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Gene- Gene And Protein -Protein Interactions In Triple Negative Breast Cancer Genes

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ABSTRACT

Six high frequency mutated proteins were identified as unique in TNBC, DNBC and SNBC and in genes BRCA1is found to be unique and highly mutated compared to others in TNBC where as EGFR is highly expressed in TNBC and FOXC1 is specific transcription factor associated with the TNBC and SOX10 is the marker for mesenchymal TNBC. CDK12 is specific to DNBC and GATA3 is specific to SNBC. AR (LAR Type) and KIT (Stem Like) specific and associated with TNBC. EGFR, Nestin, SOX10 and Vimentin are the proteins found uniquely in TNBC and GRB7 in DNBC and FOX A1 in SNBC.Online tools and databases like Gene mania, STRING and PINA are used for the study of Gene- Gene interactions and Protein-Protein interactions and protein coexpression and colocalization and the proteins sharing common signaling pathways. Vimentin found to coexpress with EGFR and SOX10 and Vimentin specifically coexpress with nestin. From the studies of gene- gene interactions BRCA1,GRB7,GATA3 and AR show physical interactions and share common interacting partners in signalling pathways.

KEYWORDS: *TNBC, DNBC and SNBC, EGFR, SOX10, GATA3, Nestin, FOX A1, BRCA1*

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1. INTRODUCTION

Triple negative breast cancer does not express plethora of genes but it is caused due to mutations leading to loss of or gain of functions. TP53 is the mostly mutated gene with ≥80% followed by PIK3CA (Weisman PS et al., 2016, Koboldt DC et al., 2012) and other notable genetic alterations with ≤ 5% include genes like *PTEN*, *KMT2C*, and *RB1*(Koboldt DC et al., 2012; Ng CK, Schultheis AM et al., 2015; Shah SP et al.,2012) Tumor microenvironment is a combination of cells including fibroblasts,TILs and connecting lymphatic vessels. Initial studies with TILs esp. TNBC IM subtype is associated with the better prognosis and response to polychemotherapy in both adjuvant and neoadjuvant types (Savas P et al., 2016; Salgado R et al., 2015).

The most frequent variant detected in 11.8% of TNBC was found to be the pathogenic variant associated with BRCA1 and in case of germline variant it depends on the genetic counsellors based on age at diagnosis, family history, the gene affected and the pathogenic variant (Kamburova ZB et al.,2024). Most of the TNBC express basal like molecular profile find out with gene expression arrays and most of the BRCA1 associated cancer are basal type like and recent research include molecular understanding of BRCA1 sporadic basal like cancer and treating it. In this article we focus on gene- gene interactions found in TNBC and interactions of TNBC genes, DNBC genes and SNBC genes and studies on Protein – Protein intercations associated with TNBC, DNBC and SNBC.

2. METHODOLOGY:

Unique genes and proteins found in TNBC,DNBC and SNBC in various cancer types were identified and the gene gene interactions were studied using Gene mania datbase. Protein – Protein interactions are studied using STRING and PINA database using online tools. Pan cancer analysis were carried out with TCGA-ACC cancer data set and gene ontology enrichment with biological process and molecular function is carried using STRING database analysis. Kalpan – Meier survival curves were generated using high values ≥ 75% and low values ≤ 30%. Gene ranking with TNBC genes was done

using Gendoo database.

3. RESULTS:

From figure 1B all the six proteins shows first shell of physical interactions and Vimentin and nestin show protein homology. EGFR and GRB7 share gene fusion mechanisms and except nestin all the Protein- Protein interaction data is derived experimentally. From Fig. 1A all the six proteins contain predicted physical interactor partners like SLC5A1, POU3F1,GPNMB,TMEFF2 and SPINK1 with ratios of 0.936,0.808,0.987,0.429 and 0.589. Sox10, EGFR and Nestin show coexpression with vimentin similarly EGFR coexpress with other proteins like Nestin, GRB7, FOXA1 and SOX10 in homosapiens.

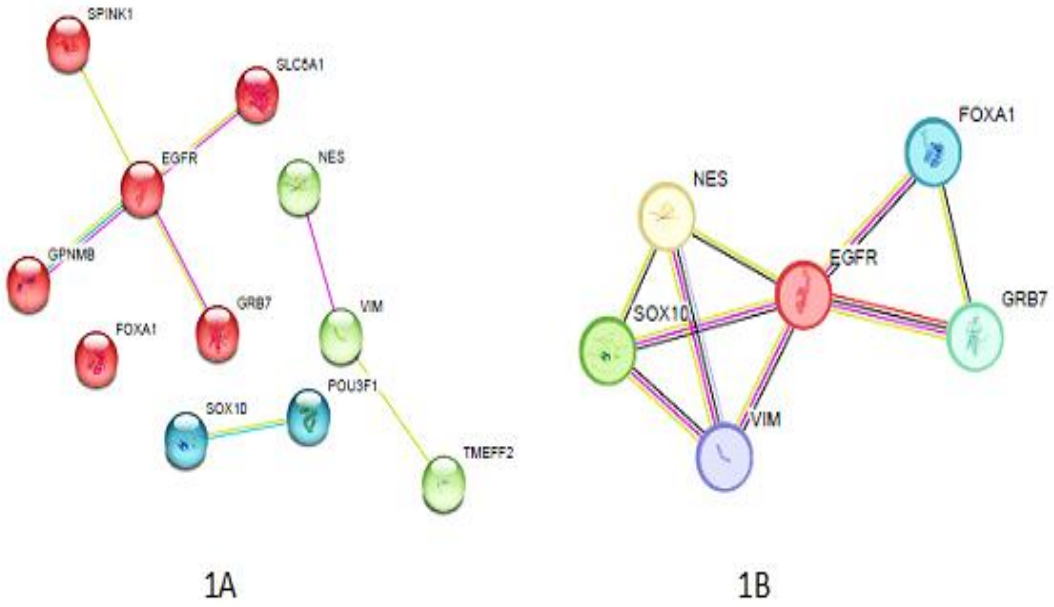


Figure: 1 Protein – Protein interactions with possible proteins (1A) and defined proteins (1B). Proteins 1B: VIM,EGFR,SOX10,FOXA1,GRB7 and NES

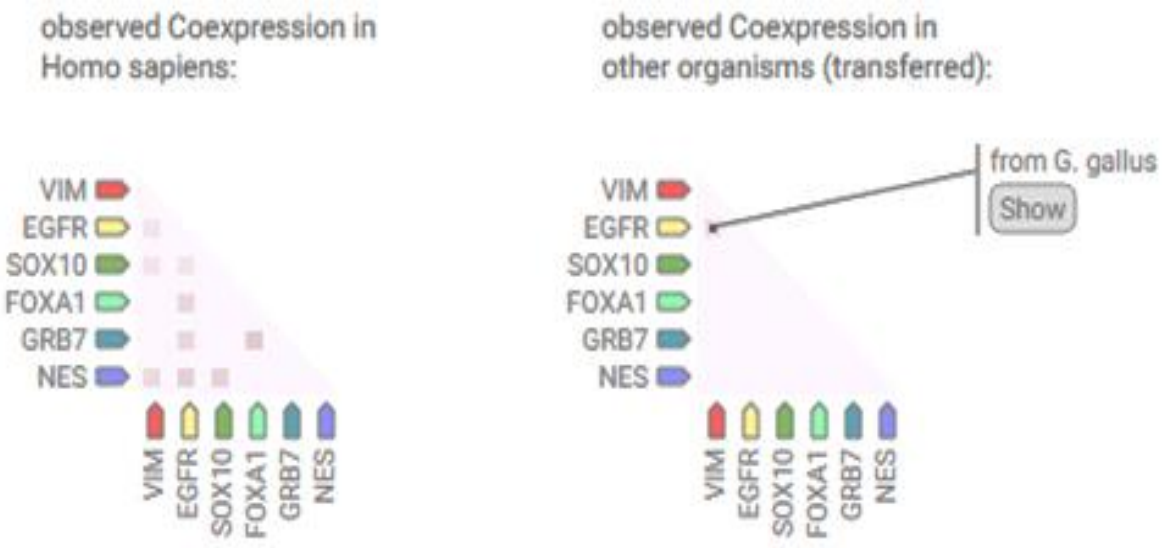
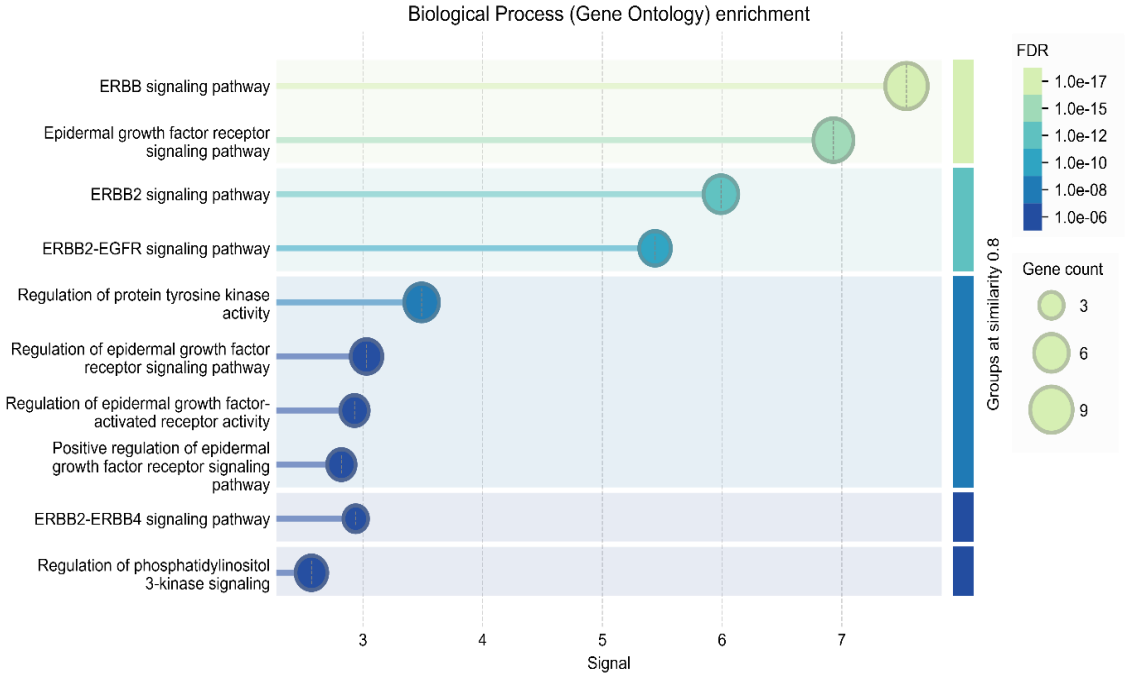


Figure: 2 Co expression pattern of proteins in Homo sapiens and other related organisms.

From the figure 3 all the six proteins regulate ERBB signalling pathway, Epidermal growth factor receptor signalling pathway, regulation of protein tyrosine kinase pathway, positive regulation of epidermal growth factor receptor signalling and regulation of PI3 Kinase signalling pathway. From the figure 4 the molecular function of the proteins like Nestin and vimentin is found to be intermediate filament binding.

Figure:3 Gene ontology enrichment of biological function of 1A



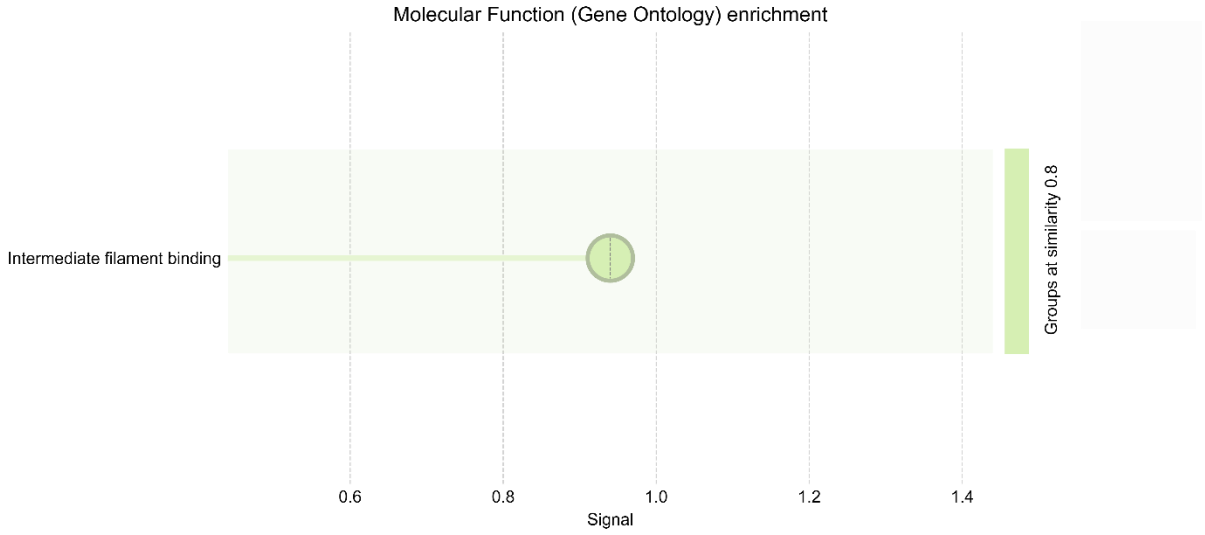


Figure:4 Gene ontology enrichment of molecular function of 1B

From the figure 5 BRCA1, EGFR and AR rank primary in neoplasms and carcinomas especially breast neoplasms. EGFR ranks tertiary in lymphoma than other parameters like Fanconi anaemia , KIT ranks secondary, Teritiary and quartenary in almost all the parameters where as FOXC1, SOX10, GATA3 and GRB7 ranks tertiary or quaternary in ranking in almost all the parameters.

From the figure 6 BRCA1 show majorly physical interactions and share some common interacting partners in signalling pathways like CCNE1 and BARD1. From figure 7 EGFR shows physical interactions with PIK3CA that co express with the other genes like CAV2 in addition to physical interactions and common signalling partners.

Gene	Link	Information Gain	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15
BRCA1	[NCBI]	0.0070688835163															
EGFR	[NCBI]	0.011753739064															
FOXC1	[NCBI]	1.0806723e-06															
SOX10	[NCBI]	1.29031618e-05															
GRB7	[NCBI]	8.35967e-05															
GATA3	[NCBI]	6.60608e-06															
AR	[NCBI]	0.007665476709															
KIT	[NCBI]	3.68507388e-05															

Figure: 5 Gene ranking according to carcinogenesis curated fro gene mania { Parameters: Neoplasms, Lymphoma, Breast neoplasms, Fanconi anaemia- Pink; Neoplasms- Radiation induced, Chromosomal instability, Lymphoma and genetic predisposition to disease- Light pink; Fibrocystic neoplasms, Skin neoplasms- Grey and Glioblastoma,medullo blastoma, Melanoma, Adenoma and Brain neoplasms – Black} Pink- Primary, Light pink- secondary; Black- Tertiary and Grey- Quaternary

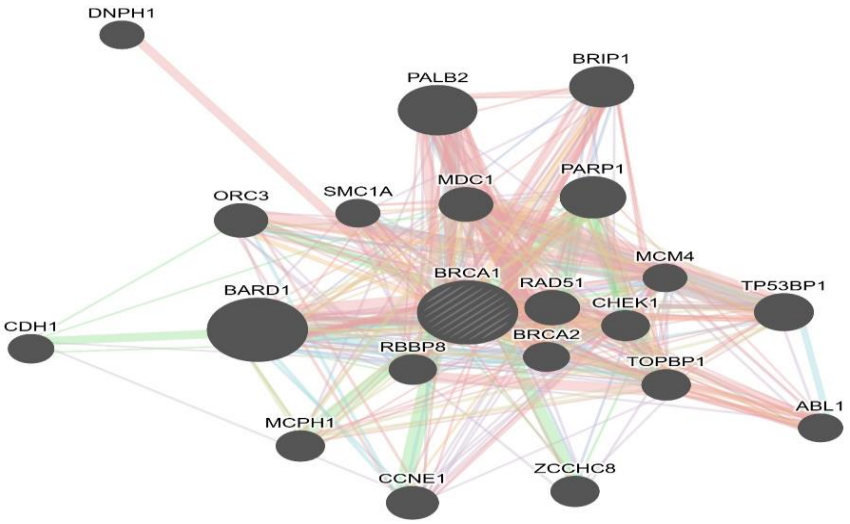


Figure: 6 Gene- Gene interactions of BRCA1 studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and sky blue lines indicate common signalling pathway partners associated with the gene

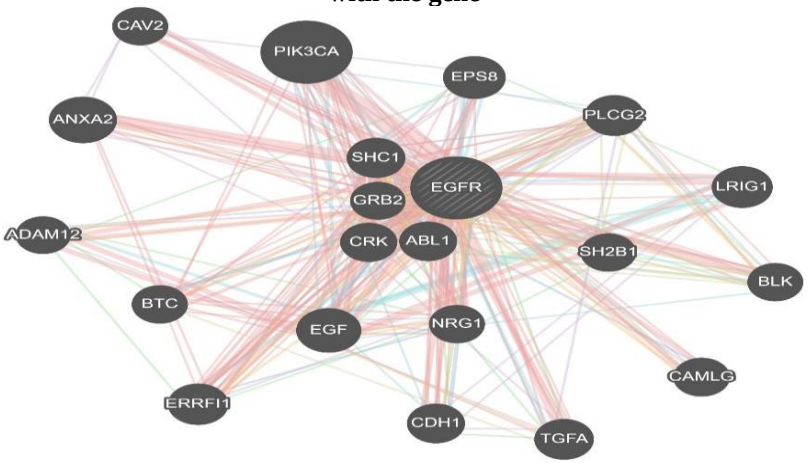


Figure: 7 Gene- Gene interactions of EGFR studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and violet lines indicate coexpression

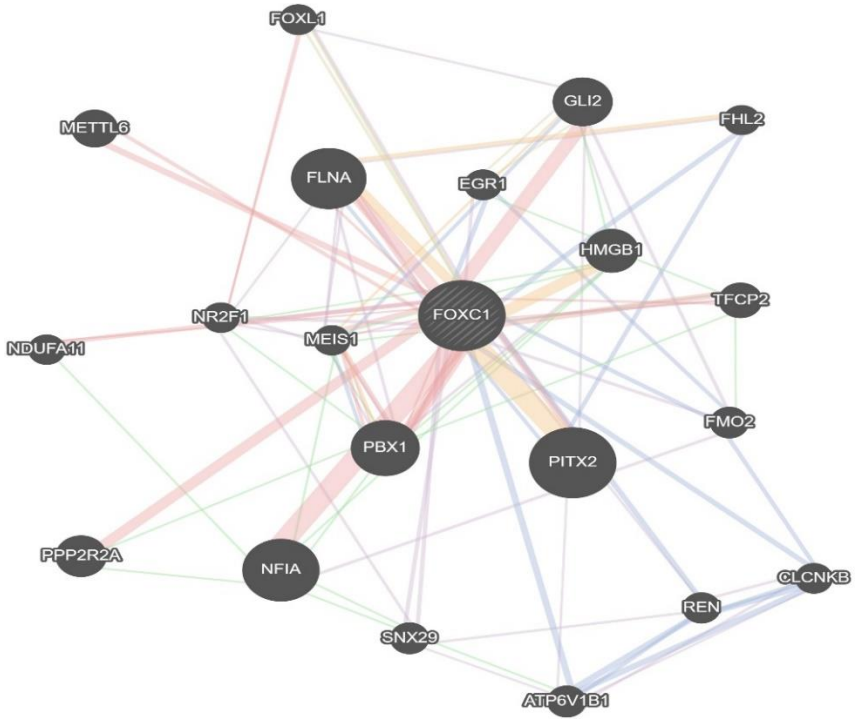


Figure: 8 Gene- Gene interactions of FOXC1 studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and violet lines indicate coexpression and dark blue lines indicate colocalization.

From Figure 8 FOXC1 co express with other genes like SNX 29 and colocalise with proteins like ATP6V1B1,FHL2 and EGR1.

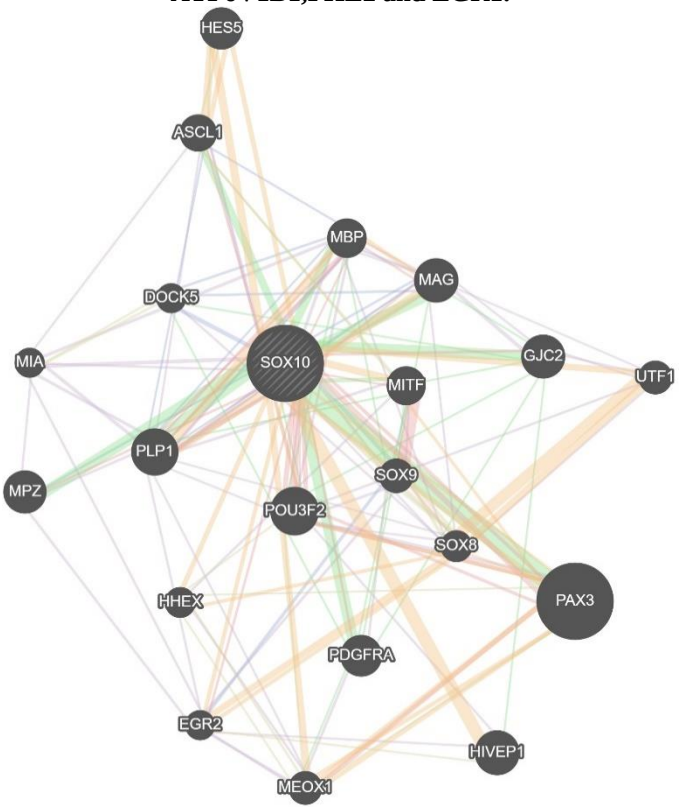


Figure: 9 Gene- Gene interactions of SOX10 studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and violet lines indicate coexpression; Green lines indicate genetic interactions

From the figure 9 SOX 10 show genetic interactions with the proteins like MPZ, PDGFRA, MBP, MAG and PAX3. From the figure 10,11,12 GRB7, GATA3 and AR shows physical interactions and common signalling pathways sharing like that of BRCA1. From the figure 13 KIT shows colocalization with proteins like CSF2RA where as it interacts with remaining genes through physical interactions and common signalling pathways.

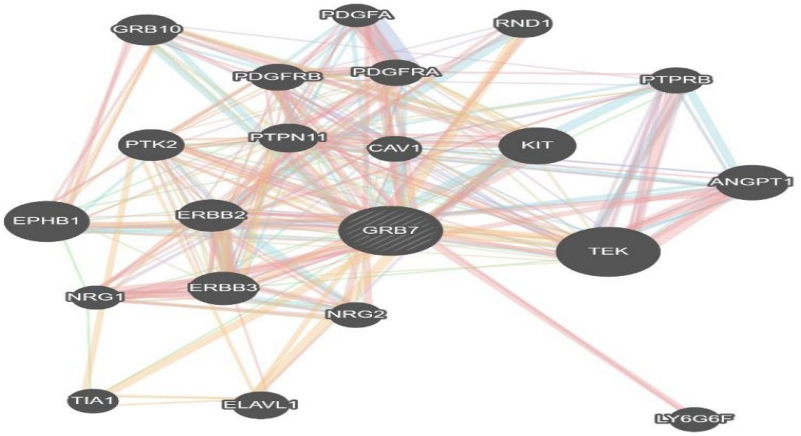


Figure: 10 Gene- Gene interactions of GRB7 studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and sky blue lines indicate common pathways

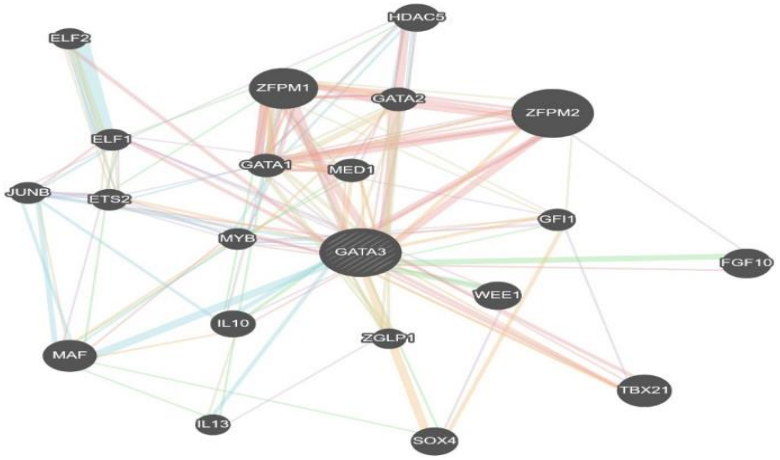


Figure: 11 Gene- Gene interactions of GATA3 studied using gene mania. Pink lines represent Physical interactions; sky blue lines indicate common pathways

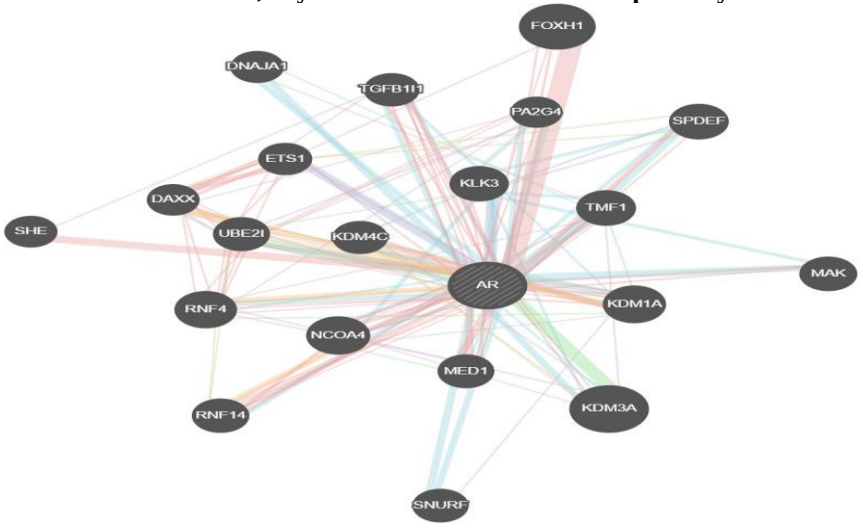


Figure: 12 Gene- Gene interactions of AR studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and sky blue lines indicate common pathways; violet lines indicate coexpression; Green lines indicate genetic interactions.

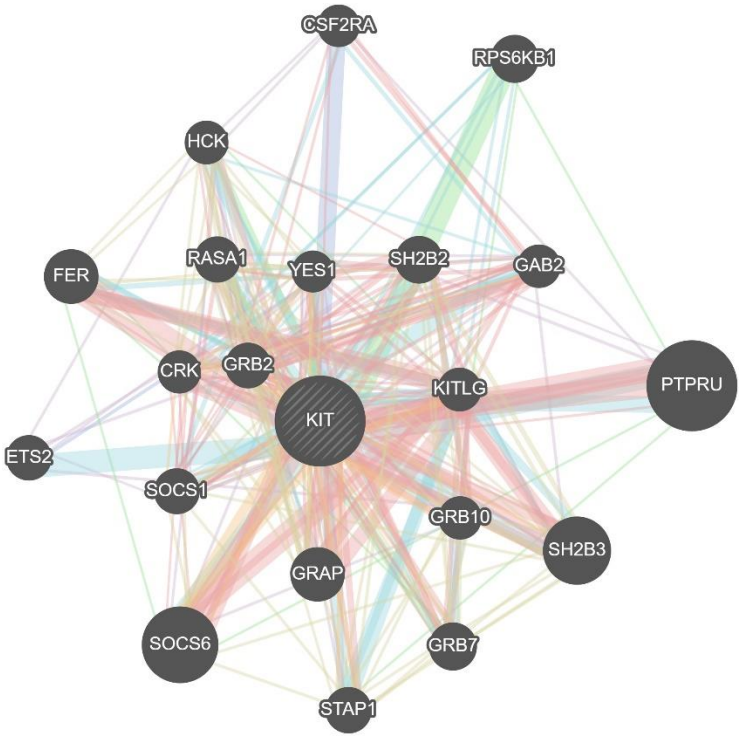


Figure: 13 Gene- Gene interactions of KIT studied using gene mania. Pink lines represent Physical interactions; orange lines indicate predicted ones and violet lines indicate coexpression; sky blue lines indicate common pathways; Green lines indicate genetic interactions.

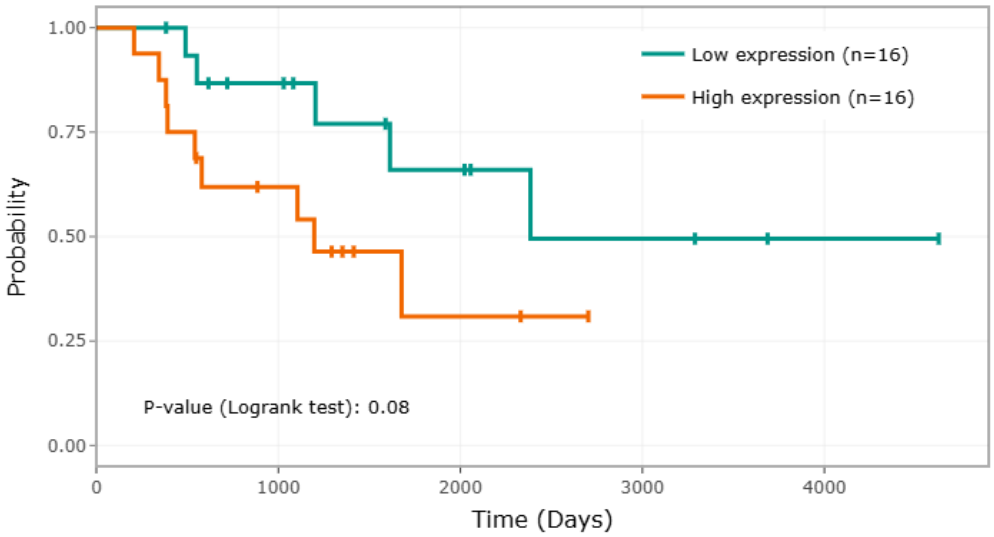


Figure:14 Kalpan – Meier survival curves based on Patients stratified by expression of Vimentin; no. of samples= 16.

From the figure 14 low probability in survival is seen with high expression of vimentin in cancer cells whereas with nestin the probability is same with both low and high expression. From the figure 16 FOXA1Shows high probability in survival with high expression of the gene.

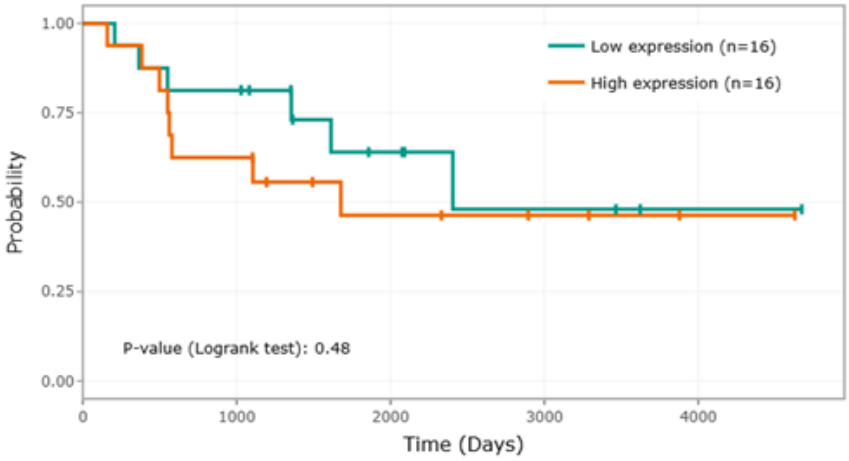


Figure:15 Kalpan – Meier survival curves based on Patients stratified by expression of protein Nestin; with p value 0.48 ; no. of samples= 16.

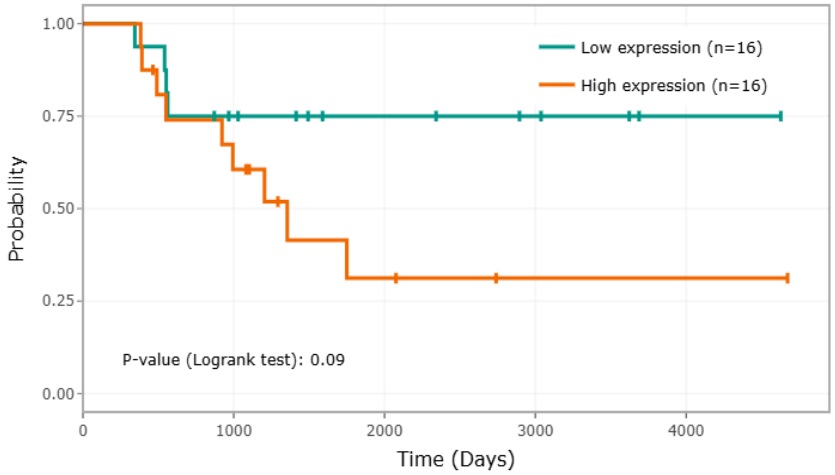


Figure:16 Kalpan – Meier survival curves based on Patients stratified by expression of protein FOXA1; with p value 0.09 and low probability ; no. of samples= 16

From the figure 16 High expression of EGFR shows higher probability during early onset of cancer and the probability in survival drops during later onset and remains same after 6.8 years of cancer onset. Pan cancer analysis of EGFR and FOXA1 using cancer data set TCGA ACC predicted in high mRNA expression with EGFR compared to FOXA1.

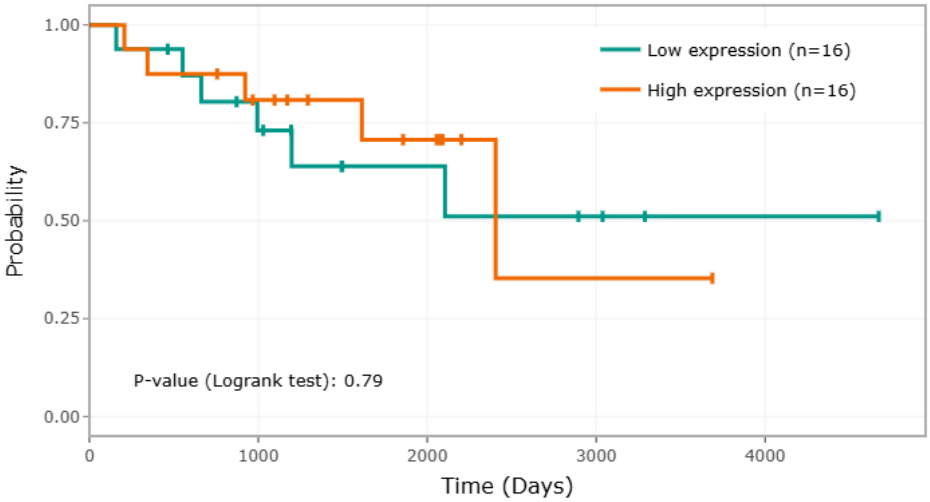


Figure:17 Kalpan – Meier survival curves based on Patients stratified by expression of protein EGFR; with p value 0.79 and low probability with high expression ; no. of samples= 16.

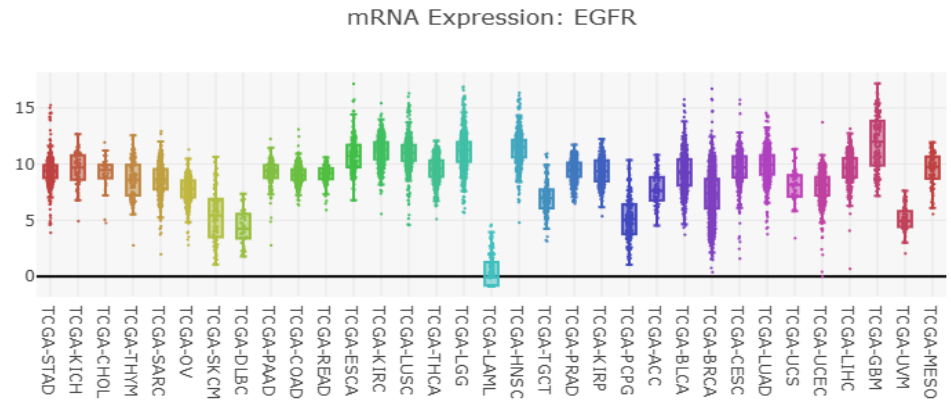


Figure:18 Pan cancer analysis with mRNA expression cancer data set TCGA- ACC across different cancer types. High expression with EGFR.

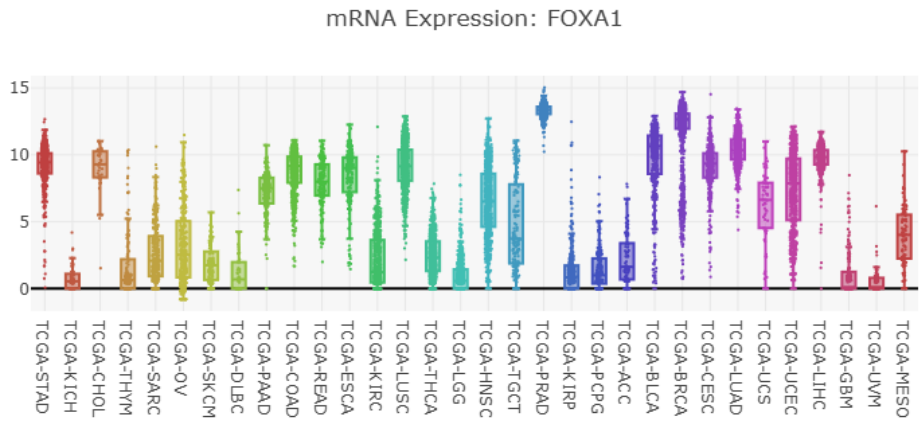


Figure: 19 Pan cancer analysis with mRNA expression cancer data set TCGA- ACC across different cancer types; Low expression with FOXA1.

4. DISCUSSION AND CONCLUSION:

TNBC is an immunohistochemistry type cancer with loss of expression of estrogen receptor, Progesterone receptor and Human Epithelial growth factor receptor 2 protein which makes the treatment by hormone therapy to be difficult and it is one of the most cancer type with high recurrence and most spread compared to other breast cancer types. TNBC is heterogenous and widely overexpressed in black and premenopausal women. Unlike other clinical subtypes treatment of TNBC is limited due to deprive in targeted therapy (Kamburova ZB et al., 2024)

TNBC clinical features include high invasiveness, high metastatic potential, proneness to relapse, and poor prognosis (Zagami, P., et al., 2022). Approximately 56% of the TNBC and BLBC are overlapping with an overlap ratio of about 60%-90% and remaining 11.5% include non-overlapping phenotype (Yin, L et al., 2020). Future therapies include based on targeted therapy with less immune invasion and socioeconomic output for better prognosis and survival.

REFERENCES:

[1] Weisman PS, Ng CK, Brogi E, Eisenberg RE, Won HH, et al. 2016. Genetic alterations of triple negative breast cancer by targeted next-generation sequencing and correlation with tumor morphology. Mod. Pathol 29:476–88 [DOI] [PMC free article] [PubMed] [Google Scholar]

[2] Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, et al. (Cancer Genome Atlas Network). 2012. Comprehensive molecular portraits of human breast tumours. Nature 490:61–70 [DOI] [PMC free article] [PubMed] [Google Scholar]

[3] Ng CK, Schultheis AM, Bidard FC, Weigelt B, Reis-Filho JS. 2015. Breast cancer genomics from microarrays to massively parallel sequencing: paradigms and new insights. J. Natl. Cancer Inst 107: djv 015. [DOI] [PubMed] [Google Scholar]
[4] Shah SP, Roth A, Goya R, Oloumi A, Ha G, et al. 2012. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. Nature 486:395–99 [DOI] [PMC free article] [PubMed] [Google Scholar]
[5] Savas P, Salgado R, Denkert C, Sotiriou C, Darcy PK, et al. 2016. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nat. Rev. Clin. Oncol 13:228–41 [DOI] [PubMed] [Google Scholar]
[6] Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, et al. 2015. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann. Oncol 26:259–71 [DOI] [PMC free article] [PubMed] [Google Scholar]
[7] Kamburova ZB, Popovska SL, Kovacheva KS, Dimitrov DD and Nikolova SE 2024.: Genetic predisposition in female patients with triple-negative breast cancer. World Acad Sci J 6: 2,
[8] Zagami, P., Carey, L.A. Triple negative breast cancer: Pitfalls and progress. npj Breast Cancer **8**, 95 (2022). https://doi.org/10.1038/s41523-022-00468-0
[9] Yin, L., Duan, JJ., Bian, XW. et al. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res **22**, 61 (2020). https://doi.org/10.1186/s13058-020-01296-5