**Supplement Table 1: List of primers used for real time RT-PCR reactions**

|  |  |  |
| --- | --- | --- |
| Gene | Primer sequence | Ref |
| HES1 F | 5’-ATGGAGAAAAATTCCTCGTCCC-3’ | 1 |
| HES1 R | 5’-TTCAGAGCATCCAAAATCAGTGT-3’ |
| HEY1 F | 5’-GAAACTTGAGTTCGGCTCTAGG-3’ |
| HEY1 R | 5’-GCTTAGCAGATCCTTGCTCCAT-3’ |
| HEY2 F | 5’-AGGGGGTAAAGGCTACTTTGA-3’ |
| HEY2 R | 5’-TGGCGCAAGTGCTGAGATG-3’ |
| GATA3 F | 5’-GTGCTTTTTAACATCGACGGTC-3’ |
| GATA3 R | 5’-AGGGGCTGAGATTCCAGGG-3’ |
| NRARP F | 5’-CAGAACATGACCAACTGCGAG-3’ |
| NRARP R | 5’-GGTGATGAGATAGAGCACGATG-3’ |
| DTX1 F | 5’-GGTGTGGGAGTGTCTGAATGA-3’ |
| DTX1 R | 5’-CCTGGCGAAACTGGTGCAT-3’ |
| PBX1 F | 5’-CATGCTGTTAGCGGAAGGC-3’ |
| PBX1 R | 5’-CAGCTCCGTATGGTAGATTTGTC-3’ |
| Dll1 F | 5’-ATCTGCCTGCCTGGATGTGATG-3’ | 2 |
| Dll1 R | 5’-AGACAGCCTGGATAGCGGATACAC-3’ |
| Dll3 F | 5’-CAATGGAGGCAGCTGTAGTG-3’ |
| Dll3 R | 5’-TCAAAGGACCTGGGTGTCTC-3’ |
| Dll4 F | 5’-TTGGATGAGCAAACCAGCACCC-3’ |
| Dll4 R | 5’-TGACAGCCCGAAAGACAGATAGG-3’ |
| JAG1 F | 5’-CAACCGTGCCAGTGACTATTTCTGC-3’ | 3 |
| JAG1 R | 5’-TGTTCCCGTGAAGCCTTTGTTACAG-3’ |
| JAG2 F | 5’-AACGATACCACCCCGAATGAGG-3’ |
| JAG2 R | 5’-GCTGCCACAGTAGTTCAGGTCTTTG-3’ |
| NOTCH 1 F | 5’-GAACCAATACAACCCTCTGC-3’ | 4 |
| NOTCH 1R | 5’-AGCTCATCATCTGGGACAGG-3’ |
| NOTCH 2 F | 5’-TGGGCTACACTGGGAAAAAC-3’ | 5 |
| NOTCH 2 R | 5’-ACATAGGCACTGGGACTCTG-3’ |
| NOTCH 3 F | 5’-TCTTGCTGCTGGTCATTCTC-3’ | 6 |
| NOTCH 3 R | 5’-TGCCTCATCCTCTTCAGTTG-3’ |
| NOTCH 4 F | 5’-AGTCCAGGCCTTGCCAGAACG-3’ | 7 |
| NOTCH 4 R | 5’-GTAGAAGGCATTGGCCAGAGAG-3’ |
| SOX2 F | 5’-CCTCCGGGACATGATCAGCATGTA-3’ | 8 |
| SOX2 R | 5’-GCAGTGTGCCGTTAATGGCCGTG-3’ |
| HES5 F | 5’-TCAGCCCCAAAGAGAAAAAC-3’ | 9 |
| HES5 R | 5’-TAGTCCTGGTGCAGGCTCTT-3’ |
| CD133 F | 5’-CTGGGGCTGCTGTTTATTATTCTG-3’ | 10 |
| CD133 R | 5’-ACGCCTTGTCCTTGGTAGTGTTG-3’ |
| BMI1 F | 5’-CTGGTTGCCCATTGACAGC-3’ | 11 |
| BMI1 R | 5’-CAGAAAATGAATGCGAGCCA-3’ |
| KLF4 F | 5’-ATCAGATGCAGCCGCAAGTCCC-3’ | 12 |
| KLF4 R | 5’-TCTTCATGTGTAAGGCGAGGTGGTCC-3’ |
| CD44 F | 5’-TGGAGCAAACACAACCTCTG-3’ | 13 |
| CD44 R | 5’-TCCACTTGGCTTTCTGTCCT-3’ |
| OCT4 F | 5’-ATTCAGCCAAACGACCATCT-3’ | 14 |
| OCT4 R | 5’-GTTTTCTTTCCCTAGCTCCTCC-3’ |
| ADAM17 F | 5’-GTCGTGGTGGTGGATGGTAAAA-3’ | 15 |
| ADAM17 R | 5’-GCCCCATCTGTGTTGATTCTGA-3’ |
| ERBB2 F | 5’-TTTGATGGTGACCTGGGAAT-3’ | 16 |
| ERBB2 R | 5’-GAACATCTGGCTGGTTCACA-3’ |
| FZD1 F | 5’-CACCTTGTGAGCCGACCAA-3’ | 17 |
| FZD1 R | 5’-CAGCACTGACCAAATGCCAAT-3’ |
| FZD6 F | 5’-ACAAGCTGAAGGTCATTTCCAAA-3’ |
| FZD6 R | 5’-GCTACTGCAGAAGTGCCATGAT-3’ |
| GLI1 F | 5’-GAAGTCATACTCACGCCTCGAA-3’ | 18 |
| GLI1 R | 5’-CAGCCAGGGAGCTTACATACAT-3’ |
| HDAC1 F | 5’-ACTGGGGACCTACGG-3’ | 19 |
| HDAC1 R | 5’-ACTTGGCGTGTCCTT-3’ |
| MMP7 F | 5’-TGAGCTACAGTGGGAACAGG-3’ | 20 |
| MMP7 R | 5’-TCATCGAAGTGAGCATCTCC-3’ |
| NCSTN F | 5’-CAAAGCACCTTCAGCATCAA-3’ | 2122 |
| NCSTN R | 5’-GGTCACATCAGGTGCCTTTT-3’ |
| PSEN1 F | 5’-TTGCGGTCCTTAGACAGCTT-3’ |
| PSEN1 R | 5’-TGCTCCTGCCGTTCTCTATT-3’ |
| PSEN2 F | 5’-CCCAGAGGATGGAGAGAACA-3’ |
| PSEN2 R | 5’-CTACCACCACGATCATGGAC-3’ |
| APH1A F | 5’-CAGCCATTATCCTGCTCCAT-3’ |
| APH1A R | 5’-CTCATACCAGGGGTTCAGGA-3’ |
| SH2D1A F | 5’-TGGGTCCACATACCAACAGA-3’ |  |
| SH2D1A R | 5’-AACACACACCCTTGCACTCA-3’ |
| SHH F | 5’-CAAGCAGTTTATCCCCAATGTG-3’ | 23 |
| SHH R | 5’-TCACCCGCAGTTTCACTC-3’ |
| SMO F | 5’-GTTCTCCATCAAGAGCAACCAC-3’ | 24 |
| SMO R | 5’-CGATTCTTGATCTCACAGTCAGG-3’ |
| SUFU F | 5’-GAGGACAGCCGGAGCATCT-3’ | 25 |
| SUFU R | 5’-AGGACAGGTTTGCTGTTGATCTC-3’ |
| TEAD1 F | 5’-AATCCCACCGCCAAAATTGAGC-3’ | 26 |
| TEAD1 R | 5’-TACCATACATTTTGCCTTCGTCT-3’ |

**List of primers used for ChIP experiments**

|  |  |
| --- | --- |
| Gene | Primer Sequence |
| HES1-P F | 5’-CCCAGAGGGAGAGTAGCAAA-3’ |
| HES1-P R | 5’-CCCAAACTTTCTTTCCCACA-3’ |
| HES1-M F | 5’-CGCAGAACCTAAAGCCTACG-3’ |
| HES1-M R | 5’-TTCAGAAATTCCTCGTTTGGA-3’ |
| HES1-D F | 5’-GCCGCTTTAACCGCAGTC-3’ |
| HES1-D R | 5’-GCCTCCAAGTTTGCTCCTC-3’ |
| HES 5-P F | 5’-TCCCTTATCTGCTCCTACGG-3’ |
| HES 5-P R | 5’-CTCGCCCTCATTAGCATCC-3’ |
| HES 5-M F | 5’-TGCTGTGGGTTACAGTGCTC-3’ |
| HES 5-M R | 5’-TCACCTGGGACTCCTGACTT-3’ |
| HES 5-D F | 5’-AGTGTCACTGCCTCCCTCTG-3’ |
| HES 5-D R | 5’-AGGACTTCAAGCCAATGCAG-3’ |
| ADAM17 F | 5’-AGGCCGCTTTCTACAGCTC-3’ |
| ADAM17 R | 5’-CTTCCTGGACGCAGACGTA-3’ |
| ERBB2 F | 5’-GTCCTGGAAGCCACAAGGTA-3’ |
| ERBB2 R | 5’-AAATTCCCTAGGCTGCCACT-3’ |
| FOS F | 5’-TAGAATTGGGGATGGGGGTA-3’ |
| FOS R | 5’-GAGAACATTCGCACCTGGTT-3’ |
| FZD1 F | 5’-GTGCCACCACCACTACTTCC-3’ |
| FZD1 R | 5’-GCCCCGTAGTCTGTCTTTCA-3’ |
| FZD6 F | 5’-CTGAAATCCGCAAGGAAGTG-3’ |
| FZD6 R | 5’-CTCCACCTTGCCGTCTGTTA-3’ |
| HDAC1 F | 5’-ATCTCCAAGCACGCTTTTCA-3’ |
| HDAC1 R | 5’-AATCAGCTTGCGCAGACAC-3’ |
| JAG2 F | 5’-GAGTAGGAGGCGGCATCTC-3’ |
| JAG2 R | 5’-CACACCTCCGCGTGAGTC-3’ |
| SH2D1A F | 5’-TCAAGATGACTGCGTGAGGT-3’ |
| SH2D1A R | 5’-GGGCAAAAACACACTGACAA-3’ |
| STIL F | 5’-TAGAGCACTTCCGGCTTCAT-3’ |
| STIL R | 5’-TCGACCAATCCCAAGTCTTC-3’ |
| TEAD1 F | 5’-AACCCAGGCTTCCAGAGTTC-3’ |
| TEAD1 R | 5’-GGTGACGTCATGGGGAATC-3’ |

**Supplementary Table2: List of overlapping genes from ChIP assay**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Gene symbol*** | ***Gene title***  | ***H3K4me3*** | ***P-value*** | ***H3K27me3*** | ***P-value*** |
| ADAM17 | ADAM metallopeptidase domain 17 | 0.52 | 5.2E-03 | 3.20 | 1.5E-04 |
| AES | Amino-terminal enhancer of split | 0.45 | 2.69E-03 | 3.78 | 1.1E-03 |
| DTX1 | Deltex homolog 1 (Drosophila) | 0.49 | 4.03E-03 | 2.12 | 3.2E-03 |
| ERBB2 | V-erb-b2 erythroblastic leukemia viral oncogene homolog 2 | 0.53 | 5.44E-03 | 5.92 | 6.6E-05 |
| FOS | FBJ murine osteosarcoma viral oncogene homolog | 0.06 | 3.03E-05 | 2.79 | 1.9E-04 |
| FZD1 | Frizzled family receptor 1 | 0.36 | 1.35E-03 | 2.14 | 3.1E-04 |
| FZD6 | Frizzled family receptor 6 | 0.43 | 2.37E-03 | 2.04 | 3.5E-05 |
| HDAC1 | Histone deacetylase 1 | 0.16 | 4.22E-04 | 2.62 | 2.0E-04 |
| HES5 | Hairy and enhancer of split 5 (Drosophila) | 0.49 | 1.29E-03 | 5.20 | 8.5E-05 |
| JAG2 | Jagged 2 | 0.56 | 7.27E-03 | 2.69 | 2.0E-04 |
| LFNG | LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase | 0.39 | 1.68E-03 | 2.28 | 2.6E-03 |
| LRP5 | Low density lipoprotein receptor-related protein 5 | 0.50 | 4.37E-03 | 1.97 | 4.0E-04 |
| MFNG | MFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase | 0.30 | 9.15E-04 | 2.71 | 1.9E-03 |
| MMP7 | Matrix metallopeptidase 7 (matrilysin, uterine) | 0.48 | 3.58E-03 | 2.41 | 2.3E-03 |
| NCSTN | Nicastrin | 0.48 | 3.45E-03 | 2.34 | 2.5E-04 |
| NOTCH1 | Notch 1 | 0.53 | 1.56E-02 | 1.95 | 4.1E-03 |
| PSEN1 | Presenilin 1 | 0.48 | 1.20E-02 | 3.81 | 1.1E-04 |
| PSEN2 | Presenilin 2 | 0.32 | 1.04E-03 | 2.32 | 2.5E-04 |
| SH2D1A | SH2 domain containing 1A | 0.44 | 2.52E-03 | 1.88 | 1.7E-03 |
| SHH | Sonic hedgehog | 0.40 | 1.87E-03 | 3.23 | 1.4E-04 |
| STIL | SCL/TAL1 interrupting locus | 0.17 | 4.43E-04 | 2.70 | 1.7E-04 |
| TEAD1 | TEA domain family member 1 (SV40 transcriptional enhancer factor) | 0.27 | 7.83E-04 | 2.60 | 1.9E-05 |

Detailed annotations of the overlapping 22 genes are presented. Fold changes and p-values were obtained from knockdown cells compared to control cells.

**Supplement Table 3: ChIP qPCR analysis confirmed by qRT-PCR**

|  |  |  |
| --- | --- | --- |
| ***Gene symbol*** | ***Fold change in HCT116*** | ***Fold change in DLD-1*** |
| ADAM17 | 0.67 | 0.38 |
| AES | 0.59 | ND |
| DTX1 | 0.63 | 0.27 |
| ERBB2 | 0.67 | 0.30 |
| FOS | 0.17 | ND |
| FZD1 | 0.53 | 0.37 |
| FZD6 | 0.59 | 0.27 |
| HES5 | 0.71 | 0.42 |
| JAG2 | 0.67 | 0.47 |
| MMP7 | 0.63 | ND |
| NCSTN | 0.63 | 0.51 |
| PSEN2 | 0.48 | 0.55 |
| SH2D1A | 0.59 | 0.38 |
| TEAD1 | 0.43 | 0.42 |

ND: No Difference

**Reference**

1. Xiao Y, Ye Y, Zou X, Jones S, Yearsley K, Shetuni B, Tellez J, Barsky SH. The lymphovascular embolus of inflammatory breast cancer exhibits a Notch 3 addiction. *Oncogene* 2010; **30**: 287-300.
2. Mittal S, Subramanyam D, Dey D, Kumar RV, Rangarajan A. Cooperation of Notch and Ras/MAPK signaling pathways in human breast carcinogenesis. *Mol Cancer* 2009; **8**:128.
3. Jason R. Rock, Xia Gao, Yan Xue, Scott H. Randell, Young-Yun Kong, and Brigid L.M. Hogan. Notch-Dependent Differentiation of Adult Airway Basal Stem Cells. *Cell Stem Cell*, 2011; **8**: 639-48.
4. Rosanò L, Cianfrocca R, Tocci P, Spinella F, Di Castro V, Caprara V, Semprucci E, Ferrandina G, Natali PG, Bagnato A. Endothelin A receptor/β-arrestin signaling to the Wnt pathway renders ovarian cancer cells resistant to chemotherapy. *Cancer Res* 2014; **74**:7453-64.
5. Rani N, Nowakowski TJ, Zhou H, Godshalk SE, Lisi V, Kriegstein AR, Kosik KS. A Primate lncRNA Mediates Notch Signaling during Neuronal Development by Sequestering miRNA. *Neuron* 2016; **90**:1174-88.
6. Ulasov IV, Nandi S, Dey M, Sonabend AM, Lesniak MS. Inhibition of Sonic hedgehog and Notch pathways enhances sensitivity of CD133(+) glioma stem cells to temozolomide therapy. *Mol Med* 2011; **17**:103-12.
7. Raghu H, Gondi CS, Dinh DH, Gujrati M, Rao JS. Specific knockdown of uPA/uPAR attenuates invasion in glioblastoma cells and xenografts by inhibition of cleavage and trafficking of Notch -1 receptor. *Mol Cancer* 2011; **10**:130-139.
8. Tian C, Li Y, Huang Y, Wang Y, Chen D, Liu J, Deng X, Sun L, Anderson K, Qi X, Li Y, Mosley RL, Chen X, Huang J, Zheng JC. Selective Generation of Dopaminergic Precursors from Mouse Fibroblasts by Direct Lineage Conversion. Sci Rep 2015; **5**:12622-21630.
9. Noisa P, Lund C, Kanduri K, Lund R, Lähdesmäki H, Lahesmaa R, Lundin K, Chokechuwattanalert H, Otonkoski T, Tuuri T, Raivio T. Notch signaling regulates the differentiation of neural crest from human pluripotent stem cells. *J Cell Sci* 2014; **127**:2083-94.
10. Wang SD1, Rath P, Lal B, Richard JP, Li Y, Goodwin CR, Laterra J, Xia S. EphB2 receptor controls proliferation/migration dichotomy of glioblastoma by interacting with focal adhesion kinase. *Oncogene* 2012 **31**:5132-43.
11. Guo BH, Feng Y, Zhang R, Xu LH, Li MZ, Kung HF, Song LB, Zeng MS. Bmi-1 promotes invasion and metastasis, and its elevated expression is correlated with an advanced stage of breast cancer. *Mol Cancer* 2011;**10**:10.
12. Yoon O, Roh J. Downregulation of KLF4 and the Bcl-2/Bax ratio in advanced epithelial ovarian cancer. *Oncol Lett* 2012; **4**:1033-1036.
13. Shimozato O, Waraya M, Nakashima K, Souda H, Takiguchi N, Yamamoto H, Takenobu H, Uehara H, Ikeda E, Matsushita S, Kubo N, Nakagawara A, Ozaki T, Kamijo T. Receptor-type protein tyrosine phosphatase κ directly dephosphorylates CD133 and regulates downstream AKT activation. *Oncogene* 2014; **34**: 1949-1960.
14. Lu Y, Lu J, Li X, Zhu H, Fan X, Zhu S, Wang Y, Guo Q, Wang L, Huang Y, Zhu M1, Wang Z. MiR-200a inhibits epithelial-mesenchymal transition of pancreatic cancer stem cell. *BMC Cancer*. 2014;**14**:85.
15. Huang HP, Chen PH, Yu CY, Chuang CY, Stone L, Hsiao WC, Li CL, Tsai SC, Chen KY, Chen HF, Ho HN, Kuo HC. Epithelial cell adhesion molecule (EpCAM) complex proteins promote transcription factor-mediated pluripotency reprogramming. *J Biol Chem* 2011; **286**: 33520-32.
16. Wang S, Huang J, Lyu H, Lee CK, Tan J, Wang J, Liu B. Functional cooperation of miR-125a, miR-125b, and miR-205 in entinostat-induced downregulation of erbB2/erbB3 and apoptosis in breast cancer cells. *Cell Death Dis* 2013; **4**: 556-560.
17. Bengochea A, de Souza MM, Lefrançois L, Le Roux E, Galy O, Chemin I, Kim M, Wands JR, Trepo C, Hainaut P, Scoazec JY, Vitvitski L, Merle P. Common Br dysregulation of Wnt/Frizzled receptor elements in human hepatocellular carcinoma *Open J Cancer* 2008; **99**: 143-150.
18. Kim DJ1, Kim J, Spaunhurst K, Montoya J, Khodosh R, Chandra K, Fu T, Gilliam A, Molgo M, Beachy PA, Tang JY. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma.J Clin Oncol. 2014; **8**:745-51.
19. Y Huang, J Chen, C Lu, J Han, G Wang, C Song, S Zhu, C Wang, G Li, J Kang and J Wang HDAC1 and Klf4 interplay critically regulates human myeloid leukemia cell proliferation Cell Death Dis 5: e1491; doi:10.1038/cddis.2014.433
20. Ito T-K, Ishii G, Chiba H, Ochiai A. The VEGF angiogenic switch of fibroblasts is regulated by MMP-7 from cancer cells. *Oncogene* 2007; **26**: 7194-7203.
21. Kang MJ, Abdelmohsen K, Hutchison ER, Mitchell SJ, Grammatikakis I, Guo R, Noh JH, Martindale JL, Yang X, Lee EK, Faghihi MA, Wahlestedt C, Troncoso JC, Pletnikova O, Perrone-Bizzozero N, Resnick SM, de Cabo R, Mattson MP, Gorospe M. HuD regulates coding and noncoding RNA to induce APP→Aβ processing. *Cell Rep.* 2014; **7**: 1401-9.
22. Schlums H, Cichocki F, Tesi B, Theorell J, Beziat V, Holmes TD, Han H, Chiang SC, Foley B, Mattsson K, Larsson S, Schaffer M, Malmberg KJ, Ljunggren HG, Miller JS, Bryceson YT. Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells with altered signaling and effector function. *Immunity*. 2015; **42**: 443-56
23. Zhan X, Wang J, Liu Y, Peng Y, Tan W. GPCR-like signaling mediated by smoothened contributes to acquired chemoresistance through activating Gli*. Mol Cancer* 2014; **13**:4-10.
24. Kurita S, Mott J L, Almada L L, Bronk S F, Werneburg N W, Sun S-Y, Roberts L R, Fernandez-Zapico M E, Gores G J. GLI3-dependent repression of DR4 mediates hedgehog antagonism of TRAIL-induced apoptosis. *Oncogene* 2010; **29**: 4848-4858.
25. Gurgel CA1, Buim ME, Carvalho KC, Sales CB, Reis MG, de Souza RO, de Faro Valverde L, de Azevedo RA, Dos Santos JN, Soares FA, Ramos EA. Transcriptional profiles of SHH pathway genes in keratocystic odontogenic tumor and ameloblastoma. *J Oral Pathol Med* 2014; **43**: 619-26.
26. Zhou GX, Li XY, Zhang Q, Zhao K, Zhang CP, Xue CH, Yang K, Tian ZB. Effects of the hippo signaling pathway in human gastric cancer. *Asian Pac J Cancer Prev* 2013; **14**: 5199-205.