Supplementary Table 1 Sequences of primers used in qRT-PCR

| Gene	Forward primer	Reverse primer
JAG1	GCCGAGGTCCTATACGTTGC	CCGAGTGAGAAGCCTTTTCA
JAG2	GCCCCGCAACGACTTTTC	TGGAGCAAATTACACCCTTGTT
PCNA	CCTGCTGGGATATTAGCTCCA	CAGCGGTAGGTGTCGAAGC
E2F1	ACGTGACGTGTCAGGACCT	GATCGGGCCTTGTTTGCTCTT
CDK2	CCAGGAGTTACTTCTATGCCTGA	TTCATCCAGGGGAGGTACAAC
CDK4	ATGGCTACCTCTCGATATGAGC	CATTGGGGACTCTCACACTCT
CDK6	TCTTCATTCACACCGAGTAGTGC	TGAGGTTAGAGCCATCTGGAAA
RB1	TTGGATCACAGCGATACAAACTT	AGCGCACGCCAATAAAGACAT
ULK1	GGCAAGTTCGAGTTCTCCCG	CGACCTCCAAATCGTGCTTCT
PIK3C 3	GTCTGGCCTAATGTAGAAGCAG	GGCAAGACGGCTCATCTGAT
BAX	CCCGAGAGGTCTTTTTCCGAG	CCAGCCCATGATGGTTCTGAT
BCL2L 1	GAGCTGGTGGTTGACTTTCTC	TCCATCTCCGATTCAGTCCCT
XIAP	AATAGTGCCACGCAGTCTACA	CAGATGGCCTGTCTAAGGCAA
CASP 8	AGAGTCTGTGCCCAAATCAAC	GCTGCTTCTCTCTTTGCTGAA
ATR	TCCCTTGAATACAGTGGCCTA	TCCTTGAAAGTACGGCAGTTC
ATM	TTGATCTTGTGCCTTGGCTAC	TATGGTGTACGTTCCCCATGT
MRE1 1	GGGGCAGATGCACTTTGTG	GAAGCAAAACCGGACTAATGTCT
RAD5 0	TTTGGTTGGACCCAATGGGG	CAGGAGGGAAATCTCCAGTACAA
18S	GAGACTCTGGCATGCTAACTAG	GGACATCTAAGGGCATCACAG

Supplementary Figure 1 The correlations between methylation status and related genes expression. The relationships between the methylation status and its genes expression from (A) cell cycle (B) Notch, (C) autophagy, (D) cell death, and (E) DNA damage associate pathways. The DNA methylation levels of CpG islands were shown as β value. Spearman correlation coefficient (ρ) is used to evaluate the significance of correlations.
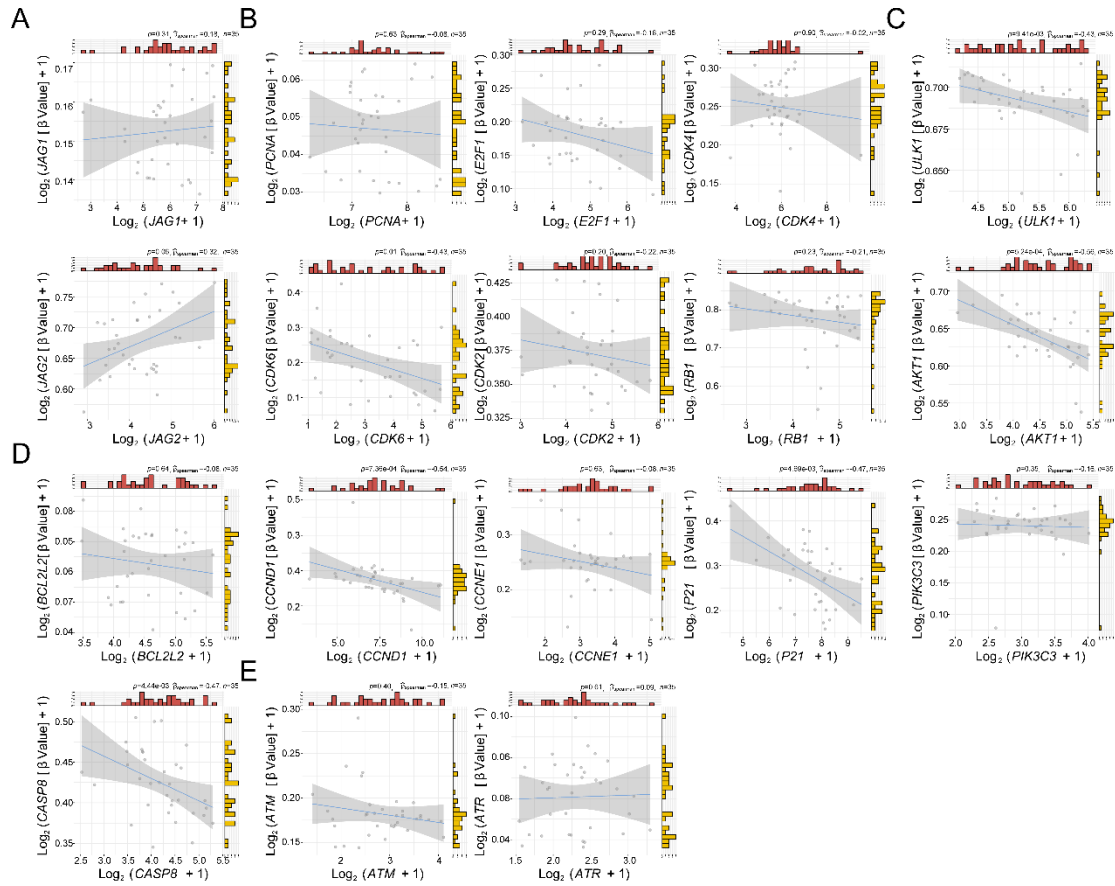
Supplementary Figure 2 The quantitative analysis of genes verified in cholangiocarcinoma cell lines. The protein quantification data of leading-edge genes relative to α-Tubulin, including (A) cell cycle, (B) Notch, (C) autophagy, (D) cell death, and (E) DNA damage associate pathways.
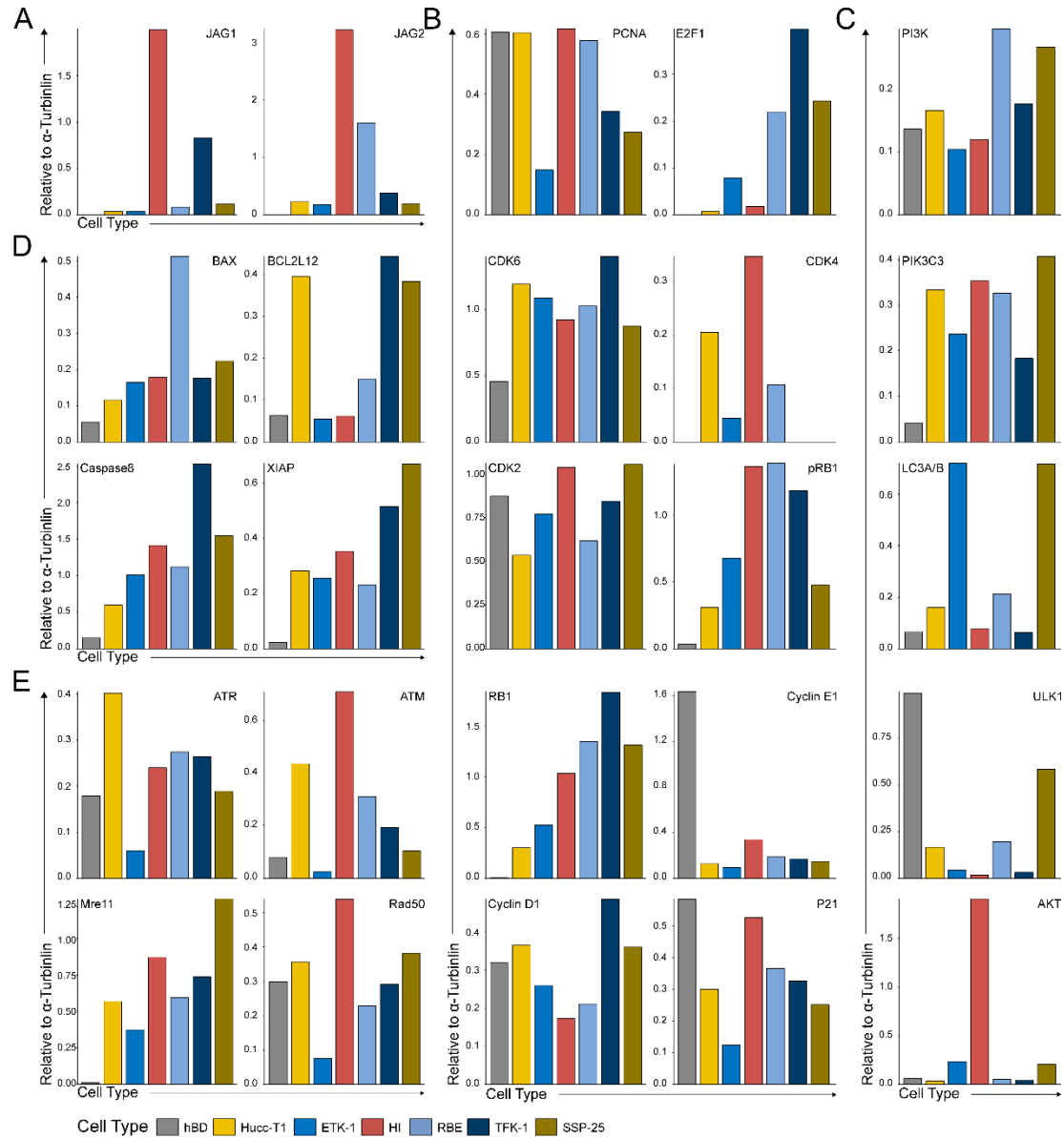
Supplementary Figure 3 The quantitative analysis of genes verified in genetically engineered mouse model. The protein quantification data of leading-edge genes relative to GAPDH, including (A) cell cycle, (B) Notch, (C) autophagy, (D) cell death, and (E) DNA damage associate pathways. P values were shown as: [a]$P < 0.05$, [b]$P < 0.01$, and [c]$P < 0.001$.
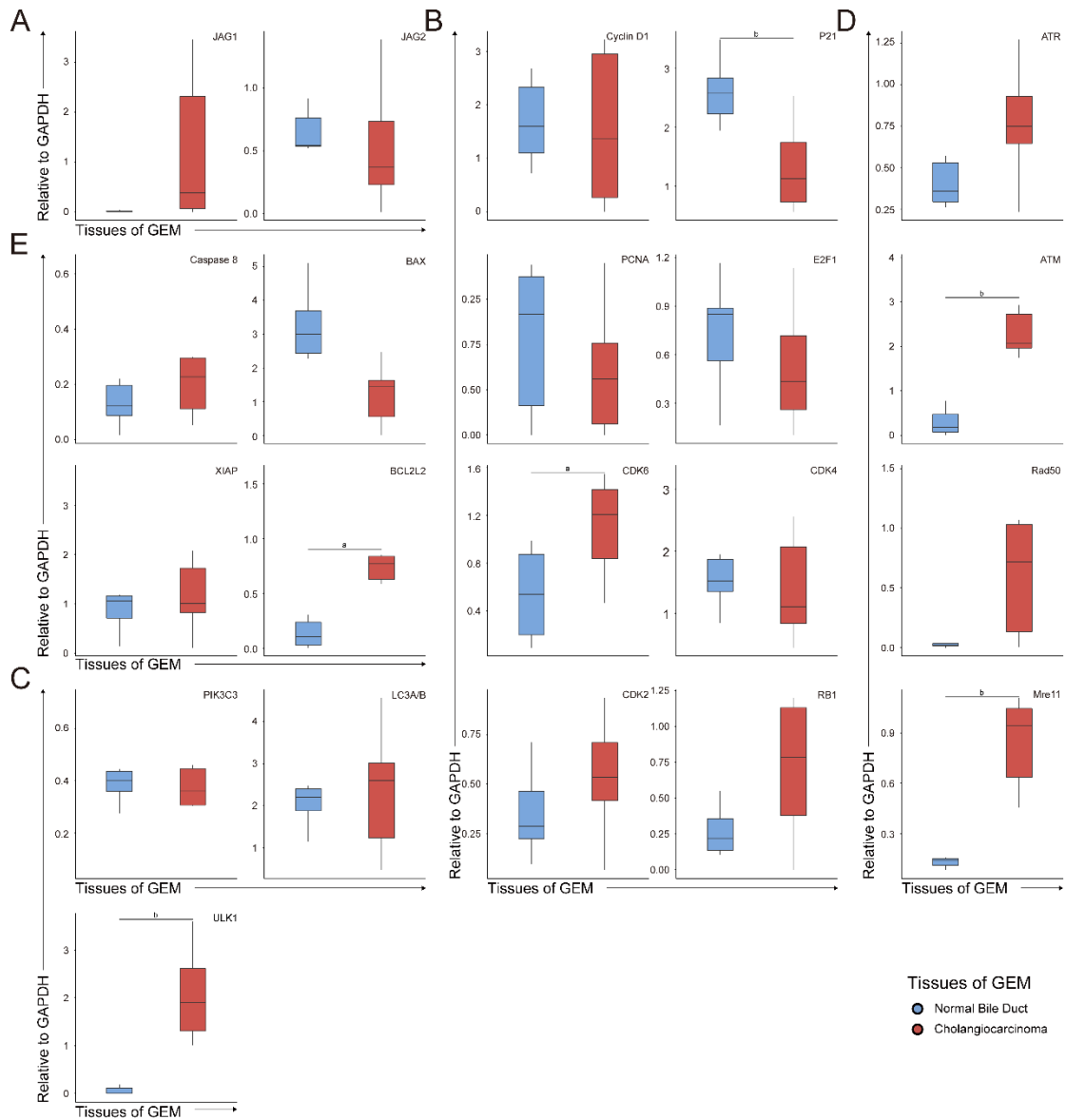
Supplementary Figure 4. Relationship between levels of tumor infiltrating immune cells and cell cycle and Notch associated genes expression. Correlations between tumor infiltration of different immune cells, (A) cell cycle, (B) Notch, (C) autophagy, (D) cell death, and (E) DNA damage associate genes. Spearman correlation is used to evaluate the relationships, and the significant levels is shown as ^aP < 0.05; ^bP < 0.01; and ^cP < 0.001. Red: Significant correlations; Black: No significant correlations.