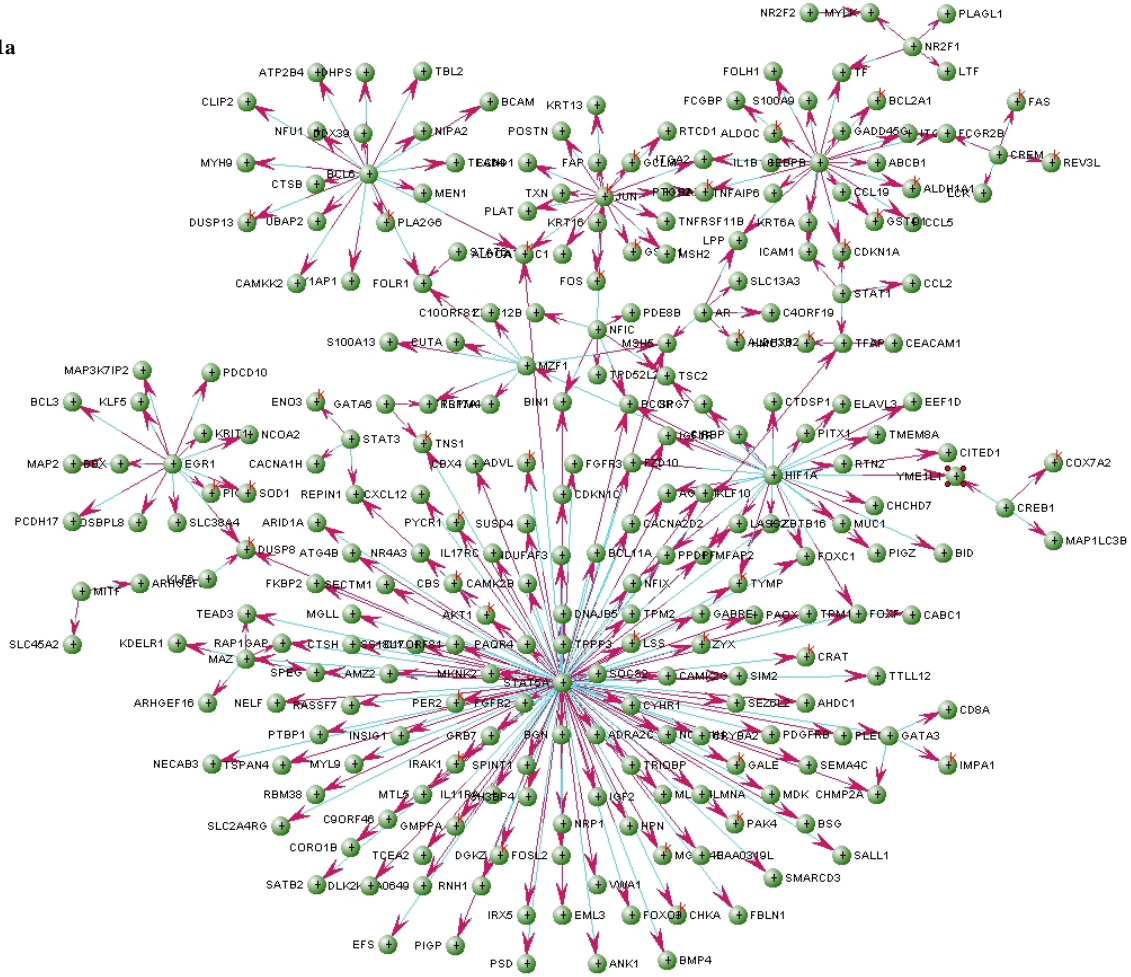
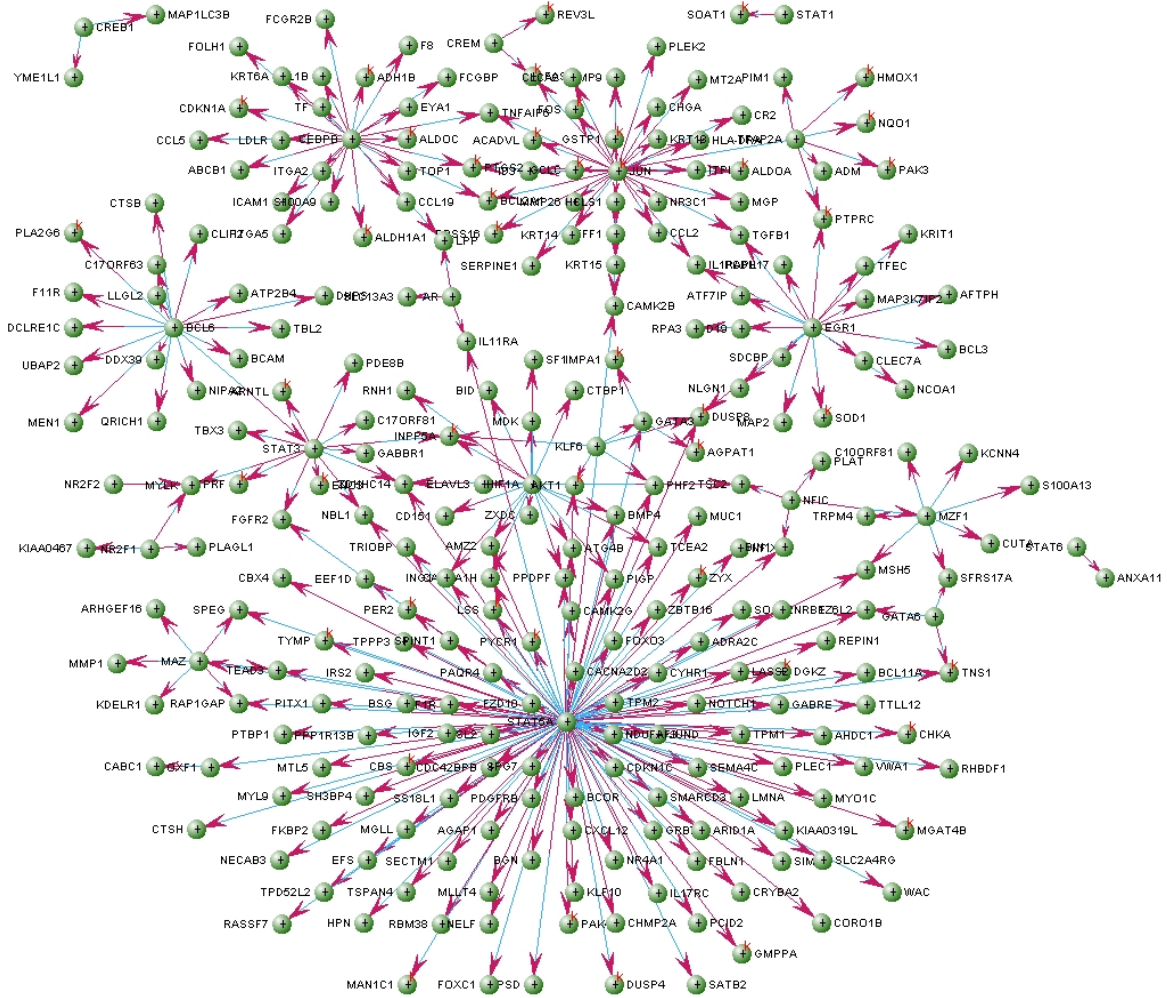


Supplementary Tables and Figures:

1a

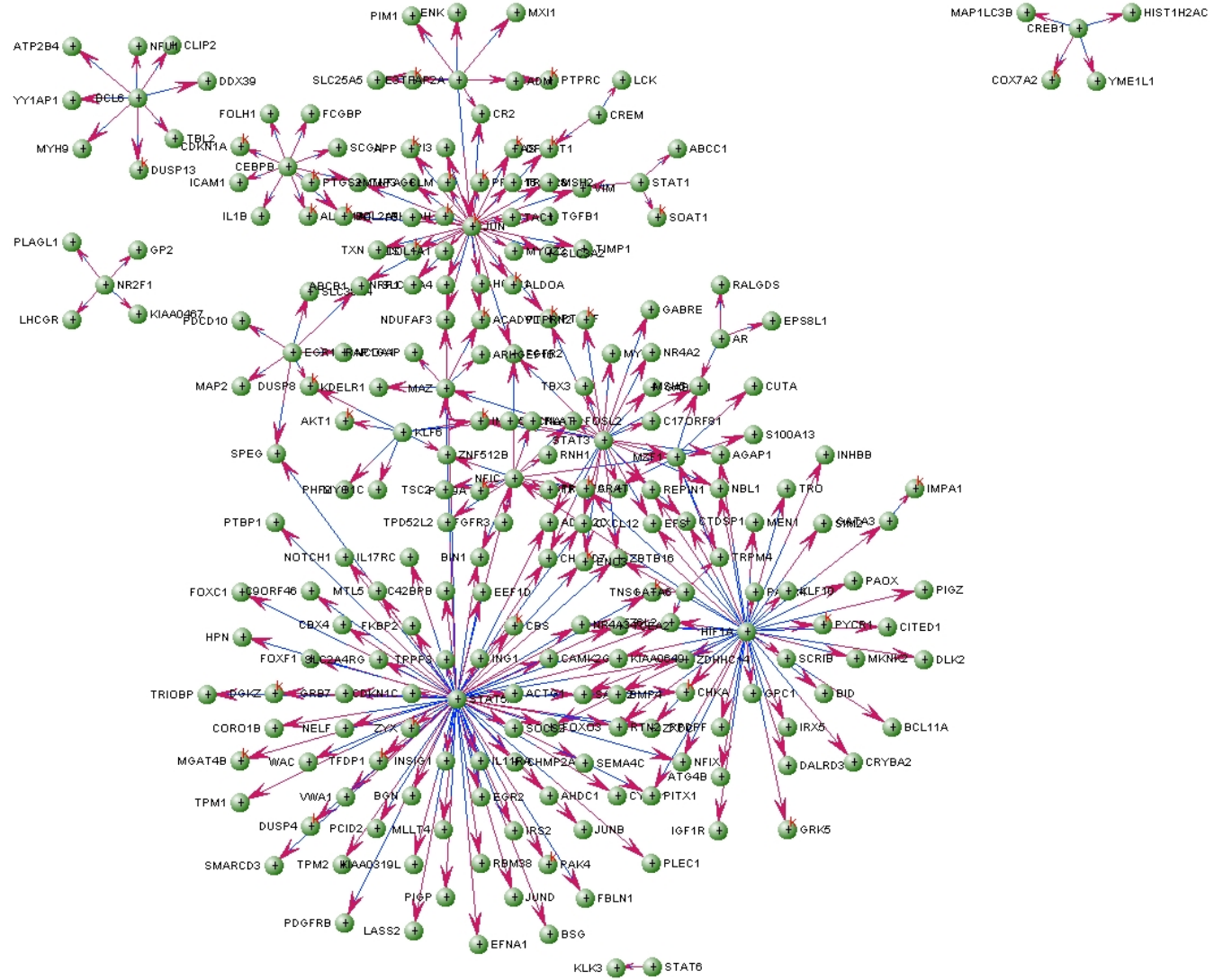


1b

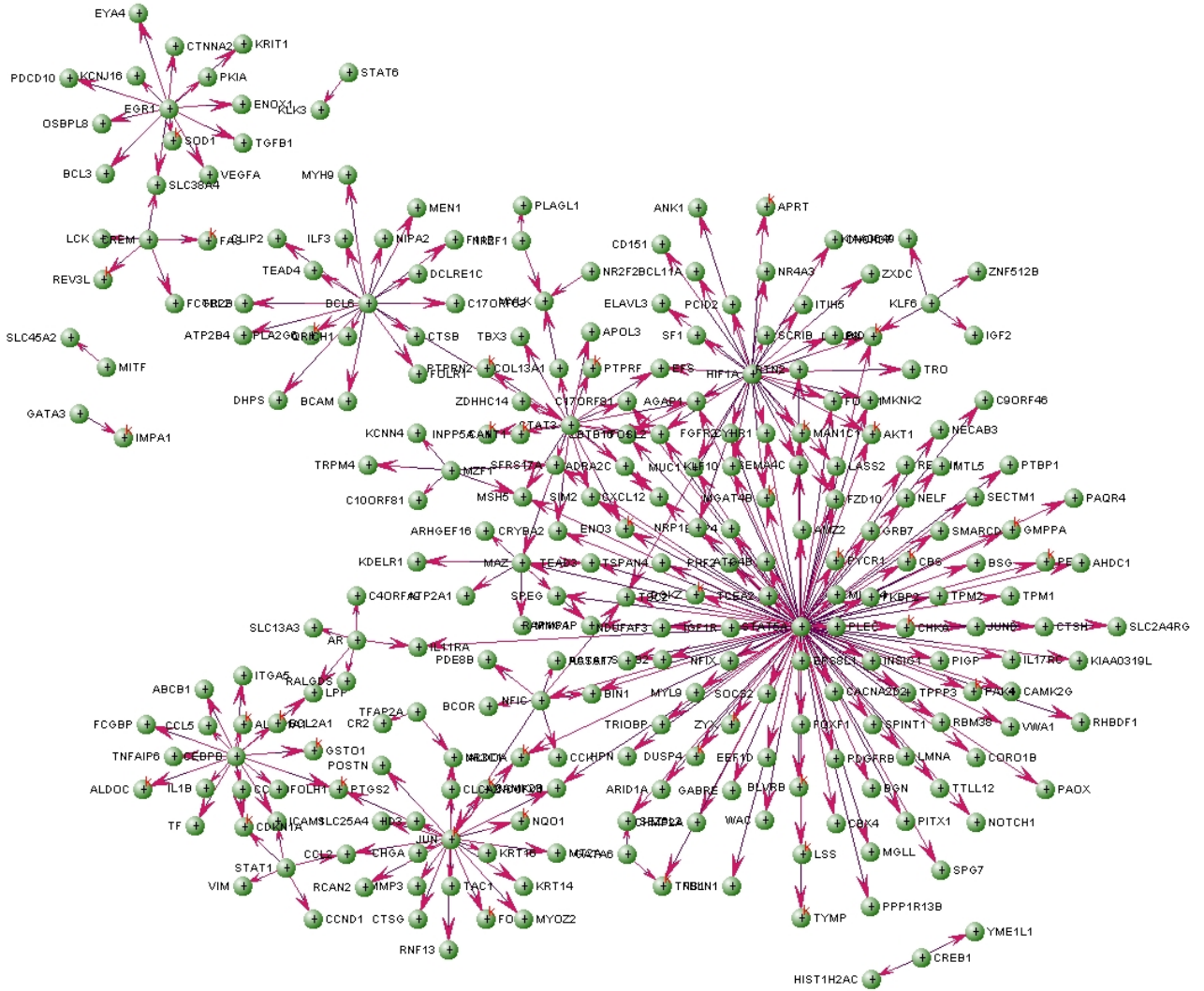


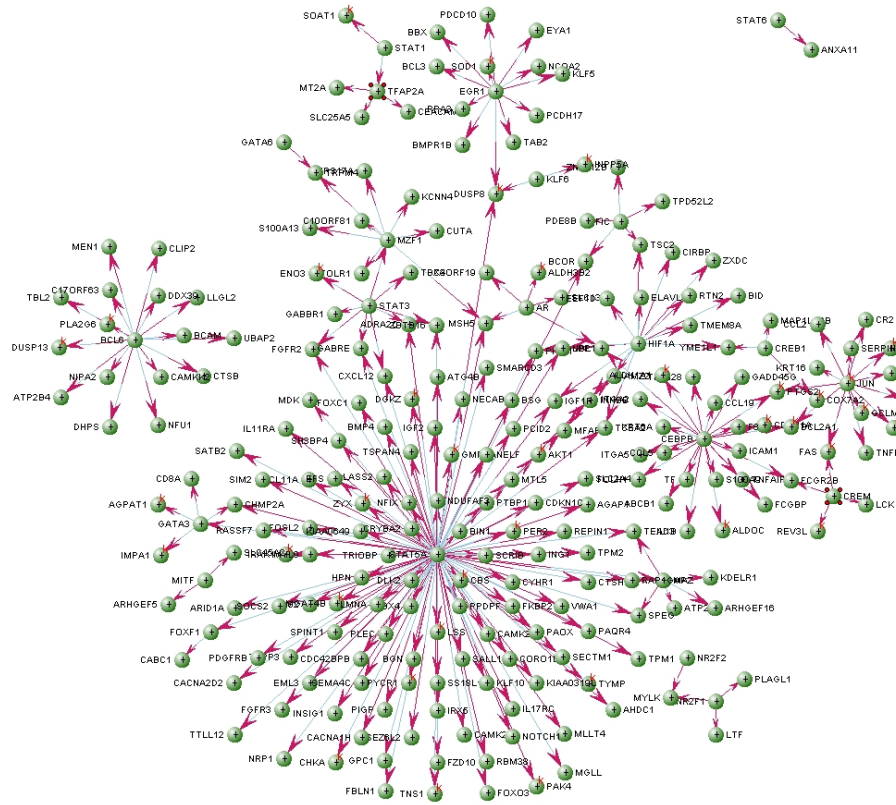
Supplementary Figure 1. Prostate cancer network in (a) African Americans (b) European Americans. The network was built using microarray data for high grade prostate samples overlaid with transcription factor data in VisANT. The hubs in the networks are STAT5a, JUN, HIF-1a, CEBPB, BCL-6 and NFIC.

2a



2b





Supplementary Figure 2. Principal networks hubs for (a) normal prostate, (b) low Gleason grade (<7) prostate cancer (c) high Gleason grade (≥ 7) prostate cancer. The central nodes (genes) in these hubs are STAT5a, HIF-1a, STAT3, JUN, CEBPB and EGR1.

Table 1. Differential expression of hubs identified in regulatory networks. Significance level of hubs associated with low and high grade tumors using single-gene analysis only. Student's t-test p-values for differentiating pair-wise between normal prostate, low grade tumor and high grade tumor are shown with those significant at p-value <0.05 shown in red (these hubs can be identified by single link analysis using the t-test). However, the rest of the hubs (those with poor p-values) can only be identified by the co-regulation analysis we present here. They are not identifiable using single gene analysis.

| Gene Name | Type of hub | Normal vs. Low grade tumors | Normal vs. High grade tumors | Low vs. High grade tumors | Pathway (KEGG, BIOCARTA database) |
|---|-------------|-----------------------------|------------------------------|---------------------------|--|
| | | t-test p-value | | | |
| STAT5a signal transducer and activator of transcription 5A | Gain | 0.036 | 0.016 | 0.819 | ErbB signaling pathway, Jak-STAT signaling pathway, Bioactive Peptide Induced Signaling Pathway, EGF Signaling Pathway, EPO Signaling Pathway, Growth Hormone Signaling Pathway, IL-10 Anti-inflammatory Signaling Pathway, IL22 Soluble Receptor Signaling Pathway, IL 2 signaling pathway, IL-2 Receptor Beta Chain in T cell Activation, IL 3 signaling pathway, IL-7 Signal Transduction, PDGF Signaling Pathway |
| CEBPB CCAAT/enhancer binding protein (C/EBP), beta | Gain | 0.570 | 0.041 | 0.237 | IL 6 signaling pathway |
| EGR1 early growth response 1 | Gain | 0.601 | 0.362 | 0.142 | Phosphorylation of MEK1 by cdk5/p35 down regulates the MAP kinase pathway |
| NFIC nuclear factor I/C (CCAAT-binding transcription factor) | | 0.897 | 0.820 | 0.776 | |
| STAT3 signal transducer and activator of transcription 3 | | 0.001 | 0.005 | 0.002 | Chemokine signaling pathway, Jak-STAT signaling pathway, Adipocytokine signaling pathway, EGF Signaling Pathway, Erk1/Erk2 Mapk Signaling pathway, Role of ERBB2 in Signal Transduction and Oncology, IL22 Soluble Receptor Signaling Pathway, IL 6 signaling pathway, Signaling of Hepatocyte Growth Factor Receptor, PDGF Signaling Pathway, Stat3 Signaling Pathway, TPO Signaling Pathway |
| JUN jun oncogene | | 0.173 | 0.070 | 0.707 | MAPK signaling pathway, ErbB signaling pathway, Wnt signaling pathway, Focal adhesion, Toll-like receptor signaling pathway, T cell receptor signaling pathway, B cell receptor signaling pathway, Neurotrophin signaling pathway, GnRH signaling pathway, Epithelial cell signaling in Helicobacter pylori infection, The 4-1BB-dependent immune response, Agrin in Postsynaptic Differentiation, Oxidative Stress Induced Gene Expression Via Nrf2, Angiotensin II mediated activation of JNK Pathway via Pyk2 dependent signaling, ATM Signaling Pathway, BCR Signaling Pathway, Pertussis toxin-insensitive CCR5 Signaling in Macrophage, Cadmium induces DNA synthesis and proliferation in macrophages, D4-GDI Signaling Pathway, EGF Signaling Pathway, EPO Signaling Pathway, METS affect on Macrophage Differentiation, FAS signaling pathway (CD95), Fc Epsilon Receptor 1 Signaling in Mast Cells, Signaling Pathway from G-Protein Families, Hypoxia-Inducible Factor in the Cardiovascular System, IGF-1 Signaling Pathway, IL12 and Stat4 Dependent Signaling Pathway in Th1 Development, Signal transduction through IL1R, IL 2 signaling pathway, IL 6 signaling pathway, Insulin Signaling Pathway, Integrin Signaling Pathway, Keratinocyte Differentiation, Nerve growth factor |

| | | | | | |
|--|------|--------------|-------|-------|---|
| | | | | | pathway (NGF),The information-processing pathway at the IFN-beta enhancer, PDGF Signaling Pathway, Proliferators via PPARa(alpha), TNF/Stress Related Signaling, T Cell Receptor Signaling Pathway, TNFR1 Signaling Pathway, Toll-Like Receptor Pathway, TPO Signaling Pathway, TSP-1 Induced Apoptosis in Microvascular Endothelial Cell |
| HIF-1a hypoxia inducible factor 1, alpha subunit | Loss | 0.026 | 0.050 | 0.464 | mTOR signaling pathway, VEGF, Hypoxia, and Angiogenesis, Erythropoietin mediated neuroprotection through NF-kB, Hypoxia-Inducible Factor in the Cardiovascular System, Hypoxia and p53 in the Cardiovascular system |

Table 2. . Gene connections gained by STAT5a from (a) normal prostate to low grade tumor and (b) in low grade to high grade progression. The p-values shown are from using single gene analysis and the Student's t-test, with significant p-values (< 0.05) marked in red. Note again that single gene analysis is unable to identify all these associations (some of the p-values are not good). However, the co-regulation analysis and transcription factor filter used in our method readily identified all these links.

Table 2a

| Gene name | Normal vs. low grade tumor | Normal vs. high grade tumor | Low vs. high grade tumor | Pathway (KEGG, BIOCARTA database) |
|---|----------------------------|-----------------------------|--------------------------|--|
| | Student's t-test p-value | | | |
| AKT1 v-akt murine thymoma viral oncogene homolog 1 | 0.001 | 0.001 | 0.770 | MAPK signaling pathway, ErbB signaling pathway, mTOR signaling pathway, Apoptosis, VEGF signaling pathway, Focal adhesion, Tight junction, Toll-like receptor signaling pathway, Jak-STAT signaling pathway, T cell receptor signaling pathway, B cell receptor signaling pathway, Fc epsilon RI signaling pathway, Insulin signaling pathway, Adipocytokine signaling pathway |
| RAP1GAP RAP1 GTPase activating protein | 0.001 | 0.000 | 0.251 | |
| APBA2BP N-terminal EF-hand calcium binding protein 3 | 0.001 | 0.001 | 0.626 | |
| ARID1A AT rich interactive domain 1A (SWI-like) | 0.001 | 0.001 | 0.047 | |
| CACNA2D2 calcium channel, voltage-dependent, alpha 2/delta subunit 2 | 0.002 | 0.022 | 0.143 | MAPK signaling pathway |
| ATG4B ATG4 autophagy related 4 homolog B (S. cerevisiae) | 0.002 | 0.001 | 0.638 | Regulation of autophagy |
| SPINT1 serine peptidase inhibitor, Kunitz type 1 | 0.002 | 0.001 | 0.465 | |
| GMPPA GDP-mannose pyrophosphorylase A | 0.003 | 0.009 | 0.169 | Fructose and mannose metabolism |
| CAMK2B calcium/calmodulin- | 0.003 | 0.000 | 0.999 | ErbB signaling pathway, Calcium signaling pathway, Wnt signaling |

| | | | | |
|--|--------------|--------------|--------------|--|
| dependent protein kinase II beta | | | | pathway, Long-term potentiation, Olfactory transduction, GnRH signaling pathway, Melanogenesis |
| AMZ2 archaelysin family metalloproteinase 2 | 0.003 | 0.002 | 0.516 | |
| TTL12 tubulin tyrosine ligase-like family, member 12 | 0.004 | 0.000 | 0.195 | |
| MSH5 mutS homolog 5 (E. coli) | 0.005 | 0.001 | 0.169 | |
| FGFR2 fibroblast growth factor receptor 2 | 0.008 | 0.114 | 0.161 | MAPK signaling pathway, Regulation of actin cytoskeleton |
| REPIN1 replication initiator 1 | 0.013 | 0.002 | 0.047 | |
| LSS lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase) | 0.014 | 0.159 | 0.023 | Biosynthesis of steroids |
| TSPAN4 tetraspanin 4 | 0.016 | 0.038 | 0.266 | |
| KLF10 Kruppel-like factor 10 | 0.020 | 0.011 | 0.371 | |
| PYCR1 sirtuin (silent mating type information regulation 2 homolog) 7 (S. cerevisiae) | 0.023 | 0.005 | 0.586 | Arginine and proline metabolism, |
| CTSH cathepsin H | 0.039 | 0.007 | 0.526 | |
| MGLL monoglyceride lipase | 0.050 | 0.208 | 0.112 | Glycerolipid metabolism, |
| CENTG2 ArfGAP with GTPase domain, ankyrin repeat and PH domain 1 | 0.051 | 0.007 | 0.175 | |
| TEAD3 TEA domain family member 3 | 0.052 | 0.135 | 0.148 | |
| IGF1R insulin-like growth factor 1 receptor | 0.053 | 0.050 | 0.823 | Focal adhesion, Adherens junction, Long-term depression |
| MYL9 myosin, light chain 9, regulatory | 0.065 | 0.542 | 0.075 | Focal adhesion, Tight junction, Leukocyte transendothelial migration, Regulation of actin cytoskeleton |
| GABRE gamma-aminobutyric acid (GABA) A receptor, epsilon | 0.073 | 0.061 | 0.918 | Neuroactive ligand-receptor interaction |
| SIM2 single-minded homolog 2 (Drosophila) | 0.083 | 0.001 | 0.186 | |
| NRP1 neuropilin 1 | 0.096 | 0.189 | 0.656 | Axon guidance |
| PAQR4 progesterone and adipoQ receptor | 0.211 | 0.944 | 0.052 | |

| | | | | |
|---|-------|--------------|-------|--|
| family member IV | | | | |
| PER2 period homolog 2 (Drosophila) | 0.250 | 0.532 | 0.525 | Circadian rhythm – mammal |
| ECGF1 sphingosine-1- phosphate receptor 1 | 0.272 | 0.086 | 0.710 | Neuroactive ligand-receptor interaction |
| FZD10 frizzled homolog 10 (Drosophila) | 0.310 | 0.049 | 0.404 | Wnt signaling pathway, Melanogenesis |
| LMNA lamin A/C | 0.406 | 0.085 | 0.427 | |
| PAOX polyamine oxidase (exo-N4- amino) | 0.422 | 0.470 | 0.858 | |
| RASSF7 Ras association (RalGDS/AF-6) domain family (N- terminal) member 7 | 0.439 | 0.031 | 0.065 | |
| SECTM1 secreted and transmembrane 1 | 0.513 | 0.030 | 0.068 | |
| DUSP8 dual specificity phosphatase 8 | 0.666 | 0.542 | 0.966 | MAPK signaling pathway |
| FOSL2 FOS-like antigen 2 | 0.776 | 0.809 | 0.605 | |
| CRYBA2 crystallin, beta A2 | 0.787 | 0.934 | 0.663 | |

Table 2b

| Gene name | Normal vs. low grade tumor | Normal vs. high grade tumor | Low vs. high grade tumor | Pathways (KEGG & BIOCARTA database) |
|---|----------------------------------|-----------------------------------|--------------------------------|---|
| | Student's t-test p-value | | | |
| EFS embryonal Fyn- associated substrate | 0.009 | 0.147 | 0.000 | |
| NBL1 neuroblastoma, suppression of tumorigenicity 1 | 0.026 | 0.179 | 0.000 | |
| GPC1 glypican 1 | 0.028 | 0.868 | 0.003 | |
| SCRIB scribbled homolog (Drosophila) | 0.035 | 0.007 | 0.005 | |
| EML3 echinoderm microtubule associated protein like 3 | 0.001 | 0.000 | 0.025 | |
| IRAK1 interleukin-1 receptor-associated kinase 1 | 0.392 | 0.049 | 0.100 | Apoptosis, Toll-like receptor signaling pathway, |
| SS18L1 synovial sarcoma translocation gene on chromosome 18- like 1 | 0.010 | 0.003 | 0.130 | |
| DLK2 delta-like 2 homolog | 0.840 | 0.179 | 0.171 | |

| | | | | |
|--|--------------|--------------|-------|---|
| (Drosophila) | | | | |
| BCOR BCL6 co-repressor | 0.089 | 0.018 | 0.209 | |
| C20orf149 pancreatic progenitor cell differentiation and proliferation factor homolog (zebrafish) | 0.074 | 0.173 | 0.223 | |
| IGF2 insulin-like growth factor 2 (somatomedin A); insulin; INS-IGF2 readthrough transcript | 0.076 | 0.317 | 0.247 | Regulation of autophagy, mTOR signaling pathway, Regulation of actin cytoskeleton, Insulin signaling pathway |
| CACNA1H calcium channel, voltage-dependent, T type, alpha 1H subunit | 0.037 | 0.172 | 0.249 | MAPK signaling pathway, Calcium signaling pathway |
| IRX5 iroquois homeobox 5 | 0.076 | 0.220 | 0.300 | |
| MDK Mesomelic dysplasia, Kantaputra type | 0.128 | 0.216 | 0.465 | |
| SALL1 sal-like 1 (Drosophila) | 0.697 | 0.623 | 0.511 | |
| FGFR3 fibroblast growth factor receptor 3 | 0.047 | 0.103 | 0.548 | MAPK signaling pathway, Regulation of actin cytoskeleton |
| INHBB inhibin, beta B | 0.938 | 0.588 | 0.585 | Cytokine-cytokine receptor interaction, TGF-beta signaling pathway |
| BCL11A B-cell CLL/lymphoma 11A (zinc finger protein) | 0.791 | 0.618 | 0.796 | |
| GATA3 GATA binding protein 3 | 0.617 | 0.468 | 0.801 | |
| MFAP2 microfibrillar- associated protein 2 | 0.007 | 0.002 | 0.909 | |
| SH3BP4 SH3-domain binding protein 4 | 0.167 | 0.165 | 0.989 | |