

Table SI. Most frequently altered genes in 66 cases of cholangiocarcinoma.

| Gene    | SNV/ShortIndel | CNV | Fusion | LongIndel | Total | Ratio, % |
|---------|----------------|-----|--------|-----------|-------|----------|
| TP53    | 41             | 0   | 1      | 0         | 42    | 62.12    |
| KRAS    | 23             | 1   | 0      | 0         | 24    | 36.36    |
| SMAD4   | 18             | 1   | 0      | 0         | 19    | 24.24    |
| TERT    | 13             | 1   | 0      | 0         | 14    | 21.21    |
| ARID1A  | 11             | 1   | 0      | 1         | 13    | 19.70    |
| CDKN2A  | 10             | 1   | 1      | 1         | 13    | 19.70    |
| RBM10   | 5              | 0   | 1      | 0         | 6     | 9.09     |
| KMT2C   | 6              | 0   | 0      | 0         | 6     | 9.09     |
| NF1     | 6              | 0   | 0      | 0         | 6     | 4.55     |
| ERBB2   | 3              | 1   | 1      | 0         | 5     | 7.58     |
| BRAF    | 4              | 1   | 0      | 0         | 5     | 7.58     |
| STK11   | 4              | 0   | 0      | 1         | 5     | 4.55     |
| SMARCA4 | 3              | 0   | 0      | 1         | 4     | 6.06     |
| FBXW7   | 4              | 0   | 0      | 0         | 4     | 6.06     |
| LRP2    | 4              | 0   | 0      | 0         | 4     | 6.06     |
| PIK3CA  | 4              | 0   | 0      | 0         | 4     | 6.06     |
| FAT3    | 4              | 0   | 0      | 0         | 4     | 6.06     |
| CCND1   | 0              | 4   | 0      | 0         | 4     | 6.06     |
| FGF19   | 0              | 4   | 0      | 0         | 4     | 6.06     |
| FGF4    | 0              | 4   | 0      | 0         | 4     | 6.06     |
| FGF3    | 0              | 4   | 0      | 0         | 4     | 6.06     |
| PBRM1   | 4              | 0   | 0      | 0         | 4     | 6.06     |
| FGFR2   | 0              | 0   | 4      | 0         | 4     | 6.06     |
| FAT1    | 3              | 0   | 0      | 0         | 3     | 4.55     |
| KDM5A   | 1              | 2   | 0      | 0         | 3     | 4.55     |
| KEAP1   | 3              | 0   | 0      | 0         | 3     | 3.03     |
| RNF43   | 3              | 0   | 0      | 0         | 3     | 4.55     |
| NSD2    | 1              | 2   | 0      | 0         | 3     | 4.55     |
| KMT2D   | 3              | 0   | 0      | 0         | 3     | 4.55     |
| ATM     | 3              | 0   | 0      | 0         | 3     | 3.03     |
| LRP1B   | 3              | 0   | 0      | 0         | 3     | 3.03     |
| MDM2    | 0              | 3   | 0      | 0         | 3     | 4.55     |
| FRS2    | 0              | 3   | 0      | 0         | 3     | 4.55     |
| TGFBR2  | 3              | 0   | 0      | 0         | 3     | 4.55     |
| MET     | 0              | 3   | 0      | 0         | 3     | 4.55     |
| GLI3    | 3              | 0   | 0      | 0         | 3     | 4.55     |
| GNAS    | 3              | 0   | 0      | 0         | 3     | 4.55     |
| MAGI2   | 3              | 0   | 0      | 0         | 3     | 4.55     |
| SPTA1   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| CTNNB1  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| U2AF1   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| NOTCH1  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| RAD52   | 0              | 2   | 0      | 0         | 2     | 3.03     |
| ARID2   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| ERBB3   | 1              | 1   | 0      | 0         | 2     | 3.03     |
| AXIN1   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| CREBBP  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| AXIN2   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| NOTCH3  | 1              | 1   | 0      | 0         | 2     | 3.03     |
| CFTR    | 1              | 1   | 0      | 0         | 2     | 3.03     |
| SMAD3   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| MAP2K2  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| MYC     | 0              | 2   | 0      | 0         | 2     | 3.03     |
| SLIT2   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| TGFBR1  | 1              | 1   | 0      | 0         | 2     | 3.03     |
| CCNE1   | 0              | 2   | 0      | 0         | 2     | 3.03     |

Table SI. Continued.

| Gene    | SNV/ShortIndel | CNV | Fusion | LongIndel | Total | Ratio, % |
|---------|----------------|-----|--------|-----------|-------|----------|
| ZNF750  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| SF3B1   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| AR      | 2              | 0   | 0      | 0         | 2     | 3.03     |
| FGFR3   | 0              | 2   | 0      | 0         | 2     | 3.03     |
| RHBDF2  | 1              | 1   | 0      | 0         | 2     | 3.03     |
| RET     | 1              | 1   | 0      | 0         | 2     | 3.03     |
| TET1    | 1              | 0   | 0      | 1         | 2     | 3.03     |
| BRCA1   | 1              | 0   | 1      | 0         | 2     | 3.03     |
| NOTCH2  | 0              | 2   | 0      | 0         | 2     | 3.03     |
| MCL1    | 0              | 2   | 0      | 0         | 2     | 3.03     |
| NTRK1   | 0              | 2   | 0      | 0         | 2     | 3.03     |
| DDR2    | 0              | 2   | 0      | 0         | 2     | 3.03     |
| MYB     | 1              | 1   | 0      | 0         | 2     | 3.03     |
| IDH1    | 2              | 0   | 0      | 0         | 2     | 3.03     |
| ATRX    | 2              | 0   | 0      | 0         | 2     | 3.03     |
| SMARCD1 | 1              | 0   | 1      | 0         | 2     | 3.03     |
| SMAD2   | 1              | 0   | 0      | 1         | 2     | 3.03     |
| MAP2K4  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| BRCA2   | 2              | 0   | 0      | 0         | 2     | 3.03     |
| EGFR    | 0              | 2   | 0      | 0         | 2     | 3.03     |
| CHEK2   | 1              | 1   | 0      | 0         | 2     | 3.03     |
| APC     | 2              | 0   | 0      | 0         | 2     | 3.03     |
| PIK3R1  | 2              | 0   | 0      | 0         | 2     | 3.03     |
| ROCK1   | 0              | 2   | 0      | 0         | 2     | 3.03     |
| GATA6   | 0              | 2   | 0      | 0         | 2     | 3.03     |
| CRKL    | 0              | 2   | 0      | 0         | 2     | 3.03     |
| MTOR    | 2              | 0   | 0      | 0         | 2     | 3.03     |
| PTEN    | 1              | 1   | 0      | 0         | 2     | 3.03     |
| TBX3    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PMS2    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FLI1    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| RARA    | 0              | 1   | 0      | 0         | 1     | 1.52     |
| TOP2A   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| CDK8    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| GRM3    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| TCF7L2  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FGF14   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| MSH2    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| STAT4   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| ERBB4   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| ABL1    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| TSC1    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| KDM6A   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| KDM5C   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| CREB3L2 | 0              | 1   | 0      | 0         | 1     | 1.52     |
| MRE11   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PTPN11  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FAM135B | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PIK3CG  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| NRAS    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| MEN1    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FLT1    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PPP2R1A | 0              | 1   | 0      | 0         | 1     | 1.52     |
| TSC2    | 0              | 0   | 0      | 1         | 1     | 1.52     |
| TP63    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PDGFRB  | 1              | 0   | 0      | 0         | 1     | 1.52     |

Table SI. Continued.

| Gene   | SNV/ShortIndel | CNV | Fusion | LongIndel | Total | Ratio, % |
|--------|----------------|-----|--------|-----------|-------|----------|
| PKD2   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| BLK    | 0              | 1   | 0      | 0         | 1     | 1.52     |
| ETV6   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| NOTCH4 | 1              | 0   | 0      | 0         | 1     | 1.52     |
| GLI1   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| CDK4   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| EMSY   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| CDK6   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| IDH2   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PARP1  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| RXRA   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| SPEN   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| CUL3   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| RAD50  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FANCA  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| MSH6   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| MACC1  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FANCL  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| MAP2K1 | 1              | 0   | 0      | 0         | 1     | 1.52     |
| ACVR1B | 1              | 0   | 0      | 0         | 1     | 1.52     |
| CCND3  | 0              | 1   | 0      | 0         | 1     | 1.52     |
| VEGFA  | 0              | 1   | 0      | 0         | 1     | 1.52     |
| JAK1   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| CDKN2B | 0              | 1   | 0      | 0         | 1     | 1.52     |
| DPYD   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| BAP1   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| EPHA7  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| SOX9   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| ACVR2A | 1              | 0   | 0      | 0         | 1     | 1.52     |
| KDR    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| CTNNA1 | 1              | 0   | 0      | 0         | 1     | 1.52     |
| JAK2   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| NTRK2  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FAS    | 0              | 1   | 0      | 0         | 1     | 1.52     |
| GLI2   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| KAT6A  | 0              | 1   | 0      | 0         | 1     | 1.52     |
| LRP1   | 0              | 0   | 0      | 1         | 1     | 1.52     |
| ERRFI1 | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FLT3   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| XPO1   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| RIT1   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| CEBPA  | 0              | 1   | 0      | 0         | 1     | 1.52     |
| AKT2   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| AXL    | 0              | 1   | 0      | 0         | 1     | 1.52     |
| ERCC1  | 0              | 1   | 0      | 0         | 1     | 1.52     |
| BCR    | 0              | 1   | 0      | 0         | 1     | 1.52     |
| BCOR   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FUBP1  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FANCG  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| ASXL1  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| STAT3  | 0              | 1   | 0      | 0         | 1     | 1.52     |
| BCORL1 | 0              | 1   | 0      | 0         | 1     | 1.52     |
| PHF6   | 0              | 1   | 0      | 0         | 1     | 1.52     |
| ESR1   | 0              | 0   | 0      | 1         | 1     | 1.52     |
| DNMT3A | 1              | 0   | 0      | 0         | 1     | 1.52     |
| ALK    | 1              | 0   | 0      | 0         | 1     | 1.52     |

Table SI. Continued.

| Gene   | SNV/ShortIndel | CNV | Fusion | LongIndel | Total | Ratio, % |
|--------|----------------|-----|--------|-----------|-------|----------|
| DDR1   | 1              | 0   | 0      | 0         | 1     | 1.52     |
| EPHA3  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FGR    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| SETD2  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PREX2  | 1              | 0   | 0      | 0         | 1     | 1.52     |
| FYN    | 1              | 0   | 0      | 0         | 1     | 1.52     |
| PRKACA | 0              | 1   | 0      | 0         | 1     | 1.52     |
| BRD4   | 0              | 1   | 0      | 0         | 1     | 1.52     |

SNV, single nucleotide variants; Indels, insertion-deletion polymorphisms; CNV, copy number variation.

Table SII. Frequency of mutated site in TP53 and KRAS.

| Gene | VAR_TYPE                           | Mutant number |
|------|------------------------------------|---------------|
| TP53 | E285V                              | 1             |
| TP53 | C135F                              | 1             |
| TP53 | N239D                              | 1             |
| TP53 | G245C                              | 1             |
| TP53 | R248Q                              | 4             |
| TP53 | K132N                              | 1             |
| TP53 | Y220C                              | 1             |
| TP53 | C141Y                              | 1             |
| TP53 | R213*                              | 2             |
| TP53 | I195T                              | 1             |
| TP53 | R342*                              | 2             |
| TP53 | R175H                              | 2             |
| TP53 | I251Hfs*13                         | 1             |
| TP53 | I332Sfs*7                          | 1             |
| TP53 | R273C                              | 1             |
| TP53 | S94*                               | 1             |
| TP53 | c.993+1_993+3delinsT (splice site) | 1             |
| TP53 | R273L                              | 1             |
| TP53 | T155Gfs*24                         | 1             |
| TP53 | G244D                              | 1             |
| TP53 | c.993+1G>A (splice site)           | 2             |
| TP53 | A159V                              | 1             |
| TP53 | R249S                              | 1             |
| TP53 | S241Y                              | 1             |
| TP53 | I255F                              | 1             |
| TP53 | L308Tfs*35                         | 1             |
| TP53 | H214Qfs*7                          | 1             |
| TP53 | c.375G>A (splice site)             | 1             |
| TP53 | L264_N268del                       | 1             |
| TP53 | G302Rfs*4                          | 1             |
| TP53 | Intergenic/TP53 (rearrangement)    | 1             |
| TP53 | D41Gfs*4                           | 1             |
| TP53 | L252P                              | 1             |
| TP53 | L308Rfs*37                         | 1             |
| TP53 | Q167Hfs*4                          | 1             |
| KRAS | G12V                               | 6             |
| KRAS | G12C                               | 1             |
| KRAS | G12D                               | 6             |
| KRAS | G12R                               | 1             |
| KRAS | G12S                               | 1             |
| KRAS | G13C                               | 2             |
| KRAS | G13D                               | 3             |
| KRAS | Q61H                               | 2             |
| KRAS | A146P                              | 1             |
| KRAS | Amplification                      | 1             |

Var\_type, variant type.

Table SIII. Altered genes in iCCA and exCCA.

| Gene   | iCCA (n=290)  |                 | exCCA (n=141) |                 | P-value   |
|--------|---------------|-----------------|---------------|-----------------|-----------|
|        | Mutant number | Mutant ratio, % | Mutant number | Mutant ratio, % |           |
| TP53   | 25            | 56.82           | 16            | 72.73           | 0.1730699 |
| KRAS   | 13            | 29.55           | 11            | 50.00           | 0.1009249 |
| SMAD4  | 8             | 18.18           | 8             | 36.36           | 0.1228768 |
| TERT   | 9             | 20.45           | 5             | 22.73           | 0.7565224 |
| CDKN2A | 8             | 18.18           | 5             | 22.73           | 0.7416156 |
| ARID1A | 6             | 13.64           | 7             | 31.82           | 0.0963127 |
| RBM10  | 1             | 2.27            | 5             | 22.73           | 0.0114968 |
| STK11  | 3             | 6.82            | 0             | 0               | 0.5451923 |
| CCND1  | 4             | 9.09            | 0             | 0               | 0.2957816 |
| FGF19  | 4             | 9.09            | 0             | 0               | 0.2957816 |
| FGF3   | 4             | 9.09            | 0             | 0               | 0.2957816 |
| FGF4   | 4             | 9.09            | 0             | 0               | 0.2957816 |
| FGFR2  | 4             | 9.09            | 0             | 0               | 0.2957816 |
| PBRM1  | 4             | 9.09            | 0             | 0               | 0.2957816 |
| FAT3   | 3             | 6.82            | 1             | 4.55            | 1         |
| FRS2   | 3             | 6.82            | 0             | 0               | 0.5451923 |
| GLI3   | 3             | 6.82            | 0             | 0               | 0.5451923 |
| GNAS   | 3             | 6.82            | 0             | 0               | 0.5451923 |
| KMT2C  | 3             | 6.82            | 3             | 13.64           | 0.3787582 |
| MAGI2  | 3             | 6.82            | 0             | 0               | 0.5451923 |
| MDM2   | 3             | 6.82            | 0             | 0               | 0.5451923 |
| MET    | 3             | 6.82            | 0             | 0               | 0.5451923 |
| NF1    | 3             | 6.82            | 3             | 13.64           | 1         |
| TGFBR2 | 3             | 6.82            | 0             | 0               | 0.5451923 |
| APC    | 2             | 4.55            | 0             | 0               | 1         |
| AR     | 2             | 4.55            | 0             | 0               | 1         |
| ATRX   | 2             | 4.55            | 0             | 0               | 1         |
| BRAF   | 2             | 4.55            | 3             | 13.64           | 0.3181492 |
| BRCA1  | 2             | 4.55            | 0             | 0               | 1         |
| BRCA2  | 2             | 4.55            | 0             | 0               | 1         |
| CHEK2  | 2             | 4.55            | 0             | 0               | 1         |
| CRKL   | 2             | 4.55            | 0             | 0               | 1         |
| DDR2   | 2             | 4.55            | 0             | 0               | 1         |
| EGFR   | 2             | 4.55            | 0             | 0               | 1         |
| ERBB2  | 2             | 4.55            | 3             | 13.64           | 0.3181492 |
| FAT1   | 2             | 4.55            | 1             | 4.55            | 1         |
| FBXW7  | 2             | 4.55            | 2             | 9.09            | 0.589206  |
| FGFR3  | 2             | 4.55            | 0             | 0               | 1         |
| GATA6  | 2             | 4.55            | 0             | 0               | 1         |
| IDH1   | 2             | 4.55            | 0             | 0               | 1         |
| KDM5A  | 2             | 4.55            | 1             | 4.55            | 1         |
| KEAP1  | 2             | 4.55            | 1             | 4.55            | 0.5451923 |
| KMT2D  | 2             | 4.55            | 1             | 4.55            | 1         |
| LRP2   | 2             | 4.55            | 2             | 9.09            | 0.589206  |
| MAP2K4 | 2             | 4.55            | 0             | 0               | 1         |
| MCL1   | 2             | 4.55            | 0             | 0               | 1         |
| MTOR   | 2             | 4.55            | 0             | 0               | 1         |
| MYB    | 2             | 4.55            | 0             | 0               | 1         |
| NOTCH2 | 2             | 4.55            | 0             | 0               | 1         |
| NSD2   | 2             | 4.55            | 1             | 4.55            | 1         |
| NTRK1  | 2             | 4.55            | 0             | 0               | 1         |
| PIK3CA | 2             | 4.55            | 2             | 9.09            | 0.589206  |
| PIK3R1 | 2             | 4.55            | 0             | 0               | 1         |
| PTEN   | 2             | 4.55            | 0             | 0               | 1         |

Table SIII. Continued.

| Gene    | iCCA (n=290)  |                 | exCCA (n=141) |                 | P-value   |
|---------|---------------|-----------------|---------------|-----------------|-----------|
|         | Mutant number | Mutant ratio, % | Mutant number | Mutant ratio, % |           |
| RET     | 2             | 4.55            | 0             | 0               | 1         |
| RHBDF2  | 2             | 4.55            | 0             | 0               | 1         |
| ROCK1   | 2             | 4.55            | 0             | 0               | 1         |
| SF3B1   | 2             | 4.55            | 0             | 0               | 1         |
| SMAD2   | 2             | 4.55            | 0             | 0               | 1         |
| SMARCA4 | 2             | 4.55            | 2             | 9.09            | 0.589206  |
| SMARCD1 | 2             | 4.55            | 0             | 0               | 1         |
| TET1    | 2             | 4.55            | 0             | 0               | 1         |
| ACVR1B  | 1             | 2.27            | 0             | 0               | 1         |
| ACVR2A  | 1             | 2.27            | 0             | 0               | 1         |
| AKT2    | 1             | 2.27            | 0             | 0               | 1         |
| ALK     | 1             | 2.27            | 0             | 0               | 1         |
| ARID2   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| ASXL1   | 1             | 2.27            | 0             | 0               | 1         |
| ATM     | 1             | 2.27            | 2             | 9.09            | 0.5451923 |
| AXIN1   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| AXIN2   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| AXL     | 1             | 2.27            | 0             | 0               | 1         |
| BAP1    | 1             | 2.27            | 0             | 0               | 1         |
| BCOR    | 1             | 2.27            | 0             | 0               | 1         |
| BCORL1  | 1             | 2.27            | 0             | 0               | 1         |
| BCR     | 1             | 2.27            | 0             | 0               | 1         |
| BLK     | 1             | 2.27            | 0             | 0               | 1         |
| BRD4    | 1             | 2.27            | 0             | 0               | 1         |
| CCND3   | 1             | 2.27            | 0             | 0               | 1         |
| CCNE1   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| CDK4    | 1             | 2.27            | 0             | 0               | 1         |
| CDK6    | 1             | 2.27            | 0             | 0               | 1         |
| CDKN2B  | 1             | 2.27            | 0             | 0               | 1         |
| CEBPA   | 1             | 2.27            | 0             | 0               | 1         |
| CFTR    | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| CTNNA1  | 1             | 2.27            | 0             | 0               | 1         |
| CTNNB1  | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| CUL3    | 1             | 2.27            | 0             | 0               | 1         |
| DDR1    | 1             | 2.27            | 0             | 0               | 1         |
| DNMT3A  | 1             | 2.27            | 0             | 0               | 1         |
| DPYD    | 1             | 2.27            | 0             | 0               | 1         |
| EMSY    | 1             | 2.27            | 0             | 0               | 1         |
| EPHA3   | 1             | 2.27            | 0             | 0               | 1         |
| EPHA7   | 1             | 2.27            | 0             | 0               | 1         |
| ERBB3   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| ERCC1   | 1             | 2.27            | 0             | 0               | 1         |
| ERRFI1  | 1             | 2.27            | 0             | 0               | 1         |
| ESR1    | 1             | 2.27            | 0             | 0               | 1         |
| ETV6    | 1             | 2.27            | 0             | 0               | 1         |
| FANCA   | 1             | 2.27            | 0             | 0               | 1         |
| FANCG   | 1             | 2.27            | 0             | 0               | 1         |
| FANCL   | 1             | 2.27            | 0             | 0               | 1         |
| FAS     | 1             | 2.27            | 0             | 0               | 1         |
| FGR     | 1             | 2.27            | 0             | 0               | 1         |
| FLT3    | 1             | 2.27            | 0             | 0               | 1         |
| FUBP1   | 1             | 2.27            | 0             | 0               | 1         |
| FYN     | 1             | 2.27            | 0             | 0               | 1         |
| GLI1    | 1             | 2.27            | 0             | 0               | 1         |

Table SIII. Continued.

| Gene    | iCCA (n=290)  |                 | exCCA (n=141) |                 | P-value   |
|---------|---------------|-----------------|---------------|-----------------|-----------|
|         | Mutant number | Mutant ratio, % | Mutant number | Mutant ratio, % |           |
| GLI2    | 1             | 2.27            | 0             | 0               | 1         |
| IDH2    | 1             | 2.27            | 0             | 0               | 1         |
| JAK1    | 1             | 2.27            | 0             | 0               | 1         |
| JAK2    | 1             | 2.27            | 0             | 0               | 1         |
| KAT6A   | 1             | 2.27            | 0             | 0               | 1         |
| KDR     | 1             | 2.27            | 0             | 0               | 1         |
| LRP1    | 1             | 2.27            | 0             | 0               | 1         |
| LRP1B   | 1             | 2.27            | 2             | 9.09            | 0.5451923 |
| MACC1   | 1             | 2.27            | 0             | 0               | 1         |
| MAP2K1  | 1             | 2.27            | 0             | 0               | 1         |
| MAP2K2  | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| MSH6    | 1             | 2.27            | 0             | 0               | 1         |
| MYC     | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| NOTCH3  | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| NOTCH4  | 1             | 2.27            | 0             | 0               | 1         |
| NTRK2   | 1             | 2.27            | 0             | 0               | 1         |
| PARP1   | 1             | 2.27            | 0             | 0               | 1         |
| PDGFRB  | 1             | 2.27            | 0             | 0               | 1         |
| PHF6    | 1             | 2.27            | 0             | 0               | 1         |
| PKD2    | 1             | 2.27            | 0             | 0               | 1         |
| PREX2   | 1             | 2.27            | 0             | 0               | 1         |
| PRKACA  | 1             | 2.27            | 0             | 0               | 1         |
| RAD50   | 1             | 2.27            | 0             | 0               | 1         |
| RAD52   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| RIT1    | 1             | 2.27            | 0             | 0               | 1         |
| RNF43   | 1             | 2.27            | 2             | 9.09            | 0.2419872 |
| RXRA    | 1             | 2.27            | 0             | 0               | 1         |
| SETD2   | 1             | 2.27            | 0             | 0               | 1         |
| SLIT2   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| SOX9    | 1             | 2.27            | 0             | 0               | 1         |
| SPEN    | 1             | 2.27            | 0             | 0               | 1         |
| SPTA1   | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| STAT3   | 1             | 2.27            | 0             | 0               | 1         |
| TGFBR1  | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| VEGFA   | 1             | 2.27            | 0             | 0               | 1         |
| XPO1    | 1             | 2.27            | 0             | 0               | 1         |
| ZNF750  | 1             | 2.27            | 1             | 4.55            | 0.5451923 |
| ABL1    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| CDK8    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| CREB3L2 | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| CREBBP  | 0             | 0.00            | 2             | 9.09            | 0.1009615 |
| ERBB4   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| FAM135B | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| FGF14   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| FLI1    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| FLT1    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| GRM3    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| KDM5C   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| KDM6A   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| MEN1    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| MRE11   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| MSH2    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| NOTCH1  | 0             | 0.00            | 2             | 9.09            | 0.1009615 |
| NRAS    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |

Table SIII. Continued.

| Gene    | iCCA (n=290)  |                 | exCCA (n=141) |                 | P-value   |
|---------|---------------|-----------------|---------------|-----------------|-----------|
|         | Mutant number | Mutant ratio, % | Mutant number | Mutant ratio, % |           |
| PIK3CG  | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| PMS2    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| PPP2R1A | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| PTPN11  | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| RARA    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| SMAD3   | 0             | 0.00            | 2             | 9.09            | 0.1009615 |
| STAT4   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| TBX3    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| TCF7L2  | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| TOP2A   | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| TP63    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| TSC1    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| TSC2    | 0             | 0.00            | 1             | 4.55            | 0.3230769 |
| U2AF1   | 0             | 0.00            | 2             | 9.09            | 0.1009615 |

iCCA, intrahepatic cholangiocarcinoma; exCCA, extrahepatic cholangiocarcinoma.

Table SIV. Highest frequency gene mutations in male and female patients with cholangiocarcinoma.

| A, Male |               |                 |
|---------|---------------|-----------------|
| Gene    | Mutant number | Mutant ratio, % |
| TP53    | 27            | 60.00           |
| KRAS    | 15            | 33.33           |
| TERT    | 11            | 24.44           |
| ARID1A  | 9             | 20.00           |
| CDKN2A  | 7             | 15.56           |
| SMAD4   | 7             | 15.56           |
| CCND1   | 4             | 8.89            |
| FBXW7   | 4             | 8.89            |
| FGF19   | 4             | 8.89            |
| FGF3    | 4             | 8.89            |
| FGF4    | 4             | 8.89            |
| PIK3CA  | 4             | 8.89            |
| NF1     | 3             | 6.67            |
| STK11   | 3             | 6.67            |
| BRAF    | 3             | 6.67            |
| FGFR2   | 3             | 6.67            |
| FRS2    | 3             | 6.67            |
| GLI3    | 3             | 6.67            |
| LRP2    | 3             | 6.67            |
| MDM2    | 3             | 6.67            |
| PBRM1   | 3             | 6.67            |
| RBM10   | 3             | 6.67            |
| SMARCA4 | 3             | 6.67            |
| ATM     | 2             | 4.44            |
| KEAP1   | 2             | 4.44            |
| LRP1B   | 2             | 4.44            |
| AR      | 2             | 4.44            |
| BRCA1   | 2             | 4.44            |
| CCNE1   | 2             | 4.44            |
| CHEK2   | 2             | 4.44            |
| CRKL    | 2             | 4.44            |
| DDR2    | 2             | 4.44            |
| FAT1    | 2             | 4.44            |
| FAT3    | 2             | 4.44            |
| FGFR3   | 2             | 4.44            |
| KMT2C   | 2             | 4.44            |
| KMT2D   | 2             | 4.44            |
| MCL1    | 2             | 4.44            |
| MET     | 2             | 4.44            |
| MYC     | 2             | 4.44            |
| NSD2    | 2             | 4.44            |
| NTRK1   | 2             | 4.44            |
| RET     | 2             | 4.44            |
| RNF43   | 2             | 4.44            |
| SF3B1   | 2             | 4.44            |
| SLIT2   | 2             | 4.44            |
| SMAD3   | 2             | 4.44            |
| SMARCD1 | 2             | 4.44            |
| TET1    | 2             | 4.44            |
| U2AF1   | 2             | 4.44            |
| ACVR1B  | 1             | 2.22            |
| AKT2    | 1             | 2.22            |
| ALK     | 1             | 2.22            |

Table SIV. Continued.

| A, Male |               |                 |
|---------|---------------|-----------------|
| Gene    | Mutant number | Mutant ratio, % |
| APC     | 1             | 2.22            |
| ARID2   | 1             | 2.22            |
| ATRX    | 1             | 2.22            |
| AXIN1   | 1             | 2.22            |
| AXL     | 1             | 2.22            |
| BCOR    | 1             | 2.22            |
| BCR     | 1             | 2.22            |
| BLK     | 1             | 2.22            |
| BRCA2   | 1             | 2.22            |
| BRD4    | 1             | 2.22            |
| CCND3   | 1             | 2.22            |
| CDK4    | 1             | 2.22            |
| CDK6    | 1             | 2.22            |
| CDK8    | 1             | 2.22            |
| CEBPA   | 1             | 2.22            |
| CFTR    | 1             | 2.22            |
| CTNNB1  | 1             | 2.22            |
| CUL3    | 1             | 2.22            |
| DDR1    | 1             | 2.22            |
| DNMT3A  | 1             | 2.22            |
| DPYD    | 1             | 2.22            |
| EGFR    | 1             | 2.22            |
| EMSY    | 1             | 2.22            |
| EPHA3   | 1             | 2.22            |
| EPHA7   | 1             | 2.22            |
| ERCC1   | 1             | 2.22            |
| ESR1    | 1             | 2.22            |
| ETV6    | 1             | 2.22            |
| FAM135B | 1             | 2.22            |
| FANCA   | 1             | 2.22            |
| FANCG   | 1             | 2.22            |
| FANCL   | 1             | 2.22            |
| FAS     | 1             | 2.22            |
| FGR     | 1             | 2.22            |
| FLT1    | 1             | 2.22            |
| FUBP1   | 1             | 2.22            |
| FYN     | 1             | 2.22            |
| GATA6   | 1             | 2.22            |
| GLI1    | 1             | 2.22            |
| GNAS    | 1             | 2.22            |
| GRM3    | 1             | 2.22            |
| IDH1    | 1             | 2.22            |
| IDH2    | 1             | 2.22            |
| JAK1    | 1             | 2.22            |
| KDM5A   | 1             | 2.22            |
| MACC1   | 1             | 2.22            |
| MAGI2   | 1             | 2.22            |
| MAP2K2  | 1             | 2.22            |
| MAP2K4  | 1             | 2.22            |
| MEN1    | 1             | 2.22            |
| MRE11   | 1             | 2.22            |
| MSH6    | 1             | 2.22            |
| NOTCH1  | 1             | 2.22            |
| NOTCH2  | 1             | 2.22            |

Table SIV. Continued.

| A, Male |               |                 |
|---------|---------------|-----------------|
| Gene    | Mutant number | Mutant ratio, % |
| NOTCH3  | 1             | 2.22            |
| NOTCH4  | 1             | 2.22            |
| NRAS    | 1             | 2.22            |
| PDGFRB  | 1             | 2.22            |
| PIK3CG  | 1             | 2.22            |
| PIK3R1  | 1             | 2.22            |
| PKD2    | 1             | 2.22            |
| PPP2R1A | 1             | 2.22            |
| PREX2   | 1             | 2.22            |
| PRKACA  | 1             | 2.22            |
| PTEN    | 1             | 2.22            |
| PTPN11  | 1             | 2.22            |
| RAD50   | 1             | 2.22            |
| RAD52   | 1             | 2.22            |
| RHBDF2  | 1             | 2.22            |
| RIT1    | 1             | 2.22            |
| ROCK1   | 1             | 2.22            |
| RXRA    | 1             | 2.22            |
| SETD2   | 1             | 2.22            |
| SMAD2   | 1             | 2.22            |
| SPEN    | 1             | 2.22            |
| SPTA1   | 1             | 2.22            |
| TGFBR1  | 1             | 2.22            |
| TGFBR2  | 1             | 2.22            |
| TSC2    | 1             | 2.22            |
| VEGFA   | 1             | 2.22            |
| ZNF750  | 1             | 2.22            |

## B, Female

| Gene   | Mutant number | Mutant ratio, % |
|--------|---------------|-----------------|
| TP53   | 14            | 66.67           |
| SMAD4  | 9             | 42.86           |
| KRAS   | 9             | 42.86           |
| CDKN2A | 6             | 28.57           |
| ERBB2  | 5             | 23.81           |
| ARID1A | 4             | 19.05           |
| KMT2C  | 4             | 19.05           |
| RBM10  | 3             | 14.29           |
| TERT   | 3             | 14.29           |
| AXIN2  | 2             | 9.52            |
| BRAF   | 2             | 9.52            |
| CREBBP | 2             | 9.52            |
| ERBB3  | 2             | 9.52            |
| FAT3   | 2             | 9.52            |
| GNAS   | 2             | 9.52            |
| KDM5A  | 2             | 9.52            |
| MAGI2  | 2             | 9.52            |
| MTOR   | 2             | 9.52            |
| MYB    | 2             | 9.52            |
| TGFBR2 | 2             | 9.52            |
| ABL1   | 1             | 4.76            |
| ACVR2A | 1             | 4.76            |

Table SIV. Continued.

| B, Female |               |                 |
|-----------|---------------|-----------------|
| Gene      | Mutant number | Mutant ratio, % |
| APC       | 1             | 4.76            |
| ARID2     | 1             | 4.76            |
| ASXL1     | 1             | 4.76            |
| ATRX      | 1             | 4.76            |
| AXIN1     | 1             | 4.76            |
| BAP1      | 1             | 4.76            |
| BCORL1    | 1             | 4.76            |
| BRCA2     | 1             | 4.76            |
| CDKN2B    | 1             | 4.76            |
| CFTR      | 1             | 4.76            |
| CREB3L2   | 1             | 4.76            |
| CTNNA1    | 1             | 4.76            |
| CTNNB1    | 1             | 4.76            |
| EGFR      | 1             | 4.76            |
| ERBB4     | 1             | 4.76            |
| ERRFI1    | 1             | 4.76            |
| FAT1      | 1             | 4.76            |
| FGF14     | 1             | 4.76            |
| FGFR2     | 1             | 4.76            |
| FLI1      | 1             | 4.76            |
| FLT3      | 1             | 4.76            |
| GATA6     | 1             | 4.76            |
| GLI2      | 1             | 4.76            |
| IDH1      | 1             | 4.76            |
| JAK2      | 1             | 4.76            |
| KAT6A     | 1             | 4.76            |
| KDM5C     | 1             | 4.76            |
| KDM6A     | 1             | 4.76            |
| KDR       | 1             | 4.76            |
| KMT2D     | 1             | 4.76            |
| LRP1      | 1             | 4.76            |
| LRP2      | 1             | 4.76            |
| MAP2K1    | 1             | 4.76            |
| MAP2K2    | 1             | 4.76            |
| MAP2K4    | 1             | 4.76            |
| MET       | 1             | 4.76            |
| MSH2      | 1             | 4.76            |
| NOTCH1    | 1             | 4.76            |
| NOTCH2    | 1             | 4.76            |
| NOTCH3    | 1             | 4.76            |
| NSD2      | 1             | 4.76            |
| NTRK2     | 1             | 4.76            |
| PARP1     | 1             | 4.76            |
| PBRM1     | 1             | 4.76            |
| PHF6      | 1             | 4.76            |
| PIK3R1    | 1             | 4.76            |
| PMS2      | 1             | 4.76            |
| PTEN      | 1             | 4.76            |
| RAD52     | 1             | 4.76            |
| RARA      | 1             | 4.76            |
| RHBDF2    | 1             | 4.76            |
| RNF43     | 1             | 4.76            |
| ROCK1     | 1             | 4.76            |
| SMAD2     | 1             | 4.76            |

Table SIV. Continued.

B, Female

| Gene    | Mutant number | Mutant ratio, % |
|---------|---------------|-----------------|
| SMARCA4 | 1             | 4.76            |
| SOX9    | 1             | 4.76            |
| SPTA1   | 1             | 4.76            |
| STAT3   | 1             | 4.76            |
| STAT4   | 1             | 4.76            |
| TBX3    | 1             | 4.76            |
| TCF7L2  | 1             | 4.76            |
| TGFBR1  | 1             | 4.76            |
| TOP2A   | 1             | 4.76            |
| TP63    | 1             | 4.76            |
| TSC1    | 1             | 4.76            |
| XPO1    | 1             | 4.76            |
| ZNF750  | 1             | 4.76            |

Table SV. Statistics of GAs/genes in patients in different age groups.

| Age group               | GAs, n | Genes, n | GAs/patient <sup>a</sup> | Genes/patient <sup>b</sup> |
|-------------------------|--------|----------|--------------------------|----------------------------|
| Group I (40-49 years)   | 36     | 29       | 7.2                      | 5.8                        |
| Group II (50-59 years)  | 119    | 84       | 6.6                      | 4.7                        |
| Group III (60-69 years) | 188    | 95       | 6.5                      | 3.3                        |
| Group IV (70-82 years)  | 88     | 59       | 6.3                      | 4.1                        |

<sup>a</sup>Average number of GAs per patient. <sup>b</sup>Average number of genes per patient. GAs, genomic alterations.