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DATA DESCRIPTOR

3' mRNA-seq dataset of human chondrocytes treated with caspase-1 and -8 inhibitors under osteoarthritis-like conditions

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About 655 million persons worldwide are affected by osteoarthritis (OA), associated with excruciating chronic pain and disability in the elderly. Inflammation and cell death are two key events in OA and also key canonical functions of caspases. Since caspases play an important role in modulating inflammation, caspase inhibitors have been widely utilized to study diseases involving inflammation in animal models and clinical trials. Among these, key caspases, which are responsible for activation of the corresponding pathways include caspase-8 for the receptor mediated apoptotic pathway and caspase-1 as the key inflammatory caspase being involved in OA pathogenesis. OA- and non-OA chondrocytes were treated with caspase-1 and -8 inhibitors and TNF- α . RNA was isolated after 3 days from three biological replicates ($n = 3$) of each group and processed for single-end RNA sequencing (1×114 bp). Data was pre-processed and analyzed with R programming language v4.2.2. Downstream analysis included identification of differentially expressed genes providing a comprehensive overview of unique and shared transcriptional changes in both OA and non-OA cohorts.

Background & Summary

Osteoarthritis (OA) is the most common joint disease, affecting cartilage and subchondral bone among other joint tissues, causing pain and disability¹ along with high social and economic impacts². According to the Global Burden of Disease Study, 595 million people worldwide were affected by OA in 2020, the number is still increasing and a critical increase is expected by 2050³. Despite its high prevalence and growing understanding of OA biology, current pharmacological therapies remain largely symptomatic and joint replacement comes as the ultimate remedy for the disease in its end-stage^{4,5}. OA is considered a multifactorial disease; therefore, successful implementation of precise personalized medicine becomes urgent. The spectrum of approaches for regenerative treatments requires complex knowledge covering underlying mechanisms, possible combinations as well as side-effects of future therapy targets.

OA is characterized by multiple pathophysiological features, with chronic, low-grade inflammation playing a central role⁶. Synovial inflammation contributes to severe pain and degradation of joint structures with a variety of molecules regulating inflammatory cytokine activity during OA progression⁷. The release of interleukin-1 β (IL-1 β) and tumour necrosis factor alpha (TNF- α) activates the key inflammatory signalling pathways driving degeneration of the articular cartilage matrix. As such, these cytokines are in focus of therapeutic strategies⁸ but also used to mimic OA-like conditions for *in vitro* investigations^{9,10}. The overproduction of active IL-1 β is dependent on processing by the ICE/caspase-1 protease. This caspase initiates the inflammasome pathways and mediates pyroptotic cell death¹¹.

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Pyroptosis contributes to OA development and progression through multiple mechanisms¹². Elevated inflammatory cytokine levels stimulate chondrocytes to secrete catabolic enzymes including matrix metalloproteinases (MMPs), disintegrins and metalloproteinases with thrombospondin motifs (ADAMTS) as the main cartilage matrix degrading proteases¹³. Chronic synovial inflammation, exacerbated by pyroptotic cell death, further accelerates cartilage degradation¹². During OA progression, increased local production of IL-1 β amplifies synovial inflammation. Additionally, elevated levels of pro-inflammatory cytokines and chemokines enhance the excitability of nociceptive neurons, leading to the intense pain that is characteristic of OA¹⁴. OA is also associated with abnormal lipid accumulation¹⁵, and caspase-1 has been shown to contribute to regulation of lipid metabolism¹⁶. Furthermore, caspase-1 plays a role in cartilage differentiation and subchondral bone remodelling, where its inhibition reduces Rankl expression and increases Opg expression¹⁷.

Although caspase-1 is a key mediator of pyroptosis and OA pathogenesis, other caspases may also participate in these processes. This applies particularly to caspase-8, the primary apoptotic initiator in the receptor mediated pathway of the programmed cell death¹⁸. Under certain pathological conditions, caspase-8 can also induce non-canonical pyroptosis by cleaving gasdermin D¹⁹. Notably, both, caspase-1 and caspase-8 are key players in the emerging concept of integrated cell death assigned as PANoptosis (Pyroptosis, Apoptosis, Necroptosis)²⁰. In the last years, papers emphasizing PANoptosis as a critical aspect in OA, keep appearing²¹. Alongside, growing evidence about broader spectrum of caspase functions such as in cell differentiation becomes important in order to understand risks and benefits of caspase inhibitors in treatment strategies, including OA²².

This study provides a transcriptomic resource for hypothesis generation regarding the non-canonical functions of caspase-1 and caspase-8 in osteoarthritis (OA). To this end, gene expression profiles of human chondrocytes were characterized following pharmacological inhibition of caspase-1 or caspase-8 activity. The comprehensive datasets based on 3' mRNA sequencing (3' mRNA-seq) follow gene expression levels in OA-patients derived chondrocytes vs. healthy non-OA chondrocytes but also in cultures under basal vs. OA-like inflammatory conditions (+TNF- α). This specific high-throughput approach was chosen as a highly cost-effective method optimized for accurate gene expression quantification.

The presented dataset represents a valuable resource for future research on OA, cell–cell interactions, cellular responses to inflammatory microenvironments, and the biological functions of caspases.

Methods

Sample collection and processing. Chondrocytes isolated from two donor classes were analyzed: 1) osteoarthritic chondrocytes (OA group) and 2) healthy chondrocytes (non-OA group).

OA cartilage was obtained from the Orthopädische Klinik für die Universität Regensburg (No. 22-2915-101; Ethikkommission bei der Universität Regensburg; email: ethikkommission@ur.de). This ethics board did not provide a consent waiver. Therefore, informed consent was obtained directly from all participants undergoing knee replacement surgery by signing a consent form for study participation and data sharing related to the above ethics approval.

Non-OA human articular cartilage explants were obtained from healthy cadaveric donors through Prof. Dr. Brian Johnstone (Oregon Health & Science University, Portland, OR, USA). No ethical approval was required because the biological samples were obtained from human cadaver knees. Information on the post-mortem interval was not available; however, the tissue was supplied as fresh cartilage before shipment.

For the OA group, chondrocytes were isolated from three donors: two males aged 72 and 88 years and one female aged 69 years. For the non-OA group, chondrocytes were isolated from three donors: one male aged 24 years and two females aged 33 and 34 years.

OA cartilage was collected from osteochondral grafts obtained during total knee arthroplasty, primarily from the lateral regions of the tibial and femoral condyles and from the patella, where the cartilage appeared macroscopically intact. At the time of surgery, OA severity was graded as Kellgren–Lawrence (KL) grade 3.5–4. Cartilage regions with a severely fissured or absent superficial zone were excluded from chondrocyte isolation. Information on donor comorbidities was not available. The average donor age was 76.3 years for the OA group and 30.3 years for the non-OA group.

The non-OA cartilage explants consisted of clinically certified pristine cartilage from osteochondral allografts, using leftover sections of femoral condyles provided by the Department of Orthopedics and Rehabilitation, Oregon Health & Science University, Portland, OR, USA. The cartilage samples were non-infectious, non-pathogenic, and non-toxic. Furthermore, they did not originate from a facility where work with exotic disease agents affecting livestock or avian species is conducted.

Material transfer information:

Processed by AlloSource; 6278 South Troy Circle, Centennial, CO 80111

Distributed by JRF Ortho; 6746 S Revere Pkwy, Ste B-125, Centennial, CO 80112

Chondrocytes from both OA and non-OA cartilage were isolated using the same protocol. Cartilage explants were cut into approximately 1 mm pieces and digested with collagenase type II (10 mg collagenase type II per 1 g cartilage in 5 mL DMEM/F12 supplemented with 1% antibiotics/antimycotics) at 37 °C for 16 h. The resulting cell suspension was filtered through a 70 μ m cell strainer, and 2×10^6 cells were seeded into T175 culture flasks containing DMEM/F12 supplemented with 10% FBS and 1% antibiotics/antimycotics. The first medium change was performed after 5 days, followed by medium changes every 2–3 days for a total culture period of 10 days²³.

Cells were cryopreserved at passage 0 (P0) in aliquots of 2×10^6 cells in complete culture medium containing 10% DMSO after stepwise freezing in a cell-freezing container at –80 °C and subsequent storage in liquid nitrogen. For thawing, cryovials were incubated in a 37 °C water bath until almost completely thawed and immediately transferred into T175 flasks containing fresh prewarmed culture medium. Cells were expanded for approximately 5–7 days until reaching a maximum confluence of 80% (P1). No further passaging was performed before experimental treatment.

Donors	Condition
OA	Unstimulated Control
	+Caspase-1 inhibitor
	+Caspase-8 inhibitor
	+TNF- α
	+Caspase-1 inhibitor + TNF- α
	+Caspase-8 inhibitor + TNF- α
non OA	Unstimulated Control
	+Caspase-1 inhibitor
	+Caspase-8 inhibitor
	+TNF- α
	+Caspase-1 inhibitor + TNF- α
	+Caspase-8 inhibitor + TNF- α

Table 1. Experimental layout.

No methods other than morphological observation by light microscopy were used to assess cell quality prior to experimental treatment.

Cells from each donor (3 OA and 3 non-OA donors) were seeded into two wells per donor (12 wells in total). Before RNA isolation and subsequent sequencing, cells from both wells belonging to the same donor were pooled. The two wells were used solely to obtain sufficient cell numbers for RNA sequencing and were therefore not considered technical replicates. Each donor represented one biological replicate ($n = 3$ for the OA group and $n = 3$ for the non-OA group).

In the present study, assays assessing cell viability, cytotoxicity, and caspase activity following pharmacological inhibition were not performed. These functional assays following caspase-1 and caspase-8 inhibition in human chondrocytes have been reported previously, and the corresponding data are available in^{9,24}.

The experimental layout is summarized in Table 1. Detailed sample metadata, including donor IDs, experimental conditions, biological replicates, and sequencing read counts, are available via Zenodo at²⁵.

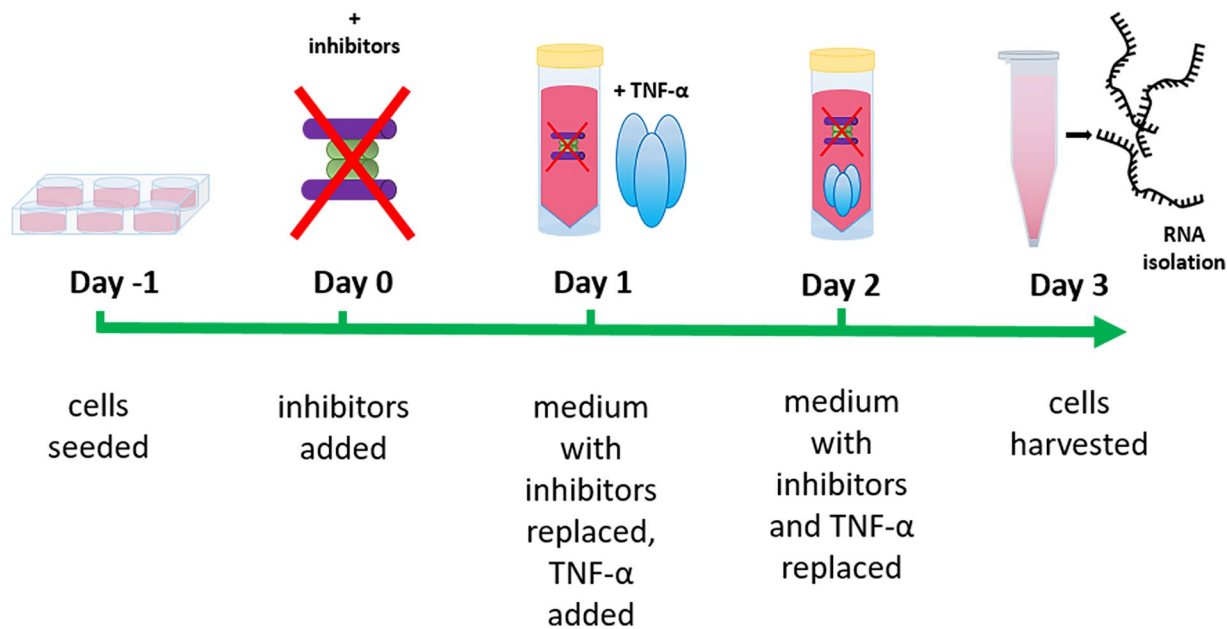
Cells were cultured in DMEM/F-12 (D8437; Sigma Aldrich) supplemented with 10% FBS (S6015; Sigma Aldrich), and 1% antibiotics/antimycotics (A5955; Sigma Aldrich). 24 hours after cell seeding, caspase-1 inhibitor VX-765 (inh-vx765i-1; Invivogen) and caspase-8 inhibitor Z-IETD-FMK (FMK007; R&D Systems) were added at a concentration of 100 μ M for 3 days⁹. VX-765 (Belnacasan) is highly potent selective caspase-1 inhibitor²⁶. Z-IETD-FMK is a cell-permeable, irreversible, selective inhibitor of caspase-8²⁷. The inhibitors were prepared in dimethyl sulfoxide (DMSO) according to the manufacturer's instructions, with DMSO serving as the vehicle control. Chondrocytes were cultured at 37 °C in a humidified atmosphere containing 5% CO₂. Inhibitors and medium were replaced every 24 h. 2 days before harvest, Recombinant Human TNF- α , (300-01 A; Peprotech) was added at a concentration 1 ng/ml. Cells were harvested and counted and RNA was isolated (Scheme 1).

RNA isolation. Samples were lysed in 350 μ l of RLT buffer (lysis buffer of RNeasy Mini Kit; Qiagen). Total RNA was isolated by the RNeasy Mini Kit (74106; Qiagen) together with the RNase-DNase-free Set (79256; Qiagen).

RNA sequencing. Total RNA samples were sent for RNA Sequencing Analysis to GeneCore Facility, Biocev, Vestec, Czech Republic, where the samples were processed and sequenced according to the standard operating procedure. Sequencing libraries were prepared from 120 ng of total RNA using the QuantSeq 3' mRNA-Seq Library Prep Kit FWD for Illumina (Lexogen), following the manufacturer's protocol. The libraries were quantified with the Qubit dsDNA assay kit and Qubit 2 fluorometer (Thermo Fisher Scientific), and their quality was evaluated using a Fragment Analyzer system with the NGS Fragment Kit (Agilent Technologies). Sequencing was performed on a NextSeq 2000 instrument using the NextSeq[™] 1000/2000 P1 XLEAP-SBS[™] Reagent Kit (100 Cycles) in 1 $\times$ 114 bp mode.

Data Preprocessing. The quality of raw sequencing reads was evaluated with FastQC v0.12.1 and potential contamination was assessed using FastQ_Screen v0.15.3²⁸. Low-quality reads and adaptors were removed with Trimmomatic (SE mode) v0.36²⁹. Low-quality reads were removed with the following parameters: LEADING:3, TRAILING:3, and SLIDINGWINDOW:4:15, MINLEN:36. Ribosomal and mitochondrial reads were filtered out using SortMeRNA v2.1b³⁰. The following ribosomal and mitochondrial genes were assessed: Mitochondrial reads, 5.8S and 5S, Archaeal: 16S, 23S, Bacterial: 16S, 23S, and Eukaryotic: 18S, 28S. All reads matching the assessed databases were removed. Reads that did not match the databases were aligned to reference Homo sapiens genome version GRCh38. Aligned reads were converted into BAM files with STAR v2.7.10b³¹. Final count tables were generated using the Python script htseq-count v0.11.3³², with the annotation file GRCh38.87.gtf, the parameter -s yes to account for the forward strandness (FWD) of the QuantSeq 3' mRNA-seq library, and the parameter -m union.

Data analysis. Data was analyzed with R programming language v4.2.2. To stabilize variance across the range of mean values and eliminate heteroscedasticity, raw counts were log-transformed using the regularized log (rlog) function from DESeq2; these transformed data were subsequently used in PCA and heatmap visualizations. org. Hs.eg.db v3.15.0 database was used for ENSEMBL ID–gene symbol conversion. Differential gene expressions were



Scheme 1 Timeline of the experiment.

Comparison	Total DEGs	Up-regulated	Down-regulated
OA Caspase-1 inhibitor/OA Unstimulated Control	13	8	5
OA Caspase-8 inhibitor/OA Unstimulated Control	0	0	0
OA TNFa/OA Unstimulated Control	796	513	283
OA Caspase-1 inhibitor + TNF-a/OA Unstimulated Control	1389	761	628
OA Caspase-8 inhibitor + TNF-a/OA Unstimulated Control	799	454	345
non OA Caspase-1 inhibitor/non OA Unstimulated Control	15	11	4
non OA Caspase-8 inhibitor/non OA Unstimulated Control	24	10	14
non OA TNFa/non OA Unstimulated Control	1054	539	515
non OA Caspase-1 inhibitor + TNF-a/non OA Unstimulated Control	1483	713	770
non OA Caspase-8 inhibitor + TNF-a/non OA Unstimulated Control	1157	549	608

Table 2. The total number of up- and down-regulated DEGs identified across the experimental conditions.

assessed using DESeq2 v1.36 package³³. Differentially expressed genes (DEGs) were identified using the following parameters: baseMean > 10, $p_{adj} < 0.05$, $|\log_2FC| > 1$. The total number of up- and down-regulated DEGs identified across the experimental conditions is summarized in Table 2 and the full list of DEGs is available via Zenodo at²⁵.

Data transformation and downstream analysis. Sequencing yielded a total of 509,085,672 high-quality reads across 36 samples (mean: 14,141,268 reads/sample). After cleaning of low-quality and rRNA-containing reads, 402,340,005 reads remained, with an average mapping rate of 90% to the Homo sapiens genome GRCh38. Detailed statistics for each sample are available via Zenodo at²⁵. To assess the consistency of the biological response across different treatments, we identified differentially expressed genes (DEGs) using a baseMean > 10, significance threshold of $p_{adj} < 0.05$ and $|\log_2FC| > 1$. The intersections of these DEGs across treatment groups were visualized using UpSet plots (Fig. 1), providing a comprehensive overview of unique and shared transcriptional changes in both OA (Fig. 1A) and non-OA (Fig. 1B) cohorts. Detailed lists of genes within each intersection are available via Zenodo at²⁵.

Data Records

The RNA sequencing datasets generated and analyzed during the current study are publicly available in the NCBI Gene Expression Omnibus (GEO) repository under accession number GSE328723³⁴. The repository contains raw fastq files of all samples and a comma-separated file with the complete raw data for all genes and all samples. The comprehensive datasets supporting the findings of this study are openly available in the Zenodo repository at²⁵.

Technical Validation

RNA integrity assessment. RNA quality and concentration was measured with the Bioanalyzer 2100 (Agilent Technologies) and RNA Nano Chips (5057-1511; Agilent Technologies). All samples showed high RNA integrity number (RIN >= 9) suitable for sequencing.

OA

non-OA

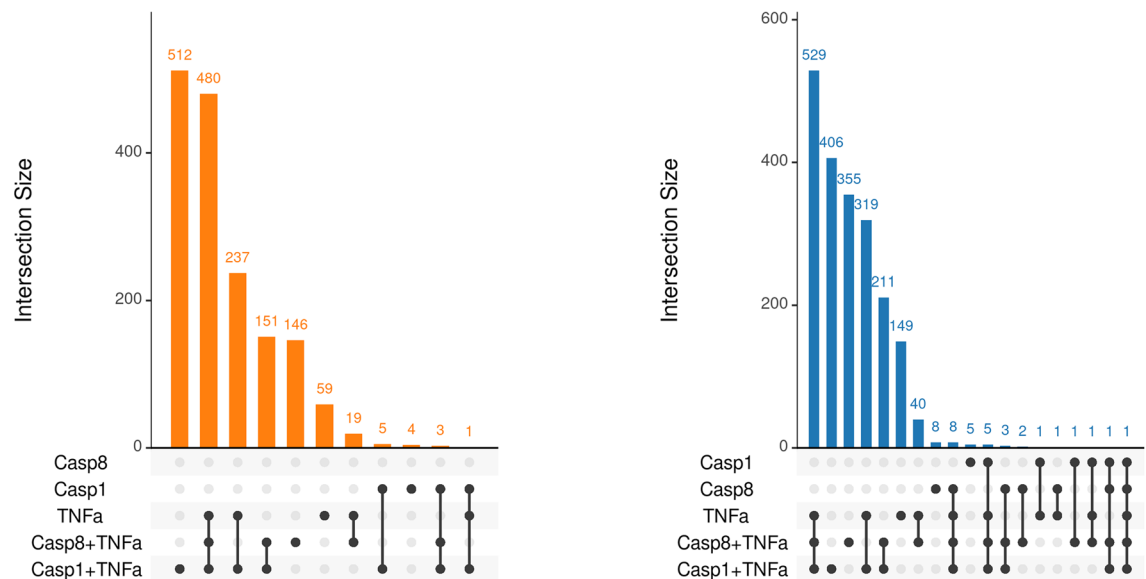


Fig. 1 Intersection analysis of differentially expressed genes across treatment conditions. UpSet plots illustrate the number of unique and shared differentially expressed genes (DEGs) in human chondrocytes. DEGs were identified using DESeq2 with the following significance criteria: baseMean > 10, padj < 0.05, and $|\log_2FC| > 1$. (OA) Osteoarthritis cohort, (non-OA) healthy. The horizontal bar chart represents the total number of DEGs for each individual treatment. The vertical bar chart displays the size of each specific intersection between treatment groups. Black dots and connecting lines indicate the specific combination of treatments included in each intersection.

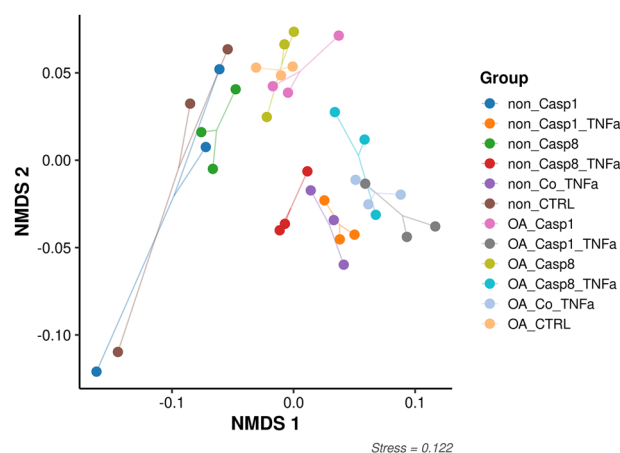


Fig. 2 Non-metric Multidimensional Scaling (NMDS) of global gene expression profiles. NMDS plot based on Bray-Curtis distances illustrating the clustering of 36 RNA-seq samples across 12 experimental groups (N = 3 biological replicates per group). The analysis was performed on filtered, non-zero gene expression data. Each point represents an individual biological replicate, with shapes and colors consistent across groups. Lines (spiders) connect individual replicates to their respective group centroid (diamond) to visualize within-group variance. A stress value of 0.122 indicates an excellent two-dimensional representation of the high-dimensional data.

RNA-seq raw data quality and filtering. Raw RNA sequencing data were processed using Trimmomatic (SE mode) for adapter trimming and quality filtering. Ribosomal RNA (rRNA) reads were removed using SortmeRNA, eliminating approximately 18% of reads per sample. After processing, between 4.34 and 15.21 million reads per sample were successfully mapped to the Homo sapiens genome version GRCh38. Non-metric Multidimensional Scaling (NMDS) was used to assess sample clustering. NMDS visualization (Stress = 0.122) confirmed high similarity among biological replicates and clear separation between experimental groups (Fig. 2).

Data availability

The RNA sequencing datasets generated and analyzed during the current study are publicly available in the NCBI Gene Expression Omnibus (GEO) repository under accession number GSE328723³⁴. Individual samples can be found under accession numbers GSM9688201 - GSM9688236. The repository contains raw fastq files of all samples and a comma-separated file with the complete raw data for all genes and all samples.

Code availability

The following freely available programs were used for quality control and data analysis, as described in the main text:

FastQC (v0.12.1) was used for quality analysis of raw FASTQ sequencing data: <https://www.bioinformatics.babraham.ac.uk/projects/fastqc/>.

FastQ_Screen (v0.15.3) was used to check potential contamination: <https://stevewingett.github.io/FastQ-Screen/>

Trimmomatic (v0.36) was used to filter and trim low quality bases from FASTQ sequencing files: <https://github.com/usadellab/Trimmomatic>

SortMeRNA (v2.1b) was used to cut rRNA reads from samples: <https://github.com/sortmerna/sortmerna>
STAR (v2.7.10b) was used to align sequencing reads to reference Homo sapiens genome version GRCh38: <https://github.com/alexdobin/STAR>

Python script htseq-count v0.11.3 was used to generate final count tables: <https://github.com/htseq/htseq>

DESeq2 (v1.36) was used to calculate and summarize differential transcript expression: <http://www.bioconductor.org/packages/release/bioc/vignettes/DESeq2/inst/doc/DESeq2.html#theory>.

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Competing interests

The authors declare no competing interests.

Additional information

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