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Comprehensive characterization of FGF/FGFR alterations in invasive breast cancers

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Introduction

FGFR signaling is central for cancer cell proliferation, migration, angiogenesis, and survival. The frequency and type of FGF/FGFR aberrations are not well-characterized across invasive breast cancer subtypes and metastatic sites of disease. In hormone receptor positive breast cancers, FGFR1 amplification correlates with early progression on endocrine therapy and promotes resistance to CDK4/6 inhibition. Our study evaluated the incidence and characterization of FGF alterations in invasive breast cancers and examined differences in histologic subtype, molecular subtype, and site.

Methods

Breast cancer samples underwent molecular profiling by Caris Life Sciences. Analyses included NGS of DNA (592 Gene Panel, NextSeq, and WES, NovaSEQ), and IHC (Caris Life Sciences, Phoenix, AX). Biomarker results were compiled from cases within the breast cohort including data from any sequencing panel, gene expression/RNA seq panel, and IHC. All results listed below were statistically significant ($p < 0.05$) as determined by chi-square test and Benjamini Hochberg correction. Real world overall survival (rwOS) was obtained from insurance claims data and was calculated from the treatment start to last contact or first treatment to last treatment (TOT) and Kaplan-Meier estimates were used for comparison.

Results and Conclusions

12058 breast cancer tumors were analyzed: 4189 from primary breast specimens (35%) and 7869 from metastatic sites (65%). 4305 (36%) were ductal and 671 (6%) were lobular histology with remaining other/unknown (**Fig 1b**). 6413 (53%) were HR+HER2-, 3504 (29%) were triple negative, 403 (3%) were HR+HER2+ and 363 (3%) were HR-HER2+ with 1375 (13%) of unknown subtype (**Fig 1c**). In the entire cohort, the most commonly amplified genes were FGF19 (11.49%), FGF3 (10.75%), FGF4 (9.98%), CCND1 (12.36%), and FGFR1 (9.08%) (**Fig 2a, b**). FGFR1-4 amplification was present in 11.01% of all cases (**Fig 2b**). FGF19 amplification was more prevalent in lobular breast cancer compared to ductal (12.1% vs 9.1%) (**Fig 2c**). FGF19, FGF23, FGF3, FGF4, and FGF6 amplifications varied across molecular subtypes, being most prevalent in HR+/HER2- (15.7%), HR+/HER2+ (12.1%), and least prevalent in HR-/HER+ tumors (3.4%) (**Fig 3a**). FGFR1 amplification was most common among FGFR1-4 amplifications and most prevalent in HR+HER2- (12%) (**Fig 3c**). Across metastatic sites, FGF ligands displayed different patterns of amplification with FGF19, FG3, and FGF4 amplifications most prevalent in liver and bone metastases (**Fig 3b**). FGFR1 amplification was statistically different across metastatic sites and most prevalent in liver metastases (16%) followed by bone (10%) (**Fig 3d**). FGFR amplification compared to wild type showed a trend towards poorer OS in both the entire breast cohort and HR+HER2- cancers (**Fig 4a, b**). Patients receiving CDK4/6 inhibitors with FGFR1 amplification had shorter time on treatment than FGFR1 wild type in the entire cohort (HR = 0.892, p = 0.03) (**Fig 4c**); and in patients with HR+/HER2- molecular subtype (HR = 0.87, p = 0.02) (**Fig 4d**).

FGF alterations in invasive breast cancers vary by molecular subtype and site of disease. FGFR1, FGF19, FGF23, FGF3, FGF4, and FGF6 amplifications were statistically different across subtypes (most prevalent in HR+/HER2- and HR+/HER2+) (**Fig. 3a, 3c**) and metastatic sites (most prevalent in liver and bone metastases) (**Fig 3b, 3d**). The prevalence in HR+ subtypes lend support to the role of FGF in endocrine resistance.

References

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Figure 1: Distribution of Tumor Specimens, Subtypes, and Metastatic Sites

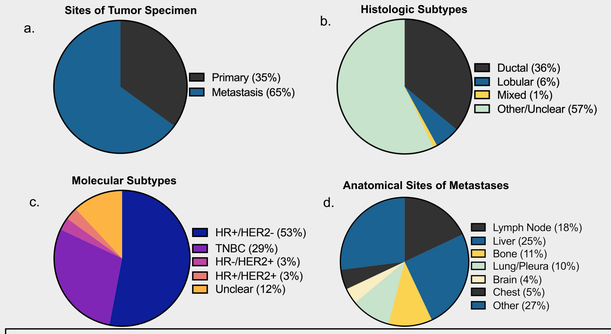

Figure 1. (1a) Study cohort contained 12058 total breast cancer tumors (1b) in various histologic subtypes. (1c) Predominant molecular subtype is HR+/HER- and Triple Negative Breast Cancer (TNBC). (1d) Most common sites of metastasis are Lymph Node, Liver, Bone, and Lung.

Figure 2: FGF and FGFR Amplification in All Cases and by Histologic Subtype

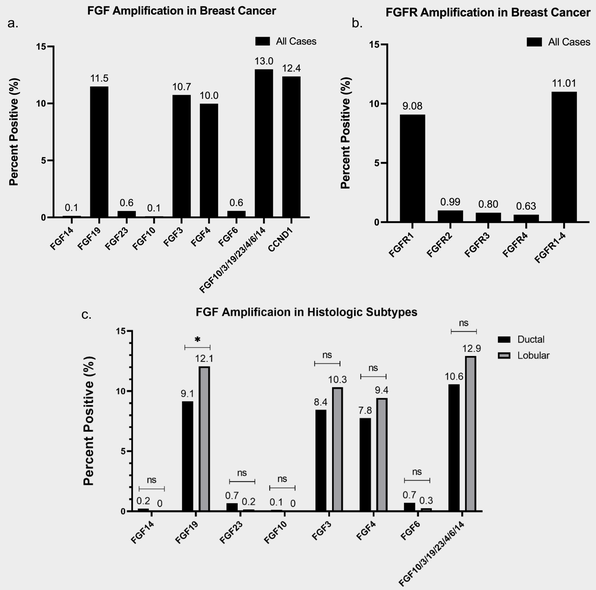

Figure 2. Distribution of FGF (2a) and FGFR (2b) alterations shown for all cases in the breast cancer cohort. FGF amplification shown by histologic subtype (2c)

Figure 3: FGF and FGFR Amplification by Breast Cancer Molecular Subtype and Site of Breast Cancer Metastasis

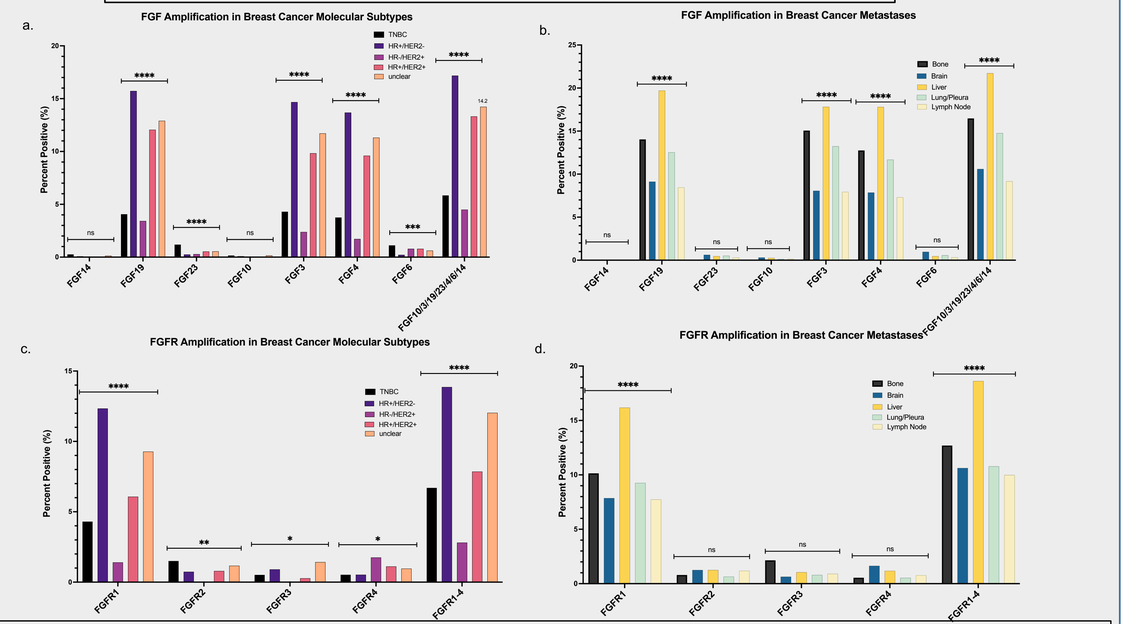

Figure 3. (3a) Amplification of FGF Subfamilies is statistically different across breast cancer molecular subtypes; most prevalent in HR+/HER2- and HR+/HER2+. (3b) FGF19, FGF3, and FGF4 amplification (all genes residing on the same amplicon) are statistically different across sites of metastases; most prevalent in Liver and Bone metastases. (3c) FGFR1 amplification is statistically different across Breast Cancer molecular subtypes; most prevalent in HR+/HER2-. (3d) FGFR1 amplification is statistically different across sites of metastases; most prevalent in Liver and Bone metastases

Figure 4. Real World Outcomes in FGFR1 Wild Type vs Amplified Breast Cancer Patients

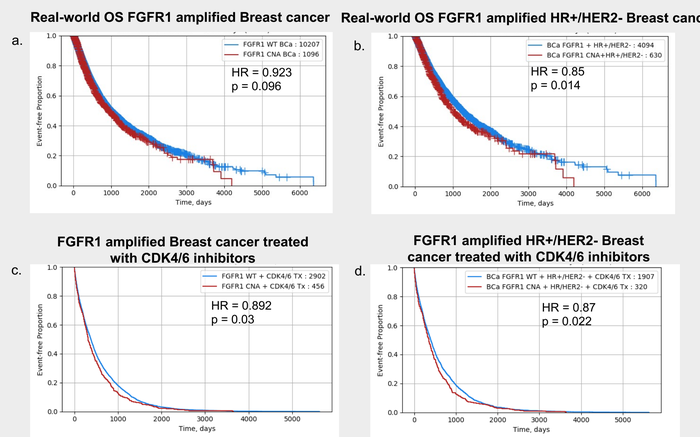

Figure 4.
4a) Overall survival for FGFR wild type vs amplified breast cancer; HR = 0.923, p = 0.096
4b) Overall survival for FGFR wild type vs amplified HR+HER2- breast cancer; HR = 0.85, p = 0.014
4c) Time of first treatment to time of last treatment for FGFR wild type vs amplified breast cancer treated with CDK4/6 inhibitors; HR = 0.092, p = 0.03
4d) Time of first treatment to time of last treatment for FGFR wild type vs amplified breast cancer treated with CDK4/6 inhibitors; HR = 0.87, p = 0.022