Ubiquitin-conjugating enzyme E2T (UBE2T) and denticleless protein homolog (DTL) are linked to poor outcome in breast and lung cancers

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Supplementary Figure 1
| Gene name                  | Gene symbol | Function                          |
|---------------------------|-------------|-----------------------------------|
| HECT, UBA and WWE domain  | HUWE1       | Ubiquitin-protein ligase which mediates ubiquitination and subsequent proteasomal degradation of target proteins. Regulates apoptosis by catalyzing the polyubiquitination and degradation of MCC1. Mediates monoubiquitination of DNA polymerase alpha (POLA) at Lys-11, Lys-61 and Lys-81, thereby playing a role in base-excision repair. Also ubiquinatizes the p53/TP53 tumor suppressor and core histones including H1, H2A, H2B, H3 and H4. Binds to an ubiquitin inhibitor-like sequence in the preproendothelin gene. May regulate polyubiquitin-dependent PTEN degradation after DNA damage by polyubiquitinating and targeting CDCC to degradation. Mediates polyubiquitination of isoform 2 of PAG2A. |
| E3 ubiquitin-protein ligase Rch ych homolog | ITCH       | Acts as an E3 ubiquitin-protein ligase which accepts ubiquitin from an E2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to target substrates. It catalyzes Lys-29-, Lys-48- and Lys-63-linked ubiquitin conjugation. It is involved in the control of inflammatory signaling pathways. Is an essential component of a ubiquitin-editing protein complex, comprising also TIFAP3, TAXIPB1 and RNF11, that ensures the transient nature of inflammatory signaling pathways. Regulates the transcriptional activity of several transcription factors, and probably plays an important role in the regulation of immune response. Involves in the regulation of apoptosis and reactive oxygen species through ubiquitination and proteasomal degradation of TXNIP. Mediates the antiapoptotic activity of epidermal growth factor through the ubiquitination and proteasomal degradation of p15 BID. |
| Ubiquitin-conjugating enzyme E2 C | UBE2C      | Accepts ubiquitin from the E1 complex and catalyzes its covalent attachment to other proteins. In vitro catalyzes Lys-11- and Lys-48-linked polyubiquitination. Acts as an essential factor of the anaphase promoting complex/cyclosome (APC/C), a cell cycle-regulated ubiquitin ligase that controls progression through mitosis. Acts by initiating Lys-11-linked polyubiquitin chains on APC/C substrates, leading to the degradation of APC/C substrates by the proteasome and promoting mitotic exit. |
| Ubiquitin-conjugating enzyme E2 S | UBE2B      | Accepts ubiquitin from the E1 complex and catalyzes its covalent attachment to other proteins. Catalyzes Lys-11-linked polyubiquitination. Acts as an essential factor of the anaphase promoting complex/cyclosome (APC/C), a cell cycle-regulated ubiquitin ligase that controls progression through mitosis. Acts by specifically elongating Lys-11-linked polyubiquitin chains initiated by the E2 enzyme UBE2C/UBCH10 on APC/C substrates, enhancing the degradation of APC/C substrates by the proteasome and promoting mitotic exit. Also acts by elongating ubiquitin chains initiated by the E2 enzyme UBE2D1/UBCH9 in vitro. It is however unclear whether UBE2D1/UBCH9 acts as an E2 enzyme for the APC/C in vivo. Also involved in ubiquitin and subsequent degradation of VHL, resulting in an accumulation of HIF1A. In vitro able to promote polyubiquitination using all 7 ubiquitin Lys residues, except Lys-48-linked polyubiquitination. |
| Ubiquitin-conjugating enzyme E2 S | UBE2H      | Accepts ubiquitin from the E1 complex and catalyzes its covalent attachment to other proteins. In vitro catalyzes Lys-11- and Lys-48-linked polyubiquitination. Capable, in vitro, to ubiquitinate histone H2A. |
| Ubiquitin-associated and SH3 domain-containing protein B | UBA3HOB    | Interferes with CBL-mediated down-regulation and degradation of receptor-type tyrosine kinases. Promotes accumulation of activated target receptors, such as T-cell receptors and EGFR, on the cell surface. Exhibits tyrosine phosphatase activity toward several substrates including EGFR, FAK, SYK, and ZAP70. Down-regulates proteins that are dually modified by both protein tyrosine phosphorylation and ubiquitination. |
| E3 ubiquitin-protein ligase TRIM71 | TRIM71     | Ubiquitin ligase that cooperates with the microRNAs (miRNAs) machinery and promotes embryonic stem cells proliferation and maintenance. Binds to miRNAs and associates with AGO2, participating in post-transcriptional repression of transcripts such as CDKN1A. Facilitates the G1-S transition to promote rapid embryonic stem cell self-renewal by repressing CDKN1A expression. |
| NEDD4-binding protein 1 | NABP1      | Inhibitor of the E3 ubiquitin-protein ligase ITCH. Acts by interacting with the second WW domain of ITCH, leading to compete with ITCH's substrates and impairing ubiquitination of substrates (By similarity). |
| E3 ubiquitin-protein ligase RNF130 | RNF130     | May have a role during the programmed cell death of hematopoietic cells (By similarity). Acts as an E3 ubiquitin-protein ligase. |
| Tubby-related protein 4 | TULP4       | May be a substrate-recognition component of a SCF-like ECS (Elongin-Cullin-SOCS-box protein) E3 ubiquitin ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins. |
| Cell division cycle-associated protein 3 | CDC6A3     | F-box-like protein which is required for entry into mitosis. Acts by participating in E3 ligases complex that mediate the ubiquitination and degradation of WEE1 kinase at G2/M phase (By similarity). |
| Cell division cycle-associated protein 20 | CDC20      | Activator protein that regulates the ubiquitin ligase activity and substrate specificity of the anaphase-promoting complex/cyclosome (APC/C). At the metaphase- to anaphase transition, recognizes and binds proteins containing a D-box including the B-type cyclins CLB2 and CLB5, HSL1 and securin PDS1, and recruits them in a C-box-dependent manner to the APC/C for ubiquitination and subsequent proteolysis. Required for sister chromatid separation and disassembly of the mitotic spindle. Target of the spindle checkpoint pathway through participation in the mitotic checkpoint complex (MCC) and the MAD2/CDC20 subcomplex. MCC and presumably the MAD2-CDC20 subcomplex inhibit the ubiquitin ligase activity of the anaphase promoting complex/cyclosome (APC/C) by preventing its activation by CDC20 until proper attachment of all chromosomes to the spindle. |
| F-box only protein 11 | FBXO11     | Substrate recognition component of a SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins, such as DTL/CD72, BCL6 and PRDM1/BLIMP1. The SCF(FBXO11) complex mediates ubiquitination and degradation of BCL6, thereby playing a role in the germline B-cells terminal differentiation toward memory B-cells and plasma cells. The SCF(FBXO11) complex also mediates ubiquitination and degradation of DTL, an important step for the regulation of TGF-beta signaling, cell migration and the timing of the cell cycle progression and exit. Binds to and neddylates phosphorylated p53/TP53, inhibiting its transcriptional activity. SCF(FBXO11) does not seem to direct ubiquitination of p53/TP53. |
| E3 ubiquitin-protein ligase UHRF1 | UHRF1      | Multidomain protein that acts as a key epigenetic regulator by bridging DNA methylation and chromatin modification. Specifically recognizes and binds hemimethylated DNA at replication forks via its YDG domain and recruits DNM1 methyltransferase to ensure faithful propagation of the DNA methylation patterns through DNA replication. In addition to its participation in maintenance of DNA methylation, also plays a key role in chromatin modification: through its tudor-like regions and PHD-type zinc fingers, specifically recognizes and binds histone H3 trimethylated at Lys-9 (H3K9me3) and unmethylated at Arg-2 (H3R2me0), respectively, and recruits chromatin proteins. Enriched in pericentric heterochromatin where it recruits different chromatin modifiers required for this chromatin replication. Also localizes to euchromatic regions where it negatively regulates transcription possibly by impeding DNA methylation and histone modifications. Has E3 ubiquitin-protein ligase activity by mediating the ubiquitination of target proteins such as histone H3 and PML. It is still unclear how E3 ubiquitin-protein ligase activity is related to its role in chromatin in vivo. May be involved in DNA repair. |

**Supplementary Table 1**
Supplementary Figure 1. Enrichment plots of the identified genes, using different gene sets showing the upregulation of the ubiquitin pathway in Basal-like breast tumors, represented by the Normalized Enrichment Score (NES).

Only gene sets at FDR <0.25 were considered significantly enriched.

Supplementary Table 1. Biological functions of the 16 identified upregulated genes.

Supplementary Table 2. Association of UBE2T and DTL with first progression and overall survival in patients with lung adenocarcinoma, lung squamous cell carcinoma, ovarian cystadenocarcinoma, and esophagus-stomach cancer.