Universitätsklinikum Hamburg-Eppendorf

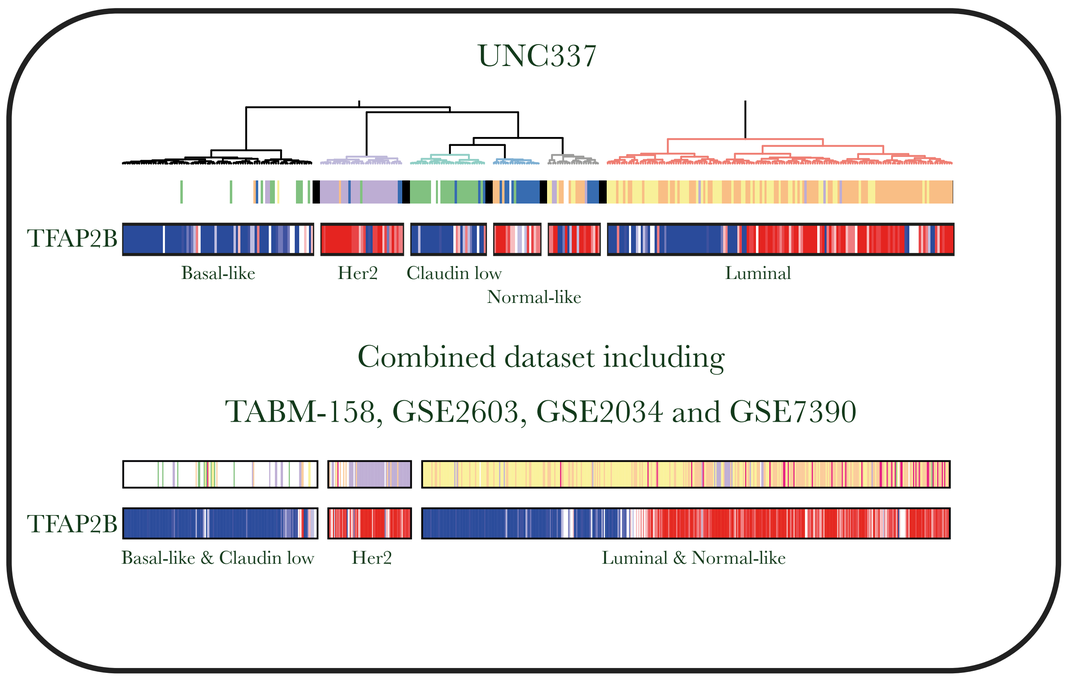
Center for Internal Medicine

TFAP2B is associated with WNT/ß-catenin pathway in luminal breast cancer

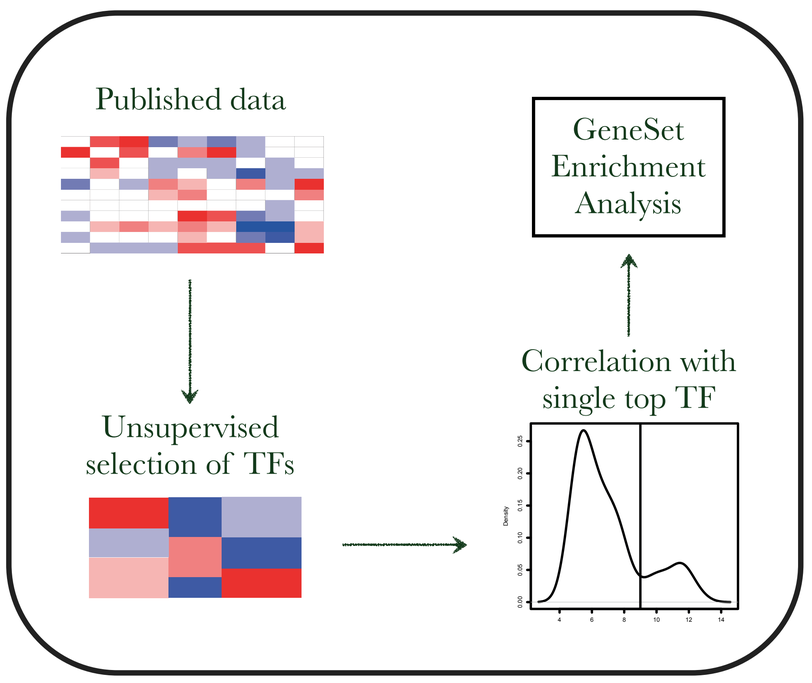
Benjamin Otto[1,2], Kristin Klätschke[2], Thomas Streichert[3], Christoph Wagener[2], Genrich Tolstonog[4]

1. Center for Internal Medicine, University Medical Center Hamburg-Eppendorf, Germany
2. Department of Clinical Chemistry, University Medical Center Hamburg-Eppendorf, Germany
3. Department of Clinical Chemistry, University Medical Center Cologne, Germany
4. Department of Otolaryngology – Head and Neck Surgery, CHUV, University of Lausanne, 1011 Lausanne, Switzerland

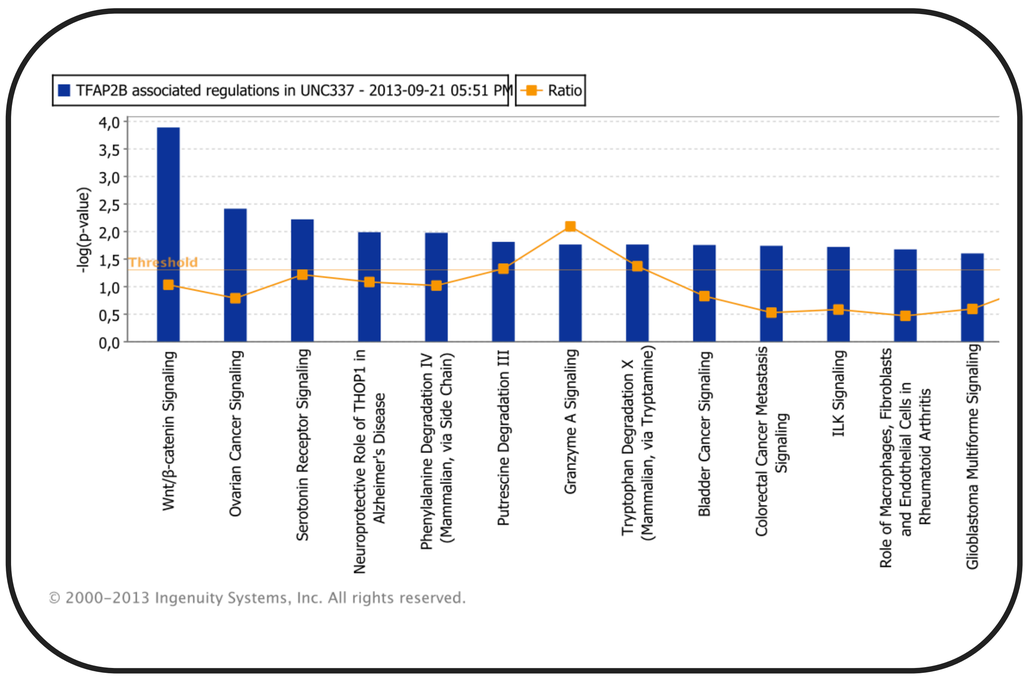
Transcription factors play a crucial role in cancer development and progression. In breast cancer some of the most important diagnostic markers used for treatment decision and outcome estimation are transcription factors. Among them are the estrogen, progesterone or androgen receptors. Because of their central role in the molecular regulatory network and their high frequency among the established diagnostic markers we put in the focus of our analysis. In a previous work we found that *TFAP2B* clearly splits luminal breast tumors into two distinct subgroups - a high expressing and a low expressing subgroup. Here we aimed to investigate which molecular mechanisms are associated with *TFAP2B* expression in luminal breast cancer.



We investigated gene expression of *TFAP2B* in several human datasets (UNC337) published in the NCBI GEO data repository. In all investigated datasets a clear expression pattern was observed. *TFAP2B* exhibited high expression in HER2 and Normal-like but not in Basal-like breast cancer. Interestingly *TFAP2B* expression clearly separated the luminal tumors into two distinct groups that did not correlate with the Luminal A or Luminal B subtypes.



Here we calculated the correlation of genes with *TFAP2B* on a whole genome basis. Afterwards we performed Gene set enrichment analysis using Ingenuity Pathway Analysis Software. We investigated biological functions, pathways and upstream regulators associated with the *TFAP2B* linked regulations in luminal breast cancer.



The analysis revealed a significant association of *TFAP2B* associated regulations with the WNT/ß-catenin signaling pathway. The pathway exhibited an enrichment p-value below 0.001. Furthermore an enrichment of a number of cancer assoiated pathways was observed, such as ovarian cancer signaling, bladder cancer signaling and colorectal cancer signaling.

Upstream Regulator	Log Ratio	Predicted Activation ...	Activation z-score	p-value of overlap
dexamethasone		Activated	3,239	1,97E-10
miR-760-3p (and oth		Activated	2,923	2,21E-03
IL1		Activated	2,917	5,63E-03
OSM	-0,093	Activated	2,858	9,92E-05
TGFB1	0,024	Activated	2,831	4,84E-05
IL6	-0,307	Activated	2,644	1,92E-03
NUPR1	0,109	Activated	2,539	2,27E-03
TGFB3	0,492	Activated	2,391	1,03E-04
IL1A	-0,036	Activated	2,189	5,00E-02
STK11	0,067	Activated	2,000	5,96E-03
STAT3	0,227		1,997	9,22E-04
tert-butyl-hydroquinor			1,987	7,04E-03
SMAD3	0,007		1,969	9,17E-03
WNT3A	-0,070		0,527	5,16E-06
diethylstilbestrol			0,246	8,26E-06
GPER	-0,368		0,415	1,10E-05
tretinoin			0,638	1,72E-05
CTNNB1	0,242		0,478	2,13E-05
tamoxifen			1,281	3,10E-05
TCF				3,46E-05
TGFB2	0,196		1,945	8,90E-03
TNF	0,037		1,825	2,59E-07

Based the on determined gene expression regulations putative upstream regulators involved in the observed expression patterns were predicted. The software predicted the activation on protein level of a number of molecules involved in WNT signaling and epithelial mesenchymal transition, such as TGFB1, TGFB3, SMAD3, WNT3A, ß-catenin, TCF and TNF.

UID	p-value	SLR	FDR
SCGB2A2	4.29E-06	1.955835174	0.001595007
CYP4Z1	9.47E-12	1.885960918	8.42E-08
ABCC11	2.17E-07	1.493971113	0.000297122
SCGB1D2	2.49E-05	1.424212404	0.005270369
TMC5	7.72E-07	1.350506372	0.000599394
CYP4X1	1.19E-06	1.223425658	0.000694092
VTCN1	4.42E-05	1.190344945	0.007473596
FAM3B	0.000950328	-1.063474936	0.041718225
GDF15	1.72E-07	-1.076870008	0.000297122
KCNJ3	4.88E-05	-1.344968564	0.007750583

Overview of the top 10 genes associated with *TFAP2B* expression based on signal-log-ratio.

Conclusions:

Identification and prediction of breast cancer subtypes is a wide and highly investigated research field. Many research groups have identified and reported subtype specific signatures. Common to many of these signatures is the supervised approach where specific phenotype associated features are provided as input. We identified *TFAP2B* in an unsupervised approach and show that the expression correlates with two distinct subgroups of luminal breast cancer which are not identical with Luminal A/B subgrouping. Though several publications describe the association of AP-2α and AP-2γ with breast cancer, AP-2β ist still hardly investigated in the context of breast cancer. Here we investigated the *TFAP2B* correlations and show that *TFAP2B* is associated with the WNT/ß-catenin signaling pathway.