High Expression of FGD3, a Putative Regulator of Cell Morphology and Motility, Is Prognostic of Favorable Outcome in Multiple Cancers

Purpose Identification of single-gene biomarkers that are prognostic of outcome can shed new insights on the molecular mechanisms that drive breast cancer and other cancers.

Methods Exploratory analysis of 20,464 single-gene messenger RNAs (mRNAs) in the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) discovery cohort indicates that low expression of FGD3 mRNA is prognostic for poor outcome. Prognostic significance of faciogenital dysplasia 3 (FGD3), SUSD3, and other single-gene proliferation markers was evaluated in breast cancer and The Cancer Genome Atlas (TCGA) cohorts.

Results A meta-analysis of Cox regression of FGD3 mRNA as a continuous variable for overall survival of estrogen receptor (ER)–positive samples in METABRIC discovery, METABRIC validation, TCGA breast cancer, and Combination Chemotherapy in Treating Women With Breast Cancer (E2197) cohorts resulted in a combined hazard ratio (HR) of 0.69 (95% CI, 0.63 to 0.75), indicating better outcome with high expression. In the ER-negative samples, the combined meta-analysis HR was 0.72 (95% CI, 0.63 to 0.82), suggesting that FGD3 is prognostic regardless of ER status. The potential of FGD3 as a biomarker for freedom from recurrence was evaluated in the Breast International Group 1-98 (BIG 1-98; Letrozole or Tamoxifen in Treating Postmenopausal Women With Breast Cancer) study (HR, 0.85; 95% CI, 0.76 to 0.93) for breast cancer–free interval. In the Hungarian Academy of Science (HAS) breast cancer cohort, splitting on the median had an HR of 0.49 (95% CI, 0.42 to 0.58) for recurrence-free survival. A comparison of the Stouffer $P$ value in five ER-positive cohorts showed that FGD3 ($P = 3.8 \times 10^{-14}$) outperformed MKI67 ($P = 1.06 \times 10^{-8}$) and AURKA ($P = 2.61 \times 10^{-5}$). A comparison of the Stouffer $P$ value in four ER-negative cohorts showed that FGD3 ($P = 3.88 \times 10^{-5}$) outperformed MKI67 ($P = .477$) and AURKA ($P = .820$).

Conclusion FGD3 was previously shown to inhibit cell migration. FGD3 mRNA is regulated by ESR1 and is associated with favorable outcome in six distinct breast cancer cohorts and four TCGA cancer cohorts. This suggests that FGD3 is an important clinical biomarker.

INTRODUCTION

An increasing collection of breast cancer cohorts have been molecularly profiled on Affymetrix and Illumina platforms, so it is now feasible to conduct an exploratory analysis to identify single-gene biomarkers in which messenger RNA (mRNA) expression is prognostic of outcome. By limiting the exploratory analysis to a single gene, we intended to identify novel gene(s) that might provide insight into biological mechanisms that drive breast cancer metastasis. The starting point for this analysis was the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) data set, which contains clinical traits, expression data, copy number variation profiles, and single nucleotide polymorphism genotypes derived from breast tumors collected from participants in the METABRIC trial. We also used the Genomic Data Commons, which incorporates The Cancer Genome Atlas (TCGA) cancer cohorts and currently spans 21 cancer types suitable for survival analysis. This type of analysis could lead to the
discovery of prognostic biomarkers that behave as oncogenic drivers and could potentially be novel therapeutic targets.

In this study, we identified FGD3 mRNA expression as a putative biomarker prognostic of outcome in the METABRIC cohort. FGD3 and SUSD3 cell motility genes were compared as a single-gene biomarker with proliferation genes MKI67, AURKA, and PCNA in six distinct breast cancer cohorts and as a pan-cancer biomarker in TCGA cancer cohorts. FGD3 protein expression was evaluated in breast cancer tissue microarrays (TMAs) as an indicator of regional lymph node status. FGD3 mRNA expression as a biomarker for an immune response was evaluated by using tumor-infiltrating lymphocyte cells in TCGA breast cancer and Breast International Group 1-98 (BIG 1-98; Letrozole or Tamoxifen in Treating Postmenopausal Women With Breast Cancer) cohorts. ESR1 transcriptional regulation of FGD3 mRNA expression in the breast cancer cell line ZR-75-1 was confirmed.

METHODS
Cohorts
Detailed description of each cohort is provided in the Data Supplement.

Survival Analysis
To illustrate the outcome benefit of low versus high expression, the Kaplan-Meier method was used to estimate the distribution of time-to-disease outcome end points by gene expression status bifurcated on the cohort mean and median (Data Supplement). An overall inference measure was determined by using a Stouffer weighted Z-test \( P \) value to combine probabilities from the cohorts. The Wald-test \( P \) values from Cox proportional hazards models for the association of cancer outcomes with gene expression status as a continuous variable for each cohort were used to determine the Stouffer weighted Z-test \( P \) value. BioJava was used to implement the R survival package for analysis. Meta-analysis data for combined hazard ratio (HR) and forest plot figures were generated by using MetaXL (http://www.epigear.com/).

FGD3 Expected Tissue Cell Profile and Tumor-Infiltrating Lymphocyte Association
Faciogenital dysplasia 3 (FGD3) protein is found to have high expression in immune response cells according to curated data in 79 human and 61 mouse tissues from the GeneAtlas using BioGPS. Tumors with high expression of FGD3 and favorable outcome could indicate an immune response. Tumor-infiltrating lymphocytes (TLs) were called in 389 samples from TCGA breast cancer high-resolution slide images using methods previously defined by the International TIL Working Group 2014. TILs were called using a similar methodology in 725 samples from the BIG 1-98 DASL cohort, and correlation to FGD3 mRNA expression was determined by using Pearson’s correlation coefficient (\( r \)).

FGD3 Protein Expression Analysis
FGD3 protein expression in tumor samples was determined by immunohistochemical (IHC) staining. Breast cancer samples were provided by Avera Cancer Institute, and breast cancer TMAs (BR1504a, BR1505b, HBre-Duc068Bch-01, and BR20837) were purchased from US Biomax (Rockville, MD).

FGD3 protein expression was quantitatively determined in the range of 0 to 4. The US Biomax metadata indicates whether the patient had no regional lymph node metastasis (N0) or degrees of metastasis in regional lymph nodes (N1 to N3). FGD3 expression levels for samples with N0 designation (n = 135) and samples with N1 to N3 designations in metastatic tissue (n = 98) were compared by using an unpaired t test. Tissues for matched lymph node metastasis (n = 103) were compared with primary tumor tissues using unpaired t test, and figures were generated using GraphPad Prism 7.0. Additional details on analysis can be found in the Data Supplement.

FGD3 mRNA Expression Regulated by Estrogen Receptors
Breast cancer cell line ZR-75-1 was grown in RPMI-1640 medium with 10% fetal bovine serum. For the treatment of estrogen, cells were deprived of hormone for 3 days in phenol-free RPMI-1640 medium with 5% charcoal-stripped fetal bovine serum and then treated with either ethanol (vehicle) or 1 nM 17\( \beta \)-estradiol (estrogen) for 16 hours. Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) was performed and is described in the Data Supplement.

mRNA Expression of Genes of Interest With Published Data
The Expression Atlas Web site was used to query RNA sequencing (RNA-seq) expression levels in breast cancer cell lines. In addition, the Web site was used to search for cancer cell line experiments with a 2.0 or greater fold change for FGD3, and downloaded experimental data were
used to illustrate differences in differential expression of the proliferation genes using Prism 7.0.

RESULTS

Discovery of FGD3

We undertook an exploratory analysis of 20,464 possible single-gene biomarkers as categorical variables split on the mean in the METABRIC discovery cohort and identified FGD3 mRNA expression as the highest ranked prognostic gene based on the *P* value for overall survival (OS), which we subsequently verified as being prognostic in the METABRIC validation cohort (data not shown). A detailed summary of the genes in this article that were used for Cox models as continuous and categorical variables, Kaplan-Meier figures split on cohort means, and expression profiles can be found in the Data Supplement.

FGD3 Breast Cancer Prognostic Marker

**IHC estrogen receptor-positive cohorts.** The results of the Cox regression analysis of *FGD3* mRNA expression as a continuous variable in five distinct estrogen receptor (ER)-positive breast cancer cohorts are shown in Figure 1A (combined HR, 0.73; 95% CI, 0.64 to 0.82) in which high expression is prognostic of favorable outcome. High expression of *SUSD3* was also prognostic of favorable outcome (HR, 0.72; 95% CI, 0.62 to 0.84; Data Supplement). High expression of
**FGD3** mRNA is highly prognostic of poor outcome in the five cohorts, but in the E2197 (Combination Chemotherapy in Treating Women With Breast Cancer) ER-positive cohort it had the opposite effect, with an HR of 0.78 (95% CI, 0.62 to 1.00), indicating that low expression is prognostic of poor outcome (Data Supplement). **PCNA** has an HR of 1.06 (95% CI, 0.94 to 1.19) and is prognostic, by virtue of the HR > 1.0, of poor outcome in the METABRIC ER-positive validation cohort (HR, 1.27; 95% CI, 1.11 to 1.45; Data Supplement). AURKA has a combined HR of 1.26 (95% CI, 1.03 to 1.54), indicating that high expression is prognostic of poor outcome in METABRIC ER-positive and ER-negative cohorts (Data Supplement). The Stouffer P value was used to rank the prognostic significance of each gene in five distinct ER-positive cohorts: **FGD3** ($P = 3.87E^{-14}$), **SUSD3** ($P = 4.15E^{-11}$), **MKI67** ($P = 1.06E^{-8}$), **AURKA** ($P = 2.61E^{-5}$), and **PCNA** ($P = .402$).

**Hungarian Academy of Science breast cancer cohort.** The Hungarian Academy of Science (HAS) breast cancer cohort represents a collection of all publicly available breast cancer cohorts profiled on the Affymetrix platform. The Kaplan-Meier Plotter Web interface allows selection of HAS cohorts on the basis of ER status using the mRNA expression level. **FGD3** is prognostic in the HAS ER-positive cohort (HR, 0.61; 95% CI, 0.5 to 0.74; $P = 6.4E^{-7}$) and in the ER-negative cohort (HR, 0.4; 95% CI, 0.3 to 0.53; $P = 1.8E^{-11}$) when split on the median (Fig 2A-B), further supporting that high expression of **FGD3** mRNA denotes favorable outcome. High mRNA expression of **SUSD3** was prognostic of favorable outcome in the HAS ER-positive cohort (HR, 0.61; 95% CI, 0.51 to 0.75; $P = 6.5E^{-7}$) and in the ER-negative cohort (HR, 0.54; 95% CI, 0.41 to 0.71; $P = 6.1E^{-11}$) split on the median (Data Supplement). Low expression of **MKI67** mRNA was prognostic of good outcome in the HAS ER-positive cohort (HR, 1.4; 95% CI, 1.23 to 1.59; $P = 2.2E^{-7}$) split on median but was not prognostic in the HAS ER-negative cohort (HR = 1.41; Data Supplement). Low expression of **PCNA** mRNA was prognostic of good outcome in the HAS ER-positive cohort (HR, 1.65; 95% CI, 1.45 to 1.87; $P = 2.3E^{-14}$)

**Fig 2.** Hungarian Academy of Science breast cancer cohort Kaplan-Meier plots for recurrence-free survival splitting on **FGD3** median messenger RNA (mRNA) expression in which estrogen receptor (ER)–positive status is derived from mRNA using the Kaplan-Meier Plotter Web interface to generate graphs. (A) ER-positive (hazard ratio [HR], 0.59; 95% CI, 0.48 to 0.72; $P = 2.5E^{-6}$) and (B) ER-negative (HR, 0.37; 95% CI, 0.28 to 0.5; $P = 5.9E^{-12}$) data indicate that low expression of **FGD3** mRNA is highly prognostic of disease progression.

**IHC ER-negative cohorts.** In the four ER-negative cohorts (BIG 1-98 was an ER-positive only cohort), the combined meta-analysis for **FGD3** had an HR of 0.72 (95% CI, 0.63 to 0.82) and was prognostic in each cohort (Fig 1B). **SUSD3** had a combined HR of 0.88 (95% CI, 0.74 to 1.05) and no single cohort had a statistically significant $P$ value (Data Supplement). **MKI67** had a combined HR of 0.93 (95% CI, 0.83 to 1.04) and no single cohort had a statistically significant $P$ value (Data Supplement). **PCNA** had a combined HR of 0.96 (95% CI, 0.80 to 1.15) and was prognostic in the E2197 ER-negative cohort (HR, 0.78; 95% CI, 0.63 to 0.97; Data Supplement). AURKA had a combined HR of 1.06 (95% CI, 0.93 to 1.20) and was not prognostic in any individual cohort (Data Supplement). The Stouffer $P$ value was used to rank the prognostic significance of each gene in four distinct ER-negative cohorts: **FGD3** ($P = 3.88E^{-5}$), **PCNA** ($P = .063$), **SUSD3** ($P = .319$), **MKI67** ($P = .477$), and **PCNA** ($P = .820$).
and the HAS ER-negative cohort (HR, 1.34; 95% CI, 1.08 to 1.65; \( P = .007 \)) split on the median (Data Supplement). Low expression of AURKA mRNA was prognostic of good outcome in the HAS ER-positive cohort (HR, 2.1; 95% CI, 1.84-2.4; \( P < 10^{-16} \)) split on the median and was not prognostic in the HAS ER-negative cohort (\( P = .87 \); Data Supplement).

**Prediction analysis of microarray 50 breast cancer prognostic marker.** To determine whether FGD3 was a prognostic biomarker in a specific prediction analysis of microarray 50 (PAM50) subtype, the HAS cohort was subdivided via the Web interface for the Kaplan-Meier Plotter. The resulting analysis indicated that FGD3 was prognostic in each subtype: basal HR, 0.44 (95% CI, 0.31 to 0.62; \( P = 910^{-7} \)); luminal A HR, 0.63 (95% CI, 0.49 to 0.8; \( P = 210^{-4} \)); luminal B HR, 0.68 (95% CI, 0.5 to 0.97; \( P = .014 \)), and human epidermal growth factor receptor 2 subtype E (HER2-E) HR, 0.44 (95% CI, 0.28 to 0.71; \( P = 5.210^{-4} \), Fig 3). FGD3 mRNA expression was prognostic in each of the HAS breast cancer–defined PAM50 subtypes in which high expression indicated favorable outcome. SUS3 mRNA was prognostic in each

---

**Fig 3.** Hungarian Academy of Science breast cancer cohort Kaplan-Meier plot for recurrence-free survival splitting on FGD3 median messenger RNA (mRNA) expression in the prediction analysis of microarray 50 subtype. (A) Basal (hazard ratio [HR], 0.44; 95% CI, 0.31 to 0.62; \( P = 910^{-7} \)); (B) luminal A (HR, 0.63; 95% CI, 0.49 to 0.8; \( P = 210^{-4} \)); (C) luminal B (HR, 0.68; 95% CI, 0.5 to 0.97; \( P = .014 \)), and (D) human epidermal growth factor receptor 2–positive (HR, 0.44; 95% CI, 0.28 to 0.71; \( P = 5.210^{-4} \)) data indicate that high expression of FGD3 mRNA is highly prognostic of favorable outcome.
subtypes: basal HR, 0.56 (95% CI, 0.4 to 0.78; \(P = 5.3 \times 10^{-4}\)), luminal A HR, 0.66 (95% CI, 0.51 to 0.84; \(P = 8.8 \times 10^{-4}\)), luminal B HR, 0.71 (95% CI, 0.52 to 0.96; \(P = .027\)), and HER2-E HR, 0.57 (95% CI, 0.35 to 0.9; \(P = .015\); Data Supplement). MKI67 was prognostic in luminal A (HR, 1.38; 95% CI, 1.17 to 1.64) and was not prognostic in the other subtypes (Data Supplement). PCNA was prognostic in luminal A (HR, 1.64; 95% CI, 1.38 to 1.95; \(P = 1.5 \times 10^{-8}\)) and luminal B (HR, 1.52; 95% CI, 1.25 to 1.85; \(P = 1.9 \times 10^{-5}\); Data Supplement). AURKA was prognostic in luminal A (HR, 2.3; 95% CI, 1.92 to 2.75; \(P < 1 \times 10^{-16}\)) and luminal B (HR, 1.47; 95% CI, 1.21 to 1.78; \(P = 9 \times 10^{-5}\); Data Supplement).

HAS lung and ovarian cancer prognostic marker. FGD3 high expression of mRNA is prognostic of favorable outcome in the HAS lung cohort\(^{23}\) (HR, 0.68; 95% CI, 0.58 to 0.81; \(P = 7.2 \times 10^{-6}\)) and the HAS ovarian cohort\(^{24}\) (HR, 0.79; 95% CI, 0.63 to 0.99; \(P = .041\)) when split on the median (Data Supplement). SUSD3 was prognostic in the HAS ovarian cohort with separation of survival after 4 years (HR, 1.22; 95% CI, 1.01 to 1.48; \(P = .035\)) in which low expression indicated favorable outcome (Data Supplement). MKI67 high expression was prognostic of poor outcome in the HAS lung cohort (HR, 1.6; 95% CI, 1.41 to 1.82; \(P = 2.6 \times 10^{-11}\); Data Supplement). PCNA was not prognostic in either the HAS lung or ovarian cohorts (Data Supplement). AURKA high expression was prognostic for poor outcome in the HAS lung cohort (HR, 1.52; 95% CI, 1.33 to 1.72; \(P = 1.2 \times 10^{-15}\)) and the HAS ovarian cohort (HR, 1.19; 95% CI, 1.05 to 1.34; \(P = .0077\); Data Supplement).

TCGA cancer cohorts prognostic marker. A complete analysis of FGD3, SUSD3, MKI67, PCNA, and AURKA mRNA expression (\(z\)-score) as a prognostic biomarker in TCGA RNA-seq cohorts is shown in the Data Supplement. Seven of the 21 TCGA cohorts did not have a single-gene biomarker from the list (FGD3, SUSD3, MKI67, PCNA, AURKA) that was prognostic. FGD3 had a combined HR of 0.91 (95% CI, 0.84 to 0.98). In summary, the statistically significant hits for FGD3 mRNA (\(z\)-score) as a continuous variable in a Cox regression model included head and neck squamous cell carcinoma (HR, 0.72; 95% CI, 0.63 to 0.81; \(P = 5.99 \times 10^{-7}\)), lung adenocarcinoma (HR, 0.78; 95% CI, 0.68 to 0.89; \(P = 3.32 \times 10^{-7}\)), cervical squamous cell carcinoma and endocervical adenocarcinoma (HR, 0.69; 95% CI, 0.54 to 0.87; \(P = .002\)), sarcoma (HR, 0.73; 95% CI, 0.60 to 0.90; \(P = .003\)), invasive breast carcinoma (HR, 0.82; 95% CI, 0.70 to 0.96; \(P = .015\)), and urothelial bladder carcinoma (HR, 0.85; 95% CI, 0.73 to 0.99; \(P = .033\)). By using the biomarker \(P\) value and the number of samples in each cohort, the Stouffer\(^{25}\) \(P\) value was calculated to rank the prognostic value as a pan-cancer biomarker. AURKA has an overall prognostic Stouffer \(P = 2.85 \times 10^{-12}\); PCNA, \(P = 8.8 \times 10^{-7}\); MKI67, \(P = 3.0 \times 10^{-6}\); FGD3, \(P = 9.04 \times 10^{-6}\); and SUSD3, \(P = 3.21 \times 10^{-5}\). A detailed analysis of each gene in the TCGA cohorts can be found in the Data Supplement.

FGD3 expected tissue expression profile. The mRNA expression profile of a gene can indicate that it might be a biomarker for a particular cell type. FGD3 is highly expressed in T cells, natural killer cells, myeloid cells, monocytes, and whole blood (Data Supplement). In addition, combined with mRNA expression of FGD3 in cell lines, high expression of FGD3 could be a positive prognostic biomarker for TILs. By using the TCGA cohort, TILs were called from high-resolution images, and FGD3 mRNA expression did not correlate with TILs evaluated on hematoxylin and eosin slides defined by using a previously published method\(^{26}\) in which TILs represented a pre-existing antitumor T-cell response (unpublished data). In addition, TIL calls from the BIG 1-98 DASL cohort did not correlate with FGD3 mRNA expression.

To further investigate whether FGD3 mRNA expression is a feature of the tumor, breast cancer TMA s were purchased from US Biomax, and IHC was used to determine FGD3 protein expression levels (scored from 0 to 4). FGD3 protein expression was determined to be a feature of the tumor and was not associated with the presence of lymphocytes. By using metadata provided by US Biomax, FGD3 protein levels in tumors (n = 135) with no regional lymph node metastasis (N0) were compared with tumors with lymph node metastasis (N1 to N3) and corresponding matched metastatic tissues (Fig 4). An unpaired \(t\) test comparing N0 with N1 to N3 suggests that lymph node metastasis is associated with lower FGD3 protein levels (\(P < 1 \times 10^{-4}\)). An unpaired \(t\) test comparing FGD3 protein expression in N1 to N3 primary tumor samples with lymph node metastatic tissue samples suggests that lower FGD3 protein level indicates metastasis (\(P = .142\)). Representative images of FGD3 IHC staining are shown in Figure 5 and the Data Supplement. Benign tumors (Fig 5A) and breast adenocarcinomas in lower stages (Fig 5B-C) showed strong expression of FGD3, whereas late-stage breast adenocarcinomas in higher stages (Fig 5D-F) showed mild to weak expression. Stage IIA invasive breast cancer (Data Supplement) showed strong FGD3 expression compared with its matched metastatic carcinoma (Data Supplement), in which FGD3 was weakly expressed. These data suggest that...
FGD3 protein expression is inversely associated with stage.

Published ESR1 chromatin immunoprecipitation sequencing data in breast cancer cell lines MCF-7\(^\text{27}\) and ZR-75-1\(^\text{28}\) identified a conserved ESR1 binding site within the gene locus of FGD3 (Data Supplement). By using RT-qPCR, we also determined that estradiol stimulation substantially increased the mRNA expression level of FGD3, as well as the known ESR1 targeted gene TFF1 in the ZR-75-1 cell line (Data Supplement). The Gene Expression Atlas\(^\text{22}\) was queried for cancer cell line experiments with a statistically significant fold change of FGD3 mRNA with a log fold change greater than 2. In a previously published ESR1 knockdown experiment in the MCF-7 ER-positive breast cancer cell line, FGD3 was down-regulated by 2.9 and SUSD3 by 1.3 on a log2 scale (Data Supplement).\(^\text{29}\) cBioPortal was used to query co-expression relationships in the METABRIC cohort, which showed a tendency toward co-occurrence with P < .001 and a log odds ratio of 1.52. The TCGA breast cohort showed a tendency toward co-occurrence with P < .001 and a log odds ratio of 2.3 in TMA expression data. These data suggest that ESR1 plays a regulatory role in FGD3 mRNA expression. Surprisingly, FGD3 mRNA expression in BT-20, a triple-negative breast cancer cell line, was upregulated to 1.99 and ESR1 was upregulated to 0.47 on a log 2 scale when treated with an EGFR inhibitor (Data Supplement).\(^\text{30}\)

**DISCUSSION**

The exploratory analysis of 20,464 possible single-gene biomarkers in the METABRIC discovery cohort identified FGD3 as a highly prognostic biomarker. Minimal research has focused on it as a possible driver of metastasis in breast cancer, and a pan-cancer analysis in TCGA cohorts found that FGD3 mRNA was a putative prognostic biomarker in other cancers. This is a significant finding in the TCGA cohorts, considering the median survival time in these cohorts was typically less than 2 years.

FGD3 has a putative guanine nucleotide exchange factor that targets cell division control protein 42 homolog (CDC42)\(^\text{31}\) and shares high sequence similarity with FGD1 in their Dbl homology (70\%) and pleckstrin homology (60.6\%) domains; however, FGD3 lacks the N-terminal proline-rich domain found in FGD1. The proline-rich domain plays a crucial role in the response to extracellular signal-responsive translocation of FGD1 to the leading-edge membrane in cells facing toward a wound during the wound-healing process.\(^\text{32}\)

Through a highly conserved recognized destruction motif (DSGIDS) in both FGD3 and FGD1 as well as in other unrelated proteins including IkBs and B-catenin, downregulation occurs through the ubiquitin/proteasome system via phosphorylation by GSK-3\(b\) of the serine residues in the DSGIDS motif.\(^\text{33}\) Thus, both FGD3 and FGD1 intracellular levels are tightly regulated by the same destruction pathway. Functionally, FGD1 is involved in the regulation of cellular structures required for invadopodia biogenesis and extra-cellular matrix degradation in an invasive cell model by modulating Cdc42 activation.\(^\text{34-37}\) In addition, mutations in FGD1 are responsible for the X-linked disorder known as faciogenital dysplasia, and FGD1 is highly expressed during bone growth and mineralization.\(^\text{36}\)

Using the HeLa Tet-Off cell system, Hayakawa et al\(^\text{31}\) showed that notwithstanding their similarity, FGD3 and FGD1 played quite different roles in regulating cellular functions. They found that full-length FGD3 could induce and activate Cdc42. Furthermore, inducible expression of FGD3 resulted in significant morphologic changes that included the formation of broad sheet-like protrusions known as lamellipodia when GTP-bound Cdc42 levels were significantly increased by the inducible expression of FGD3, whereas high expression of FGD1 led to the formation of filopodia, which are found in migrating cells.\(^\text{31}\) Thus, cell motility seemed to be inversely regulated by FGD3 and FGD1: FGD3 inhibited cell migration and FGD1 stimulated it.

The FGD3-SUSD3 metagene (these genes share the same chromosomal location directly adjacent to each other at Chr9q22.31) was ranked with the highest concordance index\(^\text{38}\) in the Sage Bionetworks-DREAM Breast Cancer Prognosis Challenge and was a key biomarker presented by
the group submitting the winning model.\textsuperscript{39} Using the METABRIC data set,\textsuperscript{3} they determined that the expression value of two genes, \textit{FGD3} and \textit{SUSD3}, was the most prognostic molecular meta-gene marker associated with a good prognosis, and they referred to it as a protective metagene because it displayed a CI that was significantly less than 0.5. They also validated the poor prognosis associated with low expression of the \textit{FGD3-SUSD3} metagene in the OsloVal data set (described in Liu et al.\textsuperscript{40}). The prognostic significance of \textit{FGD3} and \textit{SUSD3} as single gene prognostic biomarker using Cox regression models in a large collection of breast cancer cohorts and TCGA cohorts has not been published.

In a follow-up study, the group developed a breast cancer prognostic test, Breast Cancer Attractor Metagenes (BCAM), which had several molecular features, including the breast cancer–specific \textit{FGD3-SUSD3} metagene, as well as tumor size, and number of positive lymph nodes.\textsuperscript{41} Notably, Ou Yang et al.\textsuperscript{41} went on to suggest that breast cancer subtype classification as well as hormone receptor and \textit{HER2} status did not add additional prognostic information when expression levels of the \textit{FGD3-SUSD3} metagene and the attractor metagenes were known and taken into consideration.

In a similar manner, \textit{SUSD3} expression was found to be regulated by \textit{ESR1} in MCF-7 cells through direct interaction of E2 with its regulatory region. Experiments in MCF-7 cells further showed that \textit{SUSD3} was implicated in E2-mediated cell proliferation, adhesion, and migration.\textsuperscript{8} However, as with \textit{FGD3}, the role that \textit{SUSD3} plays in ER-positive breast cancer has not been fully established.

On the basis of normal tissue expression profiles, \textit{FGD3} is highly expressed in T cells, natural killer cells, monocytes associated with immune response, and myeloid whole blood cells. A characteristic of these cell types is that they are mobile, and evidence from the HeLa Tet-Off wound healing assay suggests that high expression of \textit{FGD3} limits cell mobility.\textsuperscript{31} \textit{FGD3} mRNA expression did not correlate with TILs in the BIG 1-98 DASL and TCGA breast cancer cohorts, suggesting that the prognostic value of \textit{FGD3} is not indicating immune cells in patients’ tumors. IHC data from breast cancer TMAs indicates that \textit{FGD3} protein expression is a feature of the tumor, and low expression indicates a higher chance of cell migration to lymph nodes. The data clearly indicate that \textit{FGD3} may have an important role in metastatic-associated phenotypes. The \textit{FGD3} cell line experiment in this study (Data Supplement) and studies by others\textsuperscript{4,29} suggests that \textit{FGD3} mRNA expression is partially regulated by \textit{ESR1}, an important treatment target in breast cancer, which requires further study.

Given the potential role of \textit{FGD3} in cell migration, it is clearly prognostic in a large collection of breast cancer and other cancer cohorts and has a
wide range of treatment options. It has been implicated as a gene that regulates cell migration in the progression of cancer. Comparing the prognostic value of FGD3 in breast cancer with the prognostic value of genes associated with proliferation such as MKI67, PCNA, and AURKA indicates that FGD3 may offer superior disease progression metrics in all clinically relevant breast cancer subtypes (Fig 6A). Overall, AURKA is the most prognostic gene in the TCGA cancer cohorts in which the median time of 2 years suggests that it is an indicator of early relapse as measured by OS (Fig 6B). FGD3 is prognostic in six TCGA cohorts, and AURKA is prognostic in nine TCGA cohorts. MKI67, PCNA, and AURKA are largely prognostic in the same cohorts with renal papillary cell carcinoma, lower-grade brain glioma, renal clear cell carcinoma, pancreatic adenocarcinoma, Ovarian serous cystadenocarcinoma, Glioblastoma multiforme, Lung squamous cell carcinoma, Skin cutaneous melanoma, Esophageal carcinoma, Colon adenocarcinoma, Prostate adenocarcinoma, Bladder urothelial carcinoma, Uterine corpus endometrial carcinoma, Thyroid carcinoma, Sarcoma, Cervical squamous cell carcinoma, Uterine corpus endometrial carcinoma, Bladder urothelial carcinoma, Prostate adenocarcinoma, Colon adenocarcinoma, Esophageal carcinoma, Skin cutaneous melanoma, Lung squamous cell carcinoma, Glioblastoma multiforme, Ovarian serous cystadenocarcinoma.

### Table A

| Cohort                               | FGD3      | SUSD3     | MKI67     | PCNA      | AURKA     |
|--------------------------------------|-----------|-----------|-----------|-----------|-----------|
| METABRIC validation ER+ OS           | 5.52E-04  | 6.83E-07  | 3.59E-03  | 2.80E-07  | 0.937     |
| METABRIC discovery ER+ OS            | 8.66E-07  | 3.20E-06  | 3.19E-05  | 6.60E-07  | 5.55E-04  |
| TCGA breast cancer ER+ RNASeq OS    | 0.001     | 2.03E-08  | 0.579     | 0.525     | 0.519     |
| BIG 1-98 BCFIE                       | 0.001     | 0.081     | 0.01      | 0.58      | 0.643     |
| E2197 ER+ OS                         | 0.018     | 0.051     | 0.387     | 0.43      | 0.709     |
| E2197 ER- OS                         | 2.95E-04  | 0.027     | 0.421     | 0.274     | 0.146     |
| METABRIC validation ER- OS           | 0.118     | 0.382     | 0.126     | 0.531     | 0.903     |
| METABRIC discovery ER- OS            | 0.119     | 0.193     | 0.803     | 0.419     | 0.882     |
| TCGA breast cancer ER- RNASeq OS    | 0.551     | 0.706     | 0.399     | 0.823     | 0.871     |
| HAS ER+                              | 2.50E-05  | 6.50E-07  | 2.20E-05  | 2.30E-04  | 1.00E-06  |
| HAS ER-                              | 5.90E-12  | 6.10E-06  | 0.41      | 0.0066    | 0.87      |
| HAS basal                            | 1.50E-07  | 0.00053   | 0.086     | 0.12      | 0.25      |
| HAS luminal A                        | 1.70E-04  | 0.00088   | 2.00E-04  | 1.50E-03  | 1.00E-06  |
| HAS luminal B                        | 3.00E-02  | 0.027     | 0.31      | 1.90E-05  | 9.00E-06  |
| HAS HER2-E                           | 4.30E-04  | 0.015     | 0.35      | 2.70E-01  | 3.30E-01  |
| HAS lung                             | 7.20E-05  | 0.17      | 2.60E-05  | 5.20E-05  | 1.20E-05  |
| HAS ovarian                          | 0.041     | 0.035     | 0.66      | 2.00E-03  | 7.70E-03  |

### Table B

| Cohort                               | FGD3      | SUSD3     | MKI67     | PCNA      | AURKA     |
|--------------------------------------|-----------|-----------|-----------|-----------|-----------|
| Kidney renal papillary cell carcinoma| 0.57      | 0.266     | 5.15E-03  | 5.62E-04  | 3.40E-07  |
| Head and neck squamous cell carcinoma| 5.99E-03  | 0.158     | 0.914     | 0.377     | 0.01      |
| Brain lower grade glioma             | 0.948     | 0.151     | 1.16E-06  | 6.19E-07  | 6.73E-07  |
| Kidney renal clear cell carcinoma    | 0.047     | 0.94      | 1.32E-06  | 0.006     | 6.29E-07  |
| Pancreatic adenocarcinoma            | 0.645     | 0.318     | 6.17E-06  | 0.009     | 1.50E-04  |
| Liver hepatocellular carcinoma       | 0.827     | 0.396     | 1.03E-04  | 0.004     | 0.007     |
| Lung adenocarcinoma                  | 3.32E-08  | 0.002     | 1.88E-04  | 0.058     | 5.17E-04  |
| Breast invasive carcinoma            | 0.015     | 4.95E-06  | 0.317     | 0.363     | 0.277     |
| Cervical squamous cell carcinoma     | 0.002     | 0.169     | 0.931     | 0.004     | 0.696     |
| Sarcoma                              | 0.003     | 0.021     | 0.064     | 0.07      | 0.031     |
| Thyroid carcinoma                    | 0.662     | 0.019     | 0.986     | 0.005     | 0.404     |
| Thymoma                               | 0.117     | 0.159     | 0.01      | 0.079     | 0.058     |
| Uterine corpus endometrial carcinoma| 0.537     | 0.962     | 0.398     | 0.598     | 0.032     |
| Bladder urothelial carcinoma         | 0.033     | 0.684     | 0.588     | 0.93      | 0.081     |
| Prostate adenocarcinoma              | 0.244     | 0.077     | 0.311     | 0.286     | 0.258     |
| Colon adenocarcinoma                 | 0.139     | 0.437     | 0.921     | 0.458     | 0.227     |
| Esophageal carcinoma                 | 0.67      | 0.722     | 0.934     | 0.154     | 0.165     |
| Skin cutaneous melanoma              | 0.282     | 0.156     | 0.18      | 0.718     | 0.829     |
| Lung squamous cell carcinoma         | 0.804     | 0.269     | 0.529     | 0.774     | 0.819     |
| Glioblastoma multiforme              | 0.538     | 0.466     | 0.328     | 0.662     | 0.363     |
| Ovarian serous cystadenocarcinoma     | 0.78      | 0.791     | 0.415     | 0.646     | 0.354     |
| Stouffer P value                     | 9.04E-06  | 3.21E-05  | 3.00E-06  | 8.80E-17  | 2.85E-13  |
and lung adenocarcinoma. *FGD3* is uniquely highly prognostic in head and neck squamous cell carcinoma and lung adenocarcinoma. *FGD3* is prognostic in breast invasive carcinoma, cervical squamous cell carcinoma, sarcoma, and bladder urothelial carcinoma. A PubMed search for *FGD3* and cancer mentioned in the abstract resulted in one publication. Repeating the PubMed search for the other proliferation genes resulted in the following publication metrics (MKI67, 92; KI67, 3,104; PCNA, 2,741; and AURKA, 284).

The key differentiator of *FGD3* as a putative biomarker is that high expression indicates favorable outcome; for other established proliferation biomarkers, high expression of *MKI67*, *KI67*, *PCNA*, and *AURKA* are prognostic of poor outcome.

The availability of a growing collection of cancer cohorts with outcome data has allowed for the confirmation of the clinical importance of *FGD3* as a prognostic biomarker and implications that can guide treatment. Given the obvious cohort differences in treatment conditions, patient populations, formalin-fixed paraffin-embedded frozen tissue, and platform differences in Illumina and RNA-seq, *FGD3* represents a robust indicator of outcome in breast cancer as well as other cancers and requires further study.

DOI: https://doi.org/10.1200/PO.17.00009
Published online on ascopubs.org/journal/po on October 13, 2017.

**AUTHOR CONTRIBUTIONS**

Conception and design: Scooter Willis, Meredith M. Regan, Myles Brown, Brian Leyland-Jones  
Financial support: Myles Brown, Brian Leyland-Jones  
Administrative support: Roswitha Kammler, Joseph A. Sparano, Brian Leyland-Jones  
Provision of study materials or patients: Joseph A. Sparano, Brian Leyland-Jones  
Collection and assembly of data: Scooter Willis, Mark Abramovitz, Teng Fei, Brandon Young, Xiaoqian Lin, Min Ni, Justin Achua, Meredith M. Regan, Kathryn P. Gray, Robert Gray, Victoria Wang, Bradley Long, Roswitha Kammler, Joseph A. Sparano, Lori J. Goldstein, Roberto Salgado, Giancarlo Pruneri, Giuseppe Viale  
Data analysis and interpretation: Scooter Willis, Yuliang Sun, Teng Fei, Min Ni, Meredith M. Regan, Kathryn P. Gray, Casey Williams, Sherene Loi, Giancarlo Pruneri, Giuseppe Viale, Brian Leyland-Jones  
Manuscript writing: All authors  
Final approval of manuscript: All authors  
Accountable for all aspects of the work: All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or po.ascopubs.org/site/ifc.

Scooter Willis  
No relationship to disclose

Yuliang Sun  
No relationship to disclose

Mark Abramovitz  
No relationship to disclose

Teng Fei  
No relationship to disclose

Brandon Young  
No relationship to disclose

Xiaoqian Lin  
No relationship to disclose

Min Ni  
No relationship to disclose

Justin Achua  
Employment: Avera Mckennan Hospital

Meredith M. Regan  
Consulting or Advisory Role: Merck, Ipsen (Inst)  
Research Funding: Veridex (Inst), OncoGenex (Inst), Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), Ferring (Inst), Celgene (Inst), AstraZeneca (Inst), Pierre Fabre (Inst), Ipsen (Inst)

Kathryn P. Gray  
Stock and Other Ownership Interests: MDGN

Robert Gray  
Research Funding: Abbott Molecular, Agios, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Genentech, Genomic Health, Genzyme, GlaxoSmithKline, InClone Systems, Janssen-Ortho, Kanisa, Millennium, Novadity, Onyx, OSI Pharmaceuticals, Pfizer, Sanofi, Sequenta, Syndax, Novartis

Victoria Wang  
No relationship to disclose

Bradley Long  
No relationship to disclose

Roswitha Kammler  
No relationship to disclose

Joseph A. Sparano  
Stock and Other Ownership Interests: Metastat  
Consulting or Advisory Role: Genentech, Novartis, AstraZeneca, Celgene, Eli Lilly, Cellnex, Pfizer, Prescient Therapeutics, Juno Therapeutics, Merrimack  
Research Funding: Prescient Therapeutics (Inst), Deciphera (Inst), Genentech (Inst), Merck (Inst), Novartis (Inst), Novartis (Inst), Merrimack (Inst)

Casey Williams  
Research Funding: Takeda (Inst), Tesaro (Inst)
Lori J. Goldstein  
**Honoraria:** Genentech, Roche Pharma AG, Puma Biotechnology, Pfizer, Glenmark  
**Consulting or Advisory Role:** Genentech, Dompé Farmaceutici, Roche Pharma AG, Puma Biotechnology, Pfizer, Merck, AstraZeneca  
**Research Funding:** Merck (Inst), Genentech (Inst)  
**Other Relationship:** Roche Pharma AG

Roberto Salgado  
**Travel, Accommodations, Expenses:** Roche

Sherene Loi  
**Research Funding:** Genentech (Inst), Pfizer (Inst), Novartis (Inst), Merck (Inst), Puma Biotechnology (Inst), Bristol-Myers Squibb (Inst)  
**Patents, Royalties, Other Intellectual Property:** PI3K pathway gene signature granted by the European and US patent offices (Inst)

Giancarlo Pruneri  
No relationship to disclose

Giuseppe Viale  
**Honoraria:** MSD Oncology  
**Consulting or Advisory Role:** Dako, Genentech, AstraZeneca, Bristol-Myers Squibb, Astellas Pharma  
**Travel, Accommodations, Expenses:** Roche, Celgene

Myles Brown  
**Consulting or Advisory Role:** Novartis  
**Research Funding:** Novartis  
**Patents, Royalties, Other Intellectual Property:** As part of my work at the Dana-Farber Cancer Institute I have made invention disclosures and the institute is filing patents on technology related to endocrine resistance in breast cancer and improved CRISPR dual sgRNA library design.  
**Travel, Accommodations, Expenses:** GTx

Brian Leyland-Jones  
**Stock and Other Ownership Interests:** Catalyst Pharmaceuticals, Progenix, Puma Biotechnology, Sucampo Pharmaceuticals, ARIAD, Zogenix  
**Consulting or Advisory Role:** GlaxoSmithKline, Amgen  
**Speakers’ Bureau:** Genentech, Exelixis  
**Research Funding:** Takeda, Tesaro  
**Expert Testimony:** Amgen

**Affiliations**

Scooter Willis, Yuliang Sun, Mark Abramovitz, Brandon Young, Xiaoqian Lin, Justin Achua, Casey Williams, and Brian Leyland-Jones, Avera Cancer Institute, Sioux Falls, SD; Teng Fei, Meredith M. Regan, Kathryn P. Gray, Robert Gray, Victoria Wang, and Myles Brown, Dana-Farber Cancer Institute, Boston, MA; Min Ni, Children’s Medical Center Research Institute, University of Texas Southwestern Medical Center, Dallas, TX; Bradley Long, Molecular Core, Scripps Florida, Jupiter, FL; Roswitha Kammler, International Breast Cancer Study Group, Bern, Switzerland; Joseph A. Sparano, Montefiore Medical Center, Bronx, NY; Lori J. Goldstein, Fox Chase Cancer Center, Philadelphia, PA; Roberto Salgado, Breast Cancer Translational Research Laboratory/Institut Jules Bordet, Brussels, Belgium; Sherene Loi, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia; and Giancarlo Pruneri and Giuseppe Viale, European Institute of Oncology, University of Milan, Milan, Italy.

**Support**

Supported by Public Health Service Grants CA23318, CA66636, CA21115, CA49883, CA14958, CA39229, CA16116, CA27525, and CA114737 (to the E2197 study) from the Breast Cancer Research Foundation, National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services; by the Susan G. Komen for the Cure Promise Grant No. KG080081 (to the BIG 1-98 trial); by Grant No. CA-75362 from NIH; and by Novartis. Biospecimens were provided by the ECOG Pathology Coordinating Office and Reference Laboratory.

**REFERENCES**

1. Curtis C: Genomic profiling of breast cancers. Curr Opin Obstet Gynecol 27:34-39, 2015  
2. Lefebvre C, Bachelor T, Filleron T, et al: Mutational profile of metastatic breast cancers: A retrospective analysis. PLoS Med 13:e1002201, 2016  
3. Curtis C, Shah SP, Turashvili G, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 486:346-352, 2012  
4. Moy I, Todorovi ´c V, Dubash AD, et al: Estrogen-dependent sushi domain containing 3 regulates cytoskeleton organization and migration in breast cancer cells. Oncogene 34:323-333, 2015  
5. Bullwinkel J, Baron-Lühr B, Lüdemann A, et al: Ki-67 protein is associated with ribosomal RNA transcription in quiescent and proliferating cells. J Cell Physiol 206:624-635, 2006  
6. Dowsett M, Nielsen TO, A’Hern R, et al: Assessment of Ki67 in breast cancer: Recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 103:1656-1664, 2011  
7. Crane R, Gadea B, Littlepage L, et al: Aurora A, meiosis and mitosis. Biol Cell 96:215-229, 2004  
8. Nouri M, Rattner E, Stylianou N, et al: Androgen-targeted therapy-induced epithelial mesenchymal plasticity and neuroendocrine transdifferentiation in prostate cancer: An opportunity for intervention. Front Oncol 4:370, 2014
9. Falchook GS, Bastida CC, Kurzrock R: Aurora kinase inhibitors in oncology clinical trials: Current state of the progress. Semin Oncol 42:832-848, 2015

10. Bianchini G, Iwamoto T, Qi Y, et al: Prognostic and therapeutic implications of distinct kinase expression patterns in different subtypes of breast cancer. Cancer Res 70:8852-8862, 2010

11. Malkas LH, Herbert BS, Abdel-Aziz W, et al: A cancer-associated PCNA expressed in breast cancer has implications as a potential biomarker. Proc Natl Acad Sci U S A 103:19472-19477, 2006

12. Lv Q, Zhang J, Yi Y, et al: Proliferating cell nuclear antigen has an association with prognosis and risks factors of cancer patients: A systematic review. Mol Neurobiol 53:6209-6217, 2016

13. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

14. Whitlock MC: Combining probability from independent tests: The weighted Z-method is superior to Fisher's approach. J Evol Biol 18:1368-1373, 2005

15. Zaykin DV: Optimally weighted Z-test is a powerful method for combining probabilities in meta-analysis. J Evol Biol 24:1836-1841, 2011

16. Prlić A, Yates A, Bliven SE, et al: BioGPS: An open-source framework for bioinformatics in 2012. Bioinformatics 28:2693-2695, 2012

17. Doi SA, Thalib L: A quality-effects model for meta-analysis. Epidemiology 19:94-100, 2008

18. Su AI, Wiltshire T, Batalov S, et al: A gene atlas of the mouse and human protein-encoding transcriptomes. Proc Natl Acad Sci U S A 101:6062-6067, 2004

19. Wu C, Orozco C, Boyer J, et al: BioGPS: An extensible and customizable portal for querying and organizing gene annotation resources. Genome Biol 10:R130, 2009

20. Salgado R, Denkert C, Demaria S, et al: The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: Recommendations by an International TILs Working Group 2014. Ann Oncol 26:259-271, 2015

21. Salkind NJ: Encyclopedia of Measurement and Statistics. Thousand Oaks, CA, Sage Publications, 2006

22. Petryszak R, Keays M, Tang YA, et al: Expression Atlas update: An integrated database of gene and protein expression in humans, animals and plants. Nucleic Acids Res 44(D1):D746-D752, 2016

23. Györffy B, Surowiak P, Budczies J, et al: Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer. PLoS One 8:e82241, 2013

24. Györffy B, Lánczky A, Szallási Z: Implementing an online tool for genome-wide validation of survival-associated biomarkers in ovarian-cancer using microarray data from 1287 patients. Endocr Relat Cancer 19:197-208, 2012

25. Stouffer SA, Suchman EA, DeVinney LC, et al: The American Soldier: Adjustment during army life—Volume 1. New York, NY, John Wiley & Sons, 1965

26. Denkert C, Wienert S, Poterie A, et al: Standardized evaluation of tumor-infiltrating lymphocytes in breast cancer: Results of the ring studies of the international immuno-oncology biomarker working group. Mod Pathol 29:1155-1164, 2016

27. Ross-Innes CS, Stark R, Teschendorff AE, et al: Differential oestrogen receptor binding is associated with clinical outcome in breast cancer. Nature 481:389-393, 2012

28. Theodorou V, Stark R, Menon S, et al: GATA3 acts upstream of FOXA1 in mediating ESR1 binding by shaping enhancer accessibility. Genome Res 23:12-22, 2013

29. Al Saleh S, Al Mulla F, Luqmani YA: Estrogen receptor silencing induces epithelial to mesenchymal transition in human breast cancer cells. PLoS One 6:e20610, 2011

30. Lee MJ, Ye AS, Gardino AK, et al: Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. Cell 149:780-794, 2012

31. Hayakawa M, Matsushima M, Hagiwara H, et al: Novel insights into FGD3, a putative GEF for Cdc42, that undergoes SCF(FWD1/beta-TrCP)-mediated proteasomal degradation analogous to that of its homologue FGD1 but regulates cell morphology and motility differently from FGD1. Genes Cells 13:329-342, 2008

32. Oshima T, Fujino T, Ando K, et al: Proline-rich domain plays a crucial role in extracellular stimuli-responsive translocation of a Cdc42 guanine nucleotide exchange factor, FGD1. Biol Pharm Bull 33:35-39, 2010

33. Karin M, Ben-Neriah Y: Phosphorylation meets ubiquitination: The control of NF-(kappa)B activity. Annu Rev Immunol 18:621-663, 2000

34. Ayala I, Giacchetti G, Caldieri G, et al: Faciogenital dysplasia protein Fgd1 regulates invadopodia biogenesis and extracellular matrix degradation and is up-regulated in prostate and breast cancer. Cancer Res 69:747-752, 2009

35. Daubon T, Bucicione R, Génot E: The Aarskog-Scott syndrome protein Fgd1 regulates podosome formation and extracellular matrix remodeling in transforming growth factor β-stimulated aortic endothelial cells. Mol Cell Biol 31:4430-4441, 2011

36. Egorov MV, Capestrano M, Vorontsova OA, et al: Faciogenital dysplasia protein (FGD1) regulates export of cargo proteins from the Golgi complex via Cdc42 activation. Mol Biol Cell 20:2413-2427, 2009
37. Genot E, Daubon T, Sorrentino V, et al: FGD1 as a central regulator of extracellular matrix remodelling: Lessons from faciogenital dysplasia. J Cell Sci 125:3265-3270, 2012
38. Pencina MJ, D’Agostino RB: Overall C as a measure of discrimination in survival analysis: Model specific population value and confidence interval estimation. Stat Med 23:2109-2123, 2004
39. Cheng WY, Ou Yang TH, Anastassiou D: Development of a prognostic model for breast cancer survival in an open challenge environment. Sci Transl Med 5:181ra50, 2013
40. Liu Z, Zhang XS, Zhang S: Breast tumor subgroups reveal diverse clinical prognostic power. Sci Rep 4:4002, 2014
41. Ou Yang TH, Cheng WY, Zheng T, et al: Breast cancer prognostic biomarker using attractor metagenes and the FGD3-SUSD3 metagene. Cancer Epidemiol Biomarkers Prev 23:2850-2856, 2014

ascopubs.org/journal/po  JCO™ Precision Oncology  13
Author/s: 
Willis, S; Sun, Y; Abramovitz, M; Fei, T; Young, B; Lin, X; Ni, M; Achua, J; Regan, MM; Gray, KP; Gray, R; Wang, V; Long, B; Kammler, R; Sparano, JA; Williams, C; Goldstein, LJ; Salgado, R; Loi, S; Pruneri, G; Viale, G; Brown, M; Leyland-Jones, B

Title: 
High Expression of FGD3, a Putative Regulator of Cell Morphology and Motility, Is Prognostic of Favorable Outcome in Multiple Cancers

Date: 
2017-01-01

Citation: 
Willis, S., Sun, Y., Abramovitz, M., Fei, T., Young, B., Lin, X., Ni, M., Achua, J., Regan, M. M., Gray, K. P., Gray, R., Wang, V., Long, B., Kammler, R., Sparano, J. A., Williams, C., Goldstein, L. J., Salgado, R., Loi, S., ..., Leyland-Jones, B. (2017). High Expression of FGD3, a Putative Regulator of Cell Morphology and Motility, Is Prognostic of Favorable Outcome in Multiple Cancers. JCO PRECISION ONCOLOGY, 1 (1), https://doi.org/10.1200/PO.17.00009.

Persistent Link: 
http://hdl.handle.net/11343/247710

File Description: 
published version

License: 
CC BY