

**Supplementary Table S1.** Genes mutated in intestinal and pancreatobiliary differentiation (number of patients)

| Intestinal differentiation |                    |                    | Pancreatobiliary differentiation |                     |
|----------------------------|--------------------|--------------------|----------------------------------|---------------------|
| <i>ALK</i> (1)             | <i>ICOSLG</i> (1)  | <i>POLE</i> (1)    | <i>ANKRD11</i> (1)               | <i>MGA</i> (1)      |
| <i>APC</i> (6)             | <i>IDH1</i> (1)    | <i>PPARG</i> (1)   | <i>APC</i> (1)                   | <i>MLH1</i> (1)     |
| <i>ARID2</i> (2)           | <i>INSR</i> (1)    | <i>PREX2</i> (1)   | <i>ARAF</i> (1)                  | <i>MSH3</i> (1)     |
| <i>ATM</i> (1)             | <i>JAK3</i> (1)    | <i>PRKARIA</i> (1) | <i>ARID2</i> (1)                 | <i>MST1R</i> (1)    |
| <i>ATRX</i> (1)            | <i>KDR</i> (1)     | <i>PTPRT</i> (2)   | <i>ATM</i> (1)                   | <i>MTOR</i> (1)     |
| <i>BAP1</i> (1)            | <i>KMT2A</i> (3)   | <i>RAD52</i> (1)   | <i>CD79A</i> (1)                 | <i>NEGR1</i> (1)    |
| <i>BMPRIA</i> (1)          | <i>KMT2B</i> (3)   | <i>RASAI</i> (1)   | <i>CTCF</i> (1)                  | <i>NFI</i> (1)      |
| <i>CTNNB1</i> (3)          | <i>KMT2C</i> (1)   | <i>RBM10</i> (1)   | <i>CTNNB1</i> (1)                | <i>NOTCH2</i> (1)   |
| <i>DDR2</i> (1)            | <i>KMT2D</i> (2)   | <i>RECQL4</i> (1)  | <i>ERBB2</i> (1)                 | <i>NUP93</i> (1)    |
| <i>DIS3</i> (1)            | <i>KRAS</i> (5)    | <i>RET</i> (1)     | <i>ERBB4</i> (1)                 | <i>PARP1</i> (1)    |
| <i>DNMT3A</i> (1)          | <i>MAP3K1</i> (1)  | <i>RICTOR</i> (2)  | <i>FAM46C</i> (1)                | <i>PDCD1LG2</i> (1) |
| <i>DROSHA</i> (1)          | <i>MAPK1</i> (1)   | <i>ROS1</i> (1)    | <i>FAT1</i> (1)                  | <i>PIK3C2G</i> (1)  |
| <i>EGFR</i> (1)            | <i>MAPKAP1</i> (1) | <i>RPS6KB2</i> (1) | <i>FOXA1</i> (1)                 | <i>PIK3R3</i> (1)   |
| <i>EPHA3</i> (2)           | <i>MDC1</i> (1)    | <i>SDHA</i> (1)    | <i>H3F3B</i> (1)                 | <i>POLE</i> (1)     |
| <i>EPHA5</i> (3)           | <i>MPL</i> (1)     | <i>SF3B1</i> (1)   | <i>HGF</i> (1)                   | <i>PRKARIA</i> (1)  |
| <i>ERBB2</i> (2)           | <i>MSH2</i> (1)    | <i>SLX4</i> (2)    | <i>HIST1H3F</i> (1)              | <i>PTPRD</i> (2)    |
| <i>ERBB3</i> (2)           | <i>MSH6</i> (1)    | <i>SMAD4</i> (5)   | <i>HNF1A</i> (1)                 | <i>ROS1</i> (2)     |
| <i>ERBB4</i> (1)           | <i>MTOR</i> (1)    | <i>SMARCB1</i> (1) | <i>ICOSLG</i> (1)                | <i>RTEL1</i> (1)    |
| <i>ERCC2</i> (1)           | <i>NOTCH3</i> (3)  | <i>STK40</i> (1)   | <i>IFNGR1</i> (1)                | <i>SHOC2</i> (1)    |
| <i>ERCC3</i> (1)           | <i>NOTCH4</i> (1)  | <i>TAP1</i> (1)    | <i>IL7R</i> (1)                  | <i>SMAD4</i> (2)    |
| <i>FAM175A</i> (1)         | <i>NUP93</i> (1)   | <i>TCF7L2</i> (1)  | <i>IRS1</i> (1)                  | <i>SPRED1</i> (1)   |
| <i>FANCA</i> (2)           | <i>PAX5</i> (1)    | <i>TMEM127</i> (1) | <i>KDM6A</i> (1)                 | <i>TAP1</i> (1)     |
| <i>FAT1</i> (2)            | <i>PGR</i> (1)     | <i>TP53</i> (8)    | <i>KMT2A</i> (1)                 | <i>TEK</i> (1)      |
| <i>FBXW7</i> (1)           | <i>PIK3C2G</i> (1) | <i>TRAF7</i> (1)   | <i>KMT2D</i> (1)                 | <i>TGFBR1</i> (1)   |
| <i>FGFR3</i> (1)           | <i>PIK3CA</i> (2)  | <i>XIAP</i> (1)    | <i>KRAS</i> (3)                  | <i>TP53</i> (4)     |
| <i>GLI1</i> (1)            | <i>PMS1</i> (1)    |                    | <i>MALT1</i> (1)                 |                     |

**Supplementary Table S2.** Patients with intestinal (INT) and pancreatobiliary (PB) differentiation with pathogenic somatic mutations

| Patient No. | Tumor differentiation | Gene  |
|-------------|-----------------------|---|
| 1           | INT                   | <i>ATM, ERCC3, KMT2b, KRAS, MAPKAP1</i>                           |
| 2           | INT                   | <i>APC, RPS6KB2, SMARCB1, TP53</i>                                |
| 3           | PB                    | <i>ARID2, ERBB4, NF1, SHOC2, TP53</i>                             |
| 4           | INT                   | <i>CTNNB1, ERBB4, NOTCH3, PTPRT, RASA1, SMAD4, TP53</i>           |
| 5           | PB                    | <i>KDM6A, KMT2D, RTEL1, SMAD4, TAP1, TP53</i>                     |
| 6           | INT                   | <i>EPHA5, KTM2B, SMAD4</i>  |
| 7           | INT                   | <i>DNMT3A, FBXW7, NOTCH3, PRKARIA, RICTOR, TP53</i>               |
| 8           | PB                    |   |
| 9           | PB                    | <i>KRAS, TGFRB1</i>   |
| 10          | PB                    | <i>FAT1, FOXA1, HGF, IRS1, MGA, SMAD4</i>                         |
| 11          | Mixed                 | <i>STK11, KEAP1, KRAS, CSF1R</i>                                  |
| 12          | INT                   | <i>KRAS</i>   |
| 13          | INT                   | <i>APC, KRAS, NOTCH3, PGR, PIK3C2G</i>                            |
| 14          | PB                    |   |
| 15          | PB                    | <i>CTNNB1, HIST1H3F, PARP1, TP53</i>                              |
| 16          |                       | <i>ATRX, CTNNB1, EPHA5, ERCC2, FAM175A, FAT1, FGFR3, MSH2,</i>    |
|             | INT                   | <i>NOTCH4, PREX2, SF3B1, SLX4, STK40, TCF7L2</i>                  |
| 17          | INT                   | <i>APC, FAT1, KMT2A, KRAS, TRAF7</i>                              |
| 18          | INT                   | <i>EPHA3, ERBB2</i>   |
| 19          | PB                    |   |
| 20          | INT                   | <i>APC, DDR2, DROSHA, TP53</i>                                    |
| 21          | PB                    | <i>NEGR1, NUP93, TP53</i>   |
| 22          |                       | <i>APC, BAP1, BMPR1A, ERBB3, FANCA, FAT1, GLI1, ICOSLG, IDH1,</i> |
|             |                       | <i>INSR, KDR, KMT2A, KMT2B, KMT2C, MDC1, MSH6, NUP93, MPL,</i>    |
|             |                       | <i>PAX5, PMS1, POLE, PPARG, RAD52, RICTOR, ROS1, SDHA, SLX4,</i>  |
|             | INT                   | <i>TAP1, TMEM127, XIAP</i>  |
| 23          | PB                    |   |
| 24          |                       | <i>ANKRD11, APC, ATM, CD79A, CTCF, ERBB2, FAM46C, H3F3B,</i>      |
|             |                       | <i>HNFI1A, ICOSLG, IFNGR1, IL7R, KMT2A, MALT1, MLH1, MSH3,</i>    |
|             |                       | <i>MST1R, MTOR, NOTCH2, PDCD1LG2, PIK3C2G, POLE, PRKARIA,</i>     |
|             | PB                    | <i>PTPRD, ROS1, SPRED1, TAP1, TEK</i>                             |
| 25          | INT                   | <i>ERBB3, JAK3</i>  |
| 26          | Mixed                 | <i>KRAS, SMAD4</i>  |
| 27          | INT                   | <i>ARID2, CTNNB1, DIS3, EGFR, KMT2D, TP53</i>                     |
| 28          | INT                   | <i>EPHA5, KMT2D, MAPK1, TP53</i>                                  |
| 29          | INT                   | <i>ALK, APC, MAP3K1, SMAD4</i>                                    |
| 30          | INT                   | <i>KRAS, SMAD4</i>  |
| 31          | INT                   | <i>EPHA3, PIK3CA</i>  |
| 32          | PB                    | <i>ARAF, KRAS, PIK3R3, PTPRD, ROS1</i>                            |
| 33          | PB                    | <i>KRAS</i>   |
| 34          | INT                   | No pathogenic somatic mutation                                    |
| 35          | INT                   | <i>IKZF1, MTOR, PTPRT, TP53</i>                                   |
| 36          | INT                   | <i>AIRD2, PIK3CA, RET, TP53</i>                                   |
| 37          | INT                   | <i>FANCA, KMT2A, RBM10, RECQL4, SMAD4</i>                         |