Supplementary Materials

MMP1/PAR1/SP/NK1R paracrine loop modulates early perineural invasion of pancreatic cancer cells

Short title: MMP1 regulates early nerve invasion

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Methods

Cell lines

Human pancreas duct epithelia cell line hTERT-HPNE, human pancreatic cancer cell lines SW1990 and BXPC-3 were purchased from ATCC and maintained with DMEM containing 10% fetal bovine serum. All cells were incubated in 5% CO2 at 37°C.

Reagents

Primary antibodies: Anti-MMP1, anti-CK19 (rabbit monoclonal), anti-twist, anti-Neurokinin 1 receptor (rabbit polyclonal) were obtained from Abcam (Cambridge, USA). Anti-PAR1 and anti-Substance P (E-15) (all goat polyclonal) were purchased from Santa Cruz Biotechnology (Texas, USA). Anti-AKT, anti-pAKT, anti-ERK1/2, anti-pERK1/2, anti-vimentin (all rabbit monoclonal), anti-CD68 (mouse monoclonal) were purchased from Cell Signaling technology (Massachusetts, USA). Recombinant human MMP1 (MMP1) and Substance P (SP) were purchased from PeproTech (NJ, USA) and Sigma-Aldrich (Saint Louis, USA), respectively. ERK1/2 inhibitor U0126 and PI3K/Akt inhibitor LY294002 were purchased from Cell Signaling Technology. PAR 1 receptor antagonist SCH 79797 and NK1-R antagonist L-732,138 were obtained from TOCRIS Bioscience (Bristol, UK).

Phorbolmyristate acetate (PMA) was purchased from Sigma-Aldrich. Recombinant human interleukin-4 (IL-4) was purchased from PeproTech. Iron oxide nanoparticles (IONPs) was purchased from Ocean NanoTech company (Springdale, AR, USA). Potassium hexacyanoferrre(II) trihydrate was purchased from Nanhua Company (Hunan, China).

Migration and invasion assays
BD were used to perform migration and invasion assays. For migration assay, PANC-1 and MIA PaCa-2 cells with/without co-cultured with TAMs were harvested and re-suspended in DMEM media. 2×10^4 cells were seeded in the upper chamber. Then complete media or DMEM containing 3% FBS and 100nM SP with/without NK1R antagonist L-732,138 (100 μM) or ERK inhibitor U0126 (10nM) was added to the bottom chamber as attractants. After incubation for 24 hours at 37°C, the migrated cells at the bottom of the chamber were fixed with 4% paraformaldehyde, stained with 0.1% crystal Violet and then counted 6 random fields under ×200 magnification using microscope. The average number of cells of per chamber was represented. Experiments were repeated three times. For invasion assay, the membrane of transwell chamber was pre-coated with Matrigel, and the incubation time was 48 hours.

**Cell transfection**

Plasmid for human MMP1 (NM_002421.3) expression was constructed by Vigene Bioscience (Shandong, China). PANC-1 and Mia PaCa-2 cells were transiently transfected with the DNAs or vectors by use of Lipofectamine 2000 (Invitrogen) following the manufacturer’s protocol. The shRNA-MMP1 and shRNA-control plasmids were constructed and packaged into lentiviral virus vectors (GenePharma, Suzhou, China). For stable transfections, 2.5 ×10^5 PANC-1 cells per well were seeded in a six-well plate for 24 h. Cells were infected by LV3-shRNA-MMP1 and LV3-shRNA-control according to the manufacturer’s protocol. Cells were selected with 500ng/ml puromycin (Invitrogen, Carlsbad, CA, USA) over 4 weeks. The MMP1 mRNA expression levels of the positive cell clones that stably expressed shRNA-MMP1 or shRNA-control were then identified using qRT-PCR. The clones stably expressing shRNA-
MMP1 or shRNA-control were maintained in DMEM medium containing 500ng/ml of puromycin for further experiments.

**RT-PCR**

Total RNA was extracted from cells using Trizol (Invitrogen), reverse-transcribed to cDNA using PrimeScript TM RT Master Mix Kit (TaKaRa, Dalian, China). And quantitative real-time PCR was performed on the LightCycler480 Real-time PCR System (F. Hoffman-La Roche Ltd, Basel, Switzerland) using SYBRTM PrimeScript RT-PCR kit (TaKaRa).

**Western blot**

Cells and DRGs were lysed in RIPA contained protease inhibitor cocktail (1:100, ComWin biotech, Beijjing, China). Proteins were quantified referring to the instruction of BCA protein assay kit (Beyotime, Jiangsu, China). Proteins were separated by electrophoresis in 10% SDS-PAGE (Beyotime), transferred to polyvinylidene fluoride (PVDF) membranes (0.45μm, Merck Millipore, Darmstadt, Germany), incubated with primary antibody overnight at 4°C, and exposed to secondary antibody. Antibody binding was visualized by enhanced chemiluminescence (Merck Millipore).

**Prepare for DRGs**

Female BABL/c Mice (5±1 weeks) were euthanized with CO2 and sterilized with 75% ethanol. The spinal cords were separated from the spinal column, and DRGs beside the spinal cords were harvested 1.
**Immunofluorescent**

Cells and DRGs were fixed and incubated with NK-1R or PAR-1 primary antibody at 4°C overnight, respectively. Then the FITC-conjugated goat anti-rabbit or FITC-conjugated rabbit anti-goat secondary antibodies were added and incubated for 2 hours at room temperature. Nuclei were stained with DAPI. The Green fluorescent of FITC-labeled cells or DRGs was observed under fluorescence microscopy.

**Cytotoxicity of IONPs on cell viability**

To detect the cytotoxicity of IONPs on cell viability, PANC-1 cells were seeded in 96-well plates at the concentration of $5.0 \times 10^3$ per well in triplicate. After serum starvation for 12 hours, cells were growth in DMEM with different concentration of IONPs (0, 12, 24, 36, and 48 mg/L) in 5% CO$_2$ at 37°C for 8 hours. Then the cell viability was detected as described as the cell proliferation assay.

**MRI T2 values measurement of various concentration of IONP**

The 100μl volume of MDEM containing IONPs in different concentration (0, 12, 24, 36, and 48 mg/L) were placed in 96-well plates ordinal. MRI was performed using a 3.0T imaging system MAGNETOM Verio (Siemenz Medical System, Erlangen, Germany) with a 40 mm Loop Coils. T2-mapping sequence (repetition time 1500 msec, echo time beginning at 13.4ms, echo spacing of 13.4ms, eight echoes, slice thickness 2.0 mm) was performed and T2 value was calculated by system automatically.
Prussian blue staining

PANC-1 cells were seeded in 24-wells plates for 24 hours, then incubated with DMEM containing IONPs (0, 12, 24, 36, and 48 mg/L) for 8 hours. Media were removed and washed twice with PBS. The cells were fixed with 4% paraformaldehyde for 30min, and then reacted with the mixture of equal 2%ferrous potassium choide Potassium hexacyanoferrte (II) trihydrate (Nanhua Company, China, Hunan) and 6% muriatic acid in 30min. The number of staining cells were counted under fluorescent inverted microscope.

Operation process of in vivo model of murine sciatic nerve invasion

Mice were anesthetized with 4% chloral hydrate (85μl/10g, intraperitoneal injection) and diethyl ether inhalation. The left sciatic nerves were exposed deep to the femorococcygeous and biceps femorismusces, and then 3μl of cells mixture in PBS were slowly microscopically injected under the perineurium using a microliter syringe (Hamilton, 10μl, 33G). The concentration of PANC-1 cells was $1 \times 10^5/\mu l$ and TAMs concentration was $1 \times 10^4/\mu l$ (PANC-1/TAMs = 10:1). $1 \times 10^5/\mu l$ TAMs in a total volume of 3μl was injected under the perineurium to exclude the neoplastic proliferation of TAMs.

H&E and immunohistochemistry staining on tissue sections

The tissues were embedded in paraffin and sectioned into 3-4μm thick slices along the nerve for H&E and immunohistochemical staining. After sequential deparaffinization, antigen retrieval, background close, the slides were incubated with primary antibodies overnight at
4 °C. Then, secondary antibodies were dropped and incubated at 37°C for 15 minutes. At last, the sections were stained with the diaminobenzidine solution for 5 minutes and hematoxylin for 1 minute. We referred to the CAP (College of American Pathologists) Immunohistochemistry Survey MK system carrying out the semi quantitative analysis. The percentage of positive cells (PP) was divided as: 1 point (6-25% cells staining), 2 point (26-50% cells staining), 3 point (51-75% cells staining), and 4 point (over 75% cells staining). And the staining intensity (SI) was determined as: 0 (no staining); 1 point (weak staining); 2 point (moderate staining), and 3 point (strong staining). Added the PP and SI, we got the immunoreactive score (ISR). The IRS as defined into 4 groups: negative (0 point),1+ (2-3 point), 2+ (4-5 point), and 3+ (6-7 point).

References:

1. Ayala GE, Wheeler TM, Shine HD, et al. In vitro dorsal root ganglia and human prostate cell line interaction: redefining perineural invasion in prostate cancer. Prostate. 2001; 49: 213-23.
Figure Legends

Figure S1. (A) Morphology and immunotype of U937 monocytes changed to TAMs after induction. Before treatment, the U937 cells are circle morphology and suspended growth under microscope. After incubation with IL-4 and PMA, cells emerged pseudopodia and began to half-adherence. Immunophenotype analyzed with qPCR showed that CD68 and CD163 expression up-regulated. (B) After co-culture with TAMs, the migration and invasion abilities of PANC-1 and Mia PaCa-2 cells were enhanced. (C) After co-culture with TAMs, the perineural invasion abilities of PANC-1 and Mia PaCa-2 cells were enhanced. (D) The MMP1 mRNA upregulated significantly after MMP1-expression vector transfection and downregulated significantly after shMMP1 vector transfection both in PANC-1 and Mia PaCa-2 cells. The upregulation of MMP1 protein was detected by ELISA. Data showed as mean±SD. ** P<0.01, and *** P<0.001 compared with control.

Figure S2. Assessment of PAR1 expression in neuron and NK1R expression in pancreatic cancer cell lines. (A) The expression of PAR1 in neurons in PDAC tissues was observed using H&E staining and IHC. The expression of PAR1 in DRGs separated from mice were observed using immunofluorescence assay. (B) PAR1 and NK1R protein expression in neuron and pancreatic cell lines were evaluated by western blot assay. Both pancreatic cancer cells and DRG expressed PAR1 and NK1R. DRGs expressed high level of PAR1 protein, and pancreatic cancer cells PANC-1, Mia Paca2, SW1990, and Bxpc-3 expressed high levels of NK1R. Whereas immortalized human pancreas duct epithelia cell line hTERT-HPNE (H-H) didn’t express PAR1 or NK1R. (C) In PANC-1 and Mia Paca-2 cells, immunofluorescence assay
exhibited that NK1R protein was expressed in the cytoplasm and on the cell membrane.

**Figure S3.** (A) SP induced phosphorylation of ERK both in PANC-1 and Mia PaCa-2 cells. SP upregulated Vimentin and TWIST1 expression both in PANC-1 (B) and Mia PaCa-2 cells (C), whereas the NK1R antagonist SP+L-732,138 and U0126 (ERK pathway inhibitor) attenuated the phosphorylation of ERK, indicating that SP enhanced pancreatic cancer cells EMT via SP/NK1R/ERK pathway. Data showed as mean±SD. * P<0.05, and ** P<0.01 compared with 0 minute in (A) and with control in (B and C). ΔP<0.05 compared to the SP+L-732,138 group.

**Figure S4.** (A) The histologic immunochemical staining of tumor sections from mice injected with PANC-1+TMAs exhibited CK19\(^+\) and CD68\(^-\). (B) Mice injected with TAMs alone didn’t exhibit paralysis. In surgical images, there was not any neoplastic growth, or any changes in nerve caliber was observed. (C) H&E staining of nerve sections did not show any neoplasm invasion. All the above results excluded TAMs proliferation. (D) PANC-1 cells were pre-co-cultured with TAMs for 24 hours in vitro, then collected and injected into perineurium of left sciatic nerves. Even TAMs were not maintained in the inoculation microenvironment, transient co-culture with TAMs robustly enhanced the nerve invasion and migration ability of PANC-1 cells.

**Figure S5.** Labeling PANC-1 cells with IONPs. (A) Endocytosis of IONPs in PANC-1 cells. Eight hours after incubation with IONPs, Prussian-blue staining was performed. Blue
particles scattered in the cells plasma represented the up-taken IONPs. (B) MR signals changed with various IONPs concentrations. As a negative MRI contrast agent, the T2-signal value decreased with the increased concentration of IONPs. (C) MTS assay exhibited that IONPs did not affect cell viability apparently when used at the concentration ranging from 0 ~ 48 mg/L.
Figure S1
Figure S2

A

PDAC tissue

H&E

PAR-1

100 μm

100 μm

DRG

Bright

PAR-1

100 μm

100 μm

B

| Cell Line | NK1R | PAR1 | GAPDH |
|-----------|------|------|-------|
| HH        |      |      |       |
| BxPc-3    |      |      |       |
| PANC-1    |      |      |       |
| SW1990    |      |      |       |
| Mia PaCa-2|      |      |       |

45 kDa

47 kDa

37 kDa

C

Mia PaCa-2

NK-1R

DAPI

Merge

100 μm

100 μm

PANC-1

100 μm

100 μm

100 μm
Figure S3
Figure S4
Figure S5

A

B

C

Cell viability (%)
Table S1. The sequences of primers and shRNA

| Gene        | Sequence                                      |
|-------------|-----------------------------------------------|
| CD68 primers| forward 5’- GACCCACGACTGCCACTC-3’            |
|             | reverse 5’- GTGCTGTTGCTTGGATG-3’             |
| CD163       | forward 5’- CGAGTT AACGCCAGTAAGG-3’          |
| primers     | reverse 5’- GAACATGTCACGCCAGC-3’             |
| MMP1        | forward 5’- ACACGCCAGATTGCCAAGAGC-3’         |
| primers     | reverse 5’- GGAGAGTTGT CCCGATGATCTCCCC-3’    |
| MMP2        | forward 5’- GATGATGCTTTGCTCGTG-3’           |
| primers     | reverse 5’- CAAAGGGGTATCCACGCCA-3’           |
| MMP9        | forward 5’- CAAA GGGGTATCCACGCCA-3’          |
| primers     | reverse 5’- TCGTAGTTGCGGTCTG-3’              |
| GAPDH       | forward 5’- AAGGTGAAGGTCTGGAGTC AAC-3’      |
| primers     | reverse 5’- CATGAGTCCTCCACAGTACC-3’         |
| MMP1        | 5’- CTGACCTACAGGATTGAAA-3’                   |
| shRNA       |                                              |
| LV3-NC      | 5’- TTCTCCGAACGTGTCACGTTTC-3’                |
Table S2. All gene and the relative expression assessed in the array

| GenbankAccession | GeneSymbol | foldchange | type |
|------------------|------------|------------|------|
| NM_001039500     | VWA5B1     | 340.5143   | mRNA |
| NM_152423        | MUM1L1     | 285.5048   | mRNA |
| S75894           |            | 242.7293   | mRNA |
| NM_002043        | GABRR2     | 236.6134   | mRNA |
| NM_002421        | MMP1       | 155.7959   | mRNA |
| NM_152337        | C16orf46   | 151.7916   | mRNA |
| BX097862         | XLOC_12_013506 | 149.8562 | mRNA |
| AK098312         | IL20RA     | 136.3074   | mRNA |
| NM_001199219     | INMT       | 89.87091   | mRNA |
| NM_175878        | XKR3       | 78.90831   | mRNA |
| AK098398         | HMP19      | 73.29284   | mRNA |
| DB550107         | XLOC_12_008396 | 69.2853 | mRNA |
| NM_016383        | LUZP4      | 64.80661   | mRNA |
| D13078           |            | 64.78482   | mRNA |
| NM_001195272     | LOC100129520 | 63.58293 | mRNA |
| NM_181610        | KRTAP19-4  | 60.12266   | mRNA |
| AK092754         | SPATA13    | 59.95894   | mRNA |
| NM_000735        | CGA        | 53.80423   | mRNA |
| NR_028045        | KLRAP1     | 52.48699   | mRNA |
| NM_005118        | TNFSF15    | 52.25233   | mRNA |
| NM_000840        | GRM3       | 52.1503    | mRNA |
| XM_001714987     | ARMCX3-AS1 | 46.9051    | mRNA |
| AK131244         | AKD1       | 44.94223   | mRNA |
|                 |            | 42.60285   | mRNA |
| AK093200         | XLOC_001259 | 42.13821 | mRNA |
| NM_002585        | PBX1       | 41.31057   | mRNA |
| NM_001144058     | NTM        | 40.67006   | mRNA |
| NM_001004440     | FAM19A3    | 39.99677   | mRNA |
| NM_007038        | ADAMTS5    | 39.68226   | mRNA |
| NM_144992        | VWA3B      | 39.50031   | mRNA |
| NM_001004472     | OR10R2     | 38.72748   | mRNA |
| JN120858         |            | 36.37209   | mRNA |
| NR_033945        | LOC647107  | 36.07351   | mRNA |
| NM_198687        | KRTAP10-4  | 34.67572   | mRNA |
| NM_001085420     | PLSCR5     | 34.1537    | mRNA |
| BX100197         |            | 33.92456   | mRNA |
| BC031871         | CSMD2      | 33.24908   | mRNA |
| EU154352         |            | 31.40358   | mRNA |
| NM_003154        | STATH      | 29.86743   | mRNA |
| Gene ID          | Gene Symbol | Expression Value | mRNA   |
|------------------|-------------|------------------|--------|
| NM_001005286     | OR6F1       | 29.55381         | mRNA   |
| NM_001193502     | TCF24       | 29.4981          | mRNA   |
|                  |             | 29.12926         | mRNA   |
| BC008001         | XLOC_003427 | 28.98743         | mRNA   |
| NM_003264        | TLR2        | 27.91328         | mRNA   |
| AK130276         |             | 26.58965         | mRNA   |
| NM_001114734     | PABPC4L     | 26.12827         | mRNA   |
|                  |             | 25.71948         | mRNA   |
| NM_001136002     | TMEM229A    | 24.66118         | mRNA   |
| NM_176817        | TAS2R38     | 24.60632         | mRNA   |
| XM_291007        | HEATR7B1    | 24.26947         | mRNA   |
| NM_173857        | VN1R4       | 23.84094         | mRNA   |
| NM_198795        | TDRD1       | 23.14781         | mRNA   |
|                  |             | 22.59221         | mRNA   |
| NM_000040        | APOC3       | 19.6467          | mRNA   |
| AK127184         | LOC100131129| 19.58904         | mRNA   |
| NM_152402        | TRAM1L1     | 19.53713         | mRNA   |
| NM_145259        | ACVR1C      | 19.53134         | mRNA   |
| NR_038239        | LOC100507629| 19.35226         | mRNA   |
| NR_033460        | PAGE3       | 19.15738         | mRNA   |
| NM_001035256     | POMC        | 19.05149         | mRNA   |
| NM_001204118     | CLEC17A     | 18.96375         | mRNA   |
| NM_020663        | RHOJ        | 18.65978         | mRNA   |
| NM_001013355     | OR2G6       | 18.53143         | mRNA   |
| NM_002196        | INSM1       | 18.29421         | mRNA   |
| NM_014058        | TMPRSS11E   | 18.23555         | mRNA   |
| BC019904         | XLOC_009358 | 18.03082         | mRNA   |
| NM_001906        | CTRB1       | 17.49797         | mRNA   |
| NM_016540        | GPR83       | 16.89886         | mRNA   |
| NR_003581        | ATP8B5P     | 16.6394          | mRNA   |
| NM_000379        | XDH         | 16.44097         | mRNA   |
| AK125988         | XLOC_004040 | 16.24305         | mRNA   |
| NM_016734        | PAX5        | 16.01752         | mRNA   |
|                  |             | 15.5648          | mRNA   |
| XR_109007        |             | 15.49039         | mRNA   |
| AK124269         | BAIAP2L1    | 15.31691         | mRNA   |
|                  |             | 14.86324         | mRNA   |
| NM_014395        | DAPP1       | 14.33479         | mRNA   |
| NR_001564        | XIST        | 14.01264         | mRNA   |
| NM_002121        | HLA-DPB1    | 13.97449         | mRNA   |
| NM_001004463     | OR10G7      | 13.70065         | mRNA   |
| NM_001080523     | ARRDC5      | 13.57659         | mRNA   |
| Gene ID       | Gene Symbol | mRNA | Exp. Value |
|--------------|-------------|------|------------|
| NM_006668    | CYP46A1     | mRNA | 13.5662    |
| NM_033181    | CNR1        | mRNA | 13.4172    |
| NR_033923    | C10orf136   | mRNA | 13.3593    |
| NR_027455    | LOC100131434| mRNA | 13.2365    |
| NM_175737    | KLB         | mRNA | 13.1259    |
| NM_001113523 | PARP15      | mRNA | 13.0691    |
| AK127982     |             | mRNA | 12.9618    |
| NR_038919    | LOC100128993| mRNA | 12.8378    |
| NM_001192    | TNFRSF17    | mRNA | 12.4277    |
| BC036297     | FLJ45983    | mRNA | 12.3999    |
|              |             | mRNA | 12.0339    |
| NM_001136219 | FCGR2A      | mRNA | 11.7522    |
| NM_000584    | IL8         | mRNA | 11.7115    |
| NM_006871    | RIPK3       | mRNA | 11.6045    |
| NM_000128    | F11         | mRNA | 11.4407    |
| NM_004666    | VNN1        | mRNA | 11.3285    |
|              |             | mRNA | 11.1578    |
| NM_032126    | C1orf49     | mRNA | 11.0263    |
| BF229395     | XLOC_12_007096| mRNA | 11.0216    |
| AY181245     | EMR4P       | mRNA | 10.9763    |
| NR_036519    | C17orf62    | mRNA | 10.8413    |
| NM_031440    | RTP3        | mRNA | 10.8277    |
|              |             | mRNA | 10.7593    |
| NR_036676    | IFNA22P     | mRNA | 10.7174    |
| AY766452     |             | mRNA | 10.6950    |
| NM_178434    | LCE3C       | mRNA | 10.6724    |
| BC035381     | XLOC_12_003414| mRNA | 10.6656    |
| NR_038839    | LOC645355   | mRNA | 10.2635    |
| CR749827     | MEIS1       | mRNA | 10.2036    |
| BX648982     | DNAJC16     | mRNA | 10.1833    |
| AK125887     | XLOC_007813 | mRNA | 9.8503     |
| NM_002425    | MMP10       | mRNA | 9.7774     |
| NM_001771    | CD22        | mRNA | 9.7593     |
| NR_015392    | FLJ40852    | mRNA | 9.6223     |
| NM_173550    | C9orf93     | mRNA | 9.6175     |
| NR_038434    | LOC100506474| mRNA | 9.5606     |
| NM_024726    | IQCA1       | mRNA | 9.3901     |
| NR_036445    | OR5AK4P     | mRNA | 9.3727     |
|              |             | mRNA | 9.2736     |
| NM_206965    | FTCD        | mRNA | 9.2604     |
| NR_034007    | LOC339894   | mRNA | 9.2509     |
| Gene ID       | Gene Symbol   | Expression | Type  |
|--------------|---------------|------------|-------|
| BC143323     | SLC17A2       | 9.21982    | mRNA  |
| BC042433     | XLOC_12_010586| 9.119917   | mRNA  |
| NR_036444    | LOC400550     | 9.082806   | mRNA  |
| NM_012072    | CD93          | 9.039419   | mRNA  |
| NM_001511    | CXCL1         | 8.807594   | mRNA  |
| NM_003155    | STC1          | 8.734215   | mRNA  |
| NM_001086    | AADAC         | 8.671047   | mRNA  |
| NM_032972    | PCDH11Y       | 8.590037   | mRNA  |
| NR_040105    | FLJ46066      | 8.367218   | mRNA  |
| NM_001141919 | XG            | 8.356159   | mRNA  |
| NM_021226    | ARHGAP22      | 8.351188   | mRNA  |
| BU570946     | XLOC_12_002271| 8.281887   | mRNA  |
| NR_026860    | LINC00473     | 8.177215   | mRNA  |
| NR_034115    | LOC729178     | 8.154344   | mRNA  |
| NM_014334    | C9orf4        | 8.1444     | mRNA  |
| AA454051     | XLOC_013796   | 8.122709   | mRNA  |
| NM_001195685 | LYPD6         | 8.10247    | mRNA  |
| AW630386     | XLOC_004430   | 8.013116   | mRNA  |
| AF547222     | LOC280665     | 7.975397   | mRNA  |
| NM_024785    | FAM124B       | 7.962754   | mRNA  |
| NM_030773    | TUBB1         | 7.946062   | mRNA  |
| NR_038388    | LOC729444     | 7.92778    | mRNA  |
| NM_000576    | IL1B          | 7.789523   | mRNA  |
| NR_027180    | MIR143HG      | 7.789169   | mRNA  |
|             | XLOC_12_013530| 7.709632   | mRNA  |
| AF090909     |               | 7.64863    | mRNA  |
| NR_027755    | LOC283867     | 7.607934   | mRNA  |
| NM_001079821 | NLRP3         | 7.558229   | mRNA  |
| NM_001163942 | ABCB5         | 7.532249   | mRNA  |
| XM_003403528 | CC2D2B        | 7.314153   | mRNA  |
| NM_005739    | RASGRP1       | 7.241734   | mRNA  |
| NM_001136566 | RAD21L1       | 7.213057   | mRNA  |
| NM_033066    | MPP4          | 7.174349   | mRNA  |
| AK090740     | MOV10L1       | 7.134998   | mRNA  |
| NM_001033677 | CABP1         | 7.078471   | mRNA  |
| NR_024593    | POM121L10P    | 7.060264   | mRNA  |
| XR_133539    |               | 7.017862   | mRNA  |
| NM_002089    | CXCL2         | 7.015612   | mRNA  |
| NM_182833    | GDPD4         | 7.005675   | mRNA  |
| NM_001077693 | ECSCR         | 6.963085   | mRNA  |
| NM_138999    | NETO1         | 6.952688   | mRNA  |
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| NM_019074  | DLL4     | 6.859059       | mRNA  |
| NM_133379  | TTN      | 6.748047       | mRNA  |
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| CF127220   | XLOC_007571 | 6.595033       | mRNA  |
| NM_031469  | SH3BGR2  | 6.541903       | mRNA  |
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| NM_001944  | DSG3     | 6.483878       | mRNA  |
| NM_001898  | CST1     | 6.482694       | mRNA  |
| NM_002432  | MND A    | 6.409205       | mRNA  |
| NM_01204352| SPOCK3   | 6.390028       | mRNA  |
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| AL389942   |          | 6.330248       | mRNA  |
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| NM_001340  | CYLC2    | 6.229466       | mRNA  |
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| NM_004591  | CCL20    | 6.055236       | mRNA  |
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| NM_022162  | NOD2     | 6.026683       | mRNA  |
| NM_203303  | ZCCHC13  | 5.977514       | mRNA  |
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| NM_006851  | GLIPR1   | 5.906463       | mRNA  |
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| NM_005282 | GPR4            | 4.615203   | mRNA |
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| NR_040112 | A2MP1           | 4.58104    | mRNA |
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| NM_001290 | LDB2            | 4.123986   | mRNA |
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| NM_015166 | MLC1            | 4.054658   | mRNA |
| NM_022349 | MS4A6A          | 3.964396   | mRNA |
| NM_018891 | LAMC2           | 3.960707   | mRNA |
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| NM_152672  | OSTalpha | 3.237616   |
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| NM_001025195 | CES1        | 3.040172 | mRNA |
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| NM_152908    | PCDHB10     | 3.016579 | mRNA |
| NM_002770    | PRSS2       | 2.997509 | mRNA |
| NM_000632    | ITGAM       | 2.988319 | mRNA |
| NM_007210    | GALNT6      | 2.979888 | mRNA |
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| NM_022842    | CDCP1       | 2.969642 | mRNA |
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| NM_004918    | TCL1B       | 2.945296 | mRNA |
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| BC033823  | DNAJC3      | 2.582146 mRNA    |
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| BC069031  | CAPZB       | 2.579237 mRNA    |
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| NM_002009 | FGF7        | 2.472532 mRNA    |
| NR_026947 | MATL2963    | 2.4717 mRNA      |
| NM_006167 | NKX3-1      | 2.467941 mRNA    |
| NM_153353 | LRRRC34     | 2.465769 mRNA    |
| NM_001005176 | SP140 | 2.46292 mRNA |
| NM_000916 | OXTR        | 2.45232 mRNA     |
| NM_000678 | ADRA1D      | 2.450529 mRNA    |
| NM_022375 | OCLM        | 2.448367 mRNA    |
| NM_005263 | GFI1        | 2.446399 mRNA    |
| NM_004049 | BCL2A1      | 2.445806 mRNA    |
| NR_003199 | SNORD114-7  | 2.444214 mRNA    |
| U88300    | XLOC_006404 | 2.43584 mRNA     |
| NM_014751 | MTSS1       | 2.432162 mRNA    |
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| NM_001145720   | ZBTB8B        | 2.431823    | mRNA            |
| BG192435       | XLOC_12_013530| 2.429597    | mRNA            |
| AK124891       | LOC100131654  | 2.422045    | mRNA            |
| NM_001012633   | IL32          | 2.420966    | mRNA            |
| NM_198529      | EFCAB5        | 2.415801    | mRNA            |
| NM_001165252   | LOC730755     | 2.413379    | mRNA            |
| NM_000428      | LTBP2         | 2.410868    | mRNA            |
| NM_004133      | HNF4G         | 2.408587    | mRNA            |
| NM_001205288   | LIMS3L        | 2.406046    | mRNA            |
| BC136808       |               | 2.406024    | mRNA            |
| NM_203330      | CD59          | 2.405792    | mRNA            |
| NM_001077244   | GRIA4         | 2.403201    | mRNA            |
| BC040855       | XLOC_010962   | 2.399689    | mRNA            |
| NM_003484      | HMGA2         | 2.397414    | mRNA            |
| NM_080801      | COL13A1       | 2.394201    | mRNA            |
| AJ312026       |               | 2.392999    | mRNA            |
| XM_003403404   | LOC100653051  | 2.377865    | mRNA            |
| NM_020344      | SLC24A2       | 2.372177    | mRNA            |
| NR_038436      | LOC145216     | 2.371689    | mRNA            |
| NM_173216      | ST6GAL1       | 2.371416    | mRNA            |
| NM_001170      | AQP7          | 2.369831    | mRNA            |
| NM_000640      | IL13RA2       | 2.369069    | mRNA            |
| XM_003403831   |               | 2.367213    | mRNA            |
| NM_006509      | RELB          | 2.366722    | mRNA            |
| NM_001013642   | TRNP1         | 2.365891    | mRNA            |
| NM_000212      | ITGB3         | 2.357236    | mRNA            |
| NM_002727      | SRGN          | 2.35228     | mRNA            |
| AF274942       |               | 2.351999    | mRNA            |
| NM_001668      | ARNT          | 2.349201    | mRNA            |
| NM_001003940   | BMF           | 2.348486    | mRNA            |
| BC040220       | LOC399875     | 2.346778    | mRNA            |
| NM_207506      | SAMD12        | 2.346339    | mRNA            |
| AK090485       |               | 2.342254    | mRNA            |
| AK000925       | RUFY2         | 2.338729    | mRNA            |
| AF264626       | LOC57399      | 2.334659    | mRNA            |
| NR_040050      | LOC100507351  | 2.333493    | mRNA            |
| NM_012073      | CCT5          | 2.331735    | mRNA            |
| BC020828       | RPL36AP33     | 2.32863     | mRNA            |
| AK129846       |               | 2.328187    | mRNA            |
| NM_001010917   | GOLGA7B       | 2.323221    | mRNA            |
| NM_005297      | MCHR1         | 2.322488    | mRNA            |
| NM_138961      | ESAM          | 2.319287    | mRNA            |
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| NR_003111  | RPL32P3     | 2.313239 mRNA |
| NM_006307  | SRPX        | 2.310348 mRNA |
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| NM_019060  | CRCT1       | 2.291655 mRNA |
| AK303870   | THSD4       | 2.289755 mRNA |
| NM_174932  | BPIFC       | 2.280021 mRNA |
| NM_001965  | EGR4        | 2.27718 mRNA |
| NM_002852  | PTX3        | 2.276701 mRNA |
| AK057247   | NEK10       | 2.274833 mRNA |
| NM_145007  | NLRP11      | 2.267307 mRNA |
| NM_183242  | BTBD8       | 2.267209 mRNA |
| NM_000347  | SPTB        | 2.267188 mRNA |
| NM_001039380 | C10orf25   | 2.267073 mRNA |
| NM_002546  | TNFRSF11B   | 2.266052 mRNA |
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| NM_005429  | VEGFC       | 2.254998 mRNA |
| NM_178140  | PDZD2       | 2.246742 mRNA |
| NM_005114  | HS3ST1      | 2.244973 mRNA |
| CR624373   | XLOC_007867 | 2.24238 mRNA |
| NM_139165  | RAET1E      | 2.241765 mRNA |
| NM_152753  | SCUBE3      | 2.241099 mRNA |
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| NR_026813  | C15orf5     | 2.238506 mRNA |
| NM_139314  | ANGPTL4     | 2.23843 mRNA |
| NM_015714  | G0S2        | 2.227522 mRNA |
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| NM_001003927 | EVI2A     | 2.220987 mRNA |
| NM_033428  | C9orf123    | 2.219907 mRNA |
| NM_000506  | F2          | 2.217818 mRNA |
| AL390167   | XLOC_12_003909 | 2.213328 mRNA |
| AF220234   | GAFA2       | 2.20996 mRNA |
| NM_145015  | MRGPRF      | 2.2096 mRNA |
| NM_001040442 | FABP6     | 2.209054 mRNA |
| NR_034119  | LINC00460   | 2.206531 mRNA |
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| NM_001195790 | SLFN12L   | 2.203564 mRNA |
| NM_152888  | COL22A1     | 2.203103 mRNA |
| NM_001198832 | PDE4DIP   | 2.202224 mRNA |
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| NM_018018  | SLC38A4     | 2.198009 mRNA |
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| AK024925  | XLOC_12_009181 | 2.196099 mRNA |
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| NM_015364 | SAA1        | 2.190554 mRNA |
| NM_000331 | DNAH5       | 2.190493 mRNA |
| NM_001369 | VWA5B2      | 2.189204 mRNA |
| AK092544  | LOC100131581| 2.186434 mRNA |
| NM_001039664| TNFRSF25  | 2.184652 mRNA |
| BC043212  | EFHB        | 2.183872 mRNA |
| NM_144727 | CRYGN       | 2.17872 mRNA |
| NM_006988 | SYTL3       | 2.178549 mRNA |
| NM_001009991| ADAMTS1    | 2.175541 mRNA |
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| NM_002769 | PRSS1       | 2.169095 mRNA |
| AV726231  | XLOC_012709 | 2.168161 mRNA |
| BC035739  | AGBL4       | 2.166407 mRNA |
| NM_017821 | RHBDL2      | 2.165725 mRNA |
| NM_001080492| PRSS54    | 2.163 mRNA |
| BX280888  | XLOC_005228 | 2.162358 mRNA |
| AF113122  | KLF12       | 2.155968 mRNA |
| NR_003223 | SNORD114-30 | 2.154124 mRNA |
| AA593742  | GPR114      | 2.152358 mRNA |
| AK096092  | FLJ38773    | 2.148231 mRNA |
| NM_002363 | MAGEB1      | 2.14705 mRNA |
| NM_032464 | LAT2        | 2.145853 mRNA |
| NM_005658 | TRAF1       | 2.143728 mRNA |
| NM_025243 | SLC19A3     | 2.142782 mRNA |
| DA110513  | TRPA1       | 2.138912 mRNA |
| NM_182614 | FAM70B      | 2.137982 mRNA |
| BC043536  | XLOC_008143 | 2.134401 mRNA |
| NM_007332 | TRPA1       | 2.130276 mRNA |
| NR_003118619| LOC100507445| 2.125606 mRNA |
| NM_198828 | MAST4       | 2.124108 mRNA |
| NM_134260 | RORA        | 2.121647 mRNA |
| NM_001657 | AREG        | 2.121242 mRNA |
| NM_003202 | TCF7        | 2.120664 mRNA |
| NR_024497 | LOC399744   | 2.119199 mRNA |
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| NM_080622    | ABHD16B         | 2.115083    |
| NM_019854    | PRMT8           | 2.113572    |
| NR_038856    | LOC100506810    | 2.111187    |
| NM_004354    | CCNG2           | 2.111024    |
| NM_182607    | VSIG1           | 2.109732    |
| NM_004624    | VIPR1           | 2.100222    |
| NM_024009    | GJB3            | 2.092583    |
| AK128128     | LOC100128348    | 2.091306    |
| NM_144718    | SPICE1          | 2.091045    |
| BC000189     | OLFM1           | 2.089607    |
| NM_023112    | OTUB2           | 2.082491    |
| NR_015410    | LINC00340       | 2.082055    |
| BG192758     |                 | 2.080761    |
| NM_002842    | PTPRH           | 2.07528     |
| NR_027002    | LOC388692       | 2.074731    |
| NM_001001786 | BLID            | 2.073993    |
| NM_007352    | CELA3B          | 2.07356     |
| NM_002923    | RGS2            | 2.071924    |
| AL512720     | DKFZp547J222    | 2.069399    |
| NM_000494    | COL17A1         | 2.069244    |
| CR738035     | XLOC_013578     | 2.066837    |
| NR_026915    | LOC201651       | 2.065149    |
| NM_001127464 | ZNF469          | 2.064132    |
| NR_003229    | SNORD113-1      | 2.061       |
| NR_026991    | H1FX-AS1        | 2.060093    |
| NR_002938    | LOC284379       | 2.055676    |
| XM_001719518 | LOC100128869    | 2.054113    |
| NM_138729    | ST7L            | 2.052951    |
| NM_205856    | SPACA5          | 2.050813    |
| XM_003403456 | LOC100652857    | 2.050529    |
| AL122087     | LOC221814       | 2.048015    |
| NM_145352    | SCARF1          | 2.047887    |
| NR_027156    | TUBBP5          | 2.046393    |
| BG189643     | XLOC_000627     | 2.041425    |
| NM_002205    | ITGA5           | 2.041186    |
|              | SLC22A2         | 2.040564    |
| NR_003222    | SNORD114-29     | 2.039749    |
| NR_038402    | LOC100507387    | 2.039711    |
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| NM_080388  | S100A16    | 2.039058   |
| NM_030924  | ACSBG2     | 2.034004   |
| AK021772   | FLJ11710   | 2.032464   |
| NR_003327  | SNORD116-12| 2.031366   |
| NM_172374  | IL4I1      | 2.030200   |
| NR_003232  | SNORD113-4 | 2.02875    |
| XM_001719518| LOC100128869| 2.025644  |
| BC040718   | DLGAP1     | 2.023824   |
| NM_001162893| KIAA0040    | 2.023002   |
| BX106239   | XLOC_003095| 2.022614   |
| AB231701   | OOSP1      | 2.019606   |
| NR_038239  | LOC100507629| 2.019237  |
| NM_001040432| ZCWPW2    | 2.015349   |
| AK124002   | LOC100131829| 2.013525  |
| NM_032449  | CC2D1B     | 2.011527   |
| AK096995   | LOC729558  | 2.009802   |
| BC063596   | PTPRK      | 2.009038   |
| NM_002619  | PF4        | 2.008041   |
| AK024142   | XLOC_i2_007644 | 2.007133 |
| NM_012194  | C11orf41   | 2.005668   |
| NM_012194  | CACNA1B    | 2.005106   |
| AL050097   | DKFZP586B0319 | 2.000449  |
| AF150244   |            | 0.499922   |
|            |            | 0.499729   |
| NM_00683   | ADRA2C     | 0.498468   |
| XM_003403734| LOC100653094| 0.49765   |
| AK054818   | C1orf86    | 0.49665    |
| NM_001856  | COL16A1    | 0.496038   |
| NM_152539  | C3orf30    | 0.493987   |
| NM_080658  | ACY3       | 0.493817   |
| NM_001136572| FAM90A7    | 0.49302    |
| NM_012114  | CASP14     | 0.492596   |
| NM_182536  | GKN2       | 0.491991   |
|            | FERMT1     | 0.491784   |
| NM_006552  | SCGB1D1    | 0.491736   |
| AK090887   | SFMBT2     | 0.49132    |
| XLOC_004308|            | 0.489806   |
| NM_020777  | SORCS2     | 0.489228   |
| NM_152401  | PDCL2      | 0.488619   |
| AK301084   | WDR45      | 0.48845    |
| NM_152762  | TSGA10IP   | 0.48809    |
| AK160370   | PHF12      | 0.488042   |
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| AK126462 | CLDN4 | 0.485673 | mRNA |
| AX794781 | MTHFD2L | 0.485242 | mRNA |
| NM_053027 | MYLK | 0.485217 | mRNA |
| NM_053280 | ODF3 | 0.485169 | mRNA |
| NM_206922 | CRIP3 | 0.483401 | mRNA |
| NM_001142594 | ITPK1 | 0.482756 | mRNA |
| NM_012074 | DPF3 | 0.482472 | mRNA |
| NM_004961 | GABRE | 0.481134 | mRNA |
| NM_198174 | GRHL3 | 0.47943 | mRNA |
| AK124483 | LOC100131242 | 0.479105 | mRNA |
| XR_133518 | LOC100131242 | 0.478499 | mRNA |
| NM_007136 | ZNF80 | 0.476081 | mRNA |
| NM_020665 | TMEM27 | 0.474738 | mRNA |
| XM_001726878 | LOC400682 | 0.471721 | mRNA |
| NR_026710 | ASMTL-AS1 | 0.469235 | mRNA |
| NM_005130 | FGFBP1 | 0.467738 | mRNA |
| CD557356 | XLOC_011672 | 0.467372 | mRNA |
| NM_001001938 | C9orf47 | 0.467329 | mRNA |
| NM_007272 | CTRC | 0.467332 | mRNA |
| NM_024776 | PEAK1 | 0.465258 | mRNA |
| NM_024080 | TRPM8 | 0.465294 | mRNA |
| NM_013251 | TAC3 | 0.463695 | mRNA |
| NM_145178 | ATOH7 | 0.463332 | mRNA |
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| NM_001145434 | ZNF880 | 0.460575 | mRNA |
| BF997934 | TM4SF4 | 0.458663 | mRNA |
| NM_004617 | PEAK1 | 0.458159 | mRNA |
| EL584821 | XLOC_12_007767 | 0.457469 | mRNA |
| NM_001080524 | C16orf90 | 0.454039 | mRNA |
| NR_040002 | LOC255654 | 0.453607 | mRNA |
| NR_003246 | GOLGA6L5 | 0.455318 | mRNA |
| NM_201648 | GLYAT | 0.452131 | mRNA |
| NM_023944 | CYP4F12 | 0.451839 | mRNA |
| NR_027693 | C1orf170 | 0.451155 | mRNA |
| NM_001128223 | ZNF717 | 0.450692 | mRNA |
| NM_020911 | PLXNA4 | 0.45045 | mRNA |
| NM_032572  | RNASE7  | 0.450426 | mRNA      |
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| NM_032747  | USMG5   | 0.449486 | mRNA      |
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| NM_031481  | SLC25A18| 0.444722 | mRNA      |
| NM_001003892 | DUPD1  | 0.443058 | mRNA      |
| NR_024041  | CETN4P  | 0.442939 | mRNA      |
| BF216856   | XLOC_001209 | 0.44214  | mRNA      |
| GAD2       |         | 0.441708 | mRNA      |
| AK126260   | LOC100129275 | 0.440155 | mRNA      |
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| AK097702   | LOC285902 | 0.433763 | mRNA      |
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| NM_002701  | POU5F1  | 0.427642 | mRNA      |
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| NM_207103  | C17orf87 | 0.426791 | mRNA      |
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| HSPB8      |         | 0.426231 | mRNA      |
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| NM_001766  | CD1D    | 0.42499  | mRNA      |
| XM_003120274 | LOC100293977 | 0.424985 | mRNA      |
| NM_170606  | MLL3    | 0.424796 | mRNA      |
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| BC066916   | WWTR1   | 0.423646 | mRNA      |
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| NM_022573  | TSPY2   | 0.422507 | mRNA      |
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| NM_001650  | AQP4    | 0.419273 | mRNA      |
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| NM_170685  | TAC4           |      | 0.409857 mRNA |
| AK094853   | LOC100129775   |      | 0.407198 mRNA |
| NR_001560  | CYCSP52        |      | 0.405999 mRNA |
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| NM_022475  | HHIP           |      | 0.398651 mRNA |
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| NM_000727  | CACNG1         |      | 0.396891 mRNA |
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| NM_033128  | SCIN           |      | 0.395696 mRNA |
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| NM_002885  | RAP1GAP        |      | 0.394678 mRNA |
| NM_014694  | ADAMTSL2       |      | 0.391989 mRNA |
| DB050195   |                |      | 0.391738 mRNA |
| NM_174977  | SEC14L4        |      | 0.39131 mRNA |
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| AK093561   | LOC100131792   |      | 0.389185 mRNA |
| AK091668   | XLOC_011117    |      | 0.388923 mRNA |
| NM_213600  | PLA2G4F        |      | 0.387905 mRNA |
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| NM_053017  | ART5           |      | 0.386659 mRNA |
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| NM_004139  | LBP            |      | 0.379808 mRNA |
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| NM_000128  | F11            |      | 0.378514 mRNA |
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| XLOC_001217 | XLOC_001217 | 0.374878 mRNA |
| USP49       | CR608042  | 0.374302 mRNA |
| GRIK1-AS1   | CR608042  | 0.372611 mRNA |
| PTGER3      | NM_014409 | 0.37051 mRNA |
| XLOC_001217 | NM_001242672 | 0.369726 mRNA |
| ZNF720      | NM_000962 | 0.367438 mRNA |
| PTGS1       | NM_001242672 | 0.366546 mRNA |
| XLOC_001217 | BI465371  | 0.365238 mRNA |
| XLOC_001217 | NM_178233 | 0.3595 mRNA |
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| XLOC_001217 | NM_0101490687 | 0.358766 mRNA |
| XLOC_001944 | NM_00101242672 | 0.358009 mRNA |
| SYTL5       | NM_138780 | 0.356517 mRNA |
| XLOC_001944 | NM_00101242672 | 0.356392 mRNA |
| GRXCR2      | NM_000144049 | 0.354825 mRNA |
| ZNF45       | NM_001190839 | 0.35482 mRNA |
| SNAR-B1     | NM_000144049 | 0.354091 mRNA |
| SNORD111B   | NR_037420 | 0.353902 mRNA |
| HIVEP3      | NM_024503 | 0.349154 mRNA |
| C18orf26    | NM_173629 | 0.348422 mRNA |
| SEC1        | NR_004401 | 0.348616 mRNA |
| GGT6        | NM_153338 | 0.345778 mRNA |
| C19orf18    | NM_152474 | 0.341244 mRNA |
| DYNLRB2     | BC054892  | 0.340081 mRNA |
| AA06        | NR_037584 | 0.339942 mRNA |
| LOC644852   | BC025398  | 0.339097 mRNA |
| AFF3        | BC025398  | 0.338276 mRNA |
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| NM_201553 | FGL1  | 0.333063   |
|          |        | 0.332739   |
| NM_001039481 | ETNK1 | 0.332551   |
| NR_034143 | LOC729177 | 0.332409 |
| NM_020989 | CRYGC | 0.332408   |
| XM_002342035 | LACTBL1 | 0.330876 |
| BC034319 |        | 0.330306   |
| NM_001004689 | OR2M3 | 0.329793   |
| BC015119 |        | 0.329736   |
| BC070329 |        | 0.329608   |
| NM_004345 | CAMP  | 0.3286     |
| GQ232939 |        | 0.324666   |
| NM_001001938 | C9orf47 | 0.324575 |
| NM_174912 | FAAH2 | 0.32419    |
| NR_002762 | PRO0611 | 0.322308  |
| NR_001541 | TTTY5 | 0.322013   |
| NM_004027 | INPP4A | 0.321487   |
| NM_207328 | GPAT2 | 0.320136   |
| BC037171 | CCL27 | 0.319574   |
| AK125138 | SH3BP5L | 0.31938   |
| NM_001080427 | THSD7B | 0.318116  |
| AK128317 | ARNTL | 0.317988   |
| NM_207325 | DPY19L3 | 0.316703  |
| NM_001024075 | HNMT | 0.313504   |
| NM_000795 | DRD2 | 0.311514   |
| NR_027790 | LINC00478 | 0.31023  |
| NM_032680 | EFCAB4B | 0.30766   |
| CF887241 | XLOC_014028 | 0.304259 |
| NM_001099294 | KIAA1644 | 0.301217  |
| NM_001189 | NKX3-2 | 0.300638   |
|          |        | 0.299059   |
|          |        | 0.298519   |
| NM_001045 | SLC6A4 | 0.297478   |
| NM_080928 | ASB15 | 0.296706   |
| NM_001166006 | EPB41 | 0.296508   |
| CR744384 | XLOC_002950 | 0.293569 |
|          |        | 0.291621   |
| NM_022449 | RAB17 | 0.29087    |
|          |        | 0.289758   |
| NM_052938 | FCRL1 | 0.289479   |
| NM_032812 | PLXDC2 | 0.288782   |
| Gene Accession | Gene Symbol | mRNA Score |
|---------------|-------------|------------|
| NM_022342     | KIF9        | 0.288156   |
|               | Q8IWW8      | 0.286515   |
| NM_022449     | RAB17       | 0.28438    |
| NM_198137     | CATSPER4    | 0.284069   |
| NR_037845     | LOC100506023| 0.283694   |
| NM_173565     | RSPH10B     | 0.283395   |
| AK096705      | HSPBAP1     | 0.281874   |
| NM_003423     | ZNF43       | 0.278615   |
| NM_015198     | COBL        | 0.276886   |
| NM_153026     | PRICKLE1    | 0.274532   |
| AK097855      | FLJ40536    | 0.272524   |
| XR_109707     | HOTAIR      | 0.270818   |
| NR_003716     | HOTAIR      | 0.270436   |
| NM_052896     | CSMD2       | 0.268237   |
| BQ637851      | XLOC_000683 | 0.268012   |
| NM_000891     | KCNJ2       | 0.263437   |
| AL832464      | GPAM        | 0.263026   |
| NM_020406     | CD177       | 0.263206   |
| NM_014810     | CEP350      | 0.261977   |
| AJ412030      | XLOC_010390 | 0.260476   |
| BG613973      | XLOC_000514 | 0.259257   |
| NR_045114     | PVRL3-AS1   | 0.258353   |
| NM_015136     | STAB1       | 0.25743    |
|               |             |            |
| NM_173681     | ATG9B       | 0.257319   |
| NM_199051     | FAM5C       | 0.256124   |
| NM_004654     | USP9Y       | 0.255862   |
| NR_033842     | TMEM72-AS1  | 0.25398    |
|               | XLOC_I2_002502| 0.252883  |
| NM_020768     | KCTD16      | 0.251974   |
| NM_001039211  | ATAD3C      | 0.251754   |
| NM_014009     | FOXP3       | 0.248978   |
|               | ARF3        | 0.248363   |
| BC061919      | XLOC_006195 | 0.247712   |
| NR_038377     | MGC39584    | 0.244239   |
| NR_033880     | LOC339822   | 0.243687   |
| NM_000962     | PTGS1       | 0.242081   |
| NM_001882     | CRHBP       | 0.241827   |
| AY044864      | ARHGAP33    | 0.234925   |
| Gene Accession | Gene Symbol | Value | Description |
|----------------|-------------|-------|-------------|
| DA953843       | XLOC_002059 | 0.234745 | mRNA |
| NM_138278      | BNIP1       | 0.234676 | mRNA |
| NM_001504      | CXCR3       | 0.229762 | mRNA |
|                |             | 0.227559 | mRNA |
|                |             | 0.227245 | mRNA |
|                |             | 0.225324 | mRNA |
| NM_006274      | CCL19       | 0.225137 | mRNA |
| NR_040078      | KIRREL3-AS3 | 0.223647 | mRNA |
|                |             | 0.222738 | mRNA |
| NM_000525      | KCNJ11      | 0.222208 | mRNA |
| NM_005299      | GPR31       | 0.221796 | mRNA |
| NM_001506      | GPR32       | 0.220095 | mRNA |
| NM_021637      | TMEM35      | 0.219886 | mRNA |
| NM_001276      | CHI3L1      | 0.219412 | mRNA |
| NM_207173      | NPSR1       | 0.219026 | mRNA |
| NM_178428      | LCE2A       | 0.218271 | mRNA |
| NM_001142287   | SEMA4D      | 0.216482 | mRNA |
| NR_026835      | FLJ37201    | 0.215296 | mRNA |
|                |             | 0.212268 | mRNA |
|                | XLOC_002066 | 0.210672 | mRNA |
| NR_036549      | LOC100129961 | 0.209832 | mRNA |
| NM_178504      | DNAH12      | 0.209123 | mRNA |
| NR_003076      | SNORD98     | 0.207590 | mRNA |
| NR_040253      | LOC282980   | 0.206610 | mRNA |
| NR_040662      | HCP5        | 0.206389 | mRNA |
| NM_144505      | KLK8        | 0.203528 | mRNA |
| U80760         |             | 0.202499 | mRNA |
| NM_004784      | NDST3       | 0.201240 | mRNA |
| NM_001164443   | ANKR3D31    | 0.199563 | mRNA |
| AK023539       |             | 0.197605 | mRNA |
| NM_144977      | DENND1B     | 0.197467 | mRNA |
| NR_015361      | LOC440896   | 0.196524 | mRNA |
| NR_026794      | LOC731789   | 0.195907 | mRNA |
|                |             | 0.194766 | mRNA |
| NM_001172831   | ZNF300      | 0.193652 | mRNA |
| NM_001017920   | DAPL1       | 0.193383 | mRNA |
| NM_001142483   | C5orf13     | 0.19287 | mRNA |
|                |             | 0.192461 | mRNA |
| AL713682       | SYNE1       | 0.192100 | mRNA |
| NR_033901      | LOC285441   | 0.191820 | mRNA |
| NM_006174      | NPY5R       | 0.190676 | mRNA |
| BI833485       |             | 0.190433 | mRNA |
| Accession Number | Gene Symbol | Gene Symbol (Preprocessed) | Value | Type  |
|------------------|-------------|---------------------------|-------|-------|
| DB045402         | XLOC_002571 | mRNA                      | 0.19023 | mRNA |
| NM_173651        | FSIP2       | mRNA                      | 0.19021 | mRNA |
| NR_036678        | LOC283299   | mRNA                      | 0.19012 | mRNA |
| BX111391         | XLOC_12_010061 | mRNA                  | 0.189691 | mRNA |
|                 | XLOC_12_014217 | mRNA                  | 0.189471 | mRNA |
| NM_001017930     | DCAF8L1     | mRNA                      | 0.188908 | mRNA |
|                 | SNTG1       | mRNA                      | 0.188607 | mRNA |
| NM_001038705     | GPR149      | mRNA                      | 0.18845 | mRNA |
| NM_005959        | MTNR1B      | mRNA                      | 0.188033 | mRNA |
| NM_003547        | HIST1H4G    | mRNA                      | 0.187409 | mRNA |
| NM_203451        | SERTM1      | mRNA                      | 0.187123 | mRNA |
|                 |             |                           | 0.185241 | mRNA |
| NM_014213        | HOXD9       | mRNA                      | 0.184699 | mRNA |
| AL705284         | XLOC_12_012983 | mRNA                  | 0.184636 | mRNA |
| NR_027713        | KRT8P41     | mRNA                      | 0.182903 | mRNA |
| NM_003638        | ITGA8       | mRNA                      | 0.182126 | mRNA |
| NM_001080467     | MYO5B       | mRNA                      | 0.182031 | mRNA |
| AL705861         | XLOC_011173 | mRNA                      | 0.179394 | mRNA |
| NM_001144871     | VSTM5       | mRNA                      | 0.178739 | mRNA |
| BC035370         | XLOC_12_000941 | mRNA                  | 0.178591 | mRNA |
|                 | XLOC_002151 | mRNA                      | 0.178356 | mRNA |
| NM_002838        | PTPRC       | mRNA                      | 0.177788 | mRNA |
| NM_001013732     | C6orf138    | mRNA                      | 0.177043 | mRNA |
| NM_001100111     | LOC286238   | mRNA                      | 0.176556 | mRNA |
| NM_001042575     | TMPRSS7     | mRNA                      | 0.176386 | mRNA |
| AK126029         |             | mRNA                      | 0.172921 | mRNA |
| NM_025213        | SPTBN4      | mRNA                      | 0.172741 | mRNA |
| NM_001207026     | POU2F2      | mRNA                      | 0.172347 | mRNA |
| AK055023         | LOC219690   | mRNA                      | 0.171691 | mRNA |
| NM_198074        | OR2C3       | mRNA                      | 0.171139 | mRNA |
| NM_016562        | TLR7        | mRNA                      | 0.170401 | mRNA |
|                 | XLOC_007458 | mRNA                      | 0.169261 | mRNA |
|                 | XLOC_000902 | mRNA                      | 0.168601 | mRNA |
| NR_024464        | LINC00426   | mRNA                      | 0.167477 | mRNA |
|                 |             | mRNA                      | 0.16733 | mRNA |
| AK126787         | ERV18-1     | mRNA                      | 0.166663 | mRNA |
| NM_015336        | ZDHHC17     | mRNA                      | 0.16662 | mRNA |
| NM_207345        | CLEC9A      | mRNA                      | 0.166353 | mRNA |
| NR_027151        | C10orf108   | mRNA                      | 0.166288 | mRNA |
| AK128720         | PKP4        | mRNA                      | 0.166071 | mRNA |
| NM_001243467     | UBASH3A     | mRNA                      | 0.165937 | mRNA |
| AK125770         | XLOC_009948 | mRNA                      | 0.164773 | mRNA |
| BC040863         | P39189      | mRNA                      | 0.164565 | mRNA |
| Accession | Symbol | Score |
|-----------|--------|-------|
| NM_001146261 | SYT14 | 0.128293 mRNA |
| NM_032944 | STK31 | 0.127537 mRNA |
|          | Q8VGA8 | 0.126373 mRNA |
| NM_052917 | GALNT13 | 0.124958 mRNA |
| NM_000359 | TGM1 | 0.123504 mRNA |
| BC048118 | XLOC_12_014219 | 0.121208 mRNA |
| NM_001166254 | TBXAS1 | 0.118243 mRNA |
| NM_01039372 | HEPACAM2 | 0.118177 mRNA |
| NM_001004745 | OR5T1 | 0.117873 mRNA |
| NM_001198834 | PDE4DIP | 0.117863 mRNA |
| BX096383 | XLOC_005105 | 0.117187 mRNA |
| NM_032598 | SPATA22 | 0.11198 mRNA |
| DB088362 | XLOC_014175 | 0.111361 mRNA |
| NM_018990 | SASH3 | 0.109885 mRNA |
| XM_003118595 | DGAT2L7 | 0.109797 mRNA |
| NM_000759 | CSF3 | 0.108037 mRNA |
| NM_001204424 | RGS6 | 0.108306 mRNA |
| NM_001136234 | FAM48B1 | 0.105726 mRNA |
| AY122474 | LOC414300 | 0.105066 mRNA |
| NM_005211 | CSF1R | 0.10351 mRNA |
| BC026225 | LOC100287221 | 0.103912 mRNA |
| NM_000359 | TGM1 | 0.103577 mRNA |
| BE875542 | LINC00165 | 0.101911 mRNA |
| NR_027038 | LOC401093 | 0.101763 mRNA |
| BC032033 | LOC414300 | 0.100106 mRNA |
| A25969 | LOC285401 | 0.098007 mRNA |
| NR_027104 | XLOC_014175 | 0.097863 mRNA |
| X95463 | AFF2 | 0.09747 mRNA |
| AL598157 | XLOC_12_010011 | 0.096695 mRNA |
| Gene ID    | Description | Expression Value |
|------------|-------------|------------------|
| NR_026838  | DSCR8       | 0.094061 mRNA    |
|            |             | 0.093461 mRNA    |
|            |             | 0.093436 mRNA    |
|            |             | 0.09161 mRNA     |
| NM_001164442 | FAM159B    | 0.091206 mRNA    |
| NR_027481  | ZNF876P     | 0.091179 mRNA    |
|            |             | 0.089869 mRNA    |
| NM_001113228 | NTNG1      | 0.086386 mRNA    |
|            |             | 0.085739 mRNA    |
| NM_003106  | SOX2        | 0.08554 mRNA     |
| NR_027276  | LOC100128239| 0.085132 mRNA    |
| NM_198451  | FOXR2       | 0.083262 mRNA    |
| NM_018280  | C22orf26    | 0.081564 mRNA    |
| NR_027249  | GNN         | 0.080676 mRNA    |
| NM_001001919 | OR13C4    | 0.080045 mRNA    |
| XM_003403488 | LOC100652763| 0.077533 mRNA    |
| NM_033976  | LOC401134   | 0.075904 mRNA    |
| NM_001143939 | ZNF534    | 0.075891 mRNA    |
| DA729442   | XLOC_006040 | 0.075802 mRNA    |
| NM_178540  | C1QTNF9     | 0.075776 mRNA    |
| CF454975   | XLOC_001070 | 0.075405 mRNA    |
| NM_014692  | SEC14L5     | 0.074674 mRNA    |
| NR_026794  | LOC731789   | 0.074365 mRNA    |
| NM_018995  | MOV10L1     | 0.07368 mRNA     |
| NM_001004473 | OR10K1    | 0.070883 mRNA    |
| NM_001462  | FPR2        | 0.069783 mRNA    |
| DB515342   | XLOC_004093 | 0.069752 mRNA    |
| NM_174914  | UGT3A2      | 0.069655 mRNA    |
| NM_000844  | GRM7        | 0.069174 mRNA    |
| NR_028137  | LOC286002   | 0.069126 mRNA    |
| NM_015009  | PDZRN3      | 0.068303 mRNA    |
| AK024188   |             | 0.068181 mRNA    |
|            |             | 0.06661 mRNA     |
| NM_052898  | XKR4        | 0.066065 mRNA    |
| NM_002924  | RGS7        | 0.065963 mRNA    |
| NM_001013646 | C20orf107  | 0.064437 mRNA    |
| XM_003403443 | LOC100509263| 0.063714 mRNA    |
| NM_000609  | CXCL12      | 0.063144 mRNA    |
| NM_001033019 | DEFB134    | 0.063084 mRNA    |
| BX486480   | XLOC_013823 | 0.062503 mRNA    |
| XM_003119104 | LOC100287188| 0.061905 mRNA    |
| NM_001166242 | C22orf39   | 0.061735 mRNA    |
| AY928977   | XLOC_001360 | 0.061417 mRNA    |

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| Accession     | Name       | Value   | Type   |
|--------------|------------|---------|--------|
| NM_025239    | PDCD1LG2   | 0.061076| mRNA   |
| AW968277     | XLOC_004534| 0.060627| mRNA   |
| NR_040013    | LOC644554  | 0.060552| mRNA   |
|              |            | 0.058791| mRNA   |
| AK092662     | LOC100132005| 0.057332| mRNA   |
| DA674107     | XLOC_013531| 0.056783| mRNA   |
| AF007131     | LOC100129973| 0.056335| mRNA   |
| NM_006258    | PRKG1      | 0.055972| mRNA   |
| NM_175721    | TPO        | 0.055177| mRNA   |
| NM_001145004 | GOLGA6L6   | 0.052473| mRNA   |
| CR625825     | XLOC_005384| 0.052343| mRNA   |
| NR_033983    | LOC400654  | 0.051705| mRNA   |
|              | C1QTNF9    | 0.051266| mRNA   |
|              |            | 0.049986| mRNA   |
| DQ983818     | C1orf81    | 0.049395| mRNA   |
|              |            | 0.048434| mRNA   |
| NM_006902    | PRRX1      | 0.047676| mRNA   |
| NR_015430    | C14orf64   | 0.045765| mRNA   |
| NM_031956    | TTC29      | 0.042656| mRNA   |
| DA760426     |            | 0.041951| mRNA   |
| AF461896     |            | 0.041617| mRNA   |
| NR_033740    | CES1P2     | 0.041542| mRNA   |
| AK123052     | LOC100131821| 0.04001 | mRNA   |
| NR_033368    | GRIK1-A52  | 0.038689| mRNA   |
| NM_033267    | IRX2       | 0.038674| mRNA   |
| NM_001184714 | SLAMF6     | 0.038288| mRNA   |
| NR_027104    | LOC285401  | 0.037551| mRNA   |
| NR_033985    | FLJ26245   | 0.037303| mRNA   |
| NR_038372    | LOC402779  | 0.037247| mRNA   |
| XM_001723012 |            | 0.037086| mRNA   |
| NM_001001952 | OR5D18     | 0.034613| mRNA   |
| NM_005302    | GPR37      | 0.032962| mRNA   |
| NM_001004064 | OR8J3      | 0.032288| mRNA   |
| NM_002761    | PRM1       | 0.032073| mRNA   |
| NM_080475    | SERPINB11  | 0.031705| mRNA   |
| AJ245419     |            | 0.031422| mRNA   |
| NM_031477    | YPEL3      | 0.031175| mRNA   |
|              | XLOC_12_013442| 0.03042 | mRNA   |
| AK307375     |            | 0.030028| mRNA   |
|              |            | 0.029993| mRNA   |
| NM_001002006 | NT5C1B     | 0.029161| mRNA   |
| AK098126     |            | 0.028933| mRNA   |
| NR_001281    | PCDHB18    | 0.027993| mRNA   |
| Accession   | Symbol     | Description | Score |
|-------------|------------|-------------|-------|
| BX096530    | XLOC_005551| mRNA        | 0.027437 |
| NM_001025076| CELF2      | mRNA        | 0.027146 |
| NM_197954   | CLEC7A     | mRNA        | 0.026969 |
| NM_001080484| KIAA1751   | mRNA        | 0.025411 |
| BC008585    |            | mRNA        | 0.025265 |
| NM_001005487| OR13G1     | mRNA        | 0.024988 |
| NM_006422   | AKAP3      | mRNA        | 0.023898 |
| NM_016366   | CABP2      | mRNA        | 0.023378 |
| NM_016945   | TAS2R16    | mRNA        | 0.023367 |
| DB307521    |            | mRNA        | 0.022601 |
| NM_001721   | BMX        | mRNA        | 0.020277 |
| NM_001005160| OR52A5     | mRNA        | 0.019971 |
| NM_033401   | CNTNAP4    | mRNA        | 0.019842 |
| NM_138379   | TIMD4      | mRNA        | 0.018530 |
| NM_080615   | GCNT7      | mRNA        | 0.014586 |
| AK097358    | FLJ40039   | mRNA        | 0.013565 |
| NR_036490   | LOC284648  | mRNA        | 0.013389 |
| NR_001591   | psITPTE22  | mRNA        | 0.012178 |
| NM_002365   | MAGEB3     | mRNA        | 0.011704 |
| AK091000    | XLOC_002322| mRNA        | 0.011671 |
| BC043541    | LOC339539  | mRNA        | 0.011127 |
| NM_001198986| SPINLW1-WFDC6| mRNA      | 0.010847 |
| NM_014996   | PLCH1      | mRNA        | 0.010108 |
| NM_001005489| OR5B17     | mRNA        | 0.010021 |
| NM_183058   | LYZL2      | mRNA        | 0.009954 |
| DA230376    | XLOC_002943| mRNA        | 0.009056 |
| NM_001206626| LOC283116  | mRNA        | 0.008698 |
| NM_014495   | ANGPTL3    | mRNA        | 0.008129 |
| NM_145027   | KIF6       | mRNA        | 0.008125 |
| NM_001102470| ADH6       | mRNA        | 0.008061 |
|             | NUBPL      | mRNA        | 0.007711 |
| NM_138715   | MSR1       | mRNA        | 0.007126 |
|             |            | mRNA        | 0.00535  |
| NM_152404   | UGT3A1     | mRNA        | 0.005332 |
| NM_001142800| EYS        | mRNA        | 0.004908 |
| NM_015393   | PARM1      | mRNA        | 0.003905 |
| NR_029389   | LOC100134317| mRNA       | 0.00334  |
| NR_024072   | MRS2P2     | mRNA        | 0.001821 |
Table S3. Clinicopathological features of PDAC patients.

| Patient | Gender | Age | Site* | MMP1 | PNI number | PNI degree (ne)** | Grade | Stage |
|---------|--------|-----|-------|------|------------|-----------------|-------|-------|
| 1       | M      | 28  | 1     | 0    | 1          | 1               | 3     | IIA   |
| 2       | F      | 66  | 1     | 0    | 0          | 0               | 1     | IV    |
| 3       | F      | 58  | 1     | 0    | 0          | 0               | 2     | IIA   |
| 4       | M      | 44  | 1     | 0    | 1          | 1               | 1     | IV    |
| 5       | M      | 65  | 2     | 0    | 3          | 1               | 2     | IIA   |
| 6       | M      | 73  | 1     | 0    | 2          | 1               | 1     | IV    |
| 7       | F      | 55  | 1     | 1    | 5          | 2               | 2     | IIA   |
| 8       | M      | 68  | 2     | 1    | 2          | 1               | 2     | IIA   |
| 9       | M      | 83  | 1     | 1    | 2          | 1               | 2     | IIA   |
| 10      | M      | 65  | 1     | 1    | 1          | 1               | 3     | IIA   |
| 11      | F      | 60  | 1     | 1    | 0          | 0               | 2     | IIA   |
| 12      | M      | 44  | 2     | 1    | 0          | 0               | 1     | IIB   |
| 13      | M      | 54  | 1     | 1    | 20         | 3               | 2     | IIA   |
| 14      | M      | 48  | 1     | 1    | 1          | 1               | 1     | IIB   |
| 15      | M      | 54  | 1     | 1    | 3          | 1               | 2     | IIA   |
| 16      | F      | 55  | 2     | 1    | 0          | 0               | 2     | IV    |
| 17      | M      | 38  | 1     | 1    | 1          | 1               | 3     | IIB   |
| 18      | F      | 44  | 1     | 1    | 4          | 2               | 1     | IIB   |
| 19      | M      | 70  | 1     | 1    | 8          | 2               | 2     | IIB   |
| 20      | M      | 58  | 1     | 1    | 6          | 2               | 1     | IIB   |
| 21      | F      | 62  | 2     | 1    | 8          | 2               | 2     | IIA   |
| 22      | M      | 68  | 2     | 2    | 12         | 3               | 3     | III   |
| 23      | F      | 49  | 1     | 2    | 12         | 3               | 3     | IIB   |
| 24      | F      | 56  | 1     | 2    | 4          | 2               | 3     | IIA   |
| 25      | M      | 51  | 1     | 2    | 10         | 3               | 3     | IIB   |
| 26      | M      | 54  | 1     | 2    | 4          | 2               | 3     | III   |
| 27      | M      | 68  | 2     | 2    | 8          | 2               | 1     | IIB   |
| 28      | M      | 63  | 1     | 3    | 3          | 1               | 3     | IIB   |
| 29      | F      | 56  | 2     | 3    | 10         | 2               | 1     | IIA   |
| 30      | M      | 63  | 1     | 4    | 6          | 2               | 2     | IIB   |

* 1 = head; 2 = body/tail

** The degree of PNI was defined microscopically as follows: ne0, no perineural invasion; ne1, perineural invasion is difficult to find, occurrences of lesions ≤ 3; ne2, perineural invasion that was easy to find and between ne1 and ne3; and ne3, perineural invasion that was even easier to find with more massive occurrences of lesions and extension beyond the border of the main tumor mass.