Genes involved in non-malignant breast phenotypes are widely expressed in multiple cancers and provide novel biomarkers of clinical outcomes and therapeutic response.

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BACKGROUND

From over two hundred driver mutations identified to date, only about a dozen are FDA-approved biomarkers, and there is an unmet need to discover novel suitable biomarkers. We selected novel biomarkers based on non-malignant breast epithelial cell phenotypes and identified 325 genes (BA325) showing 32 significant oncology drug associations. A total of 251 genes out of 325 are unique and not found in any of 9 other oncology panels investigated, suggesting that BA325 may yield novel insights regarding tumor biology, clinical outcomes, and novel therapeutic targets, not covered by current tools. While prior work has validated the utility of BA325 in breast cancer, the current study investigates BA325 expression in other tumor types beyond breast.

OBJECTIVE

Can BA325 genes originally identified in breast tissue function as biomarkers in other tissues and cancers?

METHODS

We tested BA325 expression in 8 tumor types (breast, colon, lung, ovarian, prostate, pancreatic, gastric cancers, and leukemia), using two independent public data sets for each, totaling 3,563 samples in 16 datasets. All used Affymetrix HG-U133A or Plus 2.0 microarrays.

Tissue	Accession	N	Tissue	Accession	N
Breast (BR1)	GSE25055	310	Lung (LU1)	GSE19188	156
Breast (BR2)	E-TABM-157	51	Lung (LU2)	GSE30219	307
Colon (CO1)	GSE39582	585	Ovarian (OV1)	GSE26712	192
Colon (CO2)	GSE68468	366	Ovarian (OV2)	GSE9891	285
Gastric (GA1)	GSE13911	69	Pancreatic (PA1)	GSE15471	78
Gastric (GA2)	GSE54129	132	Pancreatic (PA2)	GSE16515	52
Leukemia (LK1)	GSE13159	568	Prostate (PR1)	GSE17951	154
Leukemia (LK2)	GSE14471	110	Prostate (PR2)	GSE8218	148

REFERENCES

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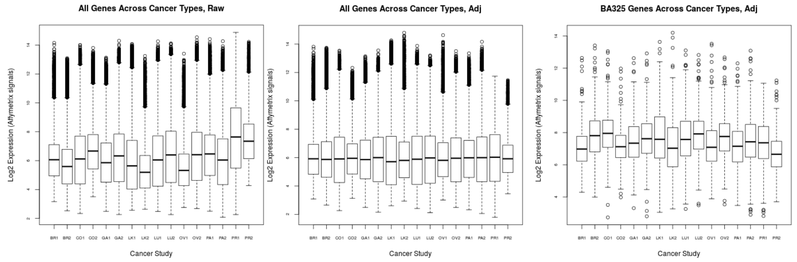
RESULTS

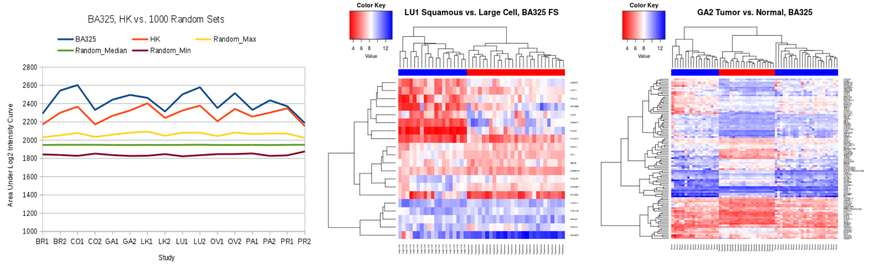
Samples were normalized within each study using RMA and batch-corrected across studies. At least 324 of the 325 genes were expressed above background (log2 > 3) in every cancer type.



119 BA325 genes were tissue-specific, having either their highest or lowest expression in both replicates of the same cancer type.

Tissue	# Genes	High	Low
Breast	10	SCD, PAGR1, DEPDC1	MBNL1, EGR1, IMPA1, …
Colon	2	EXPH5	MT2A
Leukemia	53	DDX39B, PFN1, NASP, …	ANXA5, PALLD, THBS1, …
Lung	7	GPNMB, RAI14, UBE2K, …	None
Ovarian	3	ITGB5, IGFBP2, BBOX1	None
Pancreatic	12	None	BIRC5, FOXM1, POLRMT, …
Prostate	42	CRYAB, KIAA1644	PSMB2, PFN1, LDHA, …

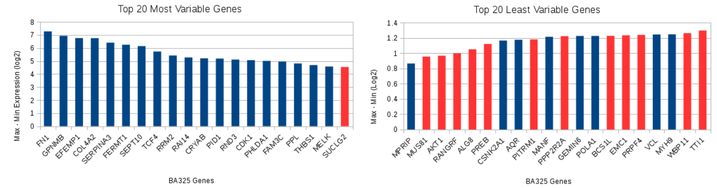
BA325 genes were more highly expressed than 1,000 random sets of 325 genes in all cancers, and could distinguish subtypes in lung cancer and tumor/normal status in gastric cancer.



Surprisingly, many of the BA325 genes were identified as housekeeping (HK) genes (Eisenberg & Levanon, 2013). HK genes were among the most variable, least variable, tissue-specific, and outcome-predicting BA325 genes.

Category	BA325	HK Subset
Most Variable	40	5
Least Variable	87	48
Tissue Specific	119	27
Outcome Predicting	32	7
Total Genes	325	102

The 20 most and 20 least variable genes are plotted here, with HK genes colored red.



These are the top GO terms for the 102 HK genes in BA325 using Enrichr.

GO Biological Process Terms (Number of Matching Genes in Parentheses)	
Spliceosomal snRNP assembly (12)	Regulation of cellular response to heat (5)
Spliceosomal conformational changes (11)	Recruitment of complex to DNA lesions (4)
Alternative mRNA splicing (11)	Mitochondrial genome maintenance (5)
Spliceosomal complex assembly (11)	Ribosomal skipping (4)
mRNA export from nucleus (9)	Regulation of NF-kappaB activity (6)
SMAD protein import into nucleus (5)	Protein import into nucleus (6)

CONCLUSIONS

We conclude that BA325 expression profiles in all datasets examined include both tissue-specific genes and genes with similar expression across tissues. Preliminary results indicate BA325 genes may have utility as biomarkers in a surprisingly wide variety of tumor types (including leukemia) in addition to breast cancer, with discriminatory power in at least gastric, ovarian, lung and breast cancers. Thus, BA325 can greatly increase the biomarker repertoire beyond oncogenes or other driver genes and may provide relevant insight in novel oncology therapeutic targets.