# Comparative transcriptome of normal and cancer-associated fibroblasts

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## Abstract

**Background** The characteristics of a tumor are largely determined by its interaction with the surrounding micro-environment (TME). TME consists of both cellular and non-cellular components. Cancer-associated fibroblasts (CAFs) are a major component of the TME. They are a source of many secreted factors that influence the survival and pro-gression of tumors as well as their response to drugs. Identification of markers either overexpressed in CAFs or unique to CAFs would pave the way for novel therapeutic strategies that in combination with conventional chemotherapy are likely to have better patient outcome.

**Methods** Fibroblasts have been derived from Benign Prostatic Hyperplasia (BPH) and prostate cancer. RNA from these has been used to perform a transcriptome analysis in order to get a comparative profile of normal and cancer-associated fibroblasts.

**Results** The study has identified 818 differentially expressed mRNAs and 17 lincRNAs between normal and cancer-associated fibroblasts. Also, 15 potential lincRNA-miRNA-mRNA combinations have been identified which may be potential biomarkers.

**Conclusions** This study identified differentially expressed markers between normal and cancer-associated fibro-blasts that would help in targeted therapy against CAFs/derived factors, in combination with conventional therapy. However, this would in future need more experimental validation.

**Keywords** Tumor microenvironment, Cancer-associated fibroblasts, Chemoresistance, Non-coding RNA, LINCRNA, Prostate cancer

## Introduction

The tumor microenvironment (TME) is a complex and dynamic ecosystem, which is shaped by the interactions between the tumor cells and the non-cancerous cells as well as the extra-cellular matrix surrounding the tumor. Although the framework and composition of the TME may vary according to the tumor type, some hallmarks of the TME remain the same. The TME is comprised of a variety of cell-types such as immune cells (T cells, B cells, Tregs, Neutrophils, Macrophages, Dendritic cells, Natural Killer cells, Mast cells etc.) cancer-associated fibroblasts (CAFs), endothelial cells (ECs), pericytes, adipocytes and neurons (Reviewed in [1]and references therin). The acellular components of the TME includes mostly secreted factors such as growth factors, cytokines, extracellular matrix (ECM) proteins, and metabolites [2]. The dynamic and reciprocal interactions between the tumor and its microenvironment influence cancer cell survival, local invasion, metastasis [3, 4], immune sur-veillance, angiogenesis [5] as well as response to therapy [6, 7].

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One of the major cell types in the TME is cancer-associated fibroblasts. CAFs are a major source of growth factors, cytokines, and other signaling molecules, which impact cancer cell behavior [6]. When subjected to chemotherapy, along with the cancer cells, the CAFs also are subjected to changes. These therapies are likely to stimulate CAFs to release factors that could influence the stemness, metabolic status, signaling cascades, etc. within the tumor, which can prevent cancer cell eradication and perhaps cause recurrence [8]. In prostate cancer models, it has been observed that there is therapy induced activation of Wnt signal which can result in drug resistance [9, 10]. In pancreatic cancer, CAFs protect cancer cells from gemcitabine-induced cell death by activating NF-κB through IL-1β and IL-1 receptor-associated kinase 4 (IRAK4) [11]. In ESCC, cisplatin resistance is conferred by IL-6/CXCR7 axis, where IL-6 is mainly secreted by the CAFs [12]. Transcriptome and proteome analysis from different models have emphasized the role of interleukins secreted by CAFs on conferring therapy resistance in various models (reviewed in [8]).

Cancer stem cells (CSC) have multiple mechanisms to overcome chemotherapy and TME has a significant influence in maintenance of CSCs. IL-17, secreted by CAFs and TGF-b signaling in CAFs have shown to influence the stemness of the CSCs [13, 14]. Besides, SHH signaling and its interaction with HIF-1a are observed to enhance the CSC properties [15, 16]. In a breast cancer model, CAF-derived miR-221 activated an ER^{low}/Notch^{high} feed-forward loop responsible for the generation of CD133^{high} CSCs [17]. Multiple studies have shown that CAF derived Interleukins, Wnt as well as ncRNAs influence the CSC population and hence therapeutic resistance (reviewed in [8]).

Metabolic changes in CAFs have received significant attention over the last few years. PI3K/AKT pathway in cancer cells, has been observed to induce Warburg effect in CAFs through cytoplasmic translocation of the nuclear G-protein-coupled estrogen receptor (GPER) and aberrant activation of the GPER signaling pathway. CAFs in turn deliver lactate transporters to cancer cells, resulting in a coupled energy metabolism process that can increase drug resistance [18]. These and other metabolic changes need to be explored further for their role in conferring resistance.

CAFs are pivotal in driving cancer progression through their involvement in processes such as extracellular matrix (ECM) deposition and remodeling, extensive communication with cancer cells, promoting epithelial-to-mesenchymal transition (EMT), facilitating invasion, metastasis, and even contributing to therapy resistance [19]. CAFs are also recognized for their involvement in developing resistance to anti-cancer therapy by providing a protective environment for tumor cells. There exists a symbiotic relationship between tumor cells and CAFs, wherein CAFs provide the necessary resources for tumor cell growth and survival, thereby contributing to the development of a chemoresistant phenotype [20]. Considering the pleiotropic effects of the tumor microenvironment, particularly CAFs, an insight into the specific factors responsible for therapeutic resistance can potentially pave the way for newer and more effective strategies for treatment. The major hurdle in this direction is the lack of distinguishing biomarkers for CAFs that would allow for their exclusive targeting. There is a high heterogeneity of CAF functions- both pro-tumorigenic and anti-tumorigenic within the same tumor [21]. Hence targeting the CAFs/derived factors has to be done with extreme caution to avoid adverse effects. Additionally, targeting CAFs might lead to significant clinical benefits, as pro-tumorigenic CAFs can support tumor progression, but they may not be indispensable for tumor growth and survival. In other words, tumor cells may not solely depend on the presence of CAFs. CAF-targeted therapy in combination with other chemotherapeutic drugs is likely to improve treatment outcomes.

Our study has used a transcriptome analysis to identify differentially expressed genes and non-coding RNAs between normal and cancer-associated fibroblasts on a human prostate model.

## Materials and methods

### Clinical specimen collection

All patient samples were collected from the Institute of Nephro-Urology (Department of Urology), Bengaluru. The study was approved by the Institutional Ethics committee of both the institutions and informed consent has been taken from all the participants. The identity of the participants has been kept anonymous. Samples were taken either by Transrectal Ultrasound scan (TRUS) or Transurethral resection of the prostate (TURP) methods. Classification of the samples as benign or malignant was done by pathologists as per standard criteria.

### Culturing of fibroblasts

Surgical or biopsy specimens were rinsed thoroughly in sterile saline and transferred to transport media (RPMI 1640 (Gibco, Cat No: 23400-021) with 2X PenStrep (Gibco, Cat No: 15140122). Subsequently, these specimens were rinsed thoroughly with RPMI media containing antibiotics, minced into fine pieces, and transferred to culture flasks keeping sufficient distance between each piece for the cells to migrate out. Media was changed periodically. Once the fibroblasts migrated out of the tissues, cells were transferred to fresh flasks and cultured in RPMI supplemented with FBS.

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### RNA isolation

Total RNA was isolated from the cultured fibroblasts using a Qiagen RNeasy kit (Cat No: 74104) according to the manufacturer's instructions. RNA was quantified on nanodrop (Thermo Scientific™ NanoDrop™). The quality of RNA samples was assessed by running them on 1% agarose gel.

### RNA sequencing

RNA sequencing was outsourced to Wipro Life Science Labs, Bengaluru. Quality assessment was done using Agilent TapeStation and all samples had RIN > 9 (Supplemenatry file). Samples were further taken for library preparation and RNA sequencing using the Illumina platform (NextSeq 2000). (The raw data files for this data set is available on GEO, accession number GSE270705).

### RNA sequencing analysis workflow

The quality assessment of the data was performed for base quality and contamination by sequencing artifacts. The adapters were trimmed and poor-quality sequences were filtered using Trim Galore. Trimmed sequence reads were mapped to reference genome (**Assembly**: hg38, GRCh38.p12 (GCA_000001405.27), Dec. 2017, **Data Source**: UCSC Genome Browser, Weblink:http://hgdownload.soe.ucsc.edu/goldenPath/hg38/bigZips/analysis-Set/hg38.analysisSet.fa.gz) with splice aware alignment tool STAR. R subread R package was used to get feature-specific expression counts. Low-count features across the samples were detected and removed using the NOISeq R package followed by expression count normalization with the TMM method (from the NOISeq R package). Differential expression analysis was performed with the NOISeq R package where the group information was used to define biological replicates. Genes/transcripts (mRNA and lincRNA) were considered differentially expressed when they showed at least a log2 fold change of 1.5 between normal and CAFs (Supplementary Fig. 1).

### qRT-PCR analysis

2 µg RNA was converted to cDNA using Verso cDNA synthesis kit (Thermo Fisher Scientific Cat no: AB1453A). 20ng RNA equivalent cDNA was used for the PCR reactions. qRT-PCR was carried out using the SYBR FAST Universal 2XqPCR Master Mix, (Roche, Cat no: KK4601). Normalization was done using RPL35. The fold changes with respect to expression level in control samples was calculated by the ddCt method. The experiment was done on 3 control samples and 2 CAF samples and the average fold change with SD has been tabulated.

### LINCRNA functional annotation

NPInter v5.0 (http://bigdata.ibp.ac.cn/npinter5/) [22, 23] is a database that provides collective information about the multidimensional interactions of ncRNAs (lincRNA, miRNA, circRNA, etc.) with protein, RNA, and DNA. This database contains information about RNA interactions based on literature mining and high-throughput sequencing data with functional annotation [22].

The list of differentially expressed lincRNAs from our experiment was fed into NPInter v5.0 database and segregated according to the interactors (proteins, mRNA, and ncRNA).

The miRNAs obtained from the lincRNA-miRNA (ncRNA) interaction (from NPInter v5.0 database) were further subjected to the miRDB database (https://mirdb.org/) [24] to predict its mRNA targets (Supplementary Fig. 2).

## Results

### Differential expression of genes between normal and cancer-associated fibroblasts

We have identified 818 genes and 17 long intergenic non-coding RNAs (lincRNAs) that exhibit differential expression between normal fibroblasts and CAFs with a minimum log2 fold of 1.5. Of these, 380 genes and 7 lincRNAs were found to be overexpressed (Table 1), while 438 genes and 10 lincRNAs were under-expressed (Table 2) in CAFs as compared to normal fibroblasts.

### qRT-PCR analysis of selected genes

Few genes from the differentially expressed gene list were selected for validation by qRT-PCR. Table 3 shows the list of genes that have been validated along with the fold changes. In the genes that have been validated, data from RNA-seq and qRT-PCR show the same pattern although fold changes are different.

### LINCRNA target prediction using npinter v5.0

LincRNA targets were predicted for differentially expressed lincRNAs in normal compared to CAFs using NP Inter V5.0. This analysis yielded 263 RNA-binding proteins (RBPs) (Table 4), 31 microRNAs (miRNAs), 1 non-coding (ncRNA) (Table 5) and 2 messenger RNA (mRNA) (Table 6) associated with a total of 14 lincRNAs. Also, there were 3 novel lincRNAs (LINC02344, LINC01670, and LINC02605) for which no data was found in the above database.

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**Table 1** List of overexpressed mRNAs and LINCRNAs in cancer-associated fibroblasts compared to normal fibroblasts

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 1 | ENSG00000184937 | 9.338678226 | WT1 |
| 2 | ENSG00000120093 | 9.066529369 | HOXB3 |
| 3 | ENSG00000182742 | 8.440665024 | HOXB4 |
| 4 | ENSG00000106483 | 7.457728693 | SFRP4 |
| 5 | ENSG00000183242 | 7.266975633 | WT1-AS |
| 6 | ENSG00000165507 | 6.8004577 | DEPP1 |
| 7 | ENSG00000163364 | 6.193836171 | LINC01116 |
| 8 | ENSG00000175879 | 5.293002219 | HOXD8 |
| 9 | ENSG00000156466 | 5.080737946 | GDF6 |
| 10 | ENSG00000169418 | 4.968358544 | NPR1 |
| 11 | ENSG00000188783 | 4.644111631 | PRELP |
| 12 | ENSG00000198774 | 4.609020395 | RASSF9 |
| 13 | ENSG00000131471 | 4.565470197 | AOC3 |
| 14 | ENSG00000106819 | 4.519034135 | ASPN |
| 15 | ENSG00000075275 | 4.434781935 | CELSR1 |
| 16 | ENSG00000196616 | 4.350248405 | ADH1B |
| 17 | ENSG00000146374 | 4.301235355 | RSPO3 |
| 18 | ENSG00000146038 | 4.29610124 | DCDC2 |
| 19 | ENSG00000112936 | 4.254281304 | C7 |
| 20 | ENSG00000244694 | 4.169584725 | PTCHD4 |
| 21 | ENSG00000135914 | 4.126018242 | HTR2B |
| 22 | ENSG00000136235 | 4.080788268 | GPNMB |
| 23 | ENSG00000005471 | 3.893427681 | ABCB4 |
| 24 | ENSG00000177363 | 3.886142424 | LRRN4CL |
| 25 | ENSG00000086289 | 3.817819494 | EPDR1 |
| 26 | ENSG00000225684 | 3.807004332 | FAM225B |
| 27 | ENSG00000146938 | 3.720873944 | NLGN4X |
| 28 | ENSG00000110076 | 3.67301846 | NRXN2 |
| 29 | ENSG00000205221 | 3.625265335 | VIT |
| 30 | ENSG00000139910 | 3.612874671 | NOVA1 |
| 31 | ENSG00000137507 | 3.593886089 | LRRC32 |
| 32 | ENSG00000167306 | 3.581243704 | MYO5B |
| 33 | ENSG00000164161 | 3.576706765 | HHIP |
| 34 | ENSG00000164318 | 3.569735487 | EGFLAM |
| 35 | ENSG00000231528 | 3.492219584 | FAM225A |
| 36 | ENSG00000172264 | 3.490561901 | MACROD2 |
| 37 | ENSG00000180777 | 3.487256802 | ANKRD30B |
| 38 | ENSG00000138449 | 3.435323115 | SLC40A1 |
| 39 | ENSG00000131370 | 3.430490091 | SH3BP5 |
| 40 | ENSG00000173917 | 3.379890194 | HOXB2 |
| 41 | ENSG00000100302 | 3.374791795 | RASD2 |
| 42 | ENSG00000157214 | 3.373774391 | STEAP2 |
| 43 | ENSG00000260552 | 3.332515698 | COSMOC |
| 44 | ENSG00000248144 | 3.324284207 | ADH1C |
| 45 | ENSG00000072041 | 3.304587859 | SLC6A15 |
| 46 | ENSG00000138135 | 3.286841035 | CH25H |
| 47 | ENSG00000183682 | 3.268320942 | BMP8A |
| 48 | ENSG00000096696 | 3.242335703 | DSP |
| 49 | ENSG00000145242 | 3.231906415 | EPHA5 |

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**Table 1**  (continued)

| SI No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 50 | ENSG00000078081 | 3.222529548 | LAMP3 |
| 51 | ENSG00000101680 | 3.21461969 | LAMA1 |
| 52 | ENSG00000166923 | 3.181087552 | GREM1 |
| 53 | ENSG00000171119 | 3.178048407 | NRTN |
| 54 | ENSG00000115252 | 3.1689023 | PDE1A |
| 55 | ENSG00000129467 | 3.164502988 | ADCY4 |
| 56 | ENSG00000145819 | 3.148256737 | ARHGAP26 |
| 57 | ENSG00000106809 | 3.147514635 | OGN |
| 58 | ENSG00000055732 | 3.103481133 | MCOLN3 |
| 59 | ENSG00000135643 | 3.087942208 | KCNMB4 |
| 60 | ENSG00000065320 | 3.080524368 | NTN1 |
| 61 | ENSG00000070193 | 3.076239219 | FGF10 |
| 62 | ENSG00000267414 | 3.070509607 | SETBP1-DT |
| 63 | ENSG00000074370 | 3.024375298 | ATP2A3 |
| 64 | ENSG00000152217 | 3.010426863 | SETBP1 |
| 65 | ENSG00000179954 | 2.984447115 | SSC5D |
| 66 | ENSG00000016082 | 2.979521208 | ISL1 |
| 67 | ENSG00000136040 | 2.979012692 | PLXNC1 |
| 68 | ENSG00000235092 | 2.971718084 | ID2-AS1 |
| 69 | ENSG00000163794 | 2.951338436 | UCN |
| 70 | ENSG00000244242 | 2.945313304 | IFITM10 |
| 71 | ENSG00000112096 | 2.940026071 | SOD2 |
| 72 | ENSG00000121005 | 2.931365251 | CRISPLD1 |
| 73 | ENSG00000139364 | 2.918854199 | TMEM132B |
| 74 | ENSG00000164106 | 2.915361292 | SCRG1 |
| 75 | ENSG00000197971 | 2.87570475 | MBP |
| 76 | ENSG00000231007 | 2.875103234 | CDC20P1 |
| 77 | ENSG00000106624 | 2.854540897 | AEBP1 |
| 78 | ENSG00000101115 | 2.849787273 | SALL4 |
| 79 | ENSG00000006210 | 2.847602797 | CX3CL1 |
| 80 | ENSG00000168427 | 2.808700829 | KLHL30 |
| 81 | ENSG00000182463 | 2.807335587 | TSHZ2 |
| 82 | ENSG00000189409 | 2.805577626 | MMP23B |
| 83 | ENSG00000117122 | 2.802217897 | MFAP2 |
| 84 | ENSG00000165959 | 2.758592315 | CLMN |
| 85 | ENSG00000131634 | 2.75181617 | TMEM204 |
| 86 | ENSG00000168477 | 2.742397705 | TNXB |
| 87 | ENSG00000248290 | 2.724225106 | TNXA |
| 88 | ENSG00000215914 | 2.718914487 | MMP23A |
| 89 | ENSG00000186868 | 2.711375311 | MAPT |
| 90 | ENSG00000170345 | 2.692482283 | FOS |
| 91 | ENSG00000154258 | 2.690792336 | ABCA9 |
| 92 | ENSG00000180481 | 2.678866617 | GLIPR1L2 |
| 93 | ENSG00000133083 | 2.661308127 | DCLK1 |
| 94 | ENSG00000082482 | 2.659723066 | KCNK2 |
| 95 | ENSG00000048052 | 2.658813636 | HDAC9 |
| 96 | ENSG00000162551 | 2.644404231 | ALPL |
| 97 | ENSG00000173805 | 2.640886128 | HAP1 |
| 98 | ENSG00000189056 | 2.639778484 | RELN |

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**Table 1** (continued)

| SI No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 99 | ENSG00000253661 | 2.63880641 | ZFHX4-AS1 |
| 100 | ENSG00000171791 | 2.610282773 | BCL2 |
| 101 | ENSG00000144837 | 2.601860367 | PLA1A |
| 102 | ENSG00000169184 | 2.599944099 | MN1 |
| 103 | ENSG00000089820 | 2.574305154 | ARHGAP4 |
| 104 | ENSG00000181634 | 2.56427507 | TNFSF15 |
| 105 | ENSG00000178015 | 2.560445983 | GPR150 |
| 106 | ENSG00000167216 | 2.537221974 | KATNAL2 |
| 107 | ENSG00000028277 | 2.532129932 | POU2F2 |
| 108 | ENSG00000178081 | 2.529858375 | ULK4P3 |
| 109 | ENSG00000004776 | 2.527119447 | HSPB6 |
| 110 | ENSG00000116675 | 2.523980391 | DNAJC6 |
| 111 | ENSG00000156804 | 2.52126043 | FBXO32 |
| 112 | ENSG00000166664 | 2.502047488 | CHRFAM7A |
| 113 | ENSG00000184292 | 2.4903466 | TACSTD2 |
| 114 | ENSG00000137942 | 2.486706943 | FNBP1L |
| 115 | ENSG00000163132 | 2.461845915 | MSX1 |
| 116 | ENSG00000230148 | 2.455525439 | HOXB-AS1 |
| 117 | ENSG00000079931 | 2.449156028 | MOXD1 |
| 118 | ENSG00000187479 | 2.449071496 | C11orf96 |
| 119 | ENSG00000172348 | 2.448876698 | RCAN2 |
| 120 | ENSG00000092929 | 2.445627941 | UNC13D |
| 121 | ENSG00000186340 | 2.420950706 | THBS2 |
| 122 | ENSG00000185567 | 2.416942281 | AHNAK2 |
| 123 | ENSG00000143387 | 2.414727514 | CTSK |
| 124 | ENSG00000165124 | 2.407244712 | SVEP1 |
| 125 | ENSG00000182379 | 2.402168936 | NXPH4 |
| 126 | ENSG00000123700 | 2.399277025 | KCNJ2 |
| 127 | ENSG00000268883 | 2.391696562 | PNMA6B |
| 128 | ENSG00000135929 | 2.390048724 | CYP27A1 |
| 129 | ENSG00000166592 | 2.388259231 | RRAD |
| 130 | ENSG00000180155 | 2.384488858 | LYNX1 |
| 131 | ENSG00000099960 | 2.384307936 | SLC7A4 |
| 132 | ENSG00000160013 | 2.37946615 | PTGIR |
| 133 | ENSG00000152049 | 2.371373176 | KCNE4 |
| 134 | ENSG00000117586 | 2.367762203 | TNFSF4 |
| 135 | ENSG00000188112 | 2.366857463 | C6orf132 |
| 136 | ENSG00000125246 | 2.366405093 | CLYBL |
| 137 | ENSG00000170873 | 2.365388741 | MTSS1 |
| 138 | ENSG00000185250 | 2.364877963 | PPIL6 |
| 139 | ENSG00000184985 | 2.360497315 | SORCS2 |
| 140 | ENSG00000053524 | 2.358290643 | MCF2L2 |
| 141 | ENSG00000064655 | 2.356374576 | EYA2 |
| 142 | ENSG00000166341 | 2.353827343 | DCHS1 |
| 143 | ENSG00000139117 | 2.331754284 | CPNE8 |
| 144 | ENSG00000164647 | 2.331093887 | STEAP1 |
| 145 | ENSG00000121898 | 2.329546823 | CPXM2 |
| 146 | ENSG00000184349 | 2.326907614 | EFNA5 |
| 147 | ENSG00000155629 | 2.319366832 | PIK3AP1 |

**Table 1**  (continued)

| SI No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 148 | ENSG00000153094 | 2.313590878 | BCL2L11 |
| 149 | ENSG00000073849 | 2.312193881 | ST6GAL1 |
| 150 | ENSG00000145911 | 2.307535495 | N4BP3 |
| 151 | ENSG00000179104 | 2.306651777 | TMTC2 |
| 152 | ENSG00000133110 | 2.304364639 | POSTN |
| 153 | ENSG00000011201 | 2.300441534 | ANOS1 |
| 154 | ENSG00000027075 | 2.299717173 | PRKCH |
| 155 | ENSG00000085563 | 2.297166128 | ABCB1 |
| 156 | ENSG00000150907 | 2.296836959 | FOXO1 |
| 157 | ENSG00000138028 | 2.295512338 | CGREF1 |
| 158 | ENSG00000122877 | 2.289440613 | EGR2 |
| 159 | ENSG00000182175 | 2.28805904 | RGMA |
| 160 | ENSG00000270441 | 2.286773813 | LAMB2P1 |
| 161 | ENSG00000116396 | 2.282150715 | KCNC4 |
| 162 | ENSG00000136960 | 2.266626397 | ENPP2 |
| 163 | ENSG00000248587 | 2.262386263 | GDNF-AS1 |
| 164 | ENSG00000185345 | 2.258116067 | PRKN |
| 165 | ENSG00000148426 | 2.256779282 | PROSER2 |
| 166 | ENSG00000061918 | 2.247439143 | GUCY1B1 |
| 167 | ENSG00000092068 | 2.24098848 | SLC7A8 |
| 168 | ENSG00000275395 | 2.234570285 | FCGBP |
| 169 | ENSG00000151490 | 2.20727056 | PTPRO |
| 170 | ENSG00000139597 | 2.207034399 | N4BP2L1 |
| 171 | ENSG00002247157 | 2.204595176 | LINC01252 |
| 172 | ENSG00000138646 | 2.203203888 | HERC5 |
| 173 | ENSG00000172403 | 2.201543978 | SYNPO2 |
| 174 | ENSG00000136404 | 2.191272623 | TM6SF1 |
| 175 | ENSG00000146555 | 2.18336527 | SDK1 |
| 176 | ENSG00000168621 | 2.178626681 | GDNF |
| 177 | ENSG00000105825 | 2.174426101 | TFPI2 |
| 178 | ENSG00000064309 | 2.174214004 | CDON |
| 179 | ENSG00000140945 | 2.169223331 | CDH13 |
| 180 | ENSG00000109610 | 2.157112704 | SOD3 |
| 181 | ENSG00000164742 | 2.156264764 | ADCY1 |
| 182 | ENSG00000141837 | 2.154368705 | CACNA1A |
| 183 | ENSG00000146950 | 2.149426889 | SHROOM2 |
| 184 | ENSG00000204967 | 2.149380077 | PCDHA4 |
| 185 | ENSG00000115457 | 2.148909168 | IGFBP2 |
| 186 | ENSG00000060718 | 2.147967361 | COL11A1 |
| 187 | ENSG00000175344 | 2.146649503 | CHRNA7 |
| 188 | ENSG00000121316 | 2.129055023 | PLBD1 |
| 189 | ENSG00000170775 | 2.127857405 | GPR37 |
| 190 | ENSG00000176723 | 2.122935457 | ZNF843 |
| 191 | ENSG00000132561 | 2.117237938 | MATN2 |
| 192 | ENSG00000132554 | 2.115887216 | RGS22 |
| 193 | ENSG00000223485 | 2.113157959 | LINC01615 |
| 194 | ENSG00000162817 | 2.110368888 | C1orf115 |
| 195 | ENSG00000088881 | 2.109274054 | EBF4 |
| 196 | ENSG00000188372 | 2.105592321 | ZP3 |

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**Table 1** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 197 | ENSG00000074181 | 2.102490156 | NOTCH3 |
| 198 | ENSG00000235961 | 2.101952544 | PNMA6A |
| 199 | ENSG00000167992 | 2.093637143 | VWCE |
| 200 | ENSG00000138650 | 2.089573305 | PCDH10 |
| 201 | ENSG00000138759 | 2.085680757 | FRAS1 |
| 202 | ENSG00000197461 | 2.081122778 | PDGFA |
| 203 | ENSG00000266714 | 2.075813496 | MYO15B |
| 204 | ENSG00000238103 | 2.074829611 | RPL9P7 |
| 205 | ENSG00000077157 | 2.074613986 | PPP1R12B |
| 206 | ENSG00000102032 | 2.07383953 | RENBP |
| 207 | ENSG00000228903 | 2.069376405 | RASA4CP |
| 208 | ENSG00000251396 | 2.068860492 | LINC01301 |
| 209 | ENSG00000151623 | 2.067577773 | NR3C2 |
| 210 | ENSG00000125510 | 2.053409396 | OPRL1 |
| 211 | ENSG00000245248 | 2.051615405 | USP2-AS1 |
| 212 | ENSG00000211445 | 2.051018294 | GPX3 |
| 213 | ENSG00000251141 | 2.046164026 | MRPS30-DT |
| 214 | ENSG00000267365 | 2.045033739 | KCNJ2-AS1 |
| 215 | ENSG00000228221 | 2.04070205 | LINC00578 |
| 216 | ENSG00000203867 | 2.032344927 | RBM20 |
| 217 | ENSG00000174945 | 2.020272513 | AMZ1 |
| 218 | ENSG00000115604 | 2.009952757 | IL18R1 |
| 219 | ENSG00000135604 | 2.00924409 | STX11 |
| 220 | ENSG00000161835 | 1.989514328 | TAMALIN |
| 221 | ENSG00000138678 | 1.980588605 | GPAT3 |
| 222 | ENSG00000099953 | 1.97665952 | MMP11 |
| 223 | ENSG00000136237 | 1.966980838 | RAPGEF5 |
| 224 | ENSG00000247317 | 1.961468975 | LY6E-DT |
| 225 | ENSG00000091137 | 1.961199971 | SLC26A4 |
| 226 | ENSG00000133106 | 1.955593857 | EPSTI1 |
| 227 | ENSG00000067606 | 1.951176918 | PRKCZ |
| 228 | ENSG00000188042 | 1.949712405 | ARL4C |
| 229 | ENSG00000121769 | 1.946715273 | FABP3 |
| 230 | ENSG00000053328 | 1.946150549 | METTL24 |
| 231 | ENSG00000119227 | 1.944119988 | PIGZ |
| 232 | ENSG00000242265 | 1.943038605 | PEG10 |
| 233 | ENSG00000158270 | 1.942012211 | COLEC12 |
| 234 | ENSG00000090339 | 1.939652022 | ICAM1 |
| 235 | ENSG00000120051 | 1.937608095 | CFAP58 |
| 236 | ENSG00000186564 | 1.934041687 | FOXD2 |
| 237 | ENSG00000170667 | 1.931915044 | RASA4B |
| 238 | ENSG00000171812 | 1.928787106 | COL8A2 |
| 239 | ENSG00000171298 | 1.918638878 | GAA |
| 240 | ENSG00000136244 | 1.914540053 | IL6 |
| 241 | ENSG00000123689 | 1.914379557 | G0S2 |
| 242 | ENSG00000116183 | 1.910021948 | PAPPA2 |
| 243 | ENSG00000070159 | 1.909849322 | PTPN3 |
| 244 | ENSG00000177989 | 1.907647864 | ODF3B |
| 245 | ENSG00000105808 | 1.901189602 | RASA4 |

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**Table 1**  (continued)

| SI No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 246 | ENSG00000143494 | 1.883805272 | VASH2 |
| 247 | ENSG00000124212 | 1.882029068 | PTGIS |
| 248 | ENSG00000017427 | 1.881716853 | IGF1 |
| 249 | ENSG00000126709 | 1.877126382 | IFI6 |
| 250 | ENSG00000054938 | 1.87640479 | CHRDL2 |
| 251 | ENSG00000160781 | 1.876267747 | PAQR6 |
| 252 | ENSG00000185522 | 1.873518829 | LMNTD2 |
| 253 | ENSG00000184489 | 1.87301321 | PTP4A3 |
| 254 | ENSG00000164440 | 1.87150095 | TXLNB |
| 255 | ENSG00000196220 | 1.870403189 | SRGAP3 |
| 256 | ENSG00000236609 | 1.86738356 | ZNF853 |
| 257 | ENSG00000124107 | 1.860586158 | SLPI |
| 258 | ENSG00000213397 | 1.860217516 | HAUS7 |
| 259 | ENSG00000230453 | 1.859718833 | ANKRD18B |
| 260 | ENSG00000111058 | 1.85627795 | ACSS3 |
| 261 | ENSG00000111728 | 1.854599204 | ST8SIA1 |
| 262 | ENSG00000167191 | 1.851559449 | GPRC5B |
| 263 | ENSG00000154262 | 1.838953254 | ABCA6 |
| 264 | ENSG00000236404 | 1.838660652 | VLDLR-AS1 |
| 265 | ENSG00000205464 | 1.83481979 | ATP6AP1L |
| 266 | ENSG00000173890 | 1.833899338 | GPR160 |
| 267 | ENSG00000163393 | 1.831146569 | SLC22A15 |
| 268 | ENSG00000083067 | 1.830961882 | TRPM3 |
| 269 | ENSG00000183160 | 1.826191137 | TMEM119 |
| 270 | ENSG00000152518 | 1.825645378 | ZFP36L2 |
| 271 | ENSG00000151322 | 1.824665719 | NPAS3 |
| 272 | ENSG00000087076 | 1.823705208 | HSD17B14 |
| 273 | ENSG00000198947 | 1.818442888 | DMD |
| 274 | ENSG00000103485 | 1.818412324 | QPRT |
| 275 | ENSG00000079337 | 1.817533512 | RAPGEF3 |
| 276 | ENSG00000261087 | 1.817317143 | ZNNT1 |
| 277 | ENSG00000137809 | 1.814823464 | ITGA11 |
| 278 | ENSG00000242759 | 1.812015961 | LINC00882 |
| 279 | ENSG00000158321 | 1.784811351 | AUTS2 |
| 280 | ENSG00000104856 | 1.780951678 | RELB |
| 281 | ENSG00000167994 | 1.778158789 | RAB3IL1 |
| 282 | ENSG00000166482 | 1.777896815 | MFAP4 |
| 283 | ENSG00000165379 | 1.769235888 | LRFN5 |
| 284 | ENSG00000138829 | 1.768396718 | FBN2 |
| 285 | ENSG00000091536 | 1.763382884 | MYO15A |
| 286 | ENSG00000261247 | 1.760534831 | GOLGA8T |
| 287 | ENSG00000159871 | 1.753151378 | LYPD5 |
| 288 | ENSG00000258057 | 1.750339825 | BCDIN3D-AS1 |
| 289 | ENSG00000141337 | 1.749006586 | ARSG |
| 290 | ENSG00000103742 | 1.745113925 | IGDCC4 |
| 291 | ENSG00000145675 | 1.74040115 | PIK3R1 |
| 292 | ENSG00000122176 | 1.737285546 | FMOD |
| 293 | ENSG00000254109 | 1.735471082 | RBPMS-AS1 |
| 294 | ENSG00000204991 | 1.726456592 | SPIRE2 |

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**Table 1** (continued)

| SI No | Gene ID | Log2FC | Symbol |
| --- | --- | --- | --- |
| 295 | ENSG00000112149 | 1.723550217 | CD83 |
| 296 | ENSG00000137573 | 1.718910062 | SULF1 |
| 297 | ENSG00000102385 | 1.71638324 | DRP2 |
| 298 | ENSG00000123358 | 1.711240172 | NR4A1 |
| 299 | ENSG00000136231 | 1.701661804 | IGF2BP3 |
| 300 | ENSG00000196189 | 1.698833406 | SEMA4A |
| 301 | ENSG00000235169 | 1.698395404 | SMIM1 |
| 302 | ENSG00000129951 | 1.697726994 | PLPPR3 |
| 303 | ENSG00000121577 | 1.696736786 | POPDC2 |
| 304 | ENSG00000136048 | 1.696574651 | DRAM1 |
| 305 | ENSG00000155093 | 1.695863189 | PTPRN2 |
| 306 | ENSG00000146021 | 1.690145464 | KLHL3 |
| 307 | ENSG00000138606 | 1.685675264 | SHF |
| 308 | ENSG00000163071 | 1.683331706 | SPATA18 |
| 309 | ENSG00000182667 | 1.681535708 | NTM |
| 310 | ENSG00000175147 | 1.675397396 | TMEM51-AS1 |
| 311 | ENSG00000131094 | 1.671463514 | C1QL1 |
| 312 | ENSG00000185950 | 1.671407837 | IRS2 |
| 313 | ENSG00000147813 | 1.667824825 | NAPRT |
| 314 | ENSG00000248932 | 1.66420747 | COPB2-DT |
| 315 | ENSG00000214530 | 1.663364842 | STARD10 |
| 316 | ENSG00000185551 | 1.661064554 | NR2F2 |
| 317 | ENSG00000101447 | 1.657930905 | FAM83D |
| 318 | ENSG00000010810 | 1.655154361 | FYN |
| 319 | ENSG00000188613 | 1.654322702 | NANOS1 |
| 320 | ENSG00000266405 | 1.652390581 | CBX3P2 |
| 321 | ENSG00000135709 | 1.651900323 | KIAA0513 |
| 322 | ENSG00000105696 | 1.648631374 | TMEM59L |
| 323 | ENSG00000130203 | 1.645917049 | APOE |
| 324 | ENSG00000196843 | 1.633503171 | ARID5A |
| 325 | ENSG00000105227 | 1.63140042 | PRX |
| 326 | ENSG00000149131 | 1.627990138 | SERPING1 |
| 327 | ENSG00000257556 | 1.627356063 | LINC02298 |
| 328 | ENSG00000154721 | 1.625716346 | JAM2 |
| 329 | ENSG00000099822 | 1.623752672 | HCN2 |
| 330 | ENSG00000184500 | 1.62244634 | PROS1 |
| 331 | ENSG00000196972 | 1.618142282 | SMIM10L2B |
| 332 | ENSG00000151468 | 1.61503098 | CCDC3 |
| 333 | ENSG00000105464 | 1.614595823 | GRIN2D |
| 334 | ENSG00000231160 | 1.612536565 | KLF3-AS1 |
| 335 | ENSG00000137103 | 1.607356621 | TMEM8B |
| 336 | ENSG00000152804 | 1.606407263 | HHEX |
| 337 | ENSG00000177406 | 1.604754837 | NINJ2-AS1 |
| 338 | ENSG00000137193 | 1.596972091 | PIM1 |
| 339 | ENSG00000064763 | 1.59577321 | FAR2 |
| 340 | ENSG00000167617 | 1.593511925 | CDC42EP5 |
| 341 | ENSG00000255052 | 1.592666461 | FAM66D |
| 342 | ENSG00000228960 | 1.59238393 | OR2A9P |
| 343 | ENSG00000162944 | 1.587186115 | RFTN2 |

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**Table 1** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 344 | ENSG00000253537 | 1.584488009 | PCDHGA7 |
| 345 | ENSG00000184160 | 1.583566455 | ADRA2C |
| 346 | ENSG00000227825 | 1.582312593 | SLC9A7P1 |
| 347 | ENSG00000130304 | 1.576658392 | SLC27A1 |
| 348 | ENSG00000182575 | 1.573523412 | NXPH3 |
| 349 | ENSG00000111961 | 1.571843412 | SASH1 |
| 350 | ENSG00000105327 | 1.571154429 | BBC3 |
| 351 | ENSG00000168405 | 1.570501551 | CMAHP |
| 352 | ENSG00000091986 | 1.567946901 | CCDC80 |
| 353 | ENSG00000115257 | 1.567912566 | PCSK4 |
| 354 | ENSG00000130513 | 1.565481009 | GDF15 |
| 355 | ENSG00000165171 | 1.561243614 | METTL27 |
| 356 | ENSG00000105088 | 1.559271564 | OLFM2 |
| 357 | ENSG00000198885 | 1.55549775 | ITPRIPL1 |
| 358 | ENSG00000164542 | 1.547170796 | KIAA0895 |
| 359 | ENSG00000176658 | 1.545536167 | MYO1D |
| 360 | ENSG00000105792 | 1.542664406 | CFAP69 |
| 361 | ENSG00000164099 | 1.54213594 | PRSS12 |
| 362 | ENSG00000166387 | 1.540636661 | PPFIBP2 |
| 363 | ENSG00000114698 | 1.535920603 | PLSCR4 |
| 364 | ENSG00000205978 | 1.532307659 | NYNRIN |
| 365 | ENSG00000226278 | 1.530617518 | PSPHP1 |
| 366 | ENSG00000086991 | 1.528440753 | NOX4 |
| 367 | ENSG00000131831 | 1.526695735 | RAI2 |
| 368 | ENSG00000107562 | 1.52621975 | CXCL12 |
| 369 | ENSG00000141458 | 1.523071138 | NPC1 |
| 370 | ENSG00000172164 | 1.522391588 | SNTB1 |
| 371 | ENSG00000125965 | 1.521256956 | GDF5 |
| 372 | ENSG00000246985 | 1.520714773 | SOCS2-AS1 |
| 373 | ENSG00000147852 | 1.519022363 | VLDLR |
| 374 | ENSG00000171877 | 1.517043034 | FRMD5 |
| 375 | ENSG00000116661 | 1.51618235 | FBXO2 |
| 376 | ENSG00000068831 | 1.515474863 | RASGRP2 |
| 377 | ENSG00000142156 | 1.514396814 | COL6A1 |
| 378 | ENSG00000233297 | 1.514139138 | RASA4DP |
| 379 | ENSG00000064989 | 1.512822057 | CALCRL |
| 380 | ENSG00000182218 | 1.512646505 | HHIPL1 |
| 381 | ENSG00000198270 | 1.512176831 | TMEM116 |
| 382 | ENSG00000143382 | 1.508260028 | ADAMTSL4 |
| 383 | ENSG00000104883 | 1.507314695 | PEX11G |
| 384 | ENSG00000205309 | 1.507255711 | NT5M |
| 385 | ENSG00000077942 | 1.506829199 | FBLN1 |
| 386 | ENSG00000246174 | 1.502096816 | KCTD21-AS1 |
| 387 | ENSG00000173262 | 1.501298345 | SLC2A14 |

List of mRNAs and LINCRNAs overexpressed in cancer associated fibroblasts as compared to normal fibroblasts. The list shows the GeneID, relative fold change values (Log$_2$FC), and gene symbol

**Table 2** List of underexpressed mRNAs and LINCRNAs in cancer-associated fibroblasts compared to normal fibroblasts

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 1 | ENSG00000164093 | -6.244899052 | PITX2 |
| 2 | ENSG00000110693 | -5.381564985 | SOX6 |
| 3 | ENSG00000171246 | -4.942383728 | NPTX1 |
| 4 | ENSG00000206432 | -4.86079173 | TMEM200C |
| 5 | ENSG00000241213 | -4.692994122 | LINC02024 |
| 6 | ENSG00000189057 | -4.682640569 | FAM111B |
| 7 | ENSG00000186493 | -4.5887501 | C5orf38 |
| 8 | ENSG00000170561 | -4.489265562 | IRX2 |
| 9 | ENSG00000065328 | -4.416019329 | MCM10 |
| 10 | ENSG00000213412 | -4.299519526 | HNRNPA1P33 |
| 11 | ENSG00000277775 | -4.280564426 | H3C7 |
| 12 | ENSG00000102755 | -4.232129614 | FLT1 |
| 13 | ENSG00000171848 | -4.211927711 | RRM2 |
| 14 | ENSG00000117525 | -4.152266428 | F3 |
| 15 | ENSG00000129173 | -4.071649074 | E2F8 |
| 16 | ENSG00000093009 | -3.993665744 | CDC45 |
| 17 | ENSG00000111816 | -3.972942656 | FRK |
| 18 | ENSG00000148773 | -3.972536202 | MKI67 |
| 19 | ENSG00000174371 | -3.960698368 | EXO1 |
| 20 | ENSG00000109805 | -3.956700161 | NCAPG |
| 21 | ENSG00000007968 | -3.919560667 | E2F2 |
| 22 | ENSG00000176049 | -3.896811197 | JAKMIP2 |
| 23 | ENSG00000109272 | -3.8826734 | PF4V1 |
| 24 | ENSG00000169607 | -3.856035805 | CKAP2L |
| 25 | ENSG00000072571 | -3.853814872 | HMMR |
| 26 | ENSG00000151150 | -3.845533978 | ANK3 |
| 27 | ENSG00000131153 | -3.815504744 | GINS2 |
| 28 | ENSG00000137812 | -3.757294903 | KNL1 |
| 29 | ENSG00000122952 | -3.742224789 | ZWINT |
| 30 | ENSG00000166803 | -3.696740654 | PCLAF |
| 31 | ENSG00000286522 | -3.665033009 | H3C2 |
| 32 | ENSG00000203811 | -3.649365262 | H3C14 |
| 33 | ENSG00000203852 | -3.645437574 | H3C15 |
| 34 | ENSG00000092853 | -3.613728714 | CLSPN |
| 35 | ENSG00000112984 | -3.590191849 | KIF20A |
| 36 | ENSG00000171241 | -3.583589781 | SHCBP1 |
| 37 | ENSG00000121152 | -3.583173772 | NCAPH |
| 38 | ENSG00000143476 | -3.558596552 | DTL |
| 39 | ENSG00000152936 | -3.557494062 | LMNTD1 |
| 40 | ENSG00000165244 | -3.557493273 | ZNF367 |
| 41 | ENSG00000165490 | -3.538556887 | DDIAS |
| 42 | ENSG00000237649 | -3.53147714 | KIFC1 |
| 43 | ENSG00000278048 | -3.530960644 | U2 |
| 44 | ENSG00000158402 | -3.511625284 | CDC25C |
| 45 | ENSG00000105011 | -3.506471129 | ASF1B |
| 46 | ENSG00000140534 | -3.501930836 | TICRR |
| 47 | ENSG00000138180 | -3.497178172 | CEP55 |
| 48 | ENSG00000134690 | -3.487940972 | CDCA8 |
| 49 | ENSG00000118193 | -3.487807903 | KIF14 |
| 50 | ENSG00000163638 | -3.463794075 | ADAMTS9 |
| 51 | ENSG00000117724 | -3.460261143 | CENPF |
| 52 | ENSG00000183598 | -3.4355466 | H3C13 |
| 53 | ENSG00000075218 | -3.43277683 | GTSE1 |

**Table 2**  (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 54 | ENSG00000166851 | -3.413367724 | PLK1 |
| 55 | ENSG00000123485 | -3.395070088 | HJURP |
| 56 | ENSG00000011426 | -3.392069201 | ANLN |
| 57 | ENSG00000090889 | -3.389812639 | KIF4A |
| 58 | ENSG00000085840 | -3.38031696 | ORC1 |
| 59 | ENSG00000163808 | -3.374288656 | KIF15 |
| 60 | ENSG00000138185 | -3.373426081 | ENTPD1 |
| 61 | ENSG00000142945 | -3.330213652 | KIF2C |
| 62 | ENSG00000238297 | -3.323221421 | U3 |
| 63 | ENSG00000068078 | -3.315141798 | FGFR3 |
| 64 | ENSG00000117399 | -3.31378088 | CDC20 |
| 65 | ENSG00000112742 | -3.310189708 | TTK |
| 66 | ENSG00000170312 | -3.308358731 | CDK1 |
| 67 | ENSG00000171320 | -3.306520946 | ESCO2 |
| 68 | ENSG00000146670 | -3.297527548 | CDCA5 |
| 69 | ENSG00000145386 | -3.282458069 | CCNA2 |
| 70 | ENSG00000166670 | -3.278837829 | MMP10 |
| 71 | ENSG00000197565 | -3.264304177 | COL4A6 |
| 72 | ENSG00000089685 | -3.2634763 | BIRC5 |
| 73 | ENSG00000168078 | -3.251635481 | PBK |
| 74 | ENSG00000183856 | -3.236451775 | IQGAP3 |
| 75 | ENSG00000145681 | -3.235820469 | HAPLN1 |
| 76 | ENSG00000109072 | -3.229022684 | VTN |
| 77 | ENSG00000273703 | -3.228440353 | H2BC14 |
| 78 | ENSG00000066279 | -3.224990555 | ASPM |
| 79 | ENSG00000184357 | -3.215486063 | H1-5 |
| 80 | ENSG00000197299 | -3.203543875 | BLM |
| 81 | ENSG00000100162 | -3.202097229 | CENPM |
| 82 | ENSG00000175305 | -3.179881376 | CCNE2 |
| 83 | ENSG00000075702 | -3.177596664 | WDR62 |
| 84 | ENSG00000011332 | -3.169273735 | DPF1 |
| 85 | ENSG00000196584 | -3.158286898 | XRCC2 |
| 86 | ENSG00000276368 | -3.147207462 | H2AC14 |
| 87 | ENSG00000134057 | -3.146004943 | CCNB1 |
| 88 | ENSG00000173320 | -3.143419433 | STOX2 |
| 89 | ENSG00000213967 | -3.137208731 | ZNF726 |
| 90 | ENSG00000094804 | -3.131644437 | CDC6 |
| 91 | ENSG00000228065 | -3.120855365 | LINC01515 |
| 92 | ENSG00000051341 | -3.118355075 | POLQ |
| 93 | ENSG00000128713 | -3.100005442 | HOXD11 |
| 94 | ENSG00000131747 | -3.09069934 | TOP2A |
| 95 | ENSG00000150551 | -3.082272486 | LYPD1 |
| 96 | ENSG00000184661 | -3.067972849 | CDCA2 |
| 97 | ENSG00000157456 | -3.063797851 | CCNB2 |
| 98 | ENSG00000281344 | -3.063460876 | HELLPAR |
| 99 | ENSG00000142731 | -3.063276977 | PLK4 |
| 100 | ENSG00000111665 | -3.060335172 | CDCA3 |
| 101 | ENSG00000087586 | -3.042747952 | AURKA |
| 102 | ENSG00000055813 | -3.03369872 | CCDC85A |
| 103 | ENSG00000164303 | -3.027403057 | ENPP6 |
| 104 | ENSG00000058866 | -3.027090567 | DGKG |
| 105 | ENSG00000275713 | -3.024102577 | H2BC9 |
| 106 | ENSG00000151725 | -3.020026322 | CENPU |

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**Table 2**  (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|-------|---------|--------|--------|
| 107 | ENSG00000196747 | -3.007422105 | H2AC13 |
| 108 | ENSG00000276043 | -3.005041466 | UHRF1 |
| 109 | ENSG00000166292 | -2.99208271 | TMEM100 |
| 110 | ENSG00000241322 | -2.984502753 | CDRT1 |
| 111 | ENSG00000111247 | -2.983780538 | RAD51AP1 |
| 112 | ENSG00000129195 | -2.977832945 | PIMREG |
| 113 | ENSG00000135451 | -2.970340448 | TROAP |
| 114 | ENSG00000120149 | -2.970262942 | MSX2 |
| 115 | ENSG00000164045 | -2.958067112 | CDC25A |
| 116 | ENSG00000076382 | -2.950383677 | SPAG5 |
| 117 | ENSG00000009694 | -2.94033935 | TENM1 |
| 118 | ENSG00000170160 | -2.934268013 | CCDC144A |
| 119 | ENSG00000287080 | -2.929684086 | H3C3 |
| 120 | ENSG00000169679 | -2.911200736 | BUB1 |
| 121 | ENSG00000227145 | -2.902745099 | IL21-AS1 |
| 122 | ENSG00000127423 | -2.89847034 | AUNIP |
| 123 | ENSG00000101412 | -2.892510405 | E2F1 |
| 124 | ENSG00000146410 | -2.866283497 | MTFR2 |
| 125 | ENSG00000154920 | -2.857083834 | EME1 |
| 126 | ENSG00000068489 | -2.845006407 | PRR11 |
| 127 | ENSG00000274641 | -2.842803264 | H2BC17 |
| 128 | ENSG00000183850 | -2.818220455 | ZNF730 |
| 129 | ENSG00000276410 | -2.814513008 | H2BC3 |
| 130 | ENSG00000261618 | -2.811451265 | LINC02605 |
| 131 | ENSG00000013810 | -2.805846132 | TACC3 |
| 132 | ENSG00000285294 | -2.799537368 | LINC00842 |
| 133 | ENSG00000100583 | -2.789283935 | SAMD15 |
| 134 | ENSG00000103522 | -2.776203635 | IL21R |
| 135 | ENSG00000163293 | -2.761734242 | NIPAL1 |
| 136 | ENSG00000138778 | -2.749900931 | CENPE |
| 137 | ENSG00000185008 | -2.739539975 | ROBO2 |
| 138 | ENSG00000164379 | -2.732731209 | FOXQ1 |
| 139 | ENSG00000167513 | -2.728991813 | CDT1 |
| 140 | ENSG00000137310 | -2.728793599 | TCF19 |
| 141 | ENSG00000144278 | -2.719986041 | GALNT13 |
| 142 | ENSG00000277224 | -2.717203571 | H2BC7 |
| 143 | ENSG00000111206 | -2.706187922 | FOXM1 |
| 144 | ENSG00000128656 | -2.701917579 | CHN1 |
| 145 | ENSG00000240809 | -2.637140463 | CAP1P1 |
| 146 | ENSG00000265190 | -2.628615159 | ANXA8 |
| 147 | ENSG00000102384 | -2.627033976 | CENPI |
| 148 | ENSG00000113368 | -2.621078132 | LMNB1 |
| 149 | ENSG00000276903 | -2.601525749 | H2AC16 |
| 150 | ENSG00002226953 | -2.595177536 | NCKAP5-AS2 |
| 151 | ENSG00000110900 | -2.590720608 | TSPAN11 |
| 152 | ENSG00000197385 | -2.580835912 | ZNF860 |
| 153 | ENSG00000180875 | -2.579367873 | GREM2 |
| 154 | ENSG00000122966 | -2.568012417 | CIT |
| 155 | ENSG00000138669 | -2.560074549 | PRKG2 |
| 156 | ENSG00000167900 | -2.558677147 | TK1 |
| 157 | ENSG00000138160 | -2.553197127 | KIF11 |
| 158 | ENSG00000134516 | -2.552103309 | DOCK2 |
| 159 | ENSG00000144554 | -2.55141711 | FANCD2 |

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**Table 2** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 160 | ENSG00000275126 | -2.55107583 | H4C13 |
| 161 | ENSG00000160223 | -2.533341384 | ICOSLG |
| 162 | ENSG00000165084 | -2.532201212 | C8orf34 |
| 163 | ENSG00000222898 | -2.531267474 | RN7SKP97 |
| 164 | ENSG00000071539 | -2.527860312 | TRIP13 |
| 165 | ENSG00000162062 | -2.52734652 | TEDC2 |
| 166 | ENSG00000117600 | -2.513999972 | PLPPR4 |
| 167 | ENSG00000138182 | -2.505030881 | KIF20B |
| 168 | ENSG00000080986 | -2.502549503 | NDC80 |
| 169 | ENSG00000176208 | -2.49026074 | ATAD5 |
| 170 | ENSG00000165891 | -2.482123055 | E2F7 |
| 171 | ENSG00000186638 | -2.46529789 | KIF24 |
| 172 | ENSG00000088756 | -2.458646519 | ARHGAP28 |
| 173 | ENSG00000215784 | -2.451244682 | FAM72D |
| 174 | ENSG00000179750 | -2.433420816 | APOBEC3B |
| 175 | ENSG00000186310 | -2.432964986 | NAP1L3 |
| 176 | ENSG00000162383 | -2.431717139 | SLC1A7 |
| 177 | ENSG00000167600 | -2.424938393 | CYP2S1 |
| 178 | ENSG00000154839 | -2.424822921 | SKA1 |
| 179 | ENSG00000101003 | -2.422973689 | GINS1 |
| 180 | ENSG00000263513 | -2.413532558 | FAM72C |
| 181 | ENSG00000164109 | -2.410394716 | MAD2L1 |
| 182 | ENSG00000184374 | -2.406516904 | COLEC10 |
| 183 | ENSG00000088325 | -2.405096136 | TPX2 |
| 184 | ENSG00000275591 | -2.397269203 | XKR5 |
| 185 | ENSG00000264230 | -2.396476922 | ANXA8L1 |
| 186 | ENSG00000109674 | -2.383348062 | NEIL3 |
| 187 | ENSG00000124882 | -2.381427676 | EREG |
| 188 | ENSG00000123219 | -2.373815709 | CENPK |
| 189 | ENSG00000179219 | -2.371344708 | LINC00311 |
| 190 | ENSG00000121904 | -2.371312009 | CSMD2 |
| 191 | ENSG00000128052 | -2.369999586 | KDR |
| 192 | ENSG00000120594 | -2.368417063 | PLXDC2 |
| 193 | ENSG00000230300 | -2.366705146 | STARD13-IT1 |
| 194 | ENSG00000278588 | -2.366083657 | H2BC10 |
| 195 | ENSG00000188662 | -2.360625481 | H1-9P |
| 196 | ENSG00000187741 | -2.359151573 | FANCA |
| 197 | ENSG00000162654 | -2.358912627 | GBP4 |
| 198 | ENSG00000250853 | -2.34035427 | RNF138P1 |
| 199 | ENSG00000248228 | -2.324670799 | SLIT2-IT1 |
| 200 | ENSG00000135476 | -2.32046519 | ESPL1 |
| 201 | ENSG00000185697 | -2.316698718 | MYBL1 |
| 202 | ENSG00000171517 | -2.316431745 | LPAR3 |
| 203 | ENSG00000166451 | -2.308405325 | CENPN |
| 204 | ENSG00000184571 | -2.302100309 | PIWIL3 |
| 205 | ENSG00000179071 | -2.298141854 | CCDC89 |
| 206 | ENSG00000161888 | -2.296025131 | SPC24 |
| 207 | ENSG00000227911 | -2.269397065 | LINC02344 |
| 208 | ENSG00000117461 | -2.26639294 | PIK3R3 |
| 209 | ENSG00000187796 | -2.266276673 | CARD9 |
| 210 | ENSG00000164850 | -2.26346959 | GPER1 |
| 211 | ENSG00000100479 | -2.263305406 | POLE2 |
| 212 | ENSG00000236532 | -2.262159728 | LINC01695 |

**Table 2** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 213 | ENSG00000104368 | -2.261503355 | PLAT |
| 214 | ENSG00000112852 | -2.255468306 | PCDHB2 |
| 215 | ENSG00000137807 | -2.254277149 | KIF23 |
| 216 | ENSG00000144395 | -2.252773294 | CCDC150 |
| 217 | ENSG00000152056 | -2.244603112 | AP1S3 |
| 218 | ENSG00000183762 | -2.234862927 | KREMEN1 |
| 219 | ENSG00000064042 | -2.233728432 | LIMCH1 |
| 220 | ENSG00000100526 | -2.226118872 | CDKN3 |
| 221 | ENSG00000207597 | -2.215978624 | MIR490 |
| 222 | ENSG00000124635 | -2.214462467 | H2BC11 |
| 223 | ENSG00000196081 | -2.207624252 | ZNF724 |
| 224 | ENSG00000133119 | -2.204999878 | RFC3 |
| 225 | ENSG00000012048 | -2.203512532 | BRCA1 |
| 226 | ENSG00000278828 | -2.197741828 | H3C10 |
| 227 | ENSG00000160957 | -2.18914984 | RECQL4 |
| 228 | ENSG00000188610 | -2.174967519 | FAM72B |
| 229 | ENSG00000164087 | -2.157773664 | POC1A |
| 230 | ENSG00000147536 | -2.154684112 | GINS4 |
| 231 | ENSG00000236824 | -2.154204019 | BCYRN1 |
| 232 | ENSG00000073111 | -2.152293569 | MCM2 |
| 233 | ENSG00000107984 | -2.137106037 | DKK1 |
| 234 | ENSG00000272674 | -2.122271421 | PCDHB16 |
| 235 | ENSG00000163535 | -2.122050767 | SGO2 |
| 236 | ENSG00000187583 | -2.103701739 | PLEKHN1 |
| 237 | ENSG00000149968 | -2.090233185 | MMP3 |
| 238 | ENSG00000161800 | -2.088807861 | RACGAP1 |
| 239 | ENSG00000162063 | -2.083000456 | CCNF |
| 240 | ENSG00000216819 | -2.070905578 | TUBB2BP1 |
| 241 | ENSG00000234383 | -2.070115996 | CTBP2P8 |
| 242 | ENSG00000164611 | -2.062477973 | PTTG1 |
| 243 | ENSG00000169247 | -2.060263012 | SH3TC2 |
| 244 | ENSG00000163507 | -2.058945689 | CIP2A |
| 245 | ENSG00000183763 | -2.05764095 | TRAIP |
| 246 | ENSG00000137135 | -2.048019992 | ARHGEF39 |
| 247 | ENSG00000168496 | -2.03889776 | FEN1 |
| 248 | ENSG00000204176 | -2.034676644 | SYT15 |
| 249 | ENSG00000144476 | -2.028952615 | ACKR3 |
| 250 | ENSG00000139618 | -2.026828243 | BRCA2 |
| 251 | ENSG00000229989 | -2.016615466 | MIR181A1HG |
| 252 | ENSG00000248019 | -2.004491042 | FAM13A-AS1 |
| 253 | ENSG00000004139 | -2.003314083 | SARM1 |
| 254 | ENSG00000240891 | -2.003055186 | PLCXD2 |
| 255 | ENSG00000274290 | -1.998795168 | H2BC6 |
| 256 | ENSG00000198692 | -1.99256031 | EIF1AY |
| 257 | ENSG00000104147 | -1.988069738 | OIP5 |
| 258 | ENSG00000274997 | -1.984906449 | H2AC12 |
| 259 | ENSG00000137267 | -1.984524033 | TUBB2A |
| 260 | ENSG00000185760 | -1.982236088 | KCNQ5 |
| 261 | ENSG00000247498 | -1.981575492 | GPRC5D-AS1 |
| 262 | ENSG00000012504 | -1.980799777 | NR1H4 |
| 263 | ENSG00000285077 | -1.973914944 | ARHGAP11B |
| 264 | ENSG00000135480 | -1.973232661 | KRT7 |
| 265 | ENSG00000144596 | -1.96748205 | GRIP2 |

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**Table 2** (continued)

| SI No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 266 | ENSG00000196787 | -1.96740556 | H2AC11 |
| 267 | ENSG00000091651 | -1.96729841 | ORC6 |
| 268 | ENSG00000131002 | -1.967122587 | TXLNGY |
| 269 | ENSG00000145861 | -1.964234961 | C1QTNF2 |
| 270 | ENSG00000248909 | -1.962396435 | HMGB1P21 |
| 271 | ENSG00000163491 | -1.955677642 | NEK10 |
| 272 | ENSG00000196550 | -1.950290978 | FAM72A |
| 273 | ENSG00000136122 | -1.950251078 | BORA |
| 274 | ENSG00000002746 | -1.94138728 | HECW1 |
| 275 | ENSG00000106537 | -1.940201039 | TSPAN13 |
| 276 | ENSG00000112029 | -1.93283442 | FBXO5 |
| 277 | ENSG00000051180 | -1.932410512 | RAD51 |
| 278 | ENSG00000100297 | -1.92766499 | MCM5 |
| 279 | ENSG00000231672 | -1.922759998 | DIRC3 |
| 280 | ENSG00000281641 | -1.919964204 | SAMD12-AS1 |
| 281 | ENSG00000079616 | -1.912111909 | KIF22 |
| 282 | ENSG00000231566 | -1.910488729 | LINC02595 |
| 283 | ENSG00000131470 | -1.908189689 | PSMC3IP |
| 284 | ENSG00000123473 | -1.899760576 | STIL |
| 285 | ENSG00000171408 | -1.89840943 | PDE7B |
| 286 | ENSG00000170624 | -1.893532203 | SGCD |
| 287 | ENSG00000214391 | -1.88992187 | TUBAP2 |
| 288 | ENSG00000197275 | -1.883502038 | RAD54B |
| 289 | ENSG00000184988 | -1.882777859 | TMEM106A |
| 290 | ENSG00000111057 | -1.871847275 | KRT18 |
| 291 | ENSG00000160229 | -1.870820281 | ZNF66 |
| 292 | ENSG00000230417 | -1.864206963 | LINC00595 |
| 293 | ENSG00000277075 | -1.862953731 | H2AC8 |
| 294 | ENSG00000214826 | -1.86155004 | DDX12P |
| 295 | ENSG00000168675 | -1.859533634 | LDLRAD4 |
| 296 | ENSG00000136492 | -1.856840499 | BRIP1 |
| 297 | ENSG00000134007 | -1.855147363 | ADAM20 |
| 298 | ENSG00000168389 | -1.840331218 | MFSD2A |
| 299 | ENSG00000124575 | -1.839002223 | H1-3 |
| 300 | ENSG00000144583 | -1.838682115 | MARCHF4 |
| 301 | ENSG00000040275 | -1.83690946 | SPDL1 |
| 302 | ENSG00000258947 | -1.835374336 | TUBB3 |
| 303 | ENSG00000274210 | -1.834128746 | RNVU1-27 |
| 304 | ENSG00000164251 | -1.833060737 | F2RL1 |
| 305 | ENSG00000077152 | -1.828725777 | UBE2T |
| 306 | ENSG00000100739 | -1.828412728 | BDKRB1 |
| 307 | ENSG00000146006 | -1.826278356 | LRRTM2 |
| 308 | ENSG00000149548 | -1.825503232 | CCDC15 |
| 309 | ENSG00000157193 | -1.817142483 | LRP8 |
| 310 | ENSG00000173894 | -1.810408037 | CBX2 |
| 311 | ENSG00000137285 | -1.808867329 | TUBB2B |
| 312 | ENSG00000125637 | -1.808350388 | PSD4 |
| 313 | ENSG00000158769 | -1.806788653 | F11R |
| 314 | ENSG00000091409 | -1.797159103 | ITGA6 |
| 315 | ENSG00000122378 | -1.795265991 | PRXL2A |
| 316 | ENSG00000160949 | -1.795003337 | TONSL |
| 317 | ENSG00000259571 | -1.794121641 | BLID |
| 318 | ENSG00000013573 | -1.783801829 | DDX11 |

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**Table 2** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 319 | ENSG00000067646 | -1.781317817 | ZFY |
| 320 | ENSG00000228485 | -1.77609442 | GRK5-IT1 |
| 321 | ENSG00000185130 | -1.775345169 | H2BC13 |
| 322 | ENSG00000135119 | -1.774610837 | RNFT2 |
| 323 | ENSG00000168961 | -1.770421979 | LGALS9 |
| 324 | ENSG00000167553 | -1.769893028 | TUBA1C |
| 325 | ENSG00000136108 | -1.767305561 | CKAP2 |
| 326 | ENSG00000275221 | -1.755721524 | H2AC15 |
| 327 | ENSG00000138772 | -1.755464656 | ANXA3 |
| 328 | ENSG00000257167 | -1.755365934 | TMPO-AS1 |
| 329 | ENSG00000119969 | -1.75451338 | HELLS |
| 330 | ENSG00000166396 | -1.748843248 | SERPINB7 |
| 331 | ENSG00000113070 | -1.7485423 | HBEGF |
| 332 | ENSG00000253669 | -1.74727492 | GASAL1 |
| 333 | ENSG00000203668 | -1.74710226 | CHML |
| 334 | ENSG00000121621 | -1.746743236 | KIF18A |
| 335 | ENSG00000143942 | -1.742138349 | CHAC2 |
| 336 | ENSG00000123416 | -1.741078217 | TUBA1B |
| 337 | ENSG00000178718 | -1.738739341 | RPP25 |
| 338 | ENSG00000135333 | -1.737844738 | EPHA7 |
| 339 | ENSG00000127586 | -1.737108616 | CHTF18 |
| 340 | ENSG00000182481 | -1.732656694 | KPNA2 |
| 341 | ENSG00000138092 | -1.727166693 | CENPO |
| 342 | ENSG00000135111 | -1.726943068 | TBX3 |
| 343 | ENSG00000003137 | -1.726195132 | CYP26B1 |
| 344 | ENSG00000050438 | -1.72618536 | SLC4A8 |
| 345 | ENSG00000104738 | -1.725725954 | MCM4 |
| 346 | ENSG00000224080 | -1.725379805 | UBE2FP1 |
| 347 | ENSG00000143248 | -1.724632404 | RGS5 |
| 348 | ENSG00000181938 | -1.72455685 | GINS3 |
| 349 | ENSG00000278463 | -1.724423695 | H2AC4 |
| 350 | ENSG00000273802 | -1.719926453 | H2BC8 |
| 351 | ENSG00000272610 | -1.718830162 | MAGI1-IT1 |
| 352 | ENSG00000276180 | -1.715080282 | H4C9 |
| 353 | ENSG00000080493 | -1.711929929 | SLC4A4 |
| 354 | ENSG00000146918 | -1.7111589 | NCAPG2 |
| 355 | ENSG00000125968 | -1.706827003 | ID1 |
| 356 | ENSG00000165304 | -1.706565279 | MELK |
| 357 | ENSG00000093072 | -1.705766917 | ADA2 |
| 358 | ENSG00000000460 | -1.704399842 | C1orf112 |
| 359 | ENSG00000203814 | -1.700700847 | H2BC18 |
| 360 | ENSG00000188229 | -1.700547122 | TUBB4B |
| 361 | ENSG00000182010 | -1.693661881 | RTKN2 |
| 362 | ENSG00000203772 | -1.693224918 | SPRN |
| 363 | ENSG00000228716 | -1.692307878 | DHFR |
| 364 | ENSG00000233695 | -1.683313672 | GAS6-AS1 |
| 365 | ENSG00000240583 | -1.681814582 | AQP1 |
| 366 | ENSG00000226887 | -1.680658527 | ERVMER34-1 |
| 367 | ENSG00000162981 | -1.680244743 | LRATD1 |
| 368 | ENSG00000155754 | -1.674128704 | C2CD6 |
| 369 | ENSG00000187764 | -1.671707352 | SEMA4D |
| 370 | ENSG00000144354 | -1.666069051 | CDCA7 |
| 371 | ENSG00000140525 | -1.665511953 | FANCI |

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**Table 2** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|---|---|---|---|
| 372 | ENSG00000198826 | -1.662405338 | ARHGAP11A |
| 373 | ENSG00000114374 | -1.66111163 | USP9Y |
| 374 | ENSG00000115687 | -1.660913272 | PASK |
| 375 | ENSG00000138641 | -1.65658816 | HERC3 |
| 376 | ENSG00000225479 | -1.650007239 | PLCB1-IT1 |
| 377 | ENSG00000171227 | -1.648342861 | TMEM37 |
| 378 | ENSG00000069011 | -1.646996033 | PITX1 |
| 379 | ENSG00000189423 | -1.645504091 | USP32P3 |
| 380 | ENSG00000106018 | -1.644722116 | VIPR2 |
| 381 | ENSG00000125885 | -1.643965568 | MCM8 |
| 382 | ENSG00000108106 | -1.641794507 | UBE2S |
| 383 | ENSG00000116741 | -1.640261558 | RGS2 |
| 384 | ENSG00000019582 | -1.637655701 | CD74 |
| 385 | ENSG00000128944 | -1.631589834 | KNSTRN |
| 386 | ENSG00000205085 | -1.629799155 | FAM71F2 |
| 387 | ENSG00000213551 | -1.629540955 | DNAJC9 |
| 388 | ENSG00000197646 | -1.628944055 | PDCD1LG2 |
| 389 | ENSG00000284770 | -1.6281093 | TBCE |
| 390 | ENSG00000175592 | -1.627413319 | FOSL1 |
| 391 | ENSG00000169255 | -1.626377071 | B3GALNT1 |
| 392 | ENSG00000256940 | -1.624938759 | PPP1R14B-AS1 |
| 393 | ENSG00000092470 | -1.624777727 | WDR76 |
| 394 | ENSG00000170396 | -1.62145823 | ZNF804A |
| 395 | ENSG00000157150 | -1.621389149 | TIMP4 |
| 396 | ENSG00000180998 | -1.620767241 | GPR137C |
| 397 | ENSG00000164342 | -1.61063564 | TLR3 |
| 398 | ENSG00000185347 | -1.608083729 | TEDC1 |
| 399 | ENSG00000185480 | -1.601104078 | PARPBP |
| 400 | ENSG00000128266 | -1.600461913 | GNAZ |
| 401 | ENSG00000138741 | -1.600042092 | TRPC3 |
| 402 | ENSG00000184524 | -1.599335578 | CEND1 |
| 403 | ENSG00000101945 | -1.599239127 | SUV39H1 |
| 404 | ENSG00000167670 | -1.597489348 | CHAF1A |
| 405 | ENSG00000120645 | -1.595159204 | IQSEC3 |
| 406 | ENSG00000274618 | -1.592827393 | H4C6 |
| 407 | ENSG00000166845 | -1.586194556 | C18orf54 |
| 408 | ENSG00000171951 | -1.584038434 | SCG2 |
| 409 | ENSG00000230397 | -1.577283347 | SPTLC1P1 |
| 410 | ENSG00000236397 | -1.570378467 | DDX11L2 |
| 411 | ENSG00000279094 | -1.568089067 | LINC01670 |
| 412 | ENSG00000161692 | -1.564584462 | DBF4B |
| 413 | ENSG00000154898 | -1.564062897 | CCDC144CP |
| 414 | ENSG00000113805 | -1.563519837 | CNTN3 |
| 415 | ENSG00000156968 | -1.563032371 | MPV17L |
| 416 | ENSG00000138658 | -1.561650456 | ZGRF1 |
| 417 | ENSG00000153956 | -1.559769347 | CACNA2D1 |
| 418 | ENSG00000072201 | -1.556754524 | LNX1 |
| 419 | ENSG00000184635 | -1.554031763 | ZNF93 |
| 420 | ENSG00000076706 | -1.550103307 | MCAM |
| 421 | ENSG00000253919 | -1.547621411 | THAP12P7 |
| 422 | ENSG00000117632 | -1.546633613 | STMN1 |
| 423 | ENSG00000169116 | -1.545012275 | PARM1 |
| 424 | ENSG00000134198 | -1.54426042 | TSPAN2 |

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**Table 2** (continued)

| Sl No | Gene ID | Log2FC | Symbol |
|-------|---------|--------|--------|
| 425 | ENSG00000145022 | -1.540861873 | TCTA |
| 426 | ENSG00000137872 | -1.538495127 | SEMA6D |
| 427 | ENSG00000151718 | -1.538300366 | WWC2 |
| 428 | ENSG00000248483 | -1.536573033 | POU5F2 |
| 429 | ENSG00000279078 | -1.53537251 | SND1-IT1 |
| 430 | ENSG00000275714 | -1.535151777 | H3C1 |
| 431 | ENSG00000054277 | -1.534516353 | OPN3 |
| 432 | ENSG00000228817 | -1.532377146 | BACH1-IT2 |
| 433 | ENSG00000106462 | -1.530310813 | EZH2 |
| 434 | ENSG00000152953 | -1.529327592 | STK32B |
| 435 | ENSG00000084710 | -1.526437542 | EFR3B |
| 436 | ENSG00000183878 | -1.526148211 | UTY |
| 437 | ENSG00000164619 | -1.522526665 | BMPER |
| 438 | ENSG00000145569 | -1.522204027 | OTULINL |
| 439 | ENSG00000124610 | -1.517949223 | H1-1 |
| 440 | ENSG00000196118 | -1.512333496 | CCDC189 |
| 441 | ENSG00000126215 | -1.510389055 | XRCC3 |
| 442 | ENSG00000233966 | -1.509072823 | UBE2SP1 |
| 443 | ENSG00000154127 | -1.508168812 | UBASH3B |
| 444 | ENSG00000176225 | -1.505171168 | RTTN |
| 445 | ENSG00000166446 | -1.504994005 | CDYL2 |
| 446 | ENSG00000270276 | -1.503539737 | H4C15 |
| 447 | ENSG00000128536 | -1.50202659 | CDHR3 |
| 448 | ENSG00000041353 | -1.501903367 | RAB27B |

List of mRNAs and LINCRNAs under-expressed in cancer-associated fibroblasts as compared to normal fibroblasts. The list shows the GeneID, relative fold change values (Log$_2$FC), and gene symbol

## Prediction of targets of the miRNAs

The 24 miRNAs obtained from the above analysis targets were fed into miRDB for mRNA target prediction. mRNA targets with a score of $>/= 95$ were chosen. We have identified 288 mRNA targets associated with the input of 24 miRNAs.

The predicted mRNA targets were cross-referenced with our dataset to identify the common mRNAs. Subsequently, we established lincRNA-miRNA-mRNA combinations Table 7.

**Table 3** Selected genes validated by qRT-PCR

| Gene symbol | Log$_2$FC (RNA-seq) | Average FC in qRT-PCR with S.D |
|-------------|---------------------|-------------------------------|
| SFRP4 | 7.457728693 | 35.45 ± 6.46 |
| DEPP1 | 6.8004577 | 48.37 ± 3.134 |
| GDF6 | 5.080737946 | 58.09 ± 4.793 |
| NPR*1* | 4.968358544 | 42.38 ± 4.161 |
| LINC00842 | -2.799537368 | 0.023 ± 0.003 |

List of differentially expressed genes validated by qRT-PCR. The list shows the Gene symbol, fold change with respect to control in RNA-seq and fold change with respect to control in qRT-PCR

## Discussion

The effect of microenvironment on the initiation, maintenance and progression of solid tumors has been established beyond doubt [25]. CAFs, which constitute a significant component of the TME are a major source of secreted factors. Interaction with the CAF and derived factors not only play a significant role in promoting tumorigenesis and metastasis but also influence the response of the tumor to drugs [10, 12]. It is likely that in response to chemotherapeutic drugs, some pro-tumorigenic actions of CAFs may be activated, which in turn aid the tumor cells in escaping from the drug challenge. Studies on prostate cancer have shown that tumor cells grown in the presence of CAFs or CAF-derived factors show much higher tolerance to drugs as compared to tumor cells grown alone [26]. Also, cells grown with CAF-derived factors have a higher potential to metastasize [27]. These highlight the possibility of targeting CAF/derived factors for therapeutic purposes.

Attempts have been made to target various components of the TME, such as ECM, exosomes, CAFs, immune cells, vascular cells etc [28].

**Table 4** List of LINCRNAs interacting with proteins

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | UniProt ID | Type |
|---|---|---|---|---|
| NONHSAG010513 | LINC01252 | IGF2BP3 | O00425 | protein |
| NONHSAG010513 | LINC01252 | SOX2 | P48431 | protein |
| NONHSAG010513 | LINC01252 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG010513 | LINC01252 | AGO2 | Q9UKV8 | protein |
| ENSG00000163364 | LINC01116 | ZC3HAV1 | Q7Z2W4 | protein |
| ENSG00000163364 | LINC01116 | IGF2BP3 | O00425 | protein |
| ENSG00000163364 | LINC01116 | CRNKL1 | Q9BZJ0 | protein |
| ENSG00000163364 | LINC01116 | IGF2BP1 | Q9NZI8 | protein |
| ENSG00000163364 | LINC01116 | DHX36 | Q9H2U1 | protein |
| ENSG00000163364 | LINC01116 | EZH2 | A0A090N8E9 | protein |
| ENSG00000223485 | LINC01615 | IGF2BP3 | O00425 | protein |
| NONHSAG099482 | LINC01301 | A1CF | Q9NQ94 | protein |
| NONHSAG099482 | LINC01301 | A1CF | Q9NQ94 | protein |
| NONHSAG099482 | LINC01301 | TRIM25 | Q14258 | protein |
| NONHSAG099482 | LINC01301 | ZC3HAV1 | Q7Z2W4 | protein |
| NONHSAG099482 | LINC01301 | ZMAT3 | Q9HA38 | protein |
| NONHSAG099482 | LINC01301 | ZMAT3 | Q9HA38 | protein |
| NONHSAG099482 | LINC01301 | SP1 | P08047 | protein |
| NONHSAG099482 | LINC01301 | IGF2BP3 | O00425 | protein |
| NONHSAG099482 | LINC01301 | RBMX | P38159 | protein |
| NONHSAG099482 | LINC01301 | SOX2 | P48431 | protein |
| NONHSAG099482 | LINC01301 | U2AF1 | Q01081 | protein |
| NONHSAG099482 | LINC01301 | ILF2 | Q12905 | protein |
| NONHSAG099482 | LINC01301 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG099482 | LINC01301 | AGO2 | Q9UKV8 | protein |
| NONHSAG099482 | LINC01301 | DHX36 | Q9H2U1 | protein |
| NONHSAG099482 | LINC01301 | DHX36 | Q9H2U1 | protein |
| NONHSAG016089 | LINC02298 | DMD | A0A075B6G3 | protein |
| NONHSAG016089 | LINC02298 | TRIM25 | Q14258 | protein |
| NONHSAG016089 | LINC02298 | IGF2BP3 | O00425 | protein |
| NONHSAG016089 | LINC02298 | SOX2 | P48431 | protein |
| NONHSAG016089 | LINC02298 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG016089 | LINC02298 | DHX36 | Q9H2U1 | protein |
| NONHSAG035677 | LINC00882 | A1CF | Q9NQ94 | protein |
| NONHSAG035677 | LINC00882 | A1CF | Q9NQ94 | protein |
| NONHSAG035677 | LINC00882 | FUBP1 | Q96AE4 | protein |
| NONHSAG035677 | LINC00882 | KHDRBS2 | Q5VWX1 | protein |
| NONHSAG035677 | LINC00882 | PUS10 | Q3MIT2 | protein |
| NONHSAG035677 | LINC00882 | TRIM25 | Q14258 | protein |
| NONHSAG035677 | LINC00882 | ZC3HAV1 | Q7Z2W4 | protein |
| NONHSAG035677 | LINC00882 | ZMAT3 | Q9HA38 | protein |
| NONHSAG035677 | LINC00882 | ZMAT3 | Q9HA38 | protein |
| NONHSAG035677 | LINC00882 | SP1 | P08047 | protein |
| NONHSAG035677 | LINC00882 | WDR4 | P57081 | protein |
| NONHSAG035677 | LINC00882 | SRSF1 | Q07955 | protein |
| NONHSAG035677 | LINC00882 | IGF2BP3 | O00425 | protein |
| NONHSAG035677 | LINC00882 | RBMX | P38159 | protein |
| NONHSAG035677 | LINC00882 | SOX2 | P48431 | protein |
| NONHSAG035677 | LINC00882 | HNRNPM | P52272 | protein |

**Table 4** (continued)

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | UniProt ID | Type |
|---|---|---|---|---|
| NONHSAG035677 | LINC00882 | U2AF1 | Q01081 | protein |
| NONHSAG035677 | LINC00882 | ILF2 | Q12905 | protein |
| NONHSAG035677 | LINC00882 | ELAVL1 | Q15717 | protein |
| NONHSAG035677 | LINC00882 | KHSRP | Q92945 | protein |
| NONHSAG035677 | LINC00882 | CRNKL1 | Q9BZJ0 | protein |
| NONHSAG035677 | LINC00882 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG035677 | LINC00882 | AGO2 | Q9UKV8 | protein |
| NONHSAG035677 | LINC00882 | AGO2 | Q9UKV8 | protein |
| NONHSAG035677 | LINC00882 | DHX36 | Q9H2U1 | protein |
| NONHSAG035677 | LINC00882 | DHX36 | Q9H2U1 | protein |
| NONHSAG035677 | LINC00882 | Rbfox1 | Q9NWB1 | protein |
| ENSG00000228221 | LINC00578 | KHDRBS2 | Q5VWX1 | protein |
| ENSG00000228221 | LINC00578 | PUS10 | Q3MIT2 | protein |
| ENSG00000228221 | LINC00578 | TRIM25 | Q14258 | protein |
| ENSG00000228221 | LINC00578 | USF2 | Q15853 | protein |
| ENSG00000228221 | LINC00578 | ZC3HAV1 | Q7Z2W4 | protein |
| ENSG00000228221 | LINC00578 | ZMAT3 | Q9HA38 | protein |
| ENSG00000228221 | LINC00578 | ZMAT3 | Q9HA38 | protein |
| ENSG00000228221 | LINC00578 | SP1 | P08047 | protein |
| ENSG00000228221 | LINC00578 | CPSF1 | Q10570 | protein |
| ENSG00000228221 | LINC00578 | IGF2BP3 | O00425 | protein |
| ENSG00000228221 | LINC00578 | SOX2 | P48431 | protein |
| ENSG00000228221 | LINC00578 | CPSF7 | Q8N684 | protein |
| ENSG00000228221 | LINC00578 | CRNKL1 | Q9BZJ0 | protein |
| ENSG00000228221 | LINC00578 | IGF2BP1 | Q9NZI8 | protein |
| ENSG00000228221 | LINC00578 | AGO2 | Q9UKV8 | protein |
| ENSG00000228221 | LINC00578 | AGO2 | Q9UKV8 | protein |
| ENSG00000228221 | LINC00578 | AGO2 | Q9UKV8 | protein |
| ENSG00000228221 | LINC00578 | PTBP1 | P26599 | protein |
| ENSG00000228221 | LINC00578 | DHX36 | Q9H2U1 | protein |
| ENSG00000228221 | LINC00578 | DHX36 | Q9H2U1 | protein |
| NONHSAG036724 | LINC00578 | ADAR | P55265 | protein |
| NONHSAG036724 | LINC00578 | WDR33 | Q9C0J8 | protein |
| NONHSAG036724 | LINC00578 | TARBP2 | Q15633 | protein |
| NONHSAG036724 | LINC00578 | RBM6 | P78332 | Tpyein |
| NONHSAG036724 | LINC00578 | RBM10 | P98175 | protein |
| NONHSAG036724 | LINC00578 | UPF1 | Q92900 | protein |
| NONHSAG036724 | LINC00578 | hnRNPA2B1 | O88569 | protein |
| NONHSAG036724 | LINC00578 | FUS | P35637 | protein |
| NONHSAG036727 | LINC00578 | HNRNPU | Q00839 | protein |
| NONHSAG036727 | LINC00578 | DDX3X | O00571 | protein |
| NONHSAG036727 | LINC00578 | EIF2C1 | Q9UL18 | protein |
| NONHSAG036727 | LINC00578 | AGO2 | Q9UKV8 | protein |
| NONHSAG036727 | LINC00578 | AGO3 | Q9H9G7 | protein |
| NONHSAG036727 | LINC00578 | AGO4 | Q9HCK5 | protein |
| NONHSAG036727 | LINC00578 | MBNL2 | Q5VZF2 | protein |
| NONHSAG036727 | LINC00578 | MOV10 | P22626 | protein |
| NONHSAG036727 | LINC00578 | SPPL3 | Q8TCT6 | protein |
| NONHSAG036727 | LINC00578 | HNRPG | P38159 | protein |

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**Table 4** (continued)

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | UniProt ID | Type |
|---|---|---|---|---|
| NONHSAG036727 | LINC00578 | YTDC1 | Q96MU7 | protein |
| NONHSAG036727 | LINC00578 | MBNL1 | Q9NR56 | protein |
| NONHSAG036727 | LINC00578 | FBL | P22087 | protein |
| NONHSAG036727 | LINC00578 | RNMT | O43148 | protein |
| NONHSAG036727 | LINC00578 | DBHS | Q15233 | protein |
| NONHSAG036727 | LINC00578 | PSF | P23246 | protein |
| NONHSAG036727 | LINC00578 | HDAC9 | Q9UKV0 | protein |
| NONHSAG036727 | LINC00578 | SMARCA4 | P51532 | protein |
| NONHSAG036727 | LINC00578 | SSB | P05455 | protein |
| NONHSAG036727 | LINC00578 | EWSR1 | Q01844 | protein |
| ENSG00000231566 | LINC02595 | DCP1B | Q8IZD4 | protein |
| ENSG00000231566 | LINC02595 | FUBP1 | Q96AE4 | protein |
| ENSG00000231566 | LINC02595 | TRIM25 | Q14258 | protein |
| ENSG00000231566 | LINC02595 | ZMAT3 | Q9HA38 | protein |
| ENSG00000231566 | LINC02595 | DDX6 | P26196 | protein |
| ENSG00000231566 | LINC02595 | AGO1 | Q9UL18 | protein |
| ENSG00000231566 | LINC02595 | FUS | P35637 | protein |
| ENSG00000231566 | LINC02595 | EWSR1 | Q01844 | protein |
| ENSG00000231566 | LINC02595 | TIA1 | P31483 | protein |
| ENSG00000231566 | LINC02595 | RBMX | P38159 | protein |
| ENSG00000231566 | LINC02595 | ILF2 | Q12905 | protein |
| ENSG00000231566 | LINC02595 | YTHDF2 | Q9Y5A9 | protein |
| ENSG00000231566 | LINC02595 | FUBP3 | Q96I24 | protein |
| ENSG00000231566 | LINC02595 | DHX36 | Q9H2U1 | protein |
| ENSG00000231566 | LINC02595 | DHX36 | Q9H2U1 | protein |
| ENSG00000231566 | LINC02595 | Rbfox1 | Q9NWB1 | protein |
| NONHSAG006313 | LINC00595 | WDR33 | Q9C0J8 | protein |
| NONHSAG006313 | LINC00595 | RTCB | Q9Y3I0 | protein |
| NONHSAG006313 | LINC00595 | RBM6 | P78332 | protein |
| NONHSAG006313 | LINC00595 | RBM10 | P98175 | protein |
| NONHSAG006313 | LINC00595 | UPF1 | Q92900 | protein |
| NONHSAG006313 | LINC00595 | hnRNPA2B1 | O88569 | protein |
| NONHSAG006313 | LINC00595 | FUS | P35637 | protein |
| NONHSAG060614 | LINC00595 | EIF2C1 | Q9UL18 | protein |
| NONHSAG060614 | LINC00595 | AGO2 | Q9UKV8 | protein |
| NONHSAG060614 | LINC00595 | AGO3 | Q9H9G7 | protein |
| NONHSAG060614 | LINC00595 | AGO4 | Q9HCK5 | protein |
| NONHSAG060614 | LINC00595 | MBNL2 | Q5VZF2 | protein |
| NONHSAG060614 | LINC00595 | MOV10 | P22626 | protein |
| NONHSAG060614 | LINC00595 | FBL | P22087 | protein |
| NONHSAG060614 | LINC00595 | RBFOX2 | O43251 | protein |
| NONHSAG060614 | LINC00595 | DBHS | Q15233 | protein |
| NONHSAG060614 | LINC00595 | PSF | P23246 | protein |
| NONHSAG060614 | LINC00595 | TRIM25 | Q14258 | protein |
| NONHSAG060614 | LINC00595 | ZC3HAV1 | Q7Z2W4 | protein |
| NONHSAG060614 | LINC00595 | ZMAT3 | Q9HA38 | protein |
| NONHSAG060614 | LINC00595 | ZMAT3 | Q9HA38 | protein |
| NONHSAG060614 | LINC00595 | SERBP1 | Q8NC51 | protein |
| NONHSAG060614 | LINC00595 | IGF2BP3 | O00425 | protein |

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**Table 4** (continued)

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | UniProt ID | Type |
|---|---|---|---|---|
| NONHSAG060614 | LINC00595 | BRCA1 | P38398 | protein |
| NONHSAG060614 | LINC00595 | SOX2 | P48431 | protein |
| NONHSAG060614 | LINC00595 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG060614 | LINC00595 | AGO2 | Q9UKV8 | protein |
| NONHSAG060614 | LINC00595 | AGO2 | Q9UKV8 | protein |
| NONHSAG060614 | LINC00595 | AGO2 | Q9UKV8 | protein |
| NONHSAG060614 | LINC00595 | DHX36 | Q9H2U1 | protein |
| NONHSAG060614 | LINC00595 | DHX36 | Q9H2U1 | protein |
| NONHSAG032603 | LINC01695 | ZMAT3 | Q9HA38 | protein |
| NONHSAG032603 | LINC01695 | SP1 | P08047 | protein |
| NONHSAG032603 | LINC01695 | IGF2BP3 | O00425 | protein |
| NONHSAG032603 | LINC01695 | SOX2 | P48431 | protein |
| NONHSAG032603 | LINC01695 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG032603 | LINC01695 | DHX36 | Q9H2U1 | protein |
| NONHSAG032603 | LINC01695 | DHX36 | Q9H2U1 | protein |
| NONHSAG020184 | LINC00311 | WDR33 | Q9C0J8 | protein |
| NONHSAG020184 | LINC00311 | TARDBP | A0A087WZM1 | protein |
| NONHSAG020184 | LINC00311 | HNRNPF | P52597 | protein |
| NONHSAG020184 | LINC00311 | CSTF2 | P33240 | protein |
| NONHSAG020184 | LINC00311 | RTCB | Q9Y3I0 | protein |
| NONHSAG020184 | LINC00311 | TIAL1 | E7ETC0 | protein |
| NONHSAG020184 | LINC00311 | TDP-43 | - | protein |
| NONHSAG020184 | LINC00311 | TARBP2 | Q15633 | protein |
| NONHSAG020184 | LINC00311 | RBM6 | P78332 | protein |
| NONHSAG020184 | LINC00311 | RBM10 | P98175 | protein |
| NONHSAG020184 | LINC00311 | MOV10 | P22626 | protein |
| NONHSAG020184 | LINC00311 | UPF1 | Q92900 | protein |
| NONHSAG020184 | LINC00311 | hnRNPA2B1 | O88569 | protein |
| NONHSAG020184 | LINC00311 | FUS | P35637 | protein |
| NONHSAG020184 | LINC00311 | CSTF2T | Q9H0L4 | protein |
| NONHSAG020184 | LINC00311 | FAM120A | Q9NZB2 | protein |
| NONHSAG020184 | LINC00311 | NCBP2 | P52298 | protein |
| NONHSAG020184 | LINC00311 | TAF15 | Q92804 | protein |
| NONHSAG020184 | LINC00311 | TIA1 | P31483 | protein |
| NONHSAG020184 | LINC00311 | AGGF1 | Q8N302 | tyein |
| NONHSAG020184 | LINC00311 | EWSR1 | Q01844 | protein |
| NONHSAG020184 | LINC00311 | DBHS | Q15233 | protein |
| NONHSAG020184 | LINC00311 | SLTM | Q9NWH9 | protein |
| NONHSAG020184 | LINC00311 | T2FA | P35269 | protein |
| NONHSAG020184 | LINC00311 | EIF2C1 | Q9UL18 | protein |
| NONHSAG020184 | LINC00311 | AGO2 | Q9UKV8 | protein |
| NONHSAG020184 | LINC00311 | AGO3 | Q9H9G7 | protein |
| NONHSAG020184 | LINC00311 | AGO4 | Q9HCK5 | protein |
| NONHSAG020184 | LINC00311 | FBL | P22087 | protein |
| NONHSAG020184 | LINC00311 | RBFOX2 | O43251 | protein |
| NONHSAG020184 | LINC00311 | HNRNPA1 | P09651 | protein |
| NONHSAG020184 | LINC00311 | U2AF2 | P26368 | protein |
| NONHSAG020184 | LINC00311 | PSF | P23246 | protein |
| NONHSAG020184 | LINC00311 | TRIM25 | Q14258 | protein |

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**Table 4** (continued)

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | UniProt ID | Type |
|---|---|---|---|---|
| NONHSAG020184 | LINC00311 | ZC3HAV1 | Q7Z2W4 | protein |
| NONHSAG020184 | LINC00311 | IGF2BP3 | O00425 | protein |
| NONHSAG020184 | LINC00311 | SOX2 | P48431 | protein |
| NONHSAG020184 | LINC00311 | FTO | Q9C0B1 | protein |
| NONHSAG020184 | LINC00311 | DHX36 | Q9H2U1 | protein |
| ENSG00000241213 | LINC02024 | ZC3HAV1 | Q7Z2W4 | protein |
| ENSG00000241213 | LINC02024 | SOX2 | P48431 | protein |
| ENSG00000241213 | LINC02024 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG006038 | LINC01515 | A1CF | Q9NQ94 | protein |
| NONHSAG006038 | LINC01515 | A1CF | Q9NQ94 | protein |
| NONHSAG006038 | LINC01515 | AIMP1 | Q12904 | protein |
| NONHSAG006038 | LINC01515 | EXOSC10 | Q01780 | protein |
| NONHSAG006038 | LINC01515 | FUBP1 | Q96AE4 | protein |
| NONHSAG006038 | LINC01515 | FUBP1 | Q96AE4 | protein |
| NONHSAG006038 | LINC01515 | KHDRBS2 | Q5VWX1 | protein |
| NONHSAG006038 | LINC01515 | KHDRBS2 | Q5VWX1 | protein |
| NONHSAG006038 | LINC01515 | METTL1 | Q9UBP6 | protein |
| NONHSAG006038 | LINC01515 | SCAF8 | Q9UPN6 | protein |
| NONHSAG006038 | LINC01515 | TRIM25 | Q14258 | protein |
| NONHSAG006038 | LINC01515 | USF2 | Q15853 | protein |
| NONHSAG006038 | LINC01515 | ZMAT3 | Q9HA38 | protein |
| NONHSAG006038 | LINC01515 | ZMAT3 | Q9HA38 | protein |
| NONHSAG006038 | LINC01515 | SP1 | P08047 | protein |
| NONHSAG006038 | LINC01515 | WDR4 | P57081 | protein |
| NONHSAG006038 | LINC01515 | CPSF1 | Q10570 | protein |
| NONHSAG006038 | LINC01515 | hnRNPD | Q14103 | protein |
| NONHSAG006038 | LINC01515 | Rbfox2 | O43251 | protein |
| NONHSAG006038 | LINC01515 | IGF2BP3 | O00425 | protein |
| NONHSAG006038 | LINC01515 | SNRPA | P09012 | protein |
| NONHSAG006038 | LINC01515 | RBMX | P38159 | protein |
| NONHSAG006038 | LINC01515 | SOX2 | P48431 | protein |
| NONHSAG006038 | LINC01515 | ELAVL1 | Q15717 | protein |
| NONHSAG006038 | LINC01515 | CPSF7 | Q8N684 | protein |
| NONHSAG006038 | LINC01515 | IGF2BP1 | Q9NZI8 | protein |
| NONHSAG006038 | LINC01515 | AGO2 | Q9UKV8 | Typein |
| NONHSAG006038 | LINC01515 | DHX36 | Q9H2U1 | protein |
| NONHSAG006038 | LINC01515 | DHX36 | Q9H2U1 | protein |
| NONHSAG006038 | LINC01515 | Rbfox1 | Q9NWB1 | protein |
| - | LINC00842 | QKI | Q96PU8 | protein |
| - | LINC00842 | SFRS2 | Q01130 | protein |
| - | LINC00842 | YTHDF1 | Q9BYJ9 | protein |
| - | LINC00842 | MBNL2 | Q5VZF2 | protein |
| - | LINC00842 | MOV10 | P22626 | protein |
| - | LINC00842 | YTDC1 | Q96MU7 | protein |
| - | LINC00842 | FBL | P22087 | protein |
| - | LINC00842 | ACIN1 | Q9UKV3 | protein |
| - | LINC00842 | HNRNPA1 | P09651 | protein |
| - | LINC00842 | UPF1 | Q92900 | protein |
| - | LINC00842 | DBHS | Q15233 | protein |

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**Table 4** (continued)

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | UniProt ID | Type |
|---|---|---|---|---|
| - | LINC00842 | PSF | P23246 | protein |
| - | LINC00842 | HDAC9 | Q9UKV0 | protein |
| - | LINC00842 | SMARCA4 | P51532 | protein |
| - | LINC00842 | EWSR1 | Q01844 | protein |
| NONHSAG005796 | LINC00842 | ADAR | P55265 | protein |
| NONHSAG005796 | LINC00842 | WDR33 | Q9C0J8 | protein |
| NONHSAG005796 | LINC00842 | SFRS1 | Q07955 | protein |
| NONHSAG005796 | LINC00842 | ELAVL1 | P70372 | protein |
| NONHSAG005796 | LINC00842 | AGO2 | Q8CJG0 | protein |
| NONHSAG005796 | LINC00842 | HNRNPU | Q00839 | protein |
| NONHSAG005796 | LINC00842 | CSTF2 | P33240 | protein |
| NONHSAG005796 | LINC00842 | hnRNPC | P07910 | protein |
| NONHSAG005796 | LINC00842 | TARBP2 | Q15633 | protein |
| NONHSAG005796 | LINC00842 | RBM6 | P78332 | protein |
| NONHSAG005796 | LINC00842 | RBM10 | P98175 | protein |
| NONHSAG005796 | LINC00842 | UPF1 | Q92900 | protein |
| NONHSAG005796 | LINC00842 | hnRNPA2B1 | O88569 | protein |
| NONHSAG005796 | LINC00842 | FUS | P35637 | protein |

The list shows Ensembl/NON CODE ID, LINCRNA and UniProt ID and type of the interacting components

Angiotensin II receptor agonists such as Losartan, Candersartan, etc. have been shown to reduce mortality in gastro-esophageal cancer patients [29]. Losartan and its analogs reduce the secretion of collagen I by interfering with transforming growth factor-β (TGF-β) signalling. This improves the delivery of chemotherapeutics to tumor cells [30, 31]. Ronespartat (SST0001), a heparanase inhibitor has shown promising results in inhibiting tumor growth when used alone or in combination at different phases of clinical trials [32, 33]. Considering the important role of Matrix Metalloproteinases (MMPs) and collagen cross-linkers in ECM remodelling several drugs have been tried to modulate MMP activity Ex: Incyclinide, JNJ0966, Fab 3369 [34–38]. However extreme caution has to be exercised while dealing with ECM as it can also promote metastases.

Several anti—angiogenic agents such as Bevacizumab, Apatinib, anti-VEGF antibodies in various combinations along with other chemotherapeutic agents such as paclitaxel and carboplatin have shown promising results in clinical trials (NCT02885753, NCT03100955). Multiple therapeutic strategies targeting the immune system, such as inhibition of macrophage recruitment and differentiation into the pro-tumoral TAMs Ex: anti-CSF-1R neutralizing antibodies or small molecule inhibitors, antibody anti-CD204, targeted-folate-receptor beta (FRβ) [39–41]; targeting chronic inflammation using IL-1R antagonists such as Anakinra (Kineret), anti-IL-1β monoclonal antibody [42, 43]; activating the anti-tumoral activity of the TME by used of GM-CSF [44], immune checkpoint therapies such as CTLA-4 and PD-1 [45, 46] have shown promise of better prognosis.

CAF being the most abundant cell type in the TME would be attractive targets for TME therapy. Fibroblast activation protein α (FAP), a membrane bound serine protease has been targeted for therapy in combination with a variety of drugs. However, these approaches have not been very successful. It is very likely due to the fact that FAP is not specific to CAFs, but also seen in normal fibroblasts. More qualitative and quantitative comparisons between normal and cancer associated fibroblasts are required to identify more effective ways of therapeutic targeting [47, 48]. Our study has tried to address this lacuna.

CAFs are distinguished from normal fibroblasts by their contractile characteristics, and metabolic and transcriptomic activity [49, 50]. Also, they are shown to express higher levels of FAP, alpha SMA and vimentin [49, 51, 52]. However, till date, there are no known unique markers of CAF. Identification of such markers becomes extremely essential if CAFs/derived factors are to be targeted for therapy, particularly because there are both pro- and anti-tumor properties of these factors. In this study, we have used the NGS platform to do a comparative analysis of fibroblasts derived from non-malignant (BPH) and cancerous prostate. This study has identified 818 genes differentially expressed between normal and

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**Table 5**  List of LINCRNAs interacting with ncRNAs

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | miRNA ID | Type |
|---|---|---|---|---|
| ENSG00000163364 | LINC01116 | miR-203 | MI0000283 | miRNA |
| ENSG00000163364 | LINC01116 | miR-3141 | MI0014165 | miRNA |
| ENSG00000163364 | LINC01116 | miR-744-5p | MI0005559 | miRNA |
| ENSG00000163364 | LINC01116 | miR-744-5p | MI0005559 | miRNA |
| ENSG00000163364 | LINC01116 | miR-3612 | MI0016002 | miRNA |
| ENSG00000163364 | LINC01116 | miR-744-5p | MI0005559 | miRNA |
| NONHSAG035677 | LINC00882 | miR-214-3p | MI0000290 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-mir-125a-3p | MI0000469 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-125b-5p | MI0000446 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-mir-150 | MI0000479 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-296-3p | MI0000747 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-4319 | MI0015848 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-455-3p | MI0003513 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-129-5p | MI0000252 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-129-2-3p | MI0000473 | miRNA |
| NONHSAG020184 | LINC00311 | hsa-miR-532-3p | MI0003205 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-1224-3p | MI0003764 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378a-5p | MI0000786 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378b | MI0014154 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378c | MI0015825 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378d | MI0016749 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378e | MI0016750 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378f | MI0016756 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378i | MI0016902 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-422a | MI0001444 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-665 | MI0005563 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-1197 | MI0006656 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-199a-5p | MI0000242 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-199b-5p | MI0000282 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-335-3p | MI0000816 | miRNA |
| NONHSAG005796 | LINC00842 | hsa-miR-378h | MI0016808 | miRNA |
| NONHSAG020184.2 | LINC00311 | SNHG4 | ENSG00000281398 | ncRNA |

The list shows Ensembl/NON CODE ID, LINCRNA and miRNA ID and type of the interacting components

cancer-associated fibroblasts. Also, there are 17 lncRNAs which show differential expression.

Long Intergenic Non-Coding RNAs (lincRNAs) are RNA molecules exceeding 200 nucleotides, lacking protein-coding functions and non-overlapping with annotated coding genes. They impact gene expression by modulating chromatin structure, regulating transcription of nearby and distant genes, and interacting with DNA, RNA, and proteins [53–55]. In cancer patients, differential lncRNA expression has been correlated with the overall survival (OS), metastasis, as well as tumor stage/grade [56–58]. LncRNAs have been detected in body fluids like plasma, serum, and urine using real-time PCR. One of the reasons lncRNAs are suitable as cancer diagnostic and prognostic biomarkers is their remarkable stability while circulating in body fluids, particularly

**Table 6**  List of LINCRNAs interacting with mRNAs

| NON CODE/ ENSEMBL ID | LINCRNA | Interacting Component | ENSEMBL ID | Type |
|---|---|---|---|---|
| ENSG00000163364 | LINC01116 | MYC | ENSG00000136997 | mRNA |
| NONHSAG020184.2 | LINC00311 | KIAA0513 | ENSG00000135709 | mRNA |

The list shows Ensembl/NON CODE ID, LINCRNA and type of the interacting components

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**Table 7** List of LINCRNA-miRNA-mRNA combinations

| LINCRNA | Log2FC (for LINCRNA) | miRNA | mRNA target | Log2FC (for mRNA) |
|---|---|---|---|---|
| LINC00882 | 1.812015961 | miR-214-3p | ATP2A3 | 3.024375 |
| | | | PIM1 | 1.596972 |
| | | | FBXO32 | 2.52126 |
| LINC00311 | -2.371344708 | hsa-mir-125a-3p | BRCA1 | -2.203512532 |
| | | | SH3TC2 | -2.060263012 |
| LINC00842 | -2.799537368 | hsa-miR-1224-3p | CDC25A | -2.958067112 |
| | | | KDR | -2.369999586 |
| | | | SLC4A8 | -1.72618536 |
| | | hsa-miR-199a-5p | HAPLN1 | -3.235820469 |
| | | hsa-miR-199b-5p | HAPLN1 | -3.235820469 |
| | | hsa-miR-335-3p | MCAM | -1.550103307 |
| | | | UTY | -1.526148211 |
| | | | CCDC85A | -3.03369872 |
| | | | KCNQ5 | -1.982236088 |
| | | | EPHA7 | -1.737844738 |

The list shows differentially expressed LINCRNA, relative fold change values of LINCRNA (Log$_2$FC (for LINCRNA)), miRNA, mRNA target and relative fold change values of target mRNA (Log$_2$FC (for mRNA)) in the same data set

when enclosed within exosomes or apoptotic bodies [59]. These characteristics of lncRNA make them attractive candidates for biomarkers. These biomarkers offer a minimally invasive alternative to conventional biopsies [60]. These markers can also be used to predict the prognosis of cancer patients, assess the risk of tumor metastasis and recurrence after surgery, and also to evaluate the success of therapeutic intervention. The distinct expression profiles of cancer-associated lncRNAs, which can vary significantly among different types of cancer, hold promise as efficient tumor biomarkers in various body fluids [57, 58, 61] (Supplementary Table 1 showing LncRNA as a prognostic and diagnostic marker in different cancers and Supplementary Fig. 3 showing tissue specific LNCRNA as potential biomarkers).

Despite the fact that lincRNAs are good biomarkers, targeting lincRNA or other ncRNA for therapeutic purposes have been extremely challenging. One of the reasons being very low conservation of lncRNAs across species. A small number of lncRNAs which are conserved between humans and mice have been discovered, while many human lncRNAs are absent in mice [62, 63].

Although it has been observed that lincRNAs show specific expression patterns in cancers, the heterogeneity in tumors makes it difficult to target them. Some studies have used in-silico approaches to identify lincRNA-miRNA-mRNA combinations. For example, a study has shown the influence of LOC101928304/miR-490-3p/LRRC2, a lincRNA-miRNA-mRNA axis on Atrial Fibrillation (AF). The levels of LOC101928304 and LRRC were elevated whereas miR-490-3p exhibited a decreased

expression in the myocardial tissue of AF patients [64]. However, there is not much experimental data available. Given the advantages of using lincRNAs as biomarkers and also the difficulties in targeting them for therapeutic intervention, identifying a combination of lincRNA-miRNA-mRNA may provide better options for targeting. In this study, we have predicted the targets of the differentially expressed lincRNAs and identified 15 lincRNA-miRNA-mRNA combinations. This would help in understanding the mechanism of action of these RNAs as well as identifying strategies for therapeutic targeting. However, this would in future need more experimental validation.

**Abbreviations**

| | |
|---|---|
| TME | Tumor microenvironment |
| CAFs | Cancer-associated fibroblasts |
| BPH | Benign Prostate Hyperplasia |
| LINCRNA | Non-Intergenic Non-Coding RNA |
| TCGA | The Cancer Genome Atlas |
| ECM | Extracellular matrix |
| TRUS | Transrectal Ultrasound Scan |
| TURP | Transurethral Resection of the Prostate |
| RPMI | Roswell Park Memorial Institute |
| PenStrep | Penicillin Streptomycin |
| RIN | RNA Integrity Number |
| ncRNA | Non-Coding RNA |
| LNCRNA | Long Non-Coding RNA |
| LINCRNA | Long-intergenic Non-Coding RNA |
| miRNA | MicroRNA |
| circRNA | CircularRNA |
| mRNA | Messenger RNA |
| FAP | Fibroblast Activation Protein |
| SMA | Smooth Muscle Actin |
| OS | Overall Survival |

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## Supplementary Information

Supplementary Material 1: Supplementary table 1: LNCRNAs as cancer prognostic and/or diagnostic marker. The table shows the type of cancer, LNCRNA involved, LNCRNA expression, and their relevance as prognostic or diagnostic markers [65–89]

Supplementary Material 2: Supplementary file. Shows the quality assessment of all the RNA samples using Tapestation

Supplementary Material 3: Supplementary Fig 1. RNA sequencing analysis workflow

Supplementary Material 4: Supplementary Fig 2. LINCRNA analysis workflow

Supplementary Material 5: Supplementary Fig 3 Tissue-specific LNCRNA as potential markers

### Clinical trial number
Not applicable.

### Availability of data and materials
The datasets generated and analyzed during this study are available on GEO, Accession Number GSE270705.

## Declarations

### Ethics approval and consent to participate
The study was approved by the Institutional Ethics Committee of both the participating institutions (CHG/077(b)/IEC/2019-20/001 and EC/01/2019). Informed consent has been obtained from all participants whose tissue samples have been used in this study. The identity of the patients has been kept confidential.
The study has been conducted in accordance with the Declaration of Helsinki. This study presented here was funded by the Indian Council for Medical Research, Govt of India (2019 – 0937), granted to PR.

### Consent for publication
Not applicable.

### Competing interests
The authors declare no competing interests.

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