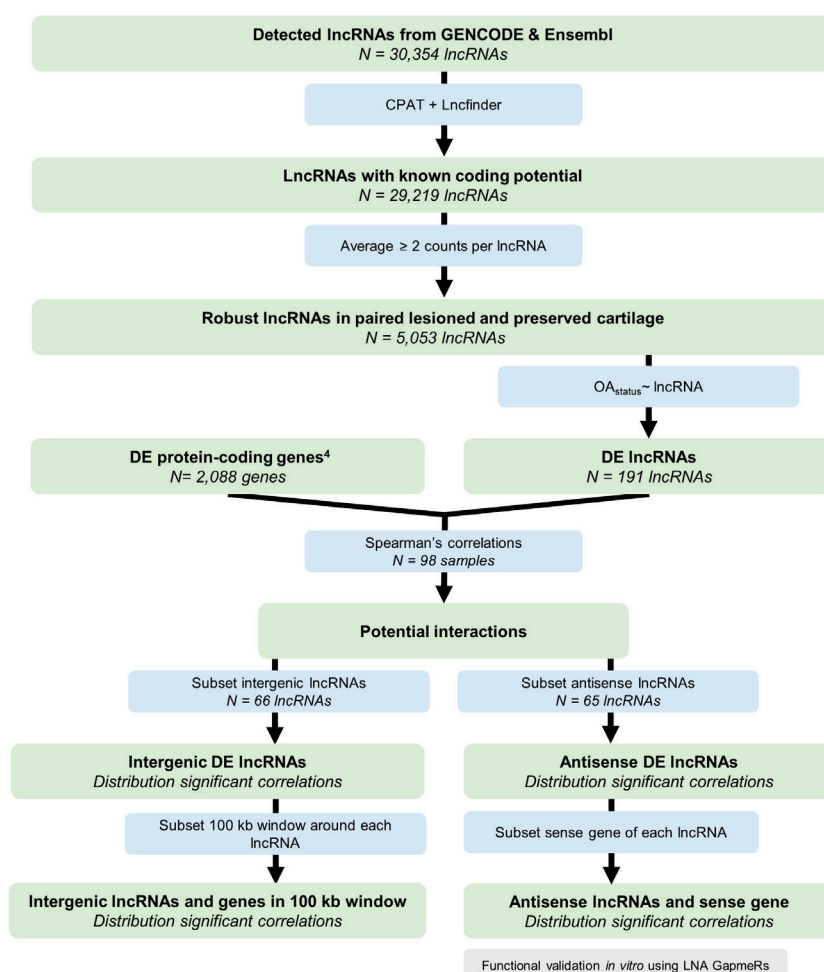


Figure 1 | Overview of applied strategy | Numbers of genes or long noncoding RNAs (lncRNAs) represent significantly differentially expressed (DE) genes or lncRNAs (according to false discovery rate). OA = osteoarthritis; LNA = locked nucleic acid.

in our dataset. To filter out possible transcripts of unknown coding potential, we integrated results from two machine learning approaches (CPAT [20] and Lncfinder, [21]). After removing these transcripts, 29,219 lncRNAs remained in the dataset and were considered for further analyses. To robustly detect lncRNAs expressed in OA cartilage, a cutoff of ≥ 2 counts per lncRNA was applied, resulting in a total of 5,053 lncRNAs expressed in cartilage (**Figure 1**). Classification of these lncRNAs based on biotype showed that 1,989 were antisense RNAs (39.4%), 249 sense RNAs (4.9%), 1,532 were pseudogenes (30.3%), and 900 were lincRNAs (17.8%) (**Figure 2**).

Differential expression of lncRNAs between lesioned and preserved OA cartilage

To identify lncRNAs associated with the OA process, differential expression analysis was performed on paired lesioned and preserved OA cartilage samples, resulting in 191 significantly differentially expressed lncRNAs ($\text{FDR} < 0.05$, **Figure 1**). Of these, 65 were antisense RNAs (34.0%), 10 were sense RNAs (5.2%), 33 were pseudogenes (17.3%), and 66 were lincRNAs (34.6%) (**Figure 2**, **Supplementary Table 3**). When comparing the biotypes of the total expressed lncRNAs to the biotypes of the differentially expressed lncRNAs (**Figure 2**), we observed an increase of lincRNAs and a decrease of pseudogenes. The most significantly differentially expressed lncRNA was lincRNA *AL139220.2* (fold change 2.2, $\text{FDR } 2.0 \times 10^{-10}$). As depicted in **Figure 3**, 114 lncRNAs were down-regulated and 77 were up-regulated, with a fold change ranging from 0.3 (*AC100782.1*, $\text{FDR } 6.5 \times 10^{-4}$) to 4.5 (*LINC01411*, $\text{FDR } 2.6 \times 10^{-6}$).

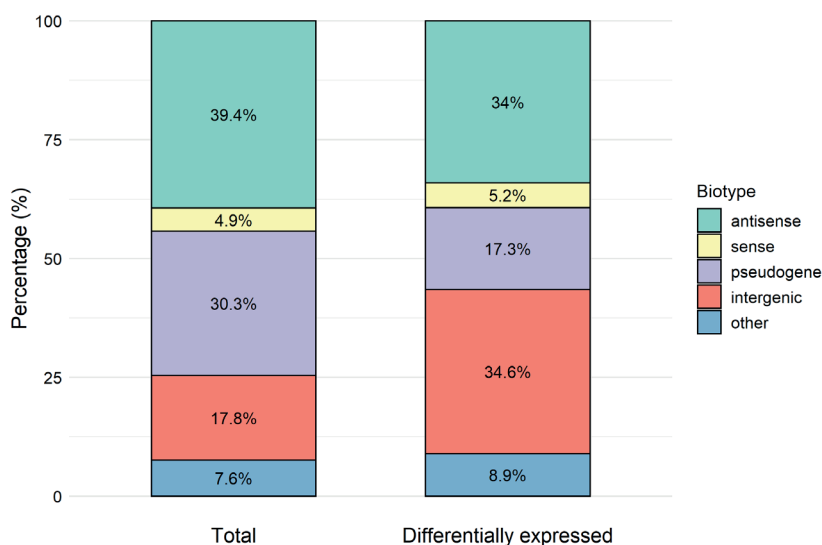


Figure 2 | Distribution of biotypes of long noncoding RNAs (lncRNAs) | Distribution of biotypes of lncRNAs expressed in cartilage compared to lncRNAs that were significantly differentially expressed (according to the false discovery rate) between lesioned osteoarthritis (OA) cartilage and preserved OA cartilage.

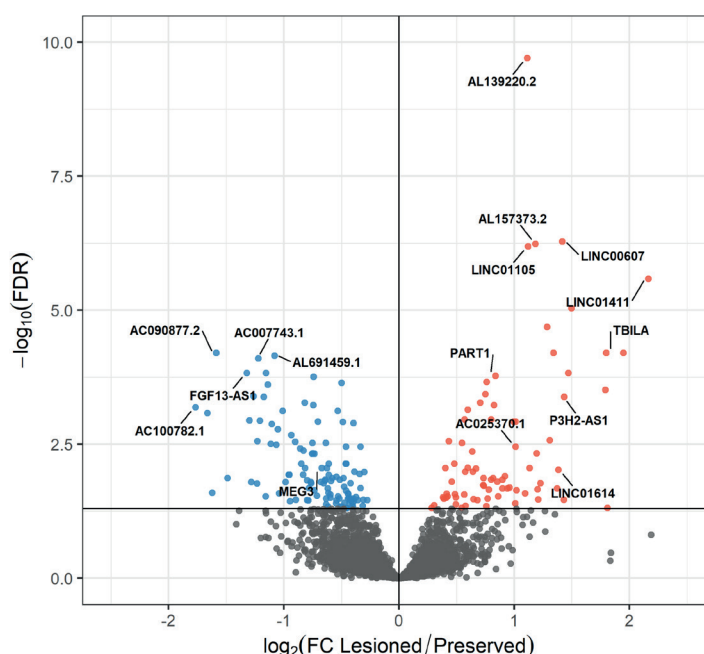


Figure 3 | Differential expression analysis of long noncoding RNAs (lncRNAs) between lesioned osteoarthritis (OA) and preserved OA cartilage. Volcano plot shows differentially expressed lncRNAs, with down-regulated lncRNAs represented by blue circles and up-regulated lncRNAs represented by red circles. Top differentially expressed lncRNAs are labeled, as are known and novel OA-associated lncRNAs. FDR = false discovery rate; FC = fold change.

The 191 identified lncRNAs in this study included several previously found to be associated to OA, such as *MEG3* (fold change 0.6, FDR 8.8×10^{-3}), *PART1* (fold change 1.8, FDR 1.7×10^{-4}), and *LINC01614* (fold change 2.6, FDR 9.5×10^{-3}) [16, 26], as well as novel OA-associated lncRNAs, including *P3H2-AS1* (fold change 2.7, FDR 4.1×10^{-4}) and *AC090877.2* (fold change 0.3, FDR 6.2×10^{-5}). Notably, previously identified lncRNAs such as *MALAT1* (fold change 1.3, FDR 0.4) [27], *TUG1* (fold change 1.1, FDR 0.7) [28], *HOTAIR* (fold change 0.8, FDR 0.5), and *GAS5* (fold change 1.1, FDR 0.8) [29] were not found to be significantly differentially expressed in the present study.

To validate the differential expression results, we selected five lncRNAs (*AC025370.1*, *AC090877.2*, *MEG3*, *P3H2-AS1*, and *TBILA*) based on highest absolute fold change and genomic location, using RT-qPCR in a cohort consisting of 10 paired samples (**Supplementary Table 1B**) overlapping with the RNA-seq samples. All five lncRNAs were detected using RT-qPCR with equal direction of effect as those found in the RNA-seq analysis (**Supplementary Table 4**). Furthermore, replication was performed in an independent cohort of 10 paired cartilage samples (**Supplementary Table 1C**), which also showed comparable effect sizes and directions (**Supplementary Table 4**).

To explore whether joint-specific lncRNAs could be detected, stratified analyses were performed for knee samples (25 pairs) and hip samples (7 pairs). Upon performing differential expression analysis on the knee samples, 90 significantly differential expressed lncRNAs were identified (**Supplementary Table 5A**), of which 12 were not found in the previous combined analysis and therefore were unique to knee cartilage (**Supplementary Table 6A**). In the hip samples, 31 lncRNAs were significantly differentially expressed (**Supplementary Table 5B**), of which 13 were unique to hip cartilage (**Supplementary Table 6B**). The most significantly differentially expressed lncRNA unique to the knee was *MSL3P1* (fold change 1.5, FDR 1.49×10^{-2}), while one of the most significantly differentially expressed lncRNAs unique to the hip was *PAPPA-AS1* (fold change 9.4, FDR 2.77×10^{-4}). Notably, the most up-regulated lncRNA in the hip, *AP001515.1* (fold change 21.5, FDR 2.8×10^{-4}), was also unique to the hip, while the most up-regulated lncRNA in the knee, *LINC01411* (fold change 5.8, FDR 6.1×10^{-6}), was not unique to the knee.

Potential interactions between lncRNAs and mRNAs relevant in OA pathophysiology

We next aimed to investigate whether mRNAs associated with the OA process are regulated by differentially expressed lncRNAs. Based on the assumption that interactions between lncRNAs and mRNAs likely show coexpression [30] among lesioned and preserved OA cartilage samples, correlations were calculated between our previously reported differentially expressed protein-coding genes [4] and differentially expressed lncRNAs (**Supplementary Table 1D**), as shown in **Figure 1**. This resulted in 343 significant correlations ($r > 0.8$) (**Supplementary Table 7**), comprising 47 unique lncRNAs, of which 17 were antisense (36%) and 14 were intergenic (30%) (**Supplementary Table 8**). This distribution is comparable to that found among all differentially expressed lncRNAs (**Figure 2**), supporting the notion that lncRNAs regulate mRNAs, independent of biotype. Notably, the most significantly differentially expressed lncRNA, *AL139220.2* (fold change 2.2, FDR 2.0×10^{-10}), showed one of the highest correlations with *COL6A3* ($r = 0.8$, $P = 2.2 \times 10^{-16}$), encoding a collagen type VI chain.

To visualize these interactions, an OA-specific lncRNA-mRNA coexpression network was generated. As shown in **Figure 4**, three relative large clusters of interacting lncRNAs and mRNAs were observed. One cluster was characterized by being highly interlinked with a cluster of the same genes (e.g., *ITGB1BP1* correlated to the six lncRNAs *IER-AS1*, *AL355075.3*, *AC234917.1*, *AC091564.4*, *AC108449.3*, and *AL450306.1*), whereas the other two were characterized by lncRNAs interlinked with mostly unique genes (e.g., *LNCsRLR* with 18 genes). In addition to the clusters, there are a number of singular interlinked lncRNAs, such as *AC090877.2* (fold change 0.3, FDR 6.2×10^{-5}) with *GREM1* ($r = 0.9$, $P = 2.2 \times 10^{-16}$), which encodes a cytokine of the BMP antagonist family (**Figure 4**). Interestingly, *GREM1* is the gene located closest to *AC090877.2*, suggesting that this lncRNA *cis*-regulates this gene.

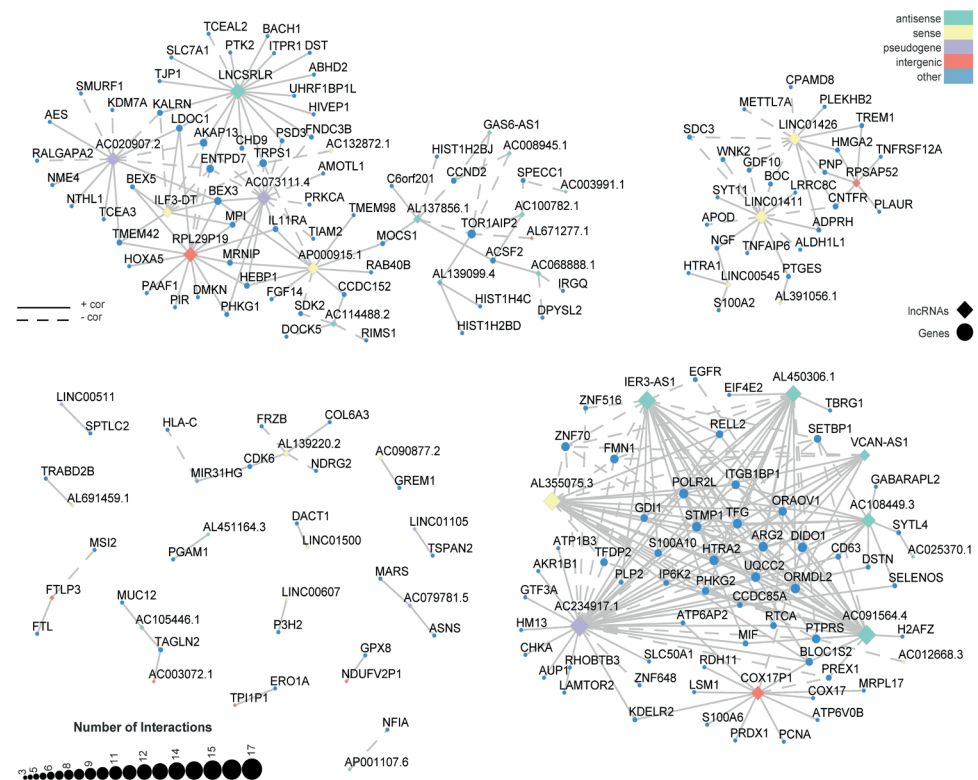


Figure 4 | Osteoarthritis (OA)-specific long noncoding RNA (lncRNA)-mRNA coexpression network. Network of differentially expressed lncRNAs and mRNAs with a correlation (cor) of >0.8 between lesioned OA and preserved OA cartilage is shown.

One of our objectives in the present study was to generalize the identification of potential *cis*-regulation of differentially expressed lncRNAs (**Figure 1**). As shown in **Figure 5A**, we compared the distribution of significant correlations between differentially expressed lncRNAs and all genes and between differentially expressed lncRNAs and genes that lie within a 100 kb window of the transcription start site. The proportion of significant correlations >0.5 with all differentially expressed genes was 11%, but this increased to 44% when we only considered the 100 kb window. Since the percentage differentially expressed antisense lncRNAs (34%) was comparable to that of intergenic lncRNAs (34.6%), we also aimed to identify potential *cis*-regulation of antisense lncRNAs. To this end, we compared the distribution of correlations between differentially expressed antisense lncRNAs and all protein-coding mRNAs and between differentially expressed antisense lncRNAs and their sense genes (**Figure 5B**). The percentage of correlations >0.5 was 10% with all genes and 61% with only the sense genes, showing that there is an enrichment for higher, positive correlations between antisense lncRNAs and their sense gene. Taken together, these data suggest that both intergenic and antisense lncRNAs are prone to regulate mRNAs in *cis* in OA cartilage.

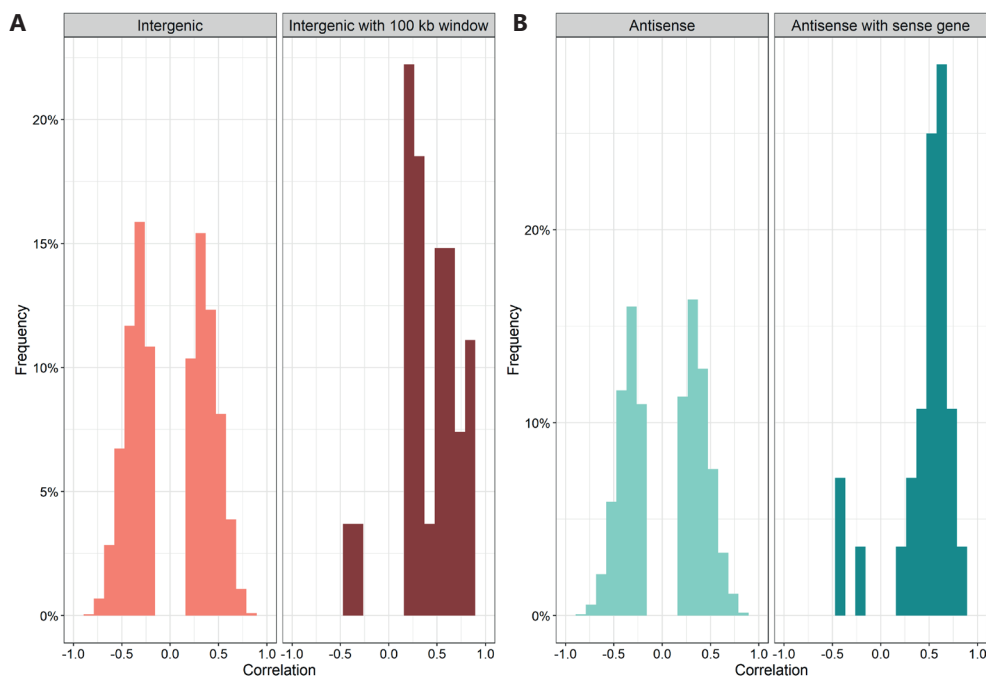


Figure 5 | Distribution of significant correlations between intergenic differentially expressed long noncoding (lncRNAs) and previously identified differentially expressed protein-coding genes or protein-coding genes in a 100 kb window (A), and between antisense differentially expressed lncRNAs and differentially expressed protein-coding genes or their sense genes (B). Correlations between lncRNA and mRNA data were calculated from the same osteoarthritis cartilage samples (n=98).

Down-regulation of lncRNA expression using LNA GapmeRs

To validate whether the previously identified *cis*-regulation between lncRNAs and their surrounding genes is caused by a direct effect, *P3H2-AS1* was selected as a proof of concept for functional validation. *P3H2-AS1* is an antisense lncRNA, which was found to be highly up-regulated in lesioned OA cartilage (fold change 2.7, FDR 4.1×10^{-4}) [4] and the highest correlation was with its sense gene *P3H2* ($r = 0.63$, $P = 1.0 \times 10^{-13}$) (**Supplementary Figure 1**). To this end, primary chondrocytes were transfected with a *P3H2-AS1* targeting LNA GapmeR. As shown in **Figure 6A**, this resulted in a significant down-regulation of *P3H2-AS1* compared to a non-targeting LNA GapmeR (fold change 0.28, $P = 0.0035$). Subsequently, *P3H2* expression levels were measured, which showed that *P3H2* expression was significantly down-regulated compared to cells transfected with non-targeting control LNA GapmeRs (fold change 0.36, $P = 0.001$) (**Figure 6B**).

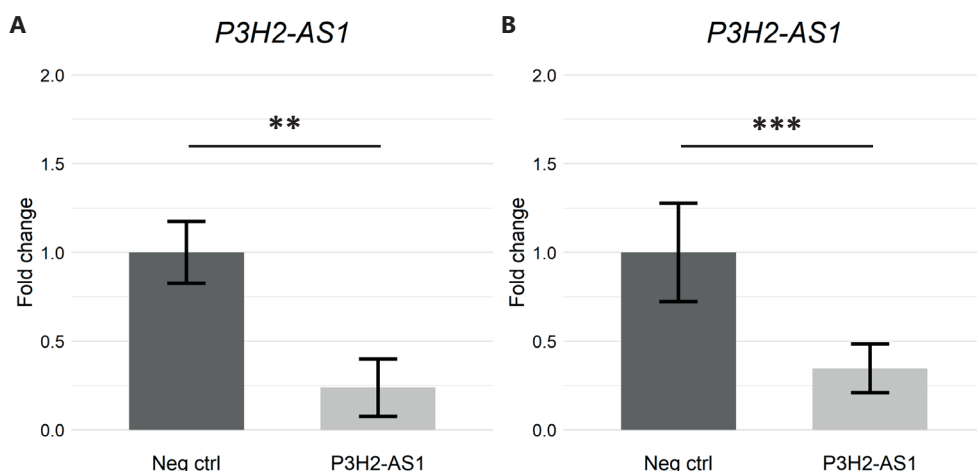


Figure 6 | Expression of long noncoding RNA (lncRNA) *P3H2-AS1* and gene *P3H2* in primary chondrocytes transfected with *P3H2-AS1* targeting antisense locked nucleic acid (LNA) GapmeRs compared to non-targeting LNA GapmeRs. (A) *P3H2-AS1* expression was significantly down-regulated by the *P3H2-AS1* targeting LNA GapmeRs. (B) *P3H2* expression was significantly down-regulated in chondrocytes transfected with *P3H2-AS1* targeting LNA GapmeRs. Bars show the mean $\pm$ SD, ** $P < 0.01$ * $P < 0.001$ by paired t-test (N = 3 donors).**

Discussion

To our knowledge, we are the first to report on robust differential expression of lncRNAs as related to OA pathophysiology, while integrating them with data on differential mRNA expression levels of the same samples using RNA sequencing. As a result, our new in-house pipeline identified 5,053 lncRNAs that were robustly expressed, 191 of which were significantly differentially expressed (according to FDR) between lesioned and preserved OA cartilage. Notably, we observed an increase in the percentage of lncRNAs, highlighting their general involvement in the OA pathophysiology process. The directions of effect of *AC025370.1* (fold change 2.0, FDR 3.5×10^{-3}), *AC090877.2* (fold change 0.3, FDR 6.2×10^{-5}), *MEG3* (fold change 0.63, FDR 8.8×10^{-3}), *P3H2-AS1* (fold change 2.7, FDR 4.1×10^{-4}), and *TBILA* (fold change 3.5, FDR 1.1×10^{-7}) was validated and replicated by RT-qPCR, indicating robustness of our lncRNA mapping strategy. Correlations were calculated to identify potential interactions between expression levels of differentially expressed lncRNAs and differentially expressed protein-coding genes [4] in the same OA cartilage samples. As a result, both intergenic and antisense differentially expressed lncRNAs showed an enrichment for higher, positive correlations with their respective flanking or sense genes compared to the total dataset. Validating this *cis*-regulation in vitro, *P3H2-AS1* levels were down-regulated in primary chondrocytes, which resulted in down-regulation of the sense gene *P3H2* expression levels, thereby confirming that *P3H2-AS1* regulates its sense gene *P3H2*.

We identified 29,219 lncRNAs that were expressed in OA cartilage. However, after applying a filter with a cutoff of an average of ≥ 2 counts per lncRNA, the detected lncRNAs were reduced by $\sim 83\%$ to 5,053. Since lncRNAs are known to be expressed at very low levels, this was to be expected, yet lncRNAs expressed at low levels can still be functional [12]. To allow exploratory analyses with lncRNAs expressed at such low levels, deeper sequencing would be necessary, with a read-depth of ~ 50 million reads per sample. Additionally, to be able to report on valid lncRNAs in OA articular cartilage and their potential target mRNAs, we prioritized reporting known lncRNAs with a predicted non-protein-coding potential. Nonetheless, by focusing on these known lncRNAs, we may have disregarded compelling novel OA-relevant lncRNAs.

Given that we had a (within patient) paired lesioned cartilage – preserved cartilage study design, with pairs sequenced on the same batch, we applied a paired Wald's test as implemented in the DESeq2 R package. Since our dataset also included lncRNAs expressed at low levels, the addition of a random effect to compensate for technical errors may have been a better, yet more conservative, approach. As such, the lncRNAs in our dataset, particularly those with low read counts, could be subject to false positive results and therefore require replication and verification.

We observed a particular enrichment of lincRNAs in the differential expression analysis compared to the total dataset (34.6% versus 17.8%) (**Figure 2**), showing that lincRNAs indeed play an important role in OA pathophysiology, as seen in previous studies [8, 16, 30]. Nonetheless, in comparison to the fraction of significantly differentially expressed lncRNAs reported by Pearson *et al.* [8], this proportion is still relative small. However, Pearson and colleagues performed RNA-seq on samples from isolated chondrocytes in contrast to the RNA isolated from cartilage in our study, and focused on profiling lncRNAs up-regulated by interleukin-1 β . The activation of chondrocyte proliferation in tissue culture will likely induce expression of RNAs involved in transcriptional regulation, compared to the transcriptome of maturational arrested chondrocytes residing in cartilage.

Of the 191 lncRNAs that were significantly differentially expressed between lesioned and preserved OA cartilage (**Figure 3**), multiple lncRNAs have been previously identified, including *MEG3*, *LINC01614*, and *PART1* [16, 26]. However, there were also examples of lncRNAs previously associated with OA, which were not significantly differentially expressed, such as *MALAT1*, *HOTAIR*, *GAS5*, and *TUG1* [27-29]. A possible explanation could be that they were found to be differentially expressed between preserved OA and healthy cartilage, as opposed to our comparison between lesioned OA cartilage and preserved OA cartilage [7]. The cross-sectional study design comparing OA cartilage and healthy cartilage provides insight into which lncRNAs are involved in the early phase of OA pathophysiology and are therefore potentially causal in the process and which lncRNAs are specific for healthy cartilage; this

was not possible with our study design. Nonetheless, the paired analysis allowed for detection of lncRNA expression changes specific to the OA pathophysiological process, independent of confounding factors such as sex and age. At least 35 differentially expressed lncRNAs in our dataset were previously found to be associated with OA [10, 16, 30], but the most significantly differentially expressed lncRNA, *AL139220.2*, and the most up- and down-regulated differentially expressed lncRNAs, *LINC01411* and *AC100782.1*, respectively, have not previously been associated with OA, showing that a paired study design allows for the detection of many more lncRNAs involved in the OA pathophysiological process [3].

Previous studies have demonstrated differences in dysregulated pathways between knee and hip OA cartilage and epigenetic differences based on DNA methylation [8, 16, 31, 32]; thus, we aimed to identify joint-specific lncRNAs. Differential expression analysis in knee samples resulted in a higher number of significantly differentially expressed lncRNAs ($N = 90$) than in hip samples ($N = 31$), which could be due to the smaller sample size of the hip samples (25 knee pairs versus 7 hip pairs). However, the number of unique lncRNAs per joint site was similar: 12 unique knee lncRNAs and 13 unique hip lncRNAs. This suggests that there is more heterogeneity in the processes in the knee, which could be due in part to anatomical joint site-specific differences. This is also supported by the fact that the average fold change of the up-regulated lncRNAs unique to the hip is 8.3, while it was 1.5 for knee. The unique lncRNAs with the highest fold change in the knee (*AC068768.1*, fold change 1.6, $FDR\ 2.3 \times 10^{-2}$) and hip (*AP001615.1*, fold change 21.5, $FDR\ 2.8 \times 10^{-4}$) were not previously found to be associated with OA. The identification of these joint specific lncRNAs are interesting for follow-up studies to determine potential joint specific therapeutic targets.

Unlike conserved microRNAs, it is difficult to predict the function of lncRNAs based solely on nucleotide sequence, due to their lack of conservation of the primary sequence [15]. To explore potential regulatory interactions between lncRNAs and mRNAs in cartilage, correlations were calculated between differentially expressed lncRNAs and differentially expressed protein-coding mRNAs (**Figure 4**). At the transcriptional level, lncRNAs can exert their function in *trans* or *cis* [13], both of which we observed in this study. The most significantly differentially expressed lncRNA, *AL139220.2*, showed one of the highest correlations with *COL6A3* ($r = 0.8$, $P = 2.2 \times 10^{-16}$), encoding one of the collagen type VI chains as part of the complete collagen type VI molecule, which is mostly present in the pericellular matrix of cartilage. *AL139220.2* is located on chromosome 1 and, at present, little is known about its function. Since *COL6A3* is located on chromosome 2, it seems likely that *AL139220.2* regulates *COL6A3* expression in *trans*. Notably, *AC090877.2* showed the highest correlation with its sense gene *GREM1* ($r = 0.9$, $P = 2.2 \times 10^{-16}$), suggesting that this lncRNA *cis*-regulates this gene. In previous studies, it has been shown that lincRNAs often regulate flanking mRNAs in *cis* in OA, in which a positive correlation was found between the expression of mRNA-flanking lincRNAs and their nearest

coding mRNA [8, 30]. This observation was confirmed by our findings, as the percentage of higher, positive correlations ($r > 0.5$) was considerably larger between lincRNAs and the differentially expressed genes that lie within a 100 kb window (44%) than with all differentially expressed genes (11%) (**Figure 5A**).

Furthermore, it is known that antisense lncRNAs can regulate their overlapping sense genes in *cis* [14], which has not previously been investigated in OA. We found an enrichment for higher, positive correlations between antisense differentially expressed lncRNAs and their sense gene ($r > 0.5$ in 61%) compared to correlations between antisense differentially expressed lncRNAs and all differentially expressed genes ($r > 0.5$ in 10%), suggesting that indeed antisense lncRNAs often regulate their sense gene in *cis* (**Figure 5B**). Therefore, to completely understand the transcriptional regulation of lncRNAs in the OA process, the total lncRNA transcriptome should be considered, not solely the lincRNAs. Of importance is the notion that these correlations are not yet proof of a (direct) downstream effect of lncRNAs on the mRNAs.

Given these observations, we selected the antisense lncRNA *P3H2-AS1* as proof of principle to establish whether it regulates its sense gene. Down-regulation of *P3H2-AS1* resulted in a significant down-regulation of *P3H2* expression levels (**Figure 6**), thereby confirming that *P3H2-AS1* regulates its sense gene in *cis*. *P3H2* encodes an enzyme that catalyzes post-translational 3-hydroxylation of proline residues and plays a critical role in collagen chain assembly, stability, and cross-linking and was recently found to be highly up-regulated in lesioned OA cartilage, and therefore likely involved in the OA process [4]. Antisense lncRNAs can affect biogenesis or mobilization of target RNA on multiple levels, such as transcription, splicing, and translation [14]. To elucidate the exact mechanism of *P3H2-AS1* regulating *P3H2* and investigate whether *P3H2-AS1* can be used as a potential preclinical target by modulating *P3H2* expression levels via *P3H2-AS1*, complementary functional studies employing e.g. CRISPR/Cas9, RNA fluorescence in situ hybridization, or crosslinked immunoprecipitation are necessary [33].

In conclusion, our improved detection strategy resulted in the characterization of lncRNAs robustly expressed in OA cartilage. Our data signify that intergenic, as well as antisense lncRNAs play an important role in regulating the pathophysiology of OA. Moreover, we observed that in addition to the previous finding that intergenic lncRNAs function in *cis*, antisense lncRNAs can exert their function in *cis*, which we confirmed in vitro. Future studies regarding lncRNAs and OA should be complemented by functional validation, e.g., by modulating lncRNA expression levels using antisense LNA GapmeRs, in order to confirm whether a correlation signifies a biological relation between lncRNA and mRNA.

Acknowledgements

We thank all the participants of the RAAK study (supported by the Leiden University Medical Center). We thank Evelyn Houtman, Enrike van der Linden, Robert van der Wal, Peter van Schie, Shaho Hasan, Maartje Meijer, Daisy Latijnhouwers, and Geert Spierenburg for their contribution to the collection of the joint tissue. Data were generated within the scope of the Medical Delta programs Regenerative Medicine 4D: Generating complex tissues with stem cells and printing technology and Improving Mobility with Technology.

Funding:

The study was funded by the Dutch Scientific Research council NWO /ZonMW VICI scheme (nr 91816631/528), the Dutch Arthritis Society (DAA-10-1-402, DAF-16-1-405), and TreatOA (grant 200800 from the European Commission Seventh Framework Program).

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Supplementary Materials

Supplementary Tables

Supplementary Table 1 | Sample characteristics included in the analysis in the (A) discovery, (B) validation (C) replication, and (D) correlation analyses.

A

Discovery						
Tissue type	Mean age (range)	# Men	# Women	# Preserved	# Lesioned	# Total
Knee	68.8 (48 -79)	6	19	25	25	50
Hip	64.4 (48 -79)	2	12	7	7	14
All	67.8 (48 -79)	7	25	32	32	64

B

Validation						
Tissue type	Mean age (range)	# Men	# Women	# Preserved	# Lesioned	# Total
Knee	69.7 (60 - 77)	2	5	7	7	14
Hip	69.7 (65 - 79)	1	2	3	3	6
All	69.7 (60 - 79)	3	7	10	10	20

C

Replication						
Tissue type	Mean age (range)	# Men	# Women	# Preserved	# Lesioned	# Total
Knee	64.6 (57 - 75)	3	2	5	5	10
Hip	68.2 (59 - 75)	2	3	5	5	10
All	66.4 (57 - 75)	5	5	10	10	20

D

Correlations						
Tissue type	Mean age (range)	# Men	# Women	# Preserved	# Lesioned	# Total
Knee	68.5 (46 - 79)	54	11	35	30	65
Hip	66.2 (48 - 82)	27	6	22	11	33
All	67.7 (46 - 82)	81	17	57	41	98

Supplementary Table 2 | Primer sequences to measure mRNA and lncRNA expression levels.

Gene	Forward primer (5' --> 3')	Reverse primer (5' --> 3')
AC025370.1	AGCCAGCTTTTAAGTGAACCTG	GTGCTATAACTCTCTCGCCA
AC090877.2	AAGCACATGGGACCCTCTCA	TGAATTGTGAAGAACCATCGCG
GAPDH	TGCCATGTAGACCCCTTGAAG	ATGGTACATGACAAGGTGCGG
MEG3	CCACCCCTCTTGCTTGTCTT	CCTGGAGTGCTGTTGGAGAA
P3H2-AS1	CACTGCCTGATGGGTACTAGC	TTGAGACTTGGAGAGGCCTTG
P3H2	AGAGAAGCCAAGCCACACAT	GCTTGTTCGAAGTGCTGAT
TBILA	CGGGACAGGAATCATGGATTTT	ACAGATGAGTGACCAAACTGGA

Supplementary Table 3 | Significant (according to false discovery rate) differentially expressed long noncoding RNAs in lesioned osteoarthritic cartilage compared to preserved osteoarthritic cartilage samples.

GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pvalue	Padj
ENSG00000230615	<i>AL139220.2</i>	52.47	1.11	2.16	3.90E-14	1.97E-10
ENSG00000235770	<i>LINC00607</i>	58.39	1.42	2.67	2.06E-10	5.20E-07
ENSG00000229896	<i>AL157373.2</i>	51.56	1.18	2.27	3.44E-10	5.80E-07
ENSG00000232044	<i>LINC01105</i>	88.54	1.12	2.17	5.06E-10	6.39E-07
ENSG00000249306	<i>LINC01411</i>	50.68	2.16	4.48	2.55E-09	2.58E-06
ENSG00000236094	<i>LINC00545</i>	18.23	1.50	2.82	1.09E-08	9.21E-06
ENSG00000258137	<i>AC079313.2</i>	6.31	1.28	2.44	2.83E-08	2.05E-05
ENSG00000184669	<i>OR7E14P</i>	4.94	1.95	3.86	1.35E-07	6.22E-05
ENSG00000261488	<i>TBILA</i>	6.10	1.80	3.48	1.14E-07	6.22E-05
ENSG00000258520	<i>AL359317.1</i>	20.67	1.34	2.53	1.34E-07	6.22E-05
ENSG00000259721	<i>AC090877.2</i>	22.03	-1.59	0.33	1.01E-07	6.22E-05
ENSG00000223814	<i>AL691459.1</i>	20.86	-1.08	0.47	1.67E-07	7.03E-05
ENSG0000023251	<i>AC007743.1</i>	86.02	-1.22	0.43	2.03E-07	7.88E-05
ENSG00000237525	<i>AC012668.3</i>	7.18	1.47	2.77	4.65E-07	1.48E-04
ENSG00000256995	<i>AC084816.1</i>	60.00	-1.16	0.45	4.70E-07	1.48E-04
ENSG00000226031	<i>FGF13-AS1</i>	3.29	-1.32	0.40	4.25E-07	1.48E-04
ENSG00000152931	<i>PART1</i>	267.61	0.84	1.78	5.62E-07	1.67E-04
ENSG00000269609	<i>RPARP-AS1</i>	24.73	-0.74	0.60	6.18E-07	1.73E-04
ENSG00000225511	<i>LINC00475</i>	28.26	0.76	1.69	8.13E-07	2.16E-04
ENSG00000257337	<i>AC068888.1</i>	268.12	-0.50	0.71	8.90E-07	2.25E-04
ENSG00000258583	<i>LINC01500</i>	20.02	-1.14	0.45	1.02E-06	2.45E-04
ENSG00000241749	<i>RPSAP52</i>	9.65	1.79	3.46	1.33E-06	3.05E-04
ENSG00000226453	<i>LINC02542</i>	11.13	0.75	1.68	1.66E-06	3.65E-04
ENSG00000228113	<i>AC003991.1</i>	78.53	-1.26	0.42	1.90E-06	4.00E-04
ENSG00000225764	<i>P3H2-AS1</i>	3.09	1.43	2.70	2.11E-06	4.12E-04
ENSG00000278869	<i>BX539320.1</i>	5.91	-1.17	0.44	2.12E-06	4.12E-04
ENSG00000231690	<i>LINC00574</i>	26.22	0.71	1.63	2.95E-06	5.32E-04
ENSG00000280007	<i>AC008079.1</i>	20.64	-0.82	0.57	2.93E-06	5.32E-04
ENSG00000234380	<i>LINC01426</i>	14.78	0.82	1.77	3.44E-06	5.91E-04
ENSG00000131797	<i>CLUHP3</i>	20.79	-0.74	0.60	3.51E-06	5.91E-04
ENSG00000254238	<i>AC100782.1</i>	196.11	-1.77	0.29	3.98E-06	6.49E-04
ENSG00000278419	<i>AL451164.3</i>	291.29	0.59	1.51	4.55E-06	7.18E-04
ENSG00000220785	<i>MTMR9LP</i>	65.31	-0.53	0.69	5.07E-06	7.53E-04
ENSG00000255471	<i>AP001528.2</i>	7.82	-1.01	0.50	4.94E-06	7.53E-04
ENSG00000266968	<i>AC023421.1</i>	3.96	-1.66	0.32	5.75E-06	8.30E-04
ENSG00000253210	<i>AC040970.1</i>	14.98	0.80	1.74	8.01E-06	1.09E-03
ENSG00000255343	<i>AC234917.1</i>	18.06	0.57	1.48	7.96E-06	1.09E-03
ENSG00000225194	<i>LINC00092</i>	15.69	-1.30	0.41	8.55E-06	1.14E-03
ENSG00000260244	<i>AC104083.1</i>	16.23	-1.21	0.43	8.93E-06	1.16E-03
ENSG00000283029	<i>AL139099.4</i>	37836.17	1.01	2.02	1.00E-05	1.20E-03
ENSG00000270412	<i>AL136084.3</i>	11.50	0.99	1.99	9.65E-06	1.20E-03
ENSG00000232677	<i>LINC00665</i>	14.12	-0.70	0.61	9.78E-06	1.20E-03
ENSG00000183935	<i>HTR7P1</i>	31.02	-0.49	0.71	1.03E-05	1.21E-03
ENSG00000188242	<i>PP7080</i>	82.64	-0.40	0.76	1.11E-05	1.28E-03
ENSG00000223561	<i>AC005165.1</i>	47.47	-1.10	0.47	1.18E-05	1.33E-03
ENSG00000271474	<i>AC106881.1</i>	8.29	-1.05	0.48	1.51E-05	1.65E-03
ENSG00000267248	<i>AC025048.2</i>	3.61	-0.94	0.52	1.99E-05	2.14E-03
ENSG00000182366	<i>FAM87A</i>	3.25	1.31	2.48	2.52E-05	2.66E-03
ENSG00000229214	<i>LINC00242</i>	18.90	0.43	1.35	2.69E-05	2.75E-03

GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pvalue	Padj
ENSG00000186466	<i>AQP7P1</i>	8.77	-1.23	0.43	2.72E-05	2.75E-03
ENSG00000225978	<i>HAR1A</i>	12.31	-0.90	0.54	2.85E-05	2.83E-03
ENSG00000227036	<i>LINC00511</i>	137.66	0.54	1.46	3.19E-05	2.99E-03
ENSG00000232368	<i>FTLP2</i>	12.62	-0.64	0.64	3.16E-05	2.99E-03
ENSG00000255153	<i>TOLLIP-AS1</i>	8.05	-0.75	0.59	3.14E-05	2.99E-03
ENSG00000197320	<i>AC060834.1</i>	122.01	-1.11	0.46	3.38E-05	3.10E-03
ENSG00000256321	<i>AC087258.1</i>	14.94	-1.07	0.48	3.61E-05	3.26E-03
ENSG00000253851	<i>AC025370.1</i>	58.50	1.01	2.02	4.08E-05	3.50E-03
ENSG00000232699	<i>BDH2P1</i>	37.99	-0.33	0.79	3.97E-05	3.50E-03
ENSG00000267100	<i>ILF3-DT</i>	143.23	-0.46	0.73	4.03E-05	3.50E-03
ENSG00000234840	<i>LINC01239</i>	9.84	-0.86	0.55	4.50E-05	3.79E-03
ENSG00000233725	<i>LINC00284</i>	9.25	-0.83	0.56	5.01E-05	4.15E-03
ENSG00000266954	<i>AP001010.1</i>	29.87	0.63	1.55	5.30E-05	4.32E-03
ENSG00000280693	<i>SH3PXD2A-AS1</i>	5.72	1.20	2.29	5.90E-05	4.67E-03
ENSG00000223652	<i>AC106786.1</i>	6.95	-0.75	0.60	5.91E-05	4.67E-03
ENSG00000251661	<i>AC136475.1</i>	10.57	-0.73	0.60	6.18E-05	4.77E-03
ENSG00000267414	<i>AC120049.1</i>	10.20	-0.76	0.59	6.23E-05	4.77E-03
ENSG00000257122	<i>RRN3P3</i>	53.03	0.48	1.39	1.00E-04	7.34E-03
ENSG00000229044	<i>AL451070.1</i>	25.71	-0.46	0.72	1.02E-04	7.34E-03
ENSG00000224729	<i>PCOLCE-AS1</i>	670.82	-0.61	0.66	9.90E-05	7.34E-03
ENSG00000162913	<i>OBSCN-AS1</i>	9.15	-0.85	0.56	9.96E-05	7.34E-03
ENSG00000266904	<i>LINC00663</i>	23.15	-0.46	0.73	1.03E-04	7.34E-03
ENSG00000260549	<i>MTLL</i>	80.60	0.59	1.51	1.23E-04	8.65E-03
ENSG00000268941	<i>LINC01711</i>	9.50	1.13	2.19	1.29E-04	8.74E-03
ENSG00000282057	<i>AC092807.3</i>	34.23	0.40	1.32	1.27E-04	8.74E-03
ENSG00000272668	<i>AL590560.1</i>	69.60	-0.63	0.65	1.31E-04	8.74E-03
ENSG00000261959	<i>AC015909.3</i>	30.43	-0.82	0.57	1.30E-04	8.74E-03
ENSG00000214548	<i>MEG3</i>	775.47	-0.67	0.63	1.34E-04	8.81E-03
ENSG00000205105	<i>COX17P1</i>	20.18	0.67	1.59	1.40E-04	9.05E-03
ENSG00000230838	<i>LINC01614</i>	21.19	1.38	2.60	1.48E-04	9.46E-03
ENSG00000273328	<i>AC099329.2</i>	20.31	0.64	1.56	1.64E-04	1.02E-02
ENSG00000231711	<i>LINC00899</i>	28.16	-0.39	0.76	1.62E-04	1.02E-02
ENSG00000250318	<i>AC003072.1</i>	13.23	0.58	1.49	1.68E-04	1.03E-02
ENSG00000225791	<i>TRAM2-AS1</i>	64.91	-0.30	0.81	1.72E-04	1.05E-02
ENSG00000204622	<i>HLA-J</i>	76.75	-0.34	0.79	1.88E-04	1.13E-02
ENSG00000237238	<i>BMS1P10</i>	5.89	-0.83	0.56	2.02E-04	1.17E-02
ENSG00000231394	<i>AC099681.2</i>	5.25	-0.95	0.52	2.02E-04	1.17E-02
ENSG00000269416	<i>LINC01224</i>	4.42	-0.96	0.52	2.02E-04	1.17E-02
ENSG00000260563	<i>AC132872.1</i>	32.58	-0.61	0.66	2.06E-04	1.18E-02
ENSG00000171889	<i>MIR31HG</i>	13.35	0.92	1.89	2.21E-04	1.26E-02
ENSG00000262580	<i>AC087741.1</i>	23.27	-0.54	0.69	2.28E-04	1.28E-02
ENSG00000273186	<i>AL359091.5</i>	5.26	0.73	1.66	2.48E-04	1.35E-02
ENSG00000259728	<i>LINC00933</i>	12.58	-0.48	0.72	2.46E-04	1.35E-02
ENSG00000271239	<i>AC007423.1</i>	3.65	-1.49	0.36	2.46E-04	1.35E-02
ENSG00000272273	<i>IER3-AS1</i>	226.80	0.81	1.76	2.53E-04	1.36E-02
ENSG00000271858	<i>CYB561D2</i>	16.03	-0.58	0.67	2.56E-04	1.36E-02
ENSG00000184385	<i>UMODL1-AS1</i>	3.95	0.90	1.86	2.82E-04	1.44E-02
ENSG00000226816	<i>AC005082.1</i>	4.92	0.80	1.74	2.77E-04	1.44E-02
ENSG00000257261	<i>AC008014.1</i>	9.40	-0.51	0.70	2.74E-04	1.44E-02
ENSG00000254693	<i>AC010768.1</i>	18.42	-0.64	0.64	2.81E-04	1.44E-02

GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pvalue	Padj
ENSG00000276791	AC092117.1	20.75	-0.80	0.58	2.92E-04	1.48E-02
ENSG00000221857	AC020907.2	252.95	-0.64	0.64	3.02E-04	1.51E-02
ENSG00000225138	SLC9A3-AS1	56.43	-0.59	0.66	3.08E-04	1.52E-02
ENSG00000224126	UBE2SP2	4.58	0.85	1.81	3.24E-04	1.59E-02
ENSG00000259607	AC108449.3	148.06	0.46	1.37	3.28E-04	1.59E-02
ENSG00000231128	AL137856.1	10.38	-0.68	0.62	3.38E-04	1.60E-02
ENSG00000285802	AL450043.1	3.83	-0.99	0.50	3.37E-04	1.60E-02
ENSG00000231324	AP000696.1	3.16	-1.28	0.41	3.37E-04	1.60E-02
ENSG00000277142	LINC00235	13.89	-0.77	0.59	3.44E-04	1.61E-02
ENSG00000285686	AL353613.2	3.72	1.22	2.34	3.65E-04	1.69E-02
ENSG00000272501	AL662844.4	27.72	-0.42	0.75	3.72E-04	1.70E-02
ENSG00000278058	AC009159.3	6.36	-0.66	0.64	3.77E-04	1.70E-02
ENSG00000259891	AC107375.1	13.49	-0.76	0.59	3.76E-04	1.70E-02
ENSG00000225492	GBP1P1	4.68	-1.23	0.43	3.82E-04	1.71E-02
ENSG00000260391	AC022336.2	8.21	0.73	1.66	4.14E-04	1.83E-02
ENSG00000260496	AC009041.1	8.79	0.73	1.66	4.26E-04	1.87E-02
ENSG00000233695	GAS6-AS1	205.80	-0.48	0.72	4.49E-04	1.96E-02
ENSG00000249835	VCAN-AS1	102.26	0.96	1.94	4.71E-04	2.03E-02
ENSG00000236213	AC006369.1	12.15	-0.78	0.58	4.89E-04	2.09E-02
ENSG00000263072	ZNF213-AS1	64.76	-0.33	0.79	4.94E-04	2.10E-02
ENSG00000227619	AL391056.1	6.94	1.37	2.59	5.07E-04	2.11E-02
ENSG00000272746	AP005131.7	5.60	0.94	1.92	5.11E-04	2.11E-02
ENSG00000236173	AL049612.1	3.97	0.90	1.86	5.13E-04	2.11E-02
ENSG00000244041	LINC01011	17.42	-0.62	0.65	5.09E-04	2.11E-02
ENSG00000230498	AL035409.1	5.15	1.20	2.30	5.36E-04	2.18E-02
ENSG00000285650	AL157827.2	8.88	0.78	1.72	5.49E-04	2.22E-02
ENSG00000255121	AP003392.4	5.91	-0.73	0.60	5.70E-04	2.28E-02
ENSG00000225913	AL138767.3	5.09	1.02	2.03	5.77E-04	2.30E-02
ENSG00000259943	AL050341.2	25.56	-0.46	0.73	5.87E-04	2.32E-02
ENSG00000235790	AC114488.2	104.36	-0.61	0.65	6.49E-04	2.54E-02
ENSG00000260433	LINC01917	3.73	-1.62	0.32	6.54E-04	2.54E-02
ENSG00000246022	ALDH1L1-AS2	3.36	-1.04	0.49	6.76E-04	2.61E-02
ENSG00000233785	AC131011.1	3.33	1.09	2.13	6.84E-04	2.62E-02
ENSG00000230091	TMEM254-AS1	11.23	-0.44	0.73	6.91E-04	2.62E-02
ENSG00000261553	AL137782.1	70.69	0.41	1.33	7.02E-04	2.65E-02
ENSG00000273038	AL365203.2	18.02	0.48	1.40	7.21E-04	2.70E-02
ENSG00000227766	AL671277.1	385.83	-0.44	0.74	7.30E-04	2.71E-02
ENSG00000254409	AC087521.3	138.82	0.57	1.48	7.44E-04	2.75E-02
ENSG00000226696	LENG8-AS1	17.80	-0.60	0.66	7.53E-04	2.76E-02
ENSG00000274925	ZKSCAN2-DT	12.47	-0.71	0.61	7.92E-04	2.88E-02
ENSG00000227053	AC105446.1	7.36	0.86	1.81	8.36E-04	2.97E-02
ENSG00000267809	NDUFV2P1	55.15	0.42	1.34	8.34E-04	2.97E-02
ENSG00000186056	MATN1-AS1	18.48	-0.53	0.69	8.36E-04	2.97E-02
ENSG00000267573	KRT8P5	8.50	-1.16	0.45	8.42E-04	2.97E-02
ENSG00000237424	FOXD2-AS1	38.23	-0.37	0.77	8.70E-04	3.05E-02
ENSG00000213383	AC104297.1	10.03	0.49	1.41	8.90E-04	3.08E-02
ENSG00000284707	AC079781.5	86.37	0.38	1.30	8.88E-04	3.08E-02
ENSG00000217648	AL136116.3	12.62	0.41	1.33	9.23E-04	3.14E-02
ENSG00000271614	ATP2B1-AS1	18.88	-0.44	0.74	9.27E-04	3.14E-02
ENSG00000264514	AP000915.1	32.45	-0.60	0.66	9.17E-04	3.14E-02

GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pvalue	Padj
ENSG00000226380	<i>LINC-PINT</i>	23.89	0.77	1.70	9.83E-04	3.24E-02
ENSG00000267321	<i>LINC02001</i>	26.49	-0.40	0.76	9.82E-04	3.24E-02
ENSG00000274828	<i>AC068473.5</i>	20.73	-0.44	0.74	9.73E-04	3.24E-02
ENSG00000260236	<i>AC099778.1</i>	10.41	-0.52	0.70	9.88E-04	3.24E-02
ENSG00000206344	<i>HCG27</i>	10.90	-0.63	0.64	9.87E-04	3.24E-02
ENSG00000255390	<i>AC091564.4</i>	185.46	0.39	1.31	9.95E-04	3.25E-02
ENSG00000240032	<i>LNCSTR</i>	19.66	0.65	1.57	1.04E-03	3.36E-02
ENSG00000230695	<i>AC012462.3</i>	2.74	1.21	2.31	1.05E-03	3.39E-02
ENSG00000204054	<i>LINC00963</i>	440.69	-0.31	0.81	1.07E-03	3.41E-02
ENSG00000225472	<i>AL136366.1</i>	3.34	-0.90	0.54	1.07E-03	3.41E-02
ENSG00000250697	<i>AC010343.3</i>	3.01	1.43	2.69	1.10E-03	3.44E-02
ENSG00000272037	<i>AP002907.1</i>	19.67	-0.42	0.75	1.09E-03	3.44E-02
ENSG00000284048	<i>AC073111.4</i>	29.55	-0.36	0.78	1.11E-03	3.48E-02
ENSG00000254756	<i>AP001107.6</i>	8.37	0.68	1.60	1.13E-03	3.49E-02
ENSG00000243431	<i>RPL5P30</i>	3.88	-0.80	0.58	1.13E-03	3.49E-02
ENSG00000235257	<i>ITGA9-AS1</i>	35.98	-0.28	0.83	1.14E-03	3.50E-02
ENSG00000226608	<i>FTLP3</i>	631.57	-0.42	0.75	1.16E-03	3.52E-02
ENSG00000272970	<i>AC107294.2</i>	12.07	-0.54	0.69	1.17E-03	3.52E-02
ENSG00000224769	<i>MUC20P1</i>	8.28	-0.79	0.58	1.17E-03	3.52E-02
ENSG00000275120	<i>AC048382.5</i>	30.50	-0.39	0.76	1.20E-03	3.60E-02
ENSG00000272234	<i>AC008945.1</i>	26.19	-0.95	0.52	1.24E-03	3.68E-02
ENSG00000277449	<i>CEBPB-AS1</i>	27.96	-0.43	0.74	1.33E-03	3.92E-02
ENSG00000220517	<i>ASS1P1</i>	30.67	-0.48	0.72	1.33E-03	3.92E-02
ENSG00000282121	<i>AL592430.2</i>	10.99	1.01	2.01	1.37E-03	4.00E-02
ENSG00000227258	<i>SMIM2-AS1</i>	6.85	-0.55	0.68	1.38E-03	4.02E-02
ENSG00000215386	<i>MIR99AHG</i>	145.01	-0.40	0.76	1.40E-03	4.05E-02
ENSG00000275549	<i>STPG3-AS1</i>	11.64	-0.63	0.64	1.45E-03	4.17E-02
ENSG00000228106	<i>AL392172.1</i>	23.57	0.49	1.41	1.46E-03	4.18E-02
ENSG00000226415	<i>TPI1P1</i>	378.41	0.31	1.24	1.53E-03	4.34E-02
ENSG00000261051	<i>AC107021.2</i>	40.06	0.58	1.49	1.59E-03	4.46E-02
ENSG00000226711	<i>FAM66C</i>	29.68	-0.31	0.80	1.58E-03	4.46E-02
ENSG00000258908	<i>AL355075.3</i>	48.27	0.76	1.69	1.61E-03	4.50E-02
ENSG00000227199	<i>ST7-AS1</i>	15.17	-0.41	0.75	1.67E-03	4.61E-02
ENSG00000277283	<i>AC004812.2</i>	9.49	-0.50	0.71	1.68E-03	4.61E-02
ENSG00000271894	<i>AC007744.1</i>	104.72	-0.51	0.70	1.67E-03	4.61E-02
ENSG00000251548	<i>AC106760.2</i>	9.07	-0.61	0.65	1.71E-03	4.67E-02
ENSG00000215241	<i>LINC02449</i>	17.55	-0.40	0.76	1.73E-03	4.71E-02
ENSG00000226812	<i>AL117382.1</i>	8.40	1.81	3.51	1.81E-03	4.88E-02
ENSG00000237276	<i>ANO7L1</i>	7.07	0.54	1.46	1.82E-03	4.88E-02
ENSG00000176998	<i>HCG4</i>	32.10	-0.46	0.73	1.82E-03	4.88E-02
ENSG00000228748	<i>AL450306.1</i>	53.91	0.28	1.22	1.84E-03	4.90E-02
ENSG00000224594	<i>RPL29P19</i>	40.38	-0.46	0.73	1.88E-03	4.96E-02

baseMean = mean of normalized counts of all samples normalized for transcript length and sequencing depth, FoldChange = fold change between lesioned and preserved OA cartilage samples, Pvalue = nominal P value, Padj = P value according to false discovery rate.

Supplementary Table 4 | Results of the validation and replication of differentially expressed long noncoding RNAs between lesioned osteoarthritic cartilage and preserved osteoarthritic cartilage, paired t-test was performed on the -ΔCt values in the validation and replication analyses.

LncRNA	Discovery		Validation		Replication	
	FC	FDR	FC	P value	FC	P value
<i>AC025370.1</i>	2.02	3.50E-03	2.33	2.16E-02	19.8	1.70E-02
<i>AC090877.2</i>	0.33	6.22E-05	0.28	1.82E-05	0.07	3.56E-04
<i>MEG3</i>	0.63	8.81E-03	0.53	6.16E-03	0.77	6.02E-02
<i>P3H2-AS1</i>	2.70	4.12E-04	2.68	6.58E-03	1.19	9.31E-01
<i>TBILA</i>	3.48	6.22E-05	2.50	9.00E-02	3.54	2.22E-03

FC = fold change, FDR = false discovery rate

Supplementary Table 5 | Significant (according to false discovery rate) differentially expressed lncRNAs in lesioned versus preserved OA cartilage in knee (A) and hip (B) samples.

A		Knee					
		GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pval
							Padj
		ENSG00000230615	<i>AL139220.2</i>	38.13	1.17	2.25	1.96E-10
		ENSG00000232044	<i>LINC01105</i>	82.83	1.24	2.37	7.43E-10
		ENSG00000152931	<i>PART1</i>	249.85	1.08	2.11	1.62E-09
		ENSG00000249306	<i>LINC01411</i>	37.45	2.53	5.78	4.91E-09
		ENSG00000235770	<i>LINC00607</i>	47.65	1.32	2.50	7.28E-09
		ENSG00000229896	<i>AL157373.2</i>	45.42	1.13	2.19	1.16E-07
		ENSG00000261488	<i>TBLA</i>	4.66	1.96	3.90	3.41E-07
		ENSG00000258520	<i>AL359317.1</i>	20.24	1.44	2.71	1.03E-06
		ENSG00000226031	<i>FGF13-AS1</i>	3.43	-1.45	0.37	1.22E-06
		ENSG00000258583	<i>LINC01500</i>	23.21	-1.20	0.44	3.14E-06
		ENSG00000225511	<i>LINC00475</i>	24.26	0.77	1.71	4.07E-06
		ENSG00000225194	<i>LINC00092</i>	16.83	-1.36	0.39	5.09E-06
		ENSG00000230838	<i>LINC01614</i>	19.89	1.83	3.56	5.31E-06
		ENSG00000226453	<i>LINC02542</i>	9.79	0.76	1.69	7.04E-06
		ENSG00000220785	<i>MTMR9LP</i>	62.84	-0.57	0.67	9.45E-06
		ENSG00000267809	<i>NDUFB2P1</i>	51.40	0.51	1.42	1.09E-05
		ENSG00000188242	<i>PP7080</i>	82.86	-0.46	0.73	1.41E-05
		ENSG00000258137	<i>AC079313.2</i>	4.86	1.16	2.24	1.40E-05
		ENSG00000269609	<i>RPAP-AS1</i>	26.79	-0.70	0.62	2.20E-05
		ENSG00000232677	<i>LINC00665</i>	14.09	-0.81	0.57	3.08E-05
		ENSG00000255471	<i>AP001528.2</i>	9.24	-0.99	0.50	2.71E-05
		ENSG00000261051	<i>AC107021.2</i>	35.12	0.69	1.61	3.01E-05
		ENSG00000283029	<i>AL139099.4</i>	37199.75	1.07	2.10	3.11E-05
		ENSG00000131797	<i>CLUHP3</i>	21.87	-0.78	0.58	4.55E-05
		ENSG00000254238	<i>AC100782.1</i>	207.35	-1.45	0.36	4.05E-05
		ENSG00000266968	<i>AC023421.1</i>	4.58	-1.67	0.32	4.53E-05
		ENSG00000278419	<i>AL451164.3</i>	240.86	0.63	1.55	4.31E-05
		ENSG00000255343	<i>AC234917.1</i>	15.44	0.62	1.53	6.14E-05
		ENSG00000259721	<i>AC090877.2</i>	24.12	-1.30	0.41	6.11E-05
		ENSG00000223814	<i>AL691459.1</i>	22.59	-1.00	0.50	6.71E-05
		ENSG00000236094	<i>LINC00545</i>	9.01	1.22	2.34	7.30E-05
		ENSG00000280007	<i>AC008079.1</i>	19.30	-0.80	0.57	8.21E-05
		ENSG00000267100	<i>ILF3-DT</i>	146.81	-0.51	0.70	9.08E-05
		ENSG00000267414	<i>AC120049.1</i>	10.19	-0.77	0.59	8.84E-05
		ENSG00000276791	<i>AC092117.1</i>	22.31	-0.96	0.51	8.96E-05
		ENSG00000261553	<i>AL137782.1</i>	65.06	0.51	1.42	1.01E-04
		ENSG00000229214	<i>LINC00242</i>	18.82	0.48	1.39	1.07E-04
		ENSG00000234380	<i>LINC01426</i>	10.59	0.75	1.68	1.11E-04
		ENSG00000251661	<i>AC136475.1</i>	11.21	-0.75	0.59	1.17E-04
		ENSG00000224287	<i>MSL3P1</i>	12.55	0.59	1.50	1.27E-04
		ENSG00000226415	<i>TP1P1</i>	323.68	0.39	1.31	1.29E-04
		ENSG00000260244	<i>AC104083.1</i>	16.76	-1.06	0.48	1.28E-04
		ENSG00000267248	<i>AC025048.2</i>	3.64	-0.99	0.50	1.28E-04
		ENSG00000228113	<i>AC003991.1</i>	78.55	-1.15	0.45	1.38E-04
		ENSG00000225138	<i>SLC9A3-AS1</i>	58.20	-0.67	0.63	1.41E-04
		ENSG00000224729	<i>PCOLCE-AS1</i>	560.41	-0.61	0.66	1.58E-04
		ENSG00000233251	<i>AC007743.1</i>	100.74	-1.04	0.48	1.55E-04
		ENSG00000225913	<i>AL138767.3</i>	4.68	1.22	2.33	1.70E-04
		ENSG00000237424	<i>FOXK2-AS1</i>	39.92	-0.46	0.73	1.68E-04
		ENSG00000255153	<i>TOLLIP-AS1</i>	8.61	-0.77	0.59	1.73E-04
		ENSG00000257337	<i>AC068888.1</i>	279.17	-0.45	0.73	1.91E-04
		ENSG00000271239	<i>AC007423.1</i>	4.29	-1.59	0.33	1.91E-04
		ENSG00000271474	<i>AC106881.1</i>	9.40	-1.00	0.50	1.94E-04
		ENSG00000182366	<i>FAM87A</i>	2.90	1.56	2.95	2.09E-04
		ENSG00000237238	<i>BMS1P10</i>	5.86	-0.99	0.50	2.08E-04
		ENSG00000269416	<i>LINC01224</i>	5.06	-1.08	0.47	2.03E-04

Knee						
GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pval	Padj
ENSG00000183935	<i>HTR7P1</i>	32.22	-0.46	0.73	2.28E-04	1.97E-02
ENSG00000226816	<i>AC005082.1</i>	4.18	0.91	1.87	2.33E-04	1.99E-02
ENSG00000182397	<i>DNM1P46</i>	8.81	-0.76	0.59	2.46E-04	2.03E-02
ENSG00000251095	<i>AC097478.1</i>	3.60	-1.46	0.36	2.44E-04	2.03E-02
ENSG00000184669	<i>OR7E14P</i>	2.75	1.46	2.76	2.56E-04	2.06E-02
ENSG00000278869	<i>BX539320.1</i>	6.19	-1.01	0.50	2.59E-04	2.06E-02
ENSG00000235423	<i>AC068768.1</i>	628.38	0.64	1.56	2.94E-04	2.31E-02
ENSG00000256995	<i>AC084816.1</i>	68.75	-0.89	0.54	3.06E-04	2.36E-02
ENSG00000272970	<i>AC107294.2</i>	12.86	-0.68	0.62	3.18E-04	2.42E-02
ENSG00000237525	<i>AC012668.3</i>	5.45	1.24	2.36	4.15E-04	2.98E-02
ENSG00000250218	<i>ALDH1L1-AS1</i>	10.22	-0.79	0.58	4.17E-04	2.98E-02
ENSG00000261959	<i>AC015909.3</i>	31.90	-0.85	0.55	4.11E-04	2.98E-02
ENSG00000270412	<i>AL136084.3</i>	10.68	0.96	1.94	4.03E-04	2.98E-02
ENSG00000267573	<i>KRT8P5</i>	9.01	-1.39	0.38	4.56E-04	3.21E-02
ENSG00000267272	<i>LINC01140</i>	119.60	0.46	1.37	4.79E-04	3.33E-02
ENSG00000231394	<i>AC099681.2</i>	5.74	-0.98	0.51	5.25E-04	3.50E-02
ENSG00000260822	<i>AC004656.1</i>	425.41	0.52	1.43	5.21E-04	3.50E-02
ENSG00000273038	<i>AL365203.2</i>	15.66	0.64	1.56	5.13E-04	3.50E-02
ENSG00000227258	<i>SMIM2-AS1</i>	7.05	-0.65	0.64	5.39E-04	3.55E-02
ENSG00000230487	<i>PSMG3-AS1</i>	59.40	-0.47	0.72	6.02E-04	3.91E-02
ENSG00000230498	<i>AL035409.1</i>	4.83	1.35	2.56	6.30E-04	4.04E-02
ENSG00000232368	<i>FTLP2</i>	10.92	-0.63	0.65	6.39E-04	4.04E-02
ENSG00000234840	<i>LINC01239</i>	11.21	-0.75	0.59	6.46E-04	4.04E-02
ENSG00000240032	<i>LNCSTRLL</i>	18.09	0.68	1.60	6.56E-04	4.05E-02
ENSG00000225472	<i>AL136366.1</i>	3.63	-1.04	0.49	6.70E-04	4.08E-02
ENSG00000225492	<i>GBP1P1</i>	5.56	-1.22	0.43	6.97E-04	4.19E-02
ENSG00000256210	<i>AC005255.1</i>	34.11	0.68	1.60	7.26E-04	4.32E-02
ENSG00000231690	<i>LINC00574</i>	24.37	0.54	1.46	7.52E-04	4.37E-02
ENSG00000231711	<i>LINC00899</i>	28.78	-0.41	0.75	7.50E-04	4.37E-02
ENSG00000221990	<i>EXOC3-AS1</i>	16.33	-0.48	0.72	7.69E-04	4.41E-02
ENSG00000171889	<i>MIR31HG</i>	10.43	0.91	1.88	7.87E-04	4.47E-02
ENSG00000282057	<i>AC092807.3</i>	36.31	0.41	1.32	8.41E-04	4.72E-02
ENSG00000227855	<i>DPY19L2P3</i>	8.18	-0.81	0.57	8.79E-04	4.88E-02
ENSG00000260139	<i>CSPG4P13</i>	40.87	-0.81	0.57	9.08E-04	4.98E-02

B	Hip						
	GeneID	GeneName	baseMean	log2FoldChange	FoldChange	Pval	Padj
	ENSG00000236094	<i>LINC00545</i>	52.87	2.23	4.68	7.03E-08	2.71E-04
	ENSG00000233251	<i>AC007743.1</i>	24.98	-1.86	0.28	2.25E-07	2.77E-04
	ENSG00000236883	<i>AP001615.1</i>	6.95	4.43	21.54	3.19E-07	2.77E-04
	ENSG00000256040	<i>PAPPA-AS1</i>	115.96	3.23	9.40	3.59E-07	2.77E-04
	ENSG00000269275	<i>AC020922.3</i>	11.20	3.79	13.87	2.54E-07	2.77E-04
	ENSG00000281371	<i>INE2</i>	136.78	1.12	2.18	9.48E-07	6.10E-04
	ENSG00000258525	<i>AL049830.3</i>	128.19	2.70	6.51	1.59E-06	8.78E-04
	ENSG00000236886	<i>AC007563.2</i>	63.43	1.92	3.78	2.33E-06	1.12E-03
	ENSG00000278192	<i>AL118505.1</i>	17.38	3.61	12.19	2.61E-06	1.12E-03
	ENSG00000241749	<i>RPSAP52</i>	36.76	2.38	5.19	4.98E-06	1.92E-03
	ENSG00000226812	<i>AL117382.1</i>	18.28	3.08	8.43	7.07E-06	2.48E-03
	ENSG00000184669	<i>OR7E14P</i>	13.19	3.46	10.97	9.94E-06	3.06E-03
	ENSG00000260231	<i>KDMA-DT</i>	116.45	1.34	2.53	1.03E-05	3.06E-03
	ENSG00000223561	<i>AC005165.1</i>	15.46	-3.03	0.12	1.64E-05	4.52E-03
	ENSG00000256995	<i>AC084816.1</i>	23.25	-2.20	0.22	1.79E-05	4.60E-03
	ENSG00000259721	<i>AC090877.2</i>	12.62	-2.73	0.15	3.73E-05	9.00E-03
	ENSG00000237525	<i>AC012668.3</i>	13.48	2.17	4.49	4.42E-05	1.00E-02
	ENSG00000230615	<i>AL139220.2</i>	109.63	0.96	1.94	5.52E-05	1.12E-02
	ENSG00000254409	<i>AC087521.3</i>	316.72	1.11	2.16	5.42E-05	1.12E-02
	ENSG00000272273	<i>IER3-AS1</i>	580.15	1.62	3.08	7.70E-05	1.49E-02
	ENSG00000231690	<i>LINC00574</i>	33.09	1.29	2.44	1.06E-04	1.95E-02
	ENSG00000224743	<i>TEX26-AS1</i>	32.18	1.92	3.78	1.17E-04	2.06E-02
	ENSG00000258908	<i>AL355075.3</i>	113.22	1.34	2.54	1.65E-04	2.77E-02
	ENSG00000271894	<i>AC007744.1</i>	68.60	-1.14	0.45	1.85E-04	2.97E-02
	ENSG00000229896	<i>AL157373.2</i>	73.33	1.37	2.59	2.45E-04	3.78E-02
	ENSG00000223855	<i>HRAT92</i>	7.66	2.57	5.95	2.77E-04	4.07E-02
	ENSG00000270547	<i>LINC01235</i>	31.37	2.68	6.39	2.85E-04	4.07E-02
	ENSG00000234964	<i>FABP5P7</i>	51.19	-1.55	0.34	3.35E-04	4.62E-02
	ENSG00000228113	<i>AC003991.1</i>	74.28	-1.64	0.32	3.66E-04	4.77E-02
	ENSG00000232530	<i>LIF-AS1</i>	4.75	3.57	11.86	3.71E-04	4.77E-02
	ENSG00000223814	<i>AL691459.1</i>	13.09	-1.38	0.38	3.84E-04	4.78E-02

baseMean = mean of normalized counts of all samples normalized for transcript length and sequencing depth, FoldChange = fold change between lesioned and preserved OA cartilage samples, Pval = nominal P value, Padj = P value according to false discovery rate.

Supplementary Table 6 | Significant (according to false discovery rate) differentially expressed long noncoding RNAs in lesioned osteoarthritic cartilage compared to preserved osteoarthritic cartilage unique for knee (A) and hip (B) samples.

A							Knee						
GeneID	GeneName	baseMean	log2FoldChange	FoldChange	pvalue	padj							
ENSG00000224287	<i>MSL3P1</i>	12.55		0.59	1.50	1.27E-04	1.49E-02						
ENSG00000182397	<i>DNM1P46</i>	8.81		-0.76	0.59	2.46E-04	2.03E-02						
ENSG00000251095	<i>AC097478.1</i>	3.60		-1.46	0.36	2.44E-04	2.03E-02						
ENSG00000235423	<i>AC068768.1</i>	628.38		0.64	1.56	2.94E-04	2.31E-02						
ENSG00000250218	<i>ALDH1L1-AS1</i>	10.22		-0.79	0.58	4.17E-04	2.98E-02						
ENSG00000267272	<i>LINC01140</i>	119.60		0.46	1.37	4.79E-04	3.33E-02						
ENSG00000260822	<i>AC004656.1</i>	425.41		0.52	1.43	5.21E-04	3.50E-02						
ENSG00000230487	<i>PSMG3-AS1</i>	59.40		-0.47	0.72	6.02E-04	3.91E-02						
ENSG00000256210	<i>AC005255.1</i>	34.11		0.68	1.60	7.26E-04	4.32E-02						
ENSG00000221990	<i>EXOC3-AS1</i>	16.33		-0.48	0.72	7.69E-04	4.41E-02						
ENSG00000227855	<i>DPY19L2P3</i>	8.18		-0.81	0.57	8.79E-04	4.88E-02						
ENSG00000260139	<i>CSPG4P13</i>	40.87		-0.81	0.57	9.08E-04	4.98E-02						

B							Hip						
GeneID	GeneName	baseMean	log2FoldChange	FoldChange	pvalue	padj							
ENSG00000236883	<i>AP001615.1</i>	6.95		4.43	21.54	3.19E-07	2.77E-04						
ENSG00000256040	<i>PAPPA-AS1</i>	115.96		3.23	9.40	3.59E-07	2.77E-04						
ENSG00000269275	<i>AC020922.3</i>	11.20		3.79	13.87	2.54E-07	2.77E-04						
ENSG00000281371	<i>INE2</i>	136.78		1.12	2.18	9.48E-07	6.10E-04						
ENSG00000258525	<i>AL049830.3</i>	128.19		2.70	6.51	1.59E-06	8.78E-04						
ENSG00000236886	<i>AC007563.2</i>	63.43		1.92	3.78	2.33E-06	1.12E-03						
ENSG00000278192	<i>AL118505.1</i>	17.38		3.61	12.19	2.61E-06	1.12E-03						
ENSG00000260231	<i>KDM7A-DT</i>	116.45		1.34	2.53	1.03E-05	3.06E-03						
ENSG00000224743	<i>TEX26-AS1</i>	32.18		1.92	3.78	1.17E-04	2.06E-02						
ENSG00000223855	<i>HRAT92</i>	7.66		2.57	5.95	2.77E-04	4.07E-02						
ENSG00000270547	<i>LINC01235</i>	31.37		2.68	6.39	2.85E-04	4.07E-02						
ENSG00000234964	<i>FABP5P7</i>	51.19		-1.55	0.34	3.35E-04	4.62E-02						
ENSG00000232530	<i>LIF-AS1</i>	4.75		3.57	11.86	3.71E-04	4.77E-02						

baseMean = mean of normalized counts of all samples normalized for transcript length and sequencing depth, FoldChange = fold change between lesioned and preserved OA cartilage samples, pvalue = nominal P value, Padj = P value according to false discovery rate.

Supplementary Table 7 | Nominal significant correlations > |0.8| between significant differentially expressed long noncoding RNAs and significant (according to false discovery rate) differentially expressed protein-coding genes in the same osteoarthritis cartilage samples.

lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000171889	MIR31HG	sense	ENSG00000105810	CDK6	0.808	2.22E-16
ENSG00000171889	MIR31HG	sense	ENSG00000204525	HLA-C	-0.808	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000158042	MRPL17	0.806	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000196072	BLOC1S2	0.830	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000117410	ATP6VoB	0.807	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000124126	PREX1	-0.815	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000175324	LSM1	0.807	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000182220	ATP6AP2	0.812	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000101191	DIDO1	-0.803	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000117450	PRDX1	0.814	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000132646	PCNA	0.805	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000197956	S100A6	0.813	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000138495	COX17	0.852	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000072042	RDH11	0.860	2.22E-16
ENSG00000205105	COX17P1	pseudogene	ENSG00000136240	KDELR2	0.801	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000103202	NME4	0.819	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000188559	RALGAP2	-0.831	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000160145	KALRN	-0.837	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000198018	ENTPD7	-0.872	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000170776	AKAP13	-0.804	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000204219	TCEA3	0.820	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000065057	TMHL1	0.802	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000169964	TMEM42	0.809	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000182195	LDOC1	0.833	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000166681	BEX3	0.826	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000104964	AES	0.801	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000006459	KDM7A	-0.850	2.22E-16
ENSG00000221857	AC020907.2	other	ENSG00000198742	SMURF1	-0.831	2.22E-16
ENSG00000223814	AL691459.1	intergenic	ENSG00000269113	TRABD2B	0.826	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000164776	PHKG1	0.840	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000166681	BEX3	0.804	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000137070	IL11RA	0.806	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000161010	MKNIP	0.855	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000170776	AKAP13	-0.810	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000087842	PIR	0.809	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000013583	HEBP1	0.810	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000178802	MPI	0.886	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000161249	DMKN	0.849	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000182195	LDOC1	0.829	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000198018	ENTPD7	-0.814	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000169964	TMEM42	0.874	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000106004	HOXA5	0.802	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000184515	BEX3	0.837	2.22E-16
ENSG00000224594	RPL29P19	pseudogene	ENSG00000175575	PAAF1	0.805	2.22E-16
ENSG00000226415	TP11P1	pseudogene	ENSG00000197930	ERO1A	0.814	2.22E-16
ENSG00000226608	FTLP3	pseudogene	ENSG00000087086	FTL	0.855	2.22E-16
ENSG00000226608	FTLP3	pseudogene	ENSG00000153944	MSI2	-0.801	2.22E-16
ENSG00000227036	LINC00511	other	ENSG00000100596	SPTLC2	0.821	2.22E-16
ENSG00000227053	AC105446.1	antisense	ENSG00000205277	MUC12	0.808	2.22E-16
ENSG00000227053	AC105446.1	antisense	ENSG00000158710	TAGLN2	0.839	2.22E-16
ENSG00000227619	AL391056.1	intergenic	ENSG00000148344	PTGES	0.804	2.22E-16
ENSG00000227766	AL671277.1	pseudogene	ENSG00000169905	TOR1AIP2	-0.813	2.22E-16
ENSG00000228113	AC003991.1	antisense	ENSG00000128487	SPECC1	-0.818	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000119185	ITGB1BP1	0.809	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000137288	UQC22	0.873	2.22E-16

lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000228748	AL450306.1	antisense	ENSG00000114354	TFG	0.837	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000156873	PHKG2	0.813	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000203879	GDI1	0.837	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000105426	PTPRS	-0.806	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000135930	EIF4E2	0.828	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000114126	TFDP2	-0.830	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000154144	TBRG1	0.805	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000137996	RTCA	0.819	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000177700	POLR2L	0.844	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000101191	DIDO1	-0.810	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000115317	HTRA2	0.825	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000123353	ORMDL2	0.846	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000248905	FMN1	-0.835	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000243317	STMP1	0.833	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000164620	RELL2	0.837	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000187792	ZNF70	-0.834	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000149716	ORAOV1	0.892	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000197747	S100A10	0.825	2.22E-16
ENSG00000228748	AL450306.1	antisense	ENSG00000081181	ARG2	0.851	2.22E-16
ENSG00000230615	AL139220.2	intergenic	ENSG00000105810	CDK6	0.818	2.22E-16
ENSG00000230615	AL139220.2	intergenic	ENSG00000163359	COL6A3	0.806	2.22E-16
ENSG00000230615	AL139220.2	intergenic	ENSG00000162998	FRZB	-0.847	2.22E-16
ENSG00000230615	AL139220.2	intergenic	ENSG00000165795	NDRG2	-0.856	2.22E-16
ENSG00000231128	AL137856.1	antisense	ENSG00000185689	C6orf201	0.840	2.22E-16
ENSG00000231128	AL137856.1	antisense	ENSG00000118971	CCND2	-0.843	2.22E-16
ENSG00000231128	AL137856.1	antisense	ENSG00000167107	ACSF2	0.830	2.22E-16
ENSG00000231128	AL137856.1	antisense	ENSG00000124635	HIST1H2BJ	-0.821	2.22E-16
ENSG00000231128	AL137856.1	antisense	ENSG00000169905	TOR1AIP2	-0.835	2.22E-16
ENSG00000231128	AL137856.1	antisense	ENSG00000124615	MOCS1	0.808	2.22E-16
ENSG00000232044	LINC01105	other	ENSG00000134198	TSPAN2	0.841	2.22E-16
ENSG00000233695	GAS6-AS1	antisense	ENSG00000118971	CCND2	-0.802	2.22E-16
ENSG00000233695	GAS6-AS1	antisense	ENSG00000169905	TOR1AIP2	-0.813	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000149948	HMG2A	0.819	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000162512	SDC3	-0.804	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000122756	CNTFR	-0.839	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000144843	ADPRH	0.848	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000144857	BOC	-0.816	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000198805	PNP	0.824	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000115762	PLEKHB2	0.804	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000160111	CPAMD8	-0.808	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000266524	GDF10	-0.835	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000165238	WNK2	-0.813	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000124731	TREM1	0.819	2.22E-16
ENSG00000234380	LINC01426	intergenic	ENSG00000185432	METTL7A	-0.803	2.22E-16
ENSG00000235770	LINC00607	intergenic	ENSG00000090530	P3H2	0.805	2.22E-16
ENSG00000235790	AC114488.2	antisense	ENSG00000198865	CCDC152	0.831	2.22E-16
ENSG00000235790	AC114488.2	antisense	ENSG00000147459	DOCK5	-0.801	2.22E-16
ENSG00000235790	AC114488.2	antisense	ENSG00000079841	RIMS1	-0.845	2.22E-16
ENSG00000235790	AC114488.2	antisense	ENSG00000069188	SDK2	-0.802	2.22E-16
ENSG00000236094	LINC00545	intergenic	ENSG00000166033	HTRA1	0.822	2.22E-16
ENSG00000236094	LINC00545	intergenic	ENSG00000196754	S100A2	0.812	2.22E-16
ENSG00000236094	LINC00545	intergenic	ENSG00000134259	NGF	0.810	2.22E-16
ENSG00000237525	AC012668.3	intergenic	ENSG00000105426	PTPRS	-0.804	2.22E-16
ENSG00000240032	LNCsRLR	antisense	ENSG00000160145	KALRN	0.846	2.22E-16
ENSG00000240032	LNCsRLR	antisense	ENSG00000156273	BACH1	0.832	2.22E-16
ENSG00000240032	LNCsRLR	antisense	ENSG00000095951	HIVEP1	0.812	2.22E-16

lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000104067	<i>TJP1</i>	0.804	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000169398	<i>PTK2</i>	0.842	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000150995	<i>ITPR1</i>	0.816	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000177200	<i>CHD9</i>	0.806	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000075420	<i>FNDC3B</i>	0.852	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000156011	<i>PSD3</i>	0.825	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000170776	<i>AKAP13</i>	0.802	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000151914	<i>DST</i>	0.849	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000104447	<i>TRPS1</i>	0.839	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000182195	<i>LDLOC1</i>	-0.817	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000198018	<i>ENTPD7</i>	0.869	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000111647	<i>UHRF1BP1L</i>	0.800	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000140526	<i>ABHD2</i>	0.805	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000184905	<i>TCEAL2</i>	-0.815	2.22E-16
ENSG00000240032	<i>LNCSTR</i>	antisense	ENSG00000139514	<i>SLC7A1</i>	0.844	2.22E-16
ENSG00000241749	<i>RPSAP52</i>	pseudogene	ENSG00000149948	<i>HMGA2</i>	0.845	2.22E-16
ENSG00000241749	<i>RPSAP52</i>	pseudogene	ENSG00000198805	<i>PNP</i>	0.832	2.22E-16
ENSG00000241749	<i>RPSAP52</i>	pseudogene	ENSG00000011422	<i>PLAUR</i>	0.844	2.22E-16
ENSG00000241749	<i>RPSAP52</i>	pseudogene	ENSG00000006327	<i>TNFRSF12A</i>	0.819	2.22E-16
ENSG00000241749	<i>RPSAP52</i>	pseudogene	ENSG00000122756	<i>CNTFR</i>	-0.813	2.22E-16
ENSG00000241749	<i>RPSAP52</i>	pseudogene	ENSG00000124731	<i>TREM1</i>	0.803	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000122756	<i>CNTFR</i>	-0.805	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000266524	<i>GDF10</i>	-0.804	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000189058	<i>APOD</i>	-0.837	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000171488	<i>LRRRC8</i>	0.836	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000123610	<i>TNFAIP6</i>	0.814	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000132718	<i>SYT11</i>	0.819	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000148344	<i>PTGES</i>	0.823	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000165238	<i>WNK2</i>	-0.814	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000144908	<i>ALDH1L1</i>	-0.815	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000162512	<i>SDC3</i>	-0.810	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000134259	<i>NGF</i>	0.836	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000144843	<i>ADPRH</i>	0.808	2.22E-16
ENSG00000249306	<i>LINC01411</i>	intergenic	ENSG00000144857	<i>BOC</i>	-0.804	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000149716	<i>ORAOV1</i>	0.843	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000114354	<i>TFG</i>	0.825	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000248905	<i>FMN1</i>	-0.806	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000177700	<i>POLR2L</i>	0.822	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000081181	<i>ARG2</i>	0.823	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000137288	<i>UQCCL2</i>	0.827	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000123353	<i>ORMDL2</i>	0.818	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000115317	<i>HTRA2</i>	0.806	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000187792	<i>ZNF70</i>	-0.837	2.22E-16
ENSG00000249835	<i>VCAN-AS1</i>	antisense	ENSG00000243317	<i>STMP1</i>	0.824	2.22E-16
ENSG00000250318	<i>AC003072.1</i>	pseudogene	ENSG00000158710	<i>TAGLN2</i>	0.805	2.22E-16
ENSG00000253851	<i>AC025370.1</i>	antisense	ENSG00000102362	<i>SYTL4</i>	0.825	2.22E-16
ENSG00000254238	<i>AC100782.1</i>	antisense	ENSG00000128487	<i>SPECC1</i>	-0.810	2.22E-16
ENSG00000254238	<i>AC100782.1</i>	antisense	ENSG00000169905	<i>TOR1AIP2</i>	-0.828	2.22E-16
ENSG00000254238	<i>AC100782.1</i>	antisense	ENSG00000167107	<i>ACSF2</i>	0.820	2.22E-16
ENSG00000254756	<i>AP001107.6</i>	antisense	ENSG00000162599	<i>NFIA</i>	-0.804	2.22E-16
ENSG00000255343	<i>AC234917.1</i>	other	ENSG00000135404	<i>CD63</i>	0.845	2.22E-16
ENSG00000255343	<i>AC234917.1</i>	other	ENSG00000119185	<i>ITGB1BP1</i>	0.835	2.22E-16
ENSG00000255343	<i>AC234917.1</i>	other	ENSG00000114126	<i>TFDP2</i>	-0.831	2.22E-16
ENSG00000255343	<i>AC234917.1</i>	other	ENSG00000149716	<i>ORAOV1</i>	0.842	2.22E-16
ENSG00000255343	<i>AC234917.1</i>	other	ENSG00000203879	<i>GDI1</i>	0.853	2.22E-16
ENSG00000255343	<i>AC234917.1</i>	other	ENSG00000182220	<i>ATP6AP2</i>	0.827	2.22E-16

lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000255343	AC234917.1	other	ENSG00000114354	TFG	0.874	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000116586	LAMTOR2	0.812	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000137996	RTCA	0.820	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000248905	FMN1	-0.850	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000115307	AUP1	0.836	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000115317	HTRA2	0.862	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000055813	CCDC85A	-0.854	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000125868	DSTN	0.809	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000240972	MIF	0.811	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000101294	HM13	0.804	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000105426	PTPRS	-0.841	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000169241	SLC50A1	0.803	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000101191	DID1	-0.852	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000101493	ZNF516	-0.809	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000131871	SELENOS	0.814	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000196072	BLOC1S2	0.834	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000187792	ZNF70	-0.824	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000152217	SETBP1	-0.851	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000197747	S100A10	0.860	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000179930	ZNF648	-0.822	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000068745	IP6K2	0.838	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000081181	ARG2	0.879	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000122034	GTF3A	0.821	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000124126	PREX1	-0.832	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000137288	UQC2	0.884	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000102007	PLP2	0.811	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000156873	PHKG2	0.855	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000177700	POLR2L	0.868	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000243317	STMP1	0.869	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000164292	RHOBTB3	-0.809	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000085662	AKR1B1	0.828	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000110721	CHKA	0.821	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000136240	KDELR2	0.809	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000164620	RELL2	0.855	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000123353	ORMDL2	0.884	2.22E-16
ENSG00000255343	AC234917.1	other	ENSG00000069849	ATP1B3	0.824	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000119185	ITGB1BP1	0.844	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000164032	H2AFZ	0.801	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000055813	CCDC85A	-0.820	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000101191	DID1	-0.846	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000137996	RTCA	0.838	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000124126	PREX1	-0.808	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000115317	HTRA2	0.884	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000114126	TTFP2	-0.834	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000203879	GDI1	0.877	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000135404	CD63	0.822	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000114354	TFG	0.860	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000196072	BLOC1S2	0.826	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000156873	PHKG2	0.854	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000068745	IP6K2	0.825	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000187792	ZNF70	-0.832	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000248905	FMN1	-0.865	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000197747	S100A10	0.843	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000240972	MIF	0.820	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000152217	SETBP1	-0.833	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000081181	ARG2	0.890	2.22E-16

lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000255390	AC091564.4	antisense	ENSG00000164620	RELL2	0.844	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000243317	STMP1	0.871	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000177700	POLR2L	0.884	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000137288	UQCC2	0.911	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000123353	ORMDL2	0.877	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000149716	ORAOV1	0.892	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000105426	PTPRS	-0.835	2.22E-16
ENSG00000255390	AC091564.4	antisense	ENSG00000146648	EGFR	-0.805	2.22E-16
ENSG00000257337	AC068888.1	antisense	ENSG00000167378	IRGQ	-0.807	2.22E-16
ENSG00000257337	AC068888.1	antisense	ENSG00000092964	DPYSL2	-0.863	2.22E-16
ENSG00000257337	AC068888.1	antisense	ENSG00000167107	ACSF2	0.813	2.22E-16
ENSG00000258583	LINC01500	intergenic	ENSG00000165617	DACT1	0.825	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000203879	GDI1	0.841	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000177700	POLR2L	0.858	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000119185	ITGB1BP1	0.808	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000114126	TFDP2	-0.840	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000055813	CCDC85A	-0.804	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000105426	PTPRS	-0.832	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000114354	TFG	0.832	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000248905	FMN1	-0.827	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000187792	ZNF70	-0.846	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000137288	UQCC2	0.890	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000152217	SETBP1	-0.809	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000149716	ORAOV1	0.899	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000081181	ARG2	0.863	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000197747	Slco0A10	0.833	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000156873	PHKG2	0.806	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000123353	ORMDL2	0.864	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000243317	STMP1	0.841	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000196072	BLOC1S2	0.808	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000115317	HTRA2	0.834	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000164620	RELL2	0.818	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000101191	DIDO1	-0.832	2.22E-16
ENSG00000258908	AL355075.3	intergenic	ENSG00000068745	IP6K2	0.807	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000125868	DSTN	0.860	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000135404	CD63	0.803	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000177700	POLR2L	0.829	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000114354	TFG	0.867	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000137288	UQCC2	0.833	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000102362	SYTL4	0.867	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000243317	STMP1	0.847	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000119185	ITGB1BP1	0.866	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000152217	SETBP1	-0.835	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000034713	GABARAPL2	0.801	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000123353	ORMDL2	0.830	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000131871	SELENOS	0.811	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000115317	HTRA2	0.883	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000101191	DIDO1	-0.806	2.22E-16
ENSG00000259607	AC108449.3	antisense	ENSG00000081181	ARG2	0.838	2.22E-16
ENSG00000259721	AC090877.2	intergenic	ENSG00000166923	GREM1	0.873	2.22E-16
ENSG00000260563	AC132872.1	intergenic	ENSG00000104447	TRPS1	-0.836	2.22E-16
ENSG00000264514	AP000915.1	intergenic	ENSG00000006042	TMEM98	0.835	2.22E-16
ENSG00000264514	AP000915.1	intergenic	ENSG00000198865	CCDC152	0.867	2.22E-16
ENSG00000264514	AP000915.1	intergenic	ENSG00000137070	IL11RA	0.801	2.22E-16
ENSG00000264514	AP000915.1	intergenic	ENSG00000141542	RAB40B	0.805	2.22E-16
ENSG00000264514	AP000915.1	intergenic	ENSG00000166681	BEX3	0.809	2.22E-16

lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000264514	<i>AP000915.1</i>	intergenic	ENSG00000013583	<i>HEBP1</i>	0.810	2.22E-16
ENSG00000264514	<i>AP000915.1</i>	intergenic	ENSG00000102466	<i>FGF14</i>	0.814	2.22E-16
ENSG00000264514	<i>AP000915.1</i>	intergenic	ENSG00000069188	<i>SDK2</i>	-0.834	2.22E-16
ENSG00000264514	<i>AP000915.1</i>	intergenic	ENSG00000104447	<i>TRPS1</i>	-0.807	2.22E-16
ENSG00000264514	<i>AP000915.1</i>	intergenic	ENSG00000161010	<i>MRNIP</i>	0.854	2.22E-16
ENSG00000264514	<i>AP000915.1</i>	intergenic	ENSG00000124615	<i>MOCS1</i>	0.842	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000104447	<i>TRPS1</i>	-0.832	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000170776	<i>AKAP13</i>	-0.827	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000160145	<i>KALRN</i>	-0.800	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000184515	<i>BEX5</i>	0.846	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000169964	<i>TMEM42</i>	0.809	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000182195	<i>LDOC1</i>	0.843	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000166681	<i>BEX3</i>	0.810	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000198018	<i>ENTPD7</i>	-0.820	2.22E-16
ENSG00000267100	<i>ILF3-DT</i>	intergenic	ENSG00000178802	<i>MPI</i>	0.801	2.22E-16
ENSG00000267809	<i>NDUFV2P1</i>	pseudogene	ENSG00000164294	<i>GPX8</i>	0.808	2.22E-16
ENSG00000272234	<i>AC008945.1</i>	antisense	ENSG00000169905	<i>TOR1AIP2</i>	-0.812	2.22E-16
ENSG00000272234	<i>AC008945.1</i>	antisense	ENSG00000118971	<i>CCND2</i>	-0.836	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000146648	<i>EGFR</i>	-0.810	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000101493	<i>ZNF516</i>	-0.808	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000105426	<i>PTPRS</i>	-0.862	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000102007	<i>PLP2</i>	0.809	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000149716	<i>ORAOV1</i>	0.873	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000248905	<i>FMN1</i>	-0.833	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000115317	<i>HTRA2</i>	0.846	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000123353	<i>ORMDL2</i>	0.865	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000114354	<i>TFG</i>	0.824	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000137996	<i>RTCA</i>	0.825	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000196072	<i>BLOC1S2</i>	0.835	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000187792	<i>ZNF70</i>	-0.833	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000156873	<i>PHKG2</i>	0.820	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000137288	<i>UQC22</i>	0.891	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000177700	<i>POLR2L</i>	0.857	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000164620	<i>RELL2</i>	0.808	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000081181	<i>ARG2</i>	0.862	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000101191	<i>DIDO1</i>	-0.842	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000114126	<i>TFDP2</i>	-0.820	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000152217	<i>SETBP1</i>	-0.823	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000119185	<i>ITGB1BP1</i>	0.802	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000203879	<i>GDI1</i>	0.832	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000197747	<i>S100A10</i>	0.828	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000240972	<i>MIF</i>	0.820	2.22E-16
ENSG00000272273	<i>IER3-AS1</i>	antisense	ENSG00000243317	<i>STMP1</i>	0.844	2.22E-16
ENSG00000278419	<i>AL451164.3</i>	antisense	ENSG00000171314	<i>PGAM1</i>	0.834	2.22E-16
ENSG00000283029	<i>AL139099.4</i>	sense	ENSG00000158373	<i>HIST1H2BD</i>	0.801	2.22E-16
ENSG00000283029	<i>AL139099.4</i>	sense	ENSG00000197061	<i>HIST1H4C</i>	0.808	2.22E-16
ENSG00000283029	<i>AL139099.4</i>	sense	ENSG00000169905	<i>TOR1AIP2</i>	0.809	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000146426	<i>TIAM2</i>	-0.836	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000156011	<i>PSD3</i>	-0.820	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000161010	<i>MRNIP</i>	0.830	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000170776	<i>AKAP13</i>	-0.837	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000137070	<i>IL1RA</i>	0.822	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000075420	<i>FNDC3B</i>	-0.835	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000104447	<i>TRPS1</i>	-0.814	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000154229	<i>PRKCA</i>	-0.811	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000177200	<i>CHD9</i>	-0.800	2.22E-16

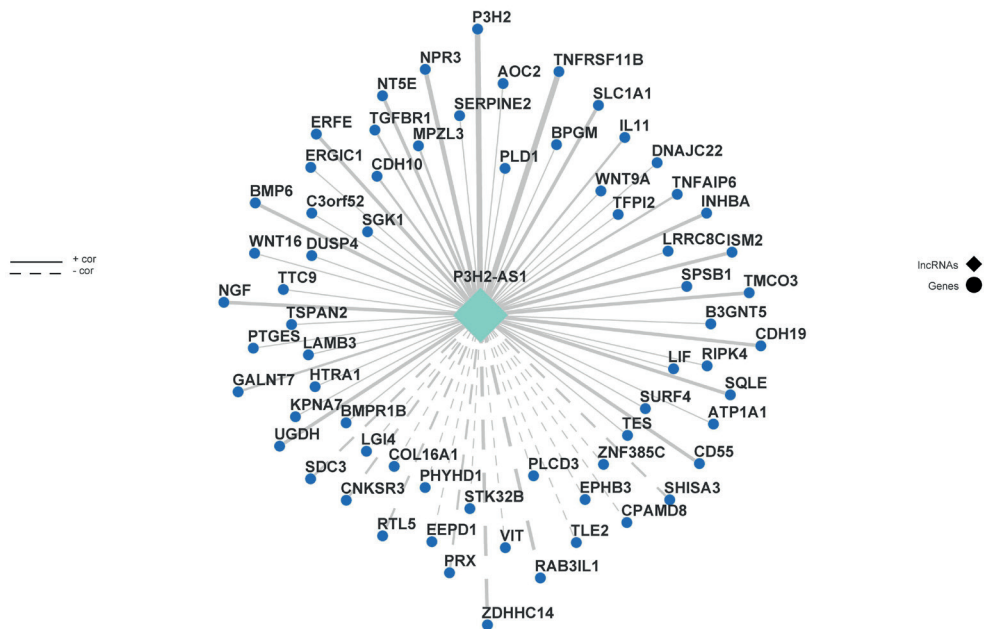
lncRNA ID	lncRNA name	Biotype	mRNA ID	mRNA name	Cor	Pval
ENSG00000284048	<i>AC073111.4</i>	other	ENSG00000013583	<i>HEBP1</i>	0.822	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG000000198018	<i>ENTPD7</i>	-0.821	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG000000166681	<i>BEX3</i>	0.811	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG000000178802	<i>MPI</i>	0.801	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG000000164776	<i>PHKG1</i>	0.815	2.22E-16
ENSG00000284048	<i>AC073111.4</i>	other	ENSG000000166025	<i>AMOTL1</i>	-0.825	2.22E-16
ENSG00000284707	<i>AC079781.5</i>	other	ENSG000000166986	<i>MARS</i>	0.841	2.22E-16
ENSG00000284707	<i>AC079781.5</i>	other	ENSG00000070669	<i>ASNS</i>	0.871	2.22E-16

Cor = correlation between lncRNA and mRNA, Pval = nominal P value.

Supplementary Table 8 | Count and percentage of unique long noncoding RNAs that have correlations > 0.8 with differentially expressed genes from the same samples.

Biotype	Number	Percentage (%)
Antisense	17	36
Sense	2	4
Pseudogene	8	17
Intergenic	14	30
Other	6	13

Supplementary Figures



Supplementary Figure 1 | *P3H2-AS1*-mRNA coexpression network

