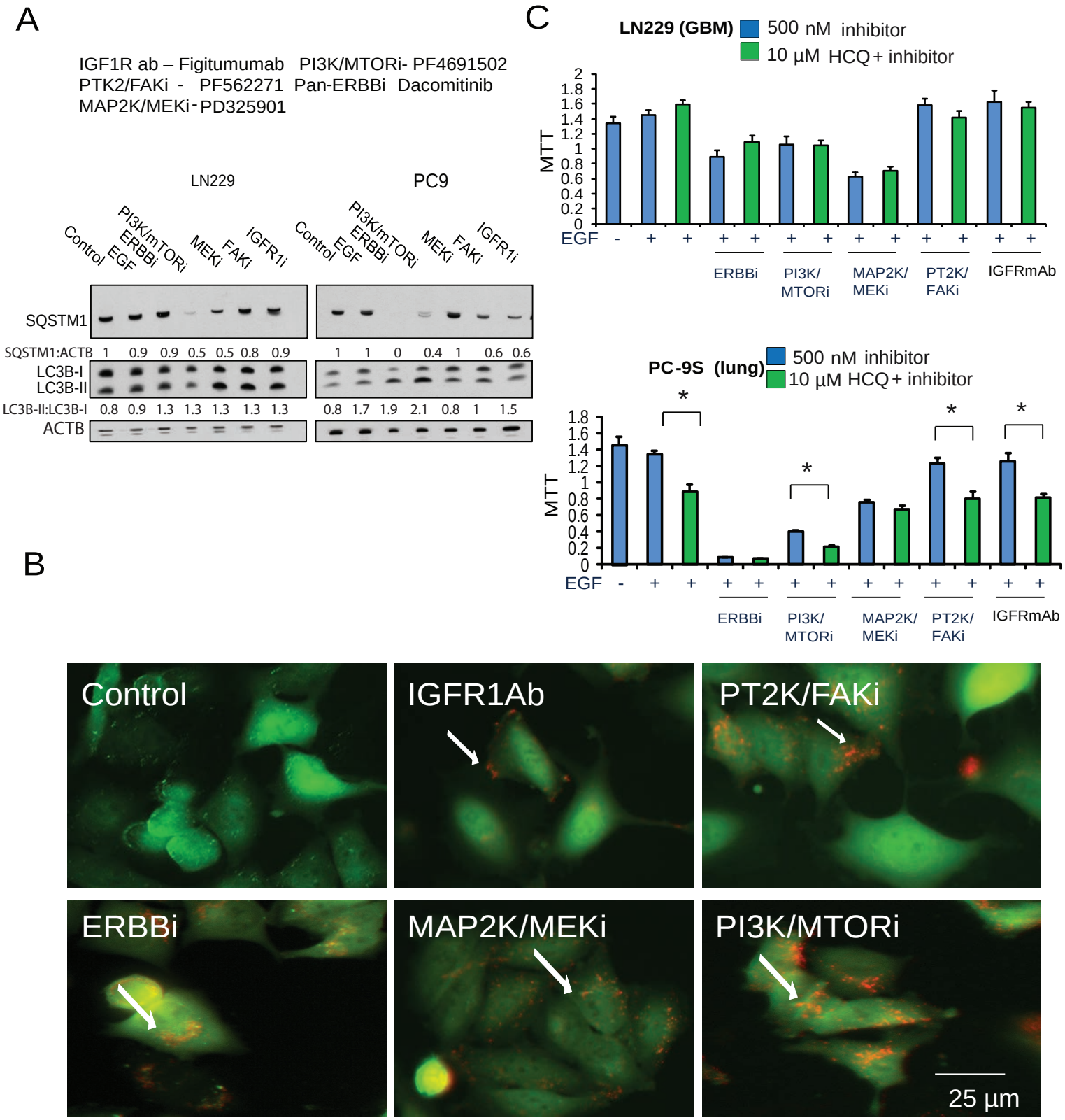


Figure S1. Autophagy induction predicts augmented cytoxicity from autophagy inhibition only in certain cell lines. (**A**) Immunoblotting against SQSTM1/p62 and LC3 in LN229 and PC9 cells treated as indicated for 24 h in the presence of EGF (epidermal growth factor) + inhibitor (500 nM). (**B**) A375P mCherry-EGFP-LC3 cells treated with the indicated inhibitors (24 h); red puncta reflects induction of autophagy. (**C**) MTT (96 h) assays. Mean +/- SD is shown; *p<0.05.

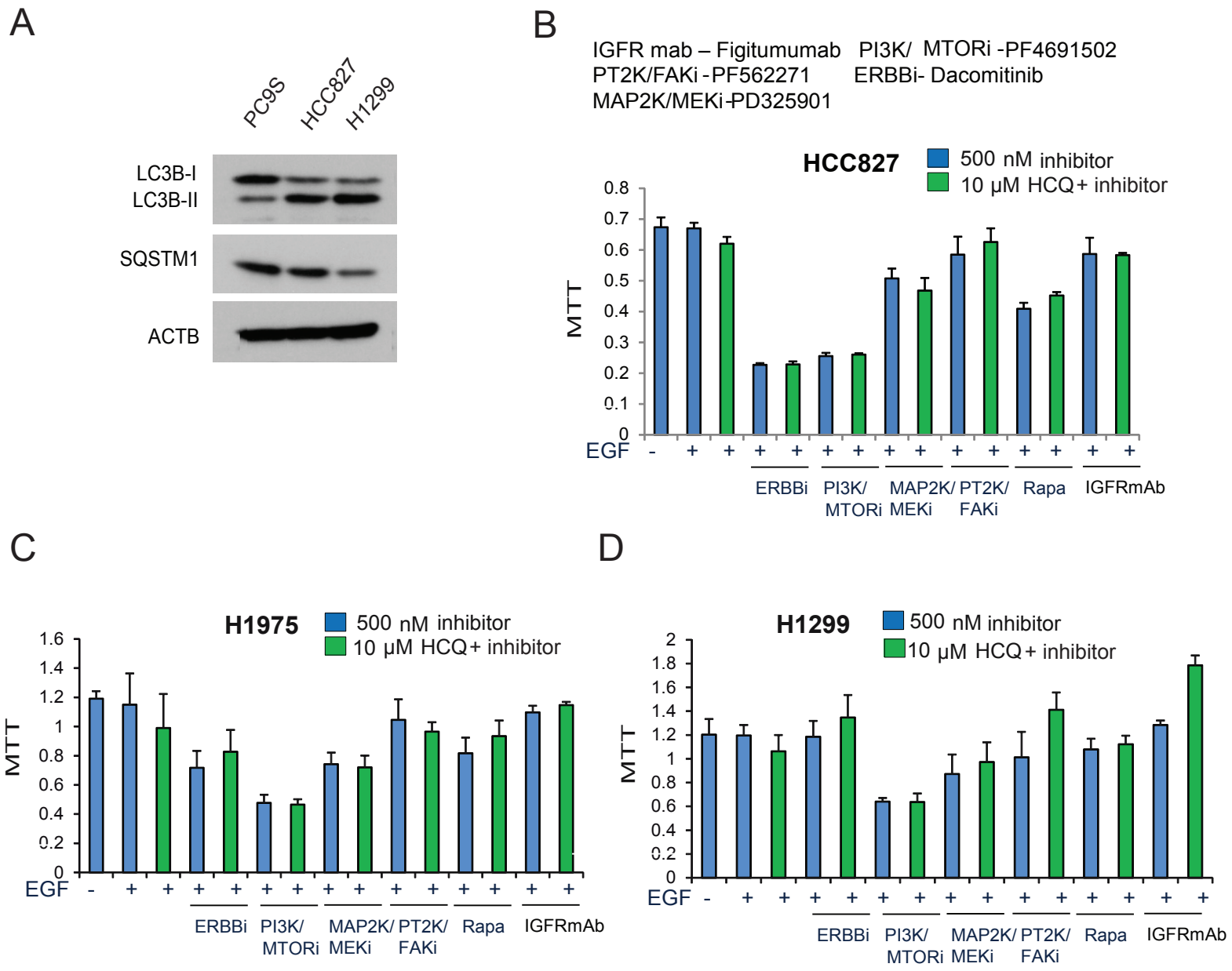


Figure S2. Addition of HCQ to targeted therapies in EGFR mutant lung cancer cell lines. (**A**) immunoblotting against LC3 and SQSTM1/p62 in the indicated cell lines. (**B-D**) MTT (96 h) assays were performed in the indicated cells simultaneously treated with inhibitor (blue), or inhibitor + HCQ (green) in the presence of EGF. Rapa, rapamycin;*p<0.05

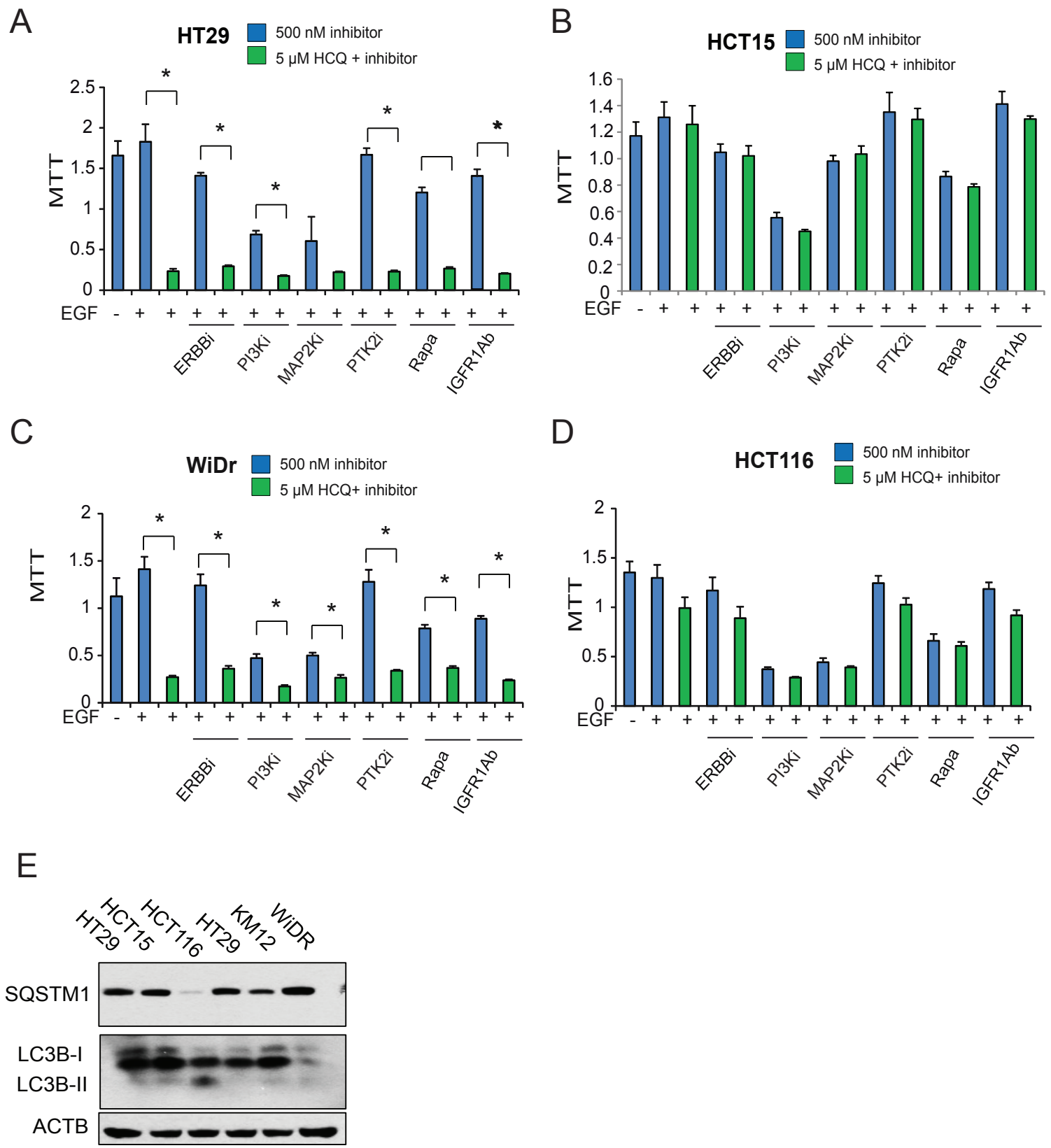
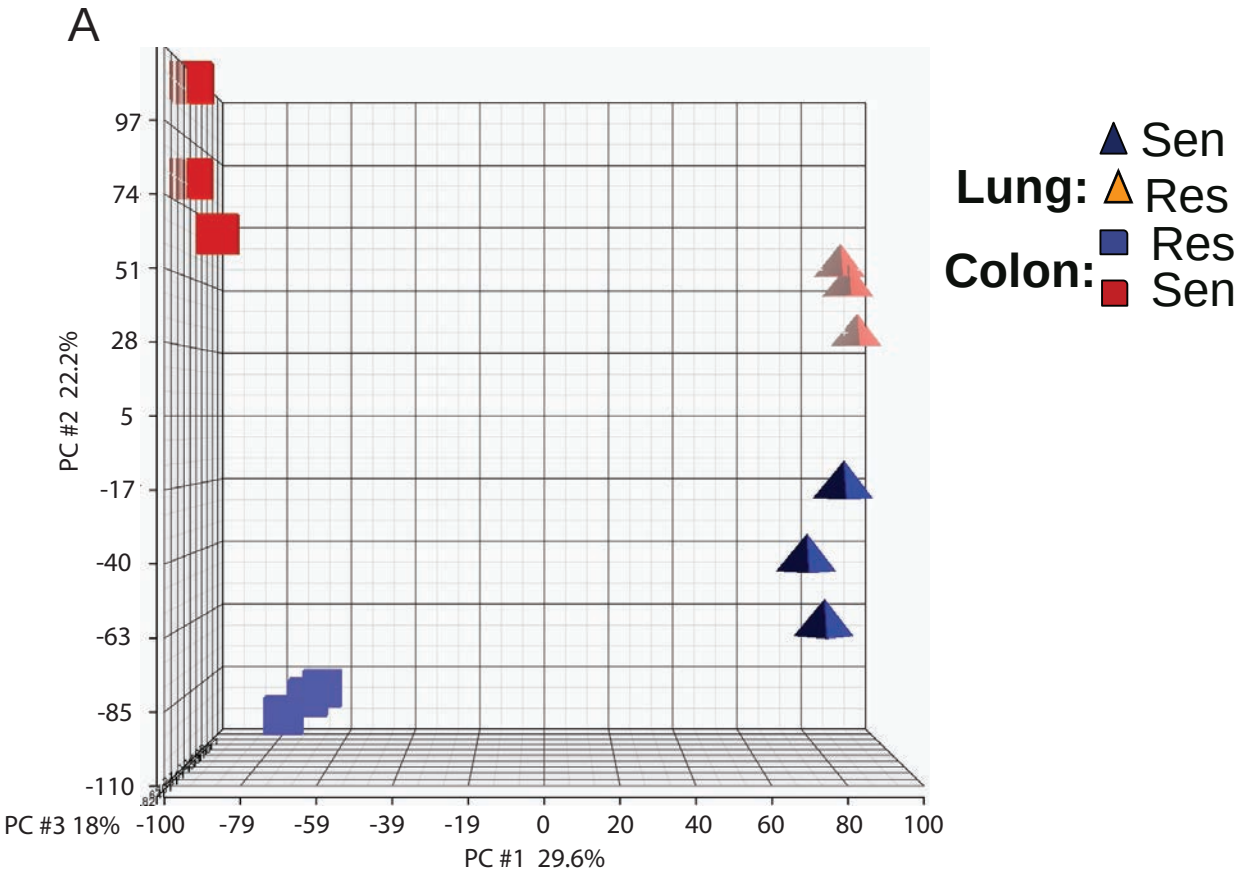


Figure S3. Colon cancer cell lines sensitive to HCQ. (**A-D**) **MTT** (96 h) assays were performed in the indicated cells simultaneously treated with inhibitor (blue), or inhibitor + HCQ (green) in the presence of EGF. Rapa, rapamycin; (**E**) Immunoblotting against LC3 and SQSTM1/p62 in the indicated cell lines. * $p<0.05$.



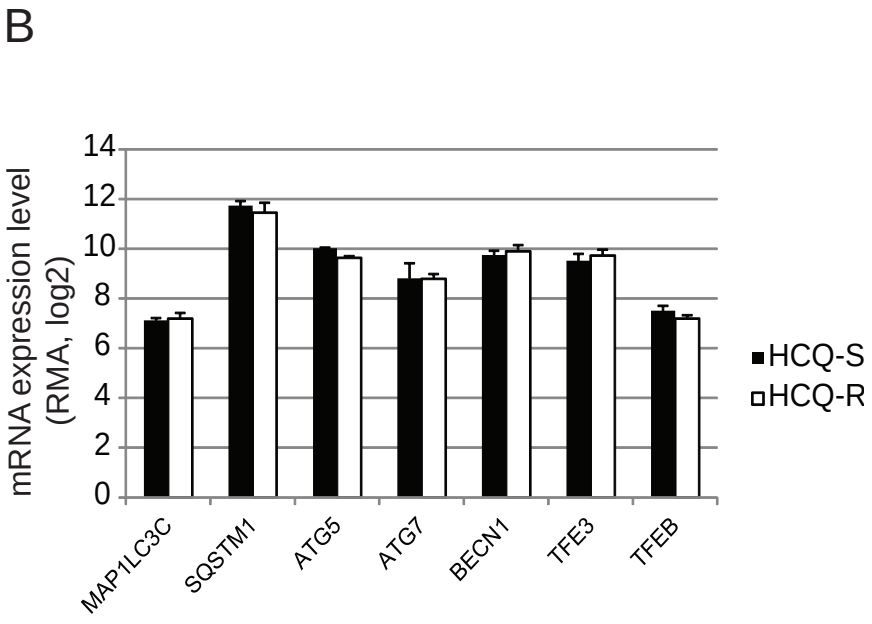


Figure S4. Expression microarray analysis in HCQ-sensitive and HCQ-resistant cells (**A**) Principal component analysis (PCA) of gene expression profile for 4 cancer cell lines (**B**) mRNA expression of essential autophagy and lysosomal biogenesis genes in 4 cancer cell lines. HCQ-S, HCQ sensitive; HCQ-R, HCQ resistant.

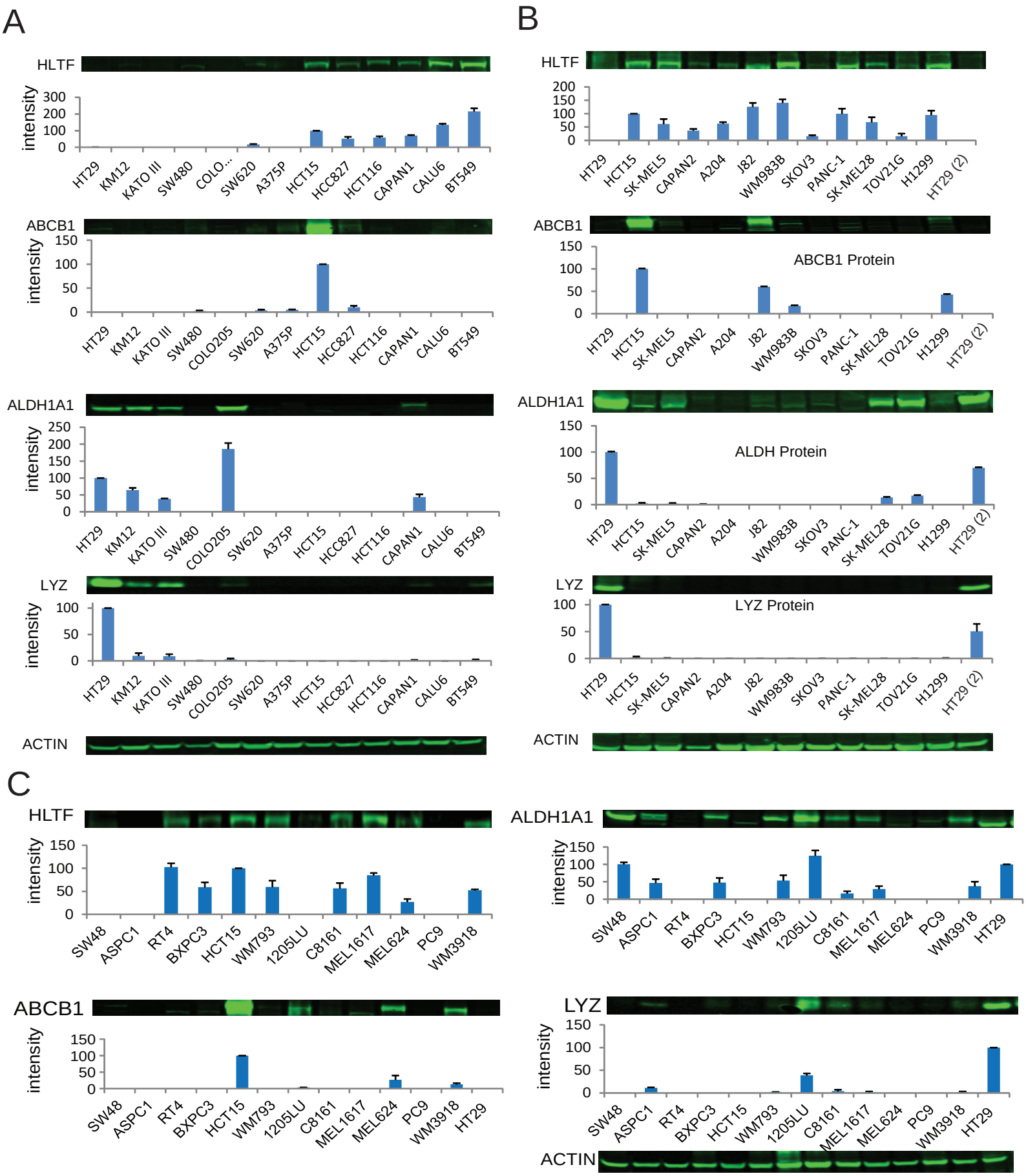


Figure S5. Licor Odyssey detection of protein expression of 4 differentially expressed genes in 33 HCQ-S and HCQ-R cell lines. (**A-C**) Separate cell lines.

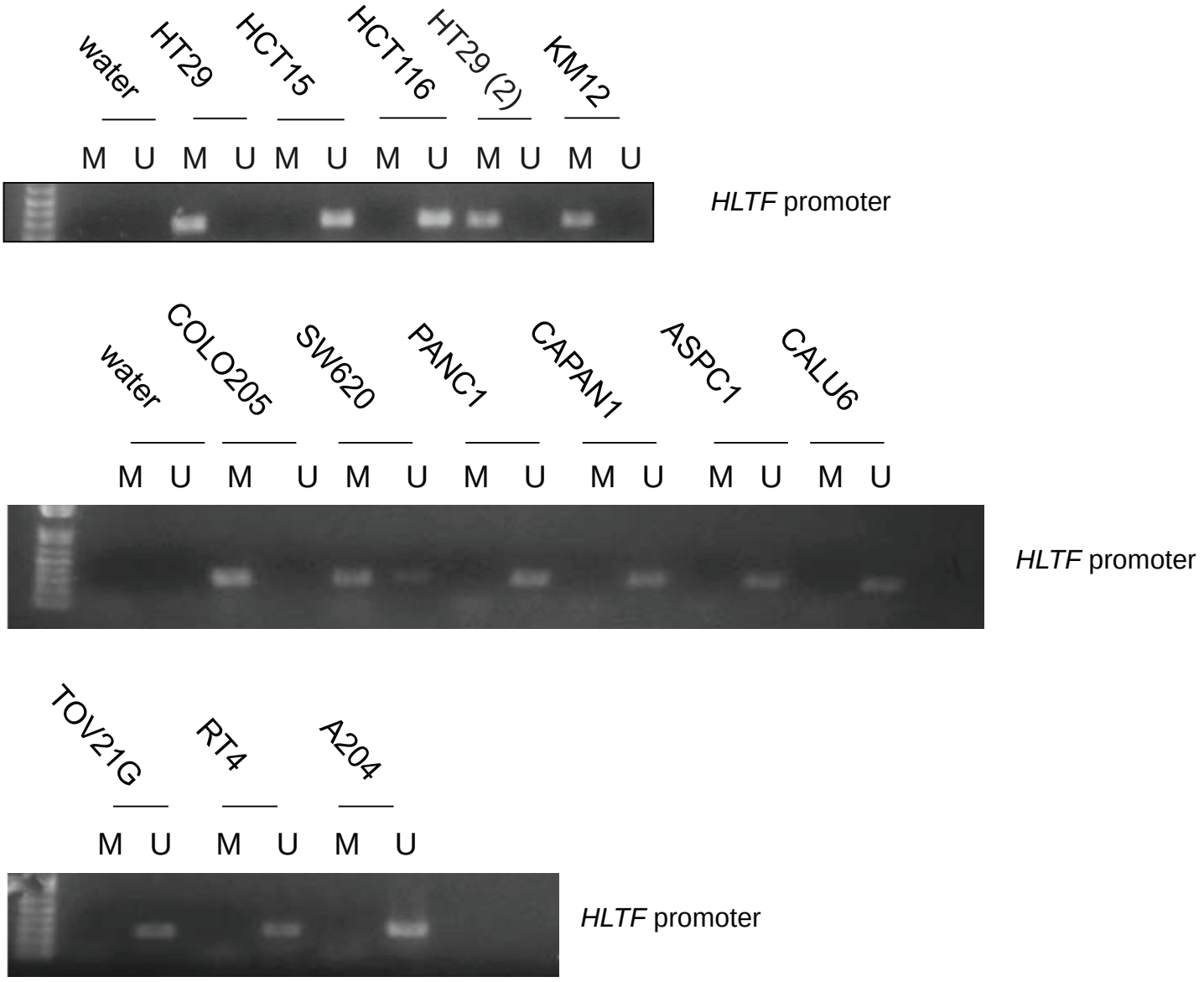


Figure S6. Methylation-specific PCR of the *HLTF* promoter in the indicated cell lines. M, methylated; U, unmethylated.

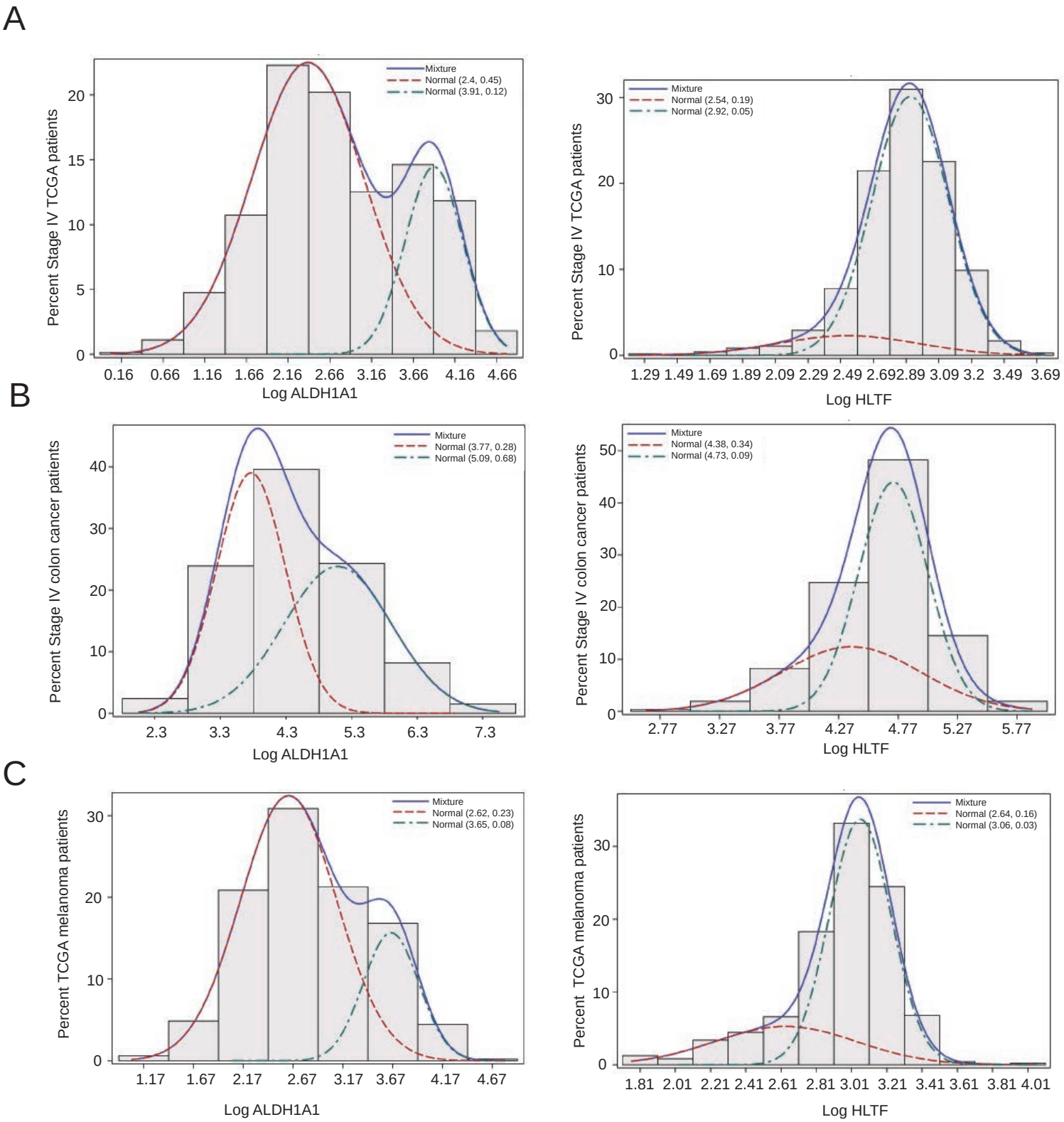


Figure S7. Histograms of expression of ALDH1A1 and HLTF. (**A**) TCGA stage IV tumors with >25 samples (N=718); (**B**) stage IV colon cancers from GSE41258, (n=255) (**C**) TCGA melanoma stage I-IV patients, (N=461). Black line, mixture model; red line, low expression; green line, high expression