

Table S4. GSEA querying Molecular Signature database (MSigDB) of DE target genes in BTC patients expressing high mRNA-181c and -181d versus low, using hallmark, wikipathways, reactome and KEGG pathways

| GENE SET | pval | FDR | ES | NES | Pathways |
|--------------------------------------|-------|-------|--------|---------|--------------|
| ANDROGEN_RESPONSE | 0.000 | 0.000 | -0.618 | -23.210 | |
| BILE_ACID_METABOLISM | 0.000 | 0.002 | -0.838 | -21.683 | |
| MYC_TARGETS_V1 | 0.039 | 0.122 | -0.396 | -15.556 | |
| MYC_TARGETS_V2 | 0.060 | 0.135 | -0.764 | -15.078 | |
| HEDGEHOG_SIGNALING | 0.062 | 0.149 | -0.723 | -14.451 | |
| ADIPOGENESIS | 0.099 | 0.135 | -0.376 | -14.394 | |
| OXIDATIVE_PHOSPHORYLATION | 0.085 | 0.229 | -0.452 | -13.198 | |
| FATTY_ACID_METABOLISM | 0.223 | 0.351 | -0.438 | -12.178 | |
| ESTROGEN_RESPONSE_EARLY | 0.231 | 0.362 | -0.220 | -11.888 | Hallmark |
| ESTROGEN_RESPONSE_LATE | 0.743 | 0.837 | -0.192 | -0.810 | |
| PEROXISOME | 0.308 | 0.458 | -0.443 | -11.096 | |
| HYPOXIA | 0.381 | 0.644 | -0.177 | -0.989 | |
| NOTCH_SIGNALING | 0.470 | 0.621 | -0.581 | -0.977 | |
| MTORC1_SIGNALING | 0.455 | 0.590 | -0.174 | -0.971 | |
| PI3K_AKT_MTOR_SIGNALING | 0.828 | 0.820 | -0.181 | -0.789 | |
| PROTEIN_SECRETION | 0.988 | 0.961 | -0.221 | -0.632 | |
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| P53_TRANSCRIPTIONAL_GENE_NETWORK | 0.014 | 0.485 | 0.680 | 16.207 | |
| APOPTOSIS | 0.463 | 0.925 | 0.484 | 0.999 | |
| ANGIOGENESIS | 0.048 | 0.238 | -0.695 | -15.721 | |
| EGFR_TYROSINE_KINASE_INHIBITOR_RESIS | 0.054 | 0.333 | -0.387 | -14.700 | |
| TARGET_OF_RAPAMYCIN_SIGNALING | 0.135 | 0.434 | -0.609 | -13.240 | |
| PI3KAKTMTOR_SIGNALING_PATHWAY_AND | 0.220 | 0.561 | -0.482 | -12.018 | |
| MODULATION_OF_PI3KAKTMTOR_SIGNALIN | 0.102 | 0.433 | -0.961 | -12.848 | |
| WNT_SIGNALING | 0.237 | 0.636 | -0.304 | -11.304 | |
| DNA_DAMAGE_RESPONSE_ONLY_ATM_DEP | 0.167 | 0.563 | -0.283 | -11.993 | |
| DNA_MISMATCH_REPAIR | 0.801 | 0.950 | -0.601 | -0.802 | |
| MAPK_CASCADE | 0.337 | 0.656 | -0.482 | -10.905 | |
| NRF2_PATHWAY | 0.018 | 0.336 | 0.811 | 15.579 | |
| NUCLEAR_RECEPTORS | 0.001 | 0.018 | -0.676 | -20.550 | |
| ESTROGEN_RECEPTOR_PATHWAY | 0.001 | 0.050 | -0.968 | -18.889 | |
| FATTY_ACID_BIOSYNTHESIS | 0.001 | 0.019 | -0.939 | -21.452 | |
| OMEGA9_FATTY_ACID_SYNTHESIS | 0.001 | 0.059 | -0.972 | -18.915 | |
| FATTY_ACID_TRANSPORTERS | 0.003 | 0.064 | -0.913 | -18.271 | |
| OXYSTEROLS_DERIVED_FROM_CHOLESTER | 0.025 | 0.411 | -0.984 | -13.213 | |
| FATTY_ACID_BETAOXIDATION | 0.210 | 0.562 | -0.523 | -11.975 | |
| MEVALONATE_ARM_OF_CHOLESTEROL_BI | 0.288 | 0.634 | -0.837 | -11.291 | WikiPathways |
| CHOLESTEROL_SYNTHESIS_DISORDERS | 0.330 | 0.641 | -0.837 | -11.101 | |
| CHOLESTEROL_BIOSYNTHESIS_PATHWAY | 0.351 | 0.635 | -0.837 | -11.027 | |
| CHOLESTEROL_METABOLISM | 0.859 | 0.962 | -0.455 | -0.749 | |
| LIPID_METABOLISM_PATHWAY | 0.820 | 0.975 | -0.385 | -0.758 | |
| CHOLESTEROL_METABOLISM | 0.005 | 0.062 | -0.731 | -18.412 | |
| SREBF_LIPID_HOMEOSTASIS | 0.028 | 0.266 | -0.803 | -15.518 | |
| STEROL_REGULATORY_ELEMENTBINDING_I | 0.196 | 0.558 | -0.311 | -12.046 | |
| TRANSCRIPTIONAL_CASCADE_REGULATING | 0.027 | 0.295 | -0.933 | -15.313 | |
| ENERGY_METABOLISM | 0.845 | 0.958 | -0.261 | -0.786 | |
| MITOCHONDRIAL_COMPLEX_IV_ASSEMBLY | 0.282 | 0.618 | -0.879 | -11.560 | |
| MITOCHONDRIAL_FATTY_ACID_BETAOXID/ | 0.006 | 0.242 | -0.967 | -15.781 | |
| MITOCHONDRIAL_COMPLEX_I_ASSEMBLY_ | 0.032 | 0.332 | -0.898 | -14.635 | |
| ELECTRON_TRANSPORT_CHAIN_OXP/OS_ | 0.042 | 0.353 | -0.880 | -14.466 | |
| GLYOXYLATE_METABOLISM | 0.003 | 0.171 | -0.979 | -16.445 | |
| GLYCOLYSIS_AND_GLUconeogenesis | 0.127 | 0.418 | -0.693 | -13.473 | |
| PPAR_SIGNALING_PATHWAY | 0.005 | 0.018 | -0.752 | -2.094 | |
| PPARALPHA_PATHWAY | 0.064 | 0.432 | -0.966 | -12.888 | |
| NAD_METABOLISM_SIRTUINS_AND_AGING | 0.406 | 0.731 | -0.779 | -10.451 | |
| NAD_METABOLISM_ | 0.965 | 1.000 | -0.328 | -0.639 | |
| FOXA2_PATHWAY | 0.621 | 0.866 | -0.538 | -0.885 | |
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| FATTY_ACYL_COA_BIOSYNTHESIS | 0.001 | 0.059 | -0.939 | -20.775 | |
| ABC_TRANSPORTER_DISORDERS | 0.005 | 0.133 | -0.737 | -1.877 | |
| NUCLEAR_RECEPTOR_TRANSCRIPTION_PA | 0.009 | 0.120 | -0.513 | -18.674 | |
| ABC_FAMILY_PROTEINS_MEDIATED_TRAN | 0.013 | 0.133 | -0.737 | -17.999 | |
| SYNTHESIS_OF_VERY_LONG_CHAIN_FATTY | 0.007 | 0.121 | -0.913 | -17.999 | |
| HEDGEHOG_LIGAND_BIOGENESIS | 0.004 | 0.179 | -0.854 | -17.229 | |
| FATTY_ACID_METABOLISM | 0.006 | 0.177 | -0.598 | -17.123 | |
| RAF_INDEPENDENT_MAPK1_3_ACTIVATION | 0.025 | 0.173 | -0.680 | -16.959 | |
| SIGNALING_BY_NOTCH3 | 0.016 | 0.245 | -0.867 | -16.342 | |
| ATF6_ATF6_ALPHA_ACTIVATES_CHAPERON | 0.018 | 0.252 | -0.841 | -16.255 | |
| ACTIVATED_NTRK2_SIGNALS_THROUGH_PI | 0.020 | 0.262 | -0.940 | -15.854 | |
| RHO_GTPASES_ACTIVATE_PKNS | 0.051 | 0.289 | -0.428 | -15.524 | |
| ACTIVATION_OF_GENE_EXPRESSION_BY_SI | 0.036 | 0.276 | -0.490 | -1.551 | |
| PKA_ACTIVATION_IN_GLUcAGON_SIGNALL | 0.066 | 0.314 | -0.767 | -15.248 | |
| RHO_GTPASES_ACTIVATE_PAKS | 0.043 | 0.318 | -0.692 | -15.190 | Reactome |
| MTOR_SIGNALING | 0.057 | 0.318 | -0.610 | -15.093 | |
| RESPIRATORY_ELECTRON_TRANSPORT_AT | 0.047 | 0.315 | -0.898 | -15.040 | |
| NICOTINAMIDE_SALVAGING | 0.036 | 0.320 | -0.888 | -14.914 | |
| RESPIRATORY_ELECTRON_TRANSPORT | 0.042 | 0.328 | -0.898 | -14.848 | |
| THE_CITRIC_ACID_TCA_CYCLE_AND_RESPI | 0.024 | 0.320 | -0.898 | -14.825 | |
| COMPLEX_I_BIOGENESIS | 0.050 | 0.334 | -0.898 | -14.703 | |
| PCP_CE_PATHWAY | 0.041 | 0.328 | -0.882 | -14.702 | |
| ENERGY_DEPENDENT_REGULATION_OF_MT | 0.045 | 0.350 | -0.862 | -14.122 | |
| NOTCH3_INTRACELLULAR_DOMAIN_REGUL | 0.075 | 0.371 | -0.866 | -13.999 | |
| MITOCHONDRIAL_PROTEIN_IMPORT | 0.068 | 0.387 | -0.625 | -13.879 | |
| RHO_GTPASES_ACTIVATE_CIT | 0.125 | 0.394 | -0.691 | -1.372 | |
| RHO_GTPASES_ACTIVATE_ROCKS | 0.102 | 0.390 | -0.691 | -13.712 | |
| MITOCHONDRIAL_TRANSLATION | 0.097 | 0.397 | -0.828 | -13.663 | |
| SENESCENCE_ASSOCIATED_SECRETORY_PI | 0.147 | 0.393 | -0.500 | -13.658 | |
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| PEROXISOME | 0.003 | 0.000 | -0.871 | -2.379 | |
| PPAR_SIGNALING_PATHWAY | 0.003 | 0.010 | -0.752 | -2.082 | |
| FATTY_ACID_METABOLISM | 0.003 | 0.048 | -0.913 | -1.838 | |
| PROTEASOME | 0.043 | 0.344 | -0.882 | -1.479 | |
| INSULIN_SIGNALING_PATHWAY | 0.043 | 0.427 | -0.298 | -1.420 | |
| GLYOXYLATE_AND_DICARBOXYLATE_MET | 0.003 | 0.379 | -1.000 | -1.343 | |
| GLYCINE_SERINE_AND_THREONINE_METAE | 0.018 | 0.469 | -0.992 | -1.305 | |
| PHENYLALANINE_METABOLISM | 0.048 | 0.475 | -0.979 | -1.297 | |
| TYROSINE_METABOLISM | 0.054 | 0.495 | -0.979 | -1.286 | |
| HEDGEHOG_SIGNALING_PATHWAY | 0.184 | 0.519 | -0.908 | -1.210 | KEGG |
| TAURINE_AND_HYPOTAURINE_METABOLIS! | 0.230 | 0.548 | -0.872 | -1.169 | |
| LYSINE_DEGRADATION | 0.289 | 0.549 | -0.592 | -1.156 | |
| GALACTOSE_METABOLISM | 0.272 | 0.540 | -0.692 | -1.153 | |
| FRUCTOSE_AND_MANNANOSE_METABOLISM | 0.307 | 0.583 | -0.513 | -1.117 | |
| CIRCADIAN_RHYTHM_MAMMAL | 0.333 | 0.603 | -0.484 | -1.102 | |
| GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_AI | 0.331 | 0.630 | -0.635 | -1.083 | |
| GLYCOLYSIS_GLUconeogenesis | 0.581 | 0.736 | -0.692 | -0.934 | |
| BIOSYNTHESIS_OF_UNSATURATED_FATTY | 0.687 | 0.881 | -0.498 | -0.821 | |