A Bioinformatics Analysis of the Transcription Interactions of Mutant p53 with Other Oncogenes

Aadi Desai
Independent Researcher

Abstract

Several studies have shown that the evolutionary conserved tumor suppressive p53 protein upon undergoing mutations acquires new oncogenic functions. Termed gain of function (GOF) mutant p53 (mtp53), this mutant gene interacts with other genes and activates their transcription to promote metastasis, contrary to its earlier suppressive functions. While the focus on p53-centric studies has increased since the turn of the century, progress has been slow. The genes associated with mtp53 in carrying out said functions remain to be accounted for or knowledge of them is incomplete at best. This research aims to use computational databases and platforms to predict some of these transcriptional hotspots. It is reported that breast cancer (BRCA), uterine cancer, and colon cancer particularly shows high expression of the gene. In BRCA, p53 has the highest expression in Triple Negative Breast Cancer (TNBC) and HER2+ subtypes, both of them invasive cancers. p53 is also reported to be an essential gene for TNBC cell lines. It is also found that mtp53 BRCA has overexpression of several oncogenes like S100A9, PSAT1, LCN2, etc., many of which have preexisting transcription associations with p53. TP53 is found to be most susceptible to PROTACS, while the other genes have shown a variety of results, ranging from antibodies to small molecules. On the basis of their over-expression in BRCA with TP53 mutant tumors and transcriptional history with p53, it is hypothesized that these genes form interactions with mtp53 in order to promote tumorigenesis.

Key Words: TP53, mtp53, GOF, BRCA, bioinformatics, over-expression, under-expression.

Introduction

Breast cancer is the most frequent case of female tumours in the world. It is also the highest cause of cancer deaths among women, followed by cancers of the lung and cervix uteri respectively (Mattiuzzi & Lippi, 2019).

Breast cancer is a clinically and genetically heterogenous tumour. One way of classifying it has widely been through the immunohistochemistry perspective, which involves the use of hormone receptors: Oestrogen (ER), Progesterone (PR), and Human Epidermal

Growth Factor (HER2). On the basis of their expression in neoplasm cells, breast cancer has been popularly classified into four subtypes, namely: Luminal A subtype (with ER+/PR+ expression and an absence of HER2+ expression), Luminal B subtype (ER+), HER2 subtype (HER2+) and TNBC (ER-, PR- and HER2-) (Orrantia-Borunda et al., 2022).

Luminal-like tumours usually have a higher frequency among women (50% in Luminal A subtype and 15% in Luminal B subtype). HER2+ type occurs in 20% of women while the Triple Negative or TNBC subtype has been found to transpire in about 15% of women (Orrantia-Borunda et al., 2022).

The TP53 gene is one of the most important hallmark genes in cancer(Sondka et al., 2024). One of the most widely studied genes in cancer history, TP53 is found on the petite arm of chromosome 17 at position 13.1 (17p13.1) (Kent et al., 2002). It is known to play important roles in tumour suppression by promoting apoptosis, preventing metastasis, and angiogenesis and suppressing tumour-promoting inflammation in cancer cells (Sondka et al., 2024), aptly gaining the title ‘Guardian of the Genome’.

It is no wonder then that TP53 is the most frequently altered gene(*Survival Outcomes by TP53 Mutation Status in Metastatic Breast Cancer: Funda-Meric Bernstam*, n.d.) in all human cancers(>50%) with loss of function mutations in p53 found to be a prerequisite for almost all of them (Zhang et al., 2020). In BRCA too, p53 has the highest incidence of mutations (30%) (Bertheau et al., 2013).

Mutations in p53 are found to be the lowest in luminal-like cancers (26%), with Luminal A subtype having less mutations than Luminal B (17% and 41% respectively). Moreover, basal-like tumours or Triple Negative subtypes have the highest expression of p53(88%), while more than half of the HER2+ subtype possesses p53 mutations (Bertheau et al., 2013; *Role of P53 in Breast Cancer Progression: An Insight into P53 Targeted Therapy*, n.d.).

Most of the gene changes that take place in TP53 are missense mutations(Cerami et al., 2012; de Bruijn et al., 2023; Gao et al., 2013; Zehir et al., 2017). So, a majority of mutations in breast cancer result in the formation of the full-length mutant p53 (mtp53) protein with a single amino acid difference from wild-type p53 (wtp53). This mtp53 has been seen to prevent the protein’s ability to bind with the DNA-binding domains of other target genes and thus, inhibits its transcriptional activity. This prevents the protein from carrying out its natural functions through the regulation of downstream genes, thus promoting tumour formation (Yue et al., 2017; Zhang et al., 2020). While most of the breast cancer cases retain wild-type p53 that is inhibited by overexpression of genes like MDM2 and MDMX, one-third of breast cancer has p53 mutations, a majority of which are of the HER2+ and basal-like subtype (*Role of P53 in Breast Cancer Progression: An Insight into P53 Targeted Therapy*, n.d.).

However, most interesting and quite controversial of all, mtp53, in addition to loss-of-function, is also seen to acquire certain new functions (Kennedy & Lowe, 2022). Termed gain-of-function (GOF),

this mutant protein harnesses its oncogenic abilities in order to promote cancer malignancy and tumorigenesis (Yue et al., 2017).

This mtp53, with its many functions, is a hallmark gene and this research paper aims to focus on a bioinformatics approach in order to understand the related pathways that mtp53 may follow in order to ensure and enhance cancer survival. It will also provide suggestions for possible therapeutic targets and the people it will most likely benefit, given their history.

Materials and Methods

3.1. GEPIA:

GEPIA (http://gepia.cancer-pku.cn/) is an interactive web server for analysing the RNA sequencing expression data of 9,736 tumours and 8,587 normal samples from the TCGA and the GTEx projects (Tang et al., 2017). This database was used to analyse the pan-cancer expression of p53.

3.2. cBioPortal:

cBio Portal (https://www.cbioportal.org/) for Cancer Genomics is a resource containing multidimensional cancer genomics data sets (Cerami et al., 2012; de Bruijn et al., 2023; Gao et al., 2013). It was used to explore pan-cancer expression of p53 and also the frequency of BRCA subtypes in altered and unaltered p53.

3.3. Depmap:

Depmap portal (https://depmap.org/) is an online analysis tool that explores the essentiality of genes across thousands of cell lines (Meyers et al., 2017). It was used to find the essentiality of TP53 gene in different BRCA subtypes.

3.4. UALCAN:

The UALCAN database (https://ualcan.path.uab.edu/) is a comprehensive, user-friendly and interactive web resource for analysing cancer OMICS data. It contains multiple readily available datasets including the TCGA dataset and data on 36 types of cancer (Chandrashekar et al., 2017, 2022). It was used to visualize heatmaps of genes over-expressed and under-expressed in BRCA with p53 mutant tumours, and also to analyse gene expression using different parameters.

3.5. STRING:

STRING (https://string-db.org/) is a web server used to depict experimentally predicted and curated protein-protein interactions (PPIs) in more than 12,000 organisms (Szklarczyk et al., 2015). It was used to find the protein-protein interactions of the TP53 protein with other proteins.

3.6. GENEMANIA:

GENEMANIA (https://genemania.org/) uses a very large set of functional association data to find related genes for the input gene or group of genes. Association data include protein and genetic interactions, pathways, co-expression, co-localization, and protein domain similarity (Warde-Farley et al., 2010). It was used to understand the protein-protein interactions of TP53 with other genes.

3.7. DrugnomeAI:

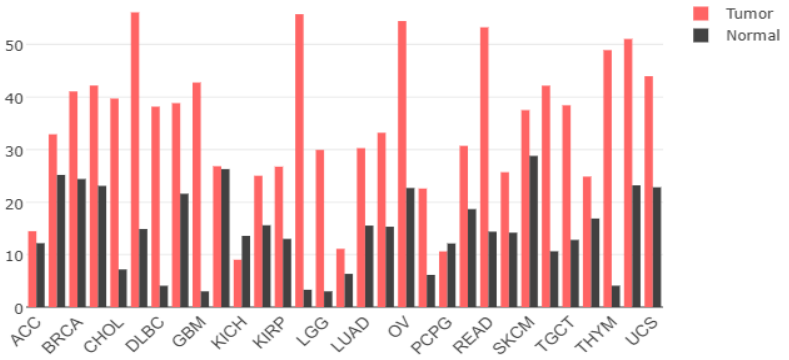
DrugnomeAI (https://astrazeneca-cgr-publications.github.io/) is a machine-learning algorithm that is an adaptation of Mantis-ML, a pre-existing machine-learning framework built to generate novel gene-disease interactions. DrugnomeAI provides both disease-agnostic and disease-specific gene druggability framework, and classifies genes as either 'druggable' or 'non-druggable' based on a subset of known examples (Raies et al., 2022). The algorithm was used to identify possible drug types that could target TP53 as well as its mutant protein along with a whole array of oncogenes.

Results

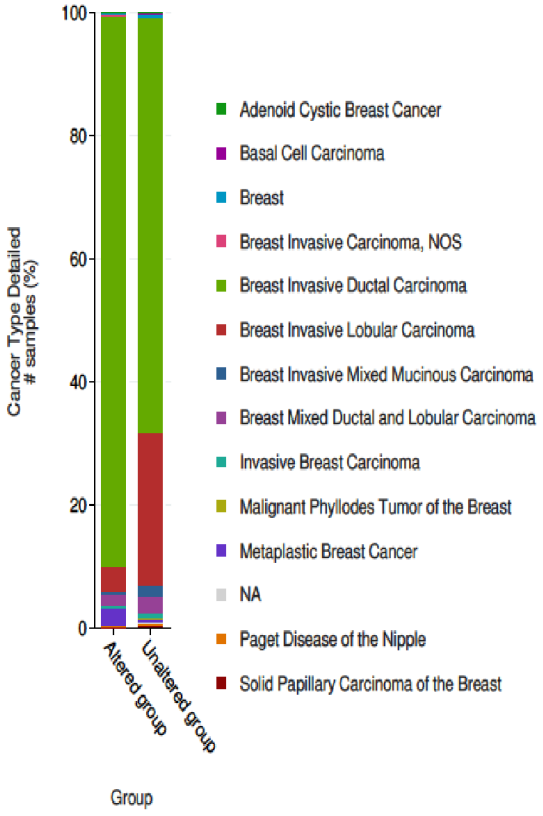
Expression of TP53 in different cancers

GEPIA (http://gepia.cancer-pku.cn/) and cBioPortal (https://www.cbioportal.org/) were used to determine the expression of TP53 in different cancer types and their subtypes. TP53 was found to be overexpressed in almost all human cancers, with the highest expression in colon, ovarian, blood, rectum, and uterine cancers whereas it was downregulated only in the Kidney Chromophobe [Fig.1(A)].

Breast cancer too held substantial expression of TP53, rounding off around 7.5 transcripts per million (Tang et al., 2017). Small cell lung cancer, colorectal cancer, and ovarian cancer had the highest alteration frequency while breast cancer had <50% frequency as per the data from the MSK-IMPACT Clinical Sequencing Cohort (41.59%) (Cerami et al., 2012; de Bruijn et al., 2023; Gao et al., 2013; Zehir et al., 2017). Overall, p53 protein levels were seen to be inconsistent across cancer types (Tang et al., 2017).



(A)



(B)

FIGURE 1. These figures (A-B) were obtained from GEPIA and cBioPortal respectively, both of which used the TCGA dataset to present the following findings. (A) Shows the expression profile of p53 across all tumour samples and paired normal tissues. The Y-axis represents the median expression of p53 in certain tumour or normal tissue. (B) Shows the frequency of different breast cancer types in the case of both altered and unaltered p53 (where altered p53 refers to any mutations in the gene and unaltered p53 refers to the p53 that has retained its wild-type status).

Expression of TP53 in BRCA subtypes

The TCGA dataset was used to further investigate the frequency of different breast cancer subtypes with respect to TP53 status [Fig.1(B)]. 311 (28%) of the patients were found to possess mutations in the queried gene. The results further showed us that the occurrence of the Breast Invasive Ductal Carcinoma (IDC) subtype for altered p53 was highest (89.42%), whereas it was significantly lower in the unaltered group (67.47%). Also, while the frequency of Breast Invasive Lobular Carcinoma was considerably high in the unaltered group at about 25%, the introduction of mutations in TP53 quite reduced its frequency to <5% (Cancer Genome Atlas Network, 2012; Cerami et al., 2012; de Bruijn et al., 2023; Gao et al., 2013).

Determining BRCA cell-line dependencies on TP53

Another study of cell line dependency on TP53 was carried out with the help of CRISPR-Cas9 knockouts on Depmap (https://depmap.org/portal/interactive/) (Fig.2) (Meyers et al., 2017). It showed that a majority of all BRCA subtypes remained unaffected in the absence of TP53. Only in Invasive Ductal Carcinoma, were cell lines found to be dependent on TP53, the cell lines being as follows- HCC1143, HCC70, and HCC1419. These three were found to have crossed the threshold while HCC1143, with a score of about -0.5 had TP53 classified as an essential gene. Meanwhile, cell lines in Breast Invasive Lobular Carcinoma, Invasive Breast Carcinoma, and Breast Ductal Carcinoma in situ remained unaffected in the absence of TP53.

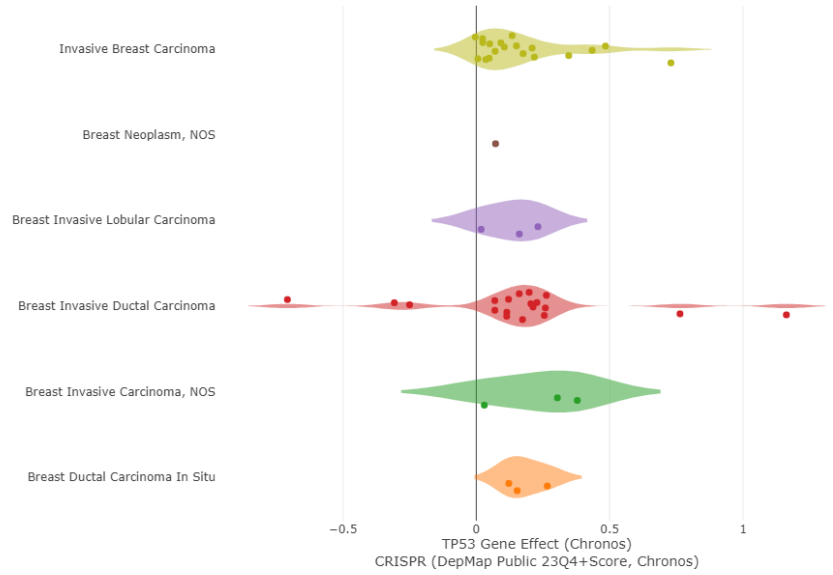


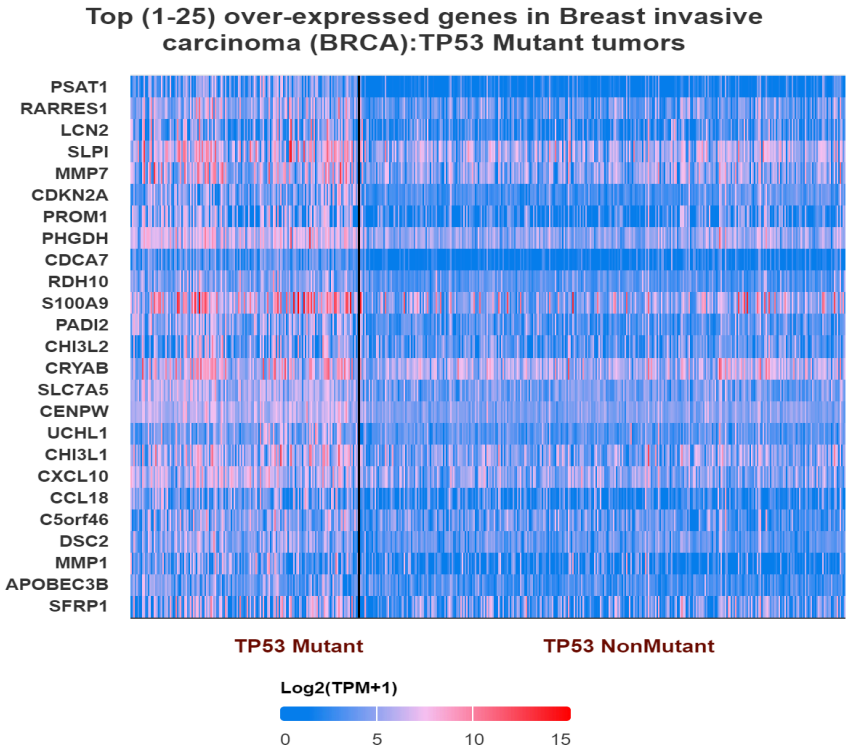
FIGURE 2. Obtained from Depmap portal using the CRISPR (Depmap Public 23Q4+Score, Chronos) dataset, this image shows the effect of TP53 gene on different BRCA subtypes. The threshold for genes to be considered essential in cell lines is -0.5.

Visualising the expression and interactions of other genes in mtp53 BRCA

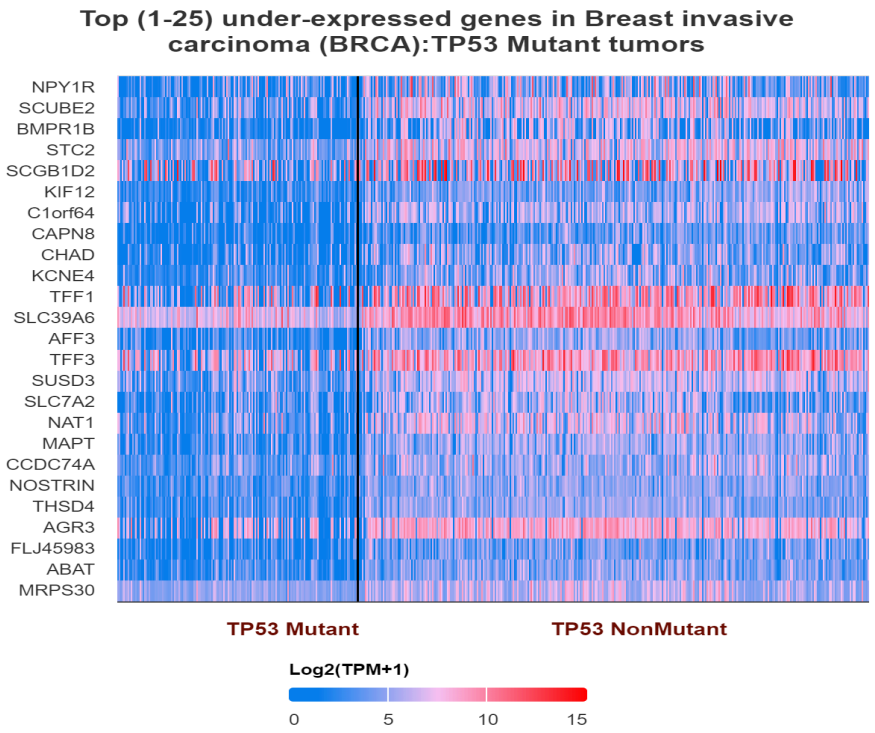
The UALCAN database was also used to visualize heatmaps regarding the genes expressed in mtp53 BRCA (Chandrashekar et al., 2017, 2022). It was found that genes with oncogenic properties-for example, PSAT1, LCN2, S100A9, etc- were expressed in higher numbers [Fig.3(A)]. Surprisingly, the tumour suppressive RARRES1 (retinoic acid receptor responder 1) was also found to be expressed in higher numbers. Furthermore, other tumour suppressor genes such as SCUBE2 and BMPR1B were few of the top 25 genes under-expressed in mtp53 BRCA [Fig.3(B)].

Additionally, the individual expression of the over-expressed genes in BRCA was also queried with respect to TP53 mutation status in UALCAN. Here, TPM response of many of these genes was seen to be higher than that of normal cells, including oncogenes like PSAT1 and LCN2. Meanwhile, other under-expressed genes like SCUBE2 and BMPR1B were down-regulated in their expression (Chandrashekar et al., 2017, 2022).

Furthermore, the STRING and GENEMANIA databases were used to check the protein-protein interactions (PPIs) of the concerned over-expressed genes (Szklarczyk et al., 2015; Warde-Farley et al., 2010) in normal Homo Sapiens cells. It was found that genes like PSAT1, LCN2, and MMP7, among many others did not form any significantly important interactions with wtp53.



(A)



(B)

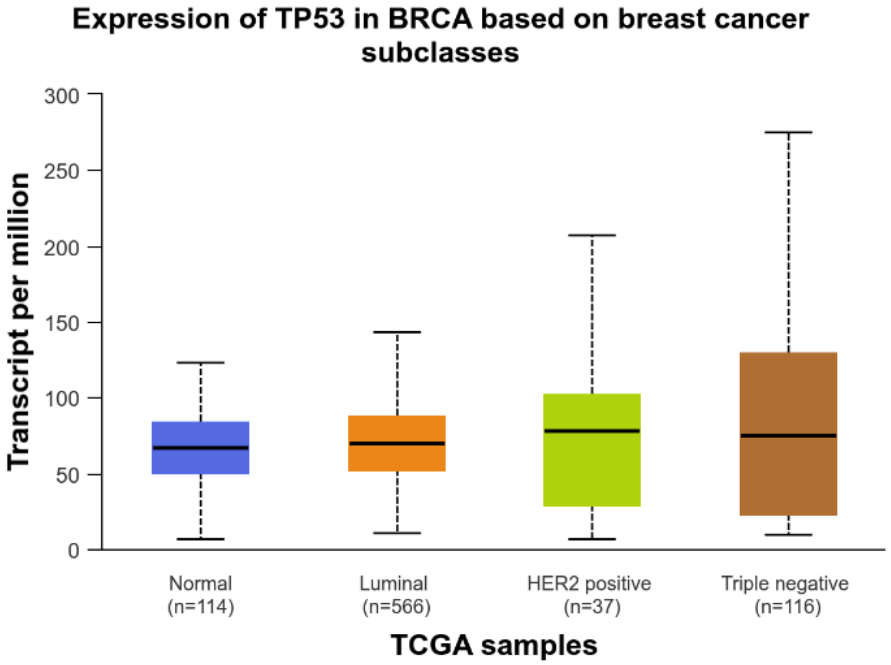
FIGURE 3. Visualized using UALCAN, these heatmaps show the expression of other genes in breast cancer with mtp53 tumours (A-B). (A) shows the genes over-expressed in mtp53 BRCA. (B) shows the genes under-expressed in mtp53 BRCA. Log2(TPM+1) was used to calculate the fold change of different gene expressions.

Exploring the expression of TP53 using clinical parameters

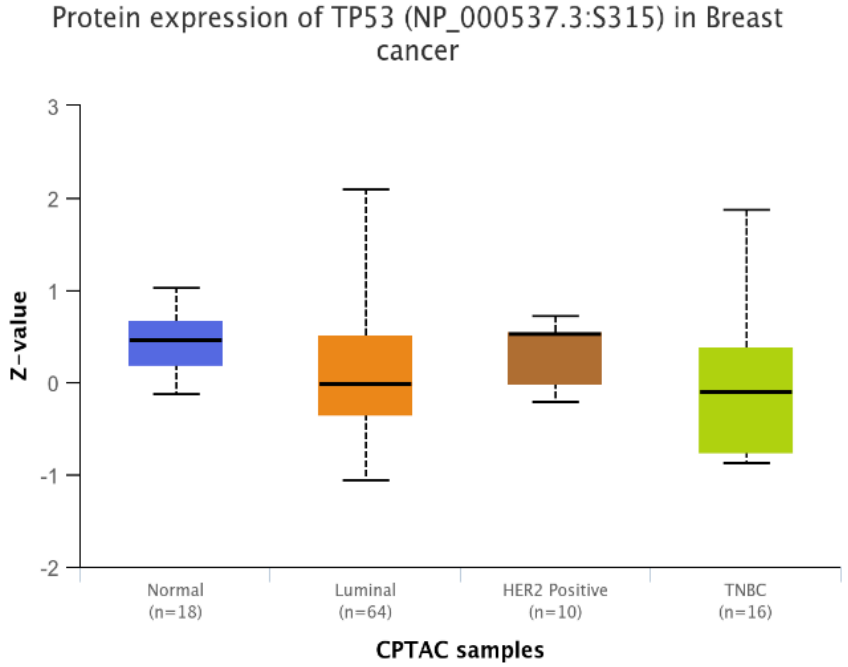
Furthermore, the UALCAN database was used to compare the expression of TP53 in different tissues comparing various clinical features (Chandrashekar et al., 2017, 2022). The results showed that expression of TP53 in the TNBC subtype was the highest in terms of expression in major subtypes with a significant statistical difference between the normal tissue and TNBC tissue (P value<0.05) [Fig.4(A)]. While luminal-like and HER2+ cancer had comparatively lower transcript expression, a statistically significant difference was also found in luminal-like cancer (Normal-vs-Luminal). However, in the TP53 protein phosphorylated at serine 315 [Fig.4(B)], its expression among the cancer subtypes was almost similar in all cases.

Furthermore, when checked for their expression in major subclasses, genes like PSAT1 [Fig.4(E)], LCN2 [Fig.4(F)], S100A9, PROM1, MMP1, MMP7, etc. had the highest expression in the TNBC and HER2+ subtype as well. While many of them maintained minimal expression in luminal-like cancers and normal cells, they were seen to be upregulated in the very cancer subtypes that possessed the highest cases of p53 mutations, that is, HER2+ and TNBC (*Role of P53 in*

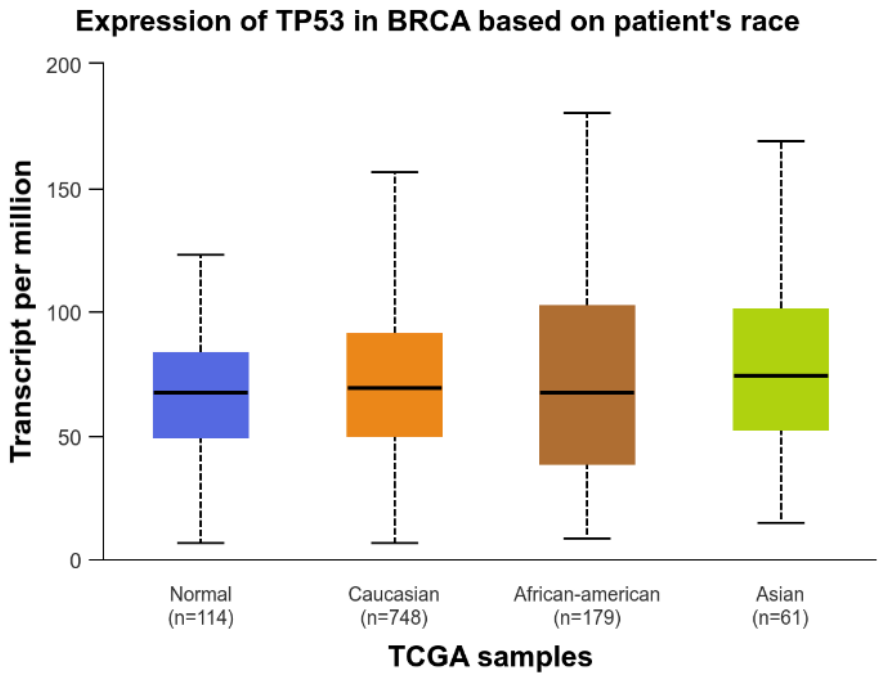
Breast Cancer Progression: An Insight into P53 Targeted Therapy, n.d.).



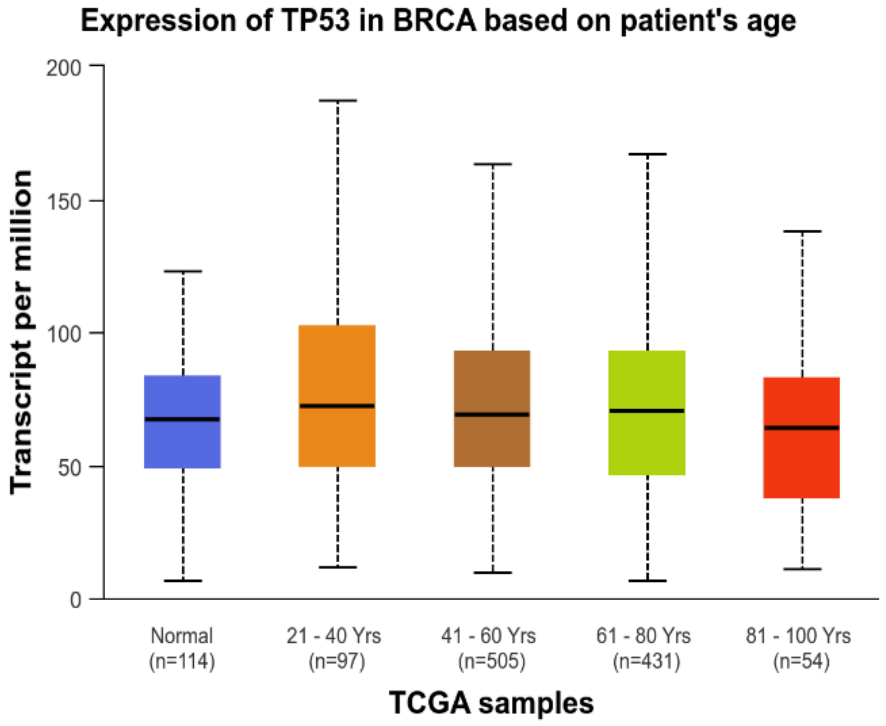
(A)



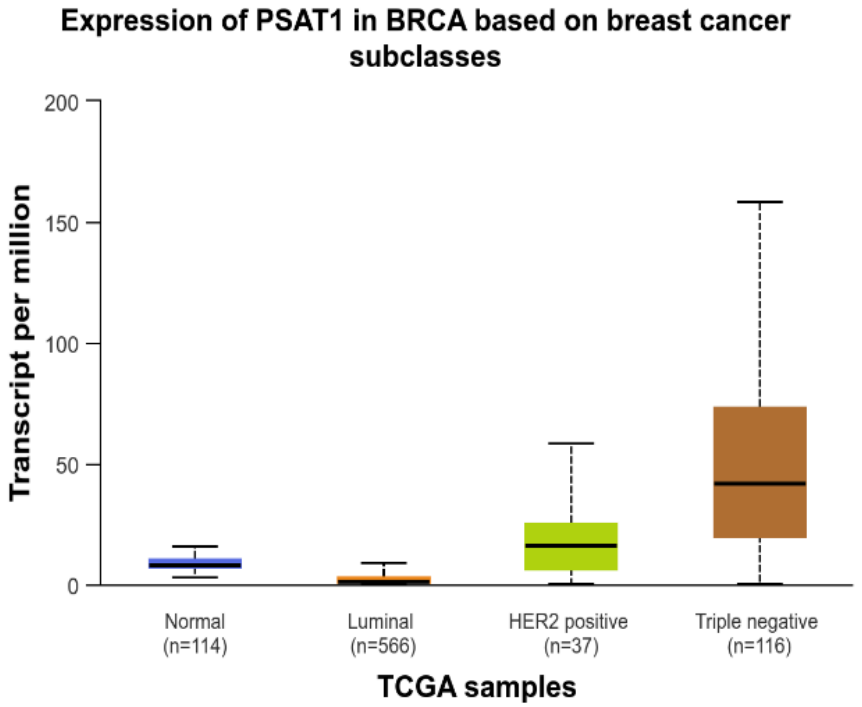
(B)


Expression of TP53 in BRCA based on patient's race
Transcript per million
200
150
100
50
0
Normal
(n=114)
Caucasian
(n=748)
African-american
(n=179)
Asian
(n=61)
TCGA samples

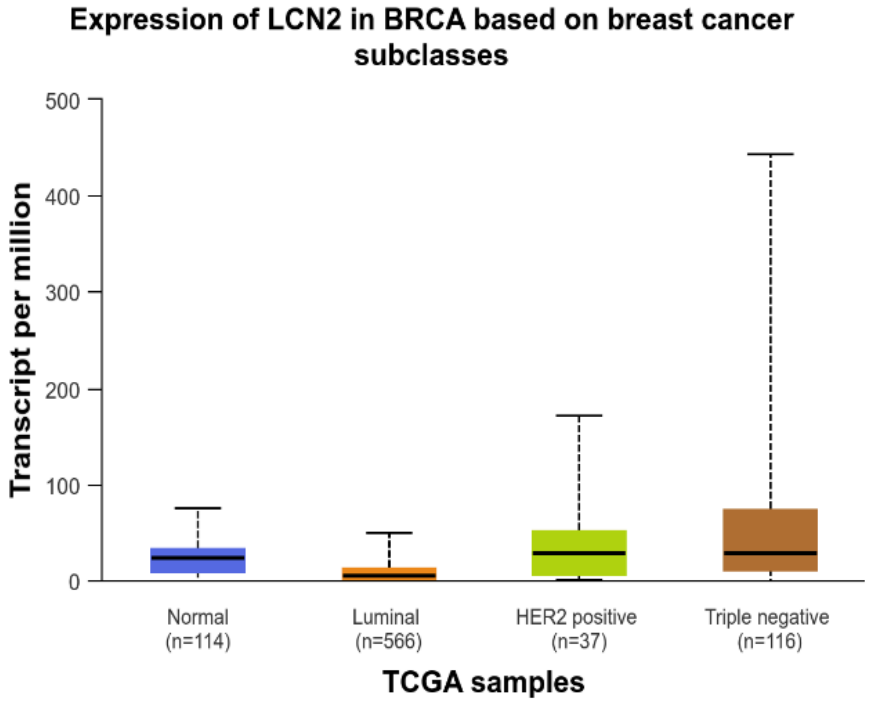
(C)


Expression of TP53 in BRCA based on patient's age
Transcript per million
200
150
100
50
0
Normal
(n=114)
21 - 40 Yrs
(n=97)
41 - 60 Yrs
(n=505)
61 - 80 Yrs
(n=431)
81 - 100 Yrs
(n=54)
TCGA samples

(D)



(E)



(F)

FIGURE 4. Obtained from UALCAN using TCGA and Proteomics data, these graphs (A-F) show the expression of concerned genes using different parameters. (A) shows expression of TP53 in BRCA based on breast cancer subclasses. (B) shows expression of phosphorylated p53 protein in breast cancer. (C) shows expression of TP53 in BRCA based on the patient's race. (D) shows expression of TP53 in BRCA based on the patient's age. (E) shows expression of PSAT1 in BRCA based on

breast cancer subclasses. (F) shows expression of LCN2 in BRCA based on breast cancer subclasses.

To further explore expression variance, the gene was queried using race as a clinical parameter [Fig.4(C)], and it was found that statistical differences were significant (P value<0.05) among all races (Normal-vs-Caucasian-vs-African American-vs-Asian). TP53 was found to be upregulated the most in African Americans followed by Asians [Fig.4(D)], although no significant differences between them were seen (African Americans-vs-Asians had a P value>0.05). Caucasians had the least expression of TP53 among the races.

Additionally, age too was used as a parameter. TP53 was upregulated the most in people between the age group of 21-40 years. The gene was downregulated only in people between the age group of 81-100 years.

Analysing the Drug Potential of p53

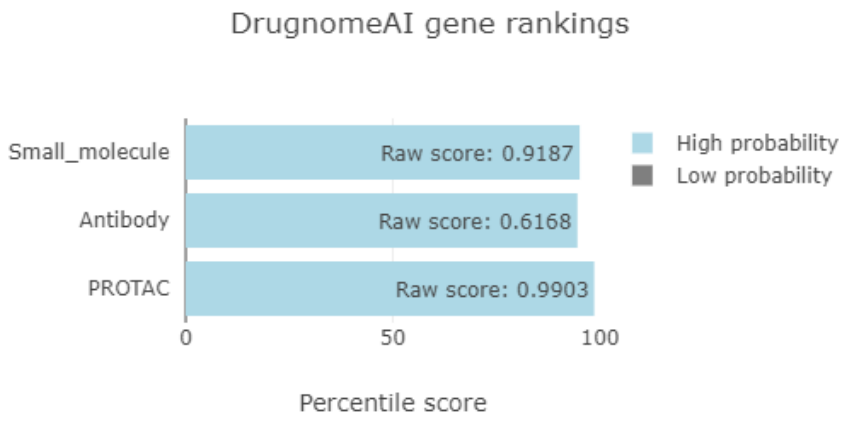


FIGURE 5. Generated using DrugnomeAI, this figure shows the highest rankings of possible drug types for the TP53 gene. This modality specific model was trained using druggable genes as examples, using one of the three modalities (Small molecule, antibody, and PROTAC).

DrugnomeAI (https://astrazeneca-cgr-publications.github.io/) was also used to analyse the scores of possible drug types in TP53 specific cancers (Fig.5) (Raies et al., 2022). The data showed that PROTACs (Proteolysis Targeting Chimeras) were the most probable drug type to develop, with a Raw score of 0.9903 as compared to scores of 0.9187 and 0.6168 for small molecules and Antibodies, respectively.

Furthermore, antibodies are seen to be the least efficient in curbing the action of p53 in these cancers. Although TP53 remains undruggable to date(Hassin & Oren, 2023), PROTACs appears to be a promising strategy.

When run through for possible drug types for the above mentioned over-expressed oncogenes, a variety of results were seen. However, a majority of them, including genes like S100A9, MMP1, MMP7, and PROM1 were found to have the highest Raw score for Antibodies, while PSAT1 and LCN2 showed low probabilities for all of the proposed modalities (drug types).

Discussion

The evolutionarily conserved p53 protein belongs to the tumour suppressors family which consists of the transcriptional genes TP53,TP63, and TP73 (Levine, 2020). The p53 protein is widely known as the 'Guardian of the Genome', particularly because of its ability to induce cell cycle arrest in response to DNA damage. This therefore, allows time for DNA repair genes to fix the damage. In the event that the repair fails, p53 accumulates, leading to apoptosis (Lane, 1992). This thereby ensures the integrity of the genome by preventing the spread of oncogenic mutations in the daughter cells (Zhu et al., 2020). However, p53, being the most frequently mutated gene in cancer, upon getting altered, not only loses its existing 'guardian of the genome' functions but also gains several new functions that help it promote tumour formation (Yue et al., 2017). These include accelerating cell proliferation, inducing genetic instability, promoting metastasis, and modifying metabolism, among many others (Zhang et al., 2020; Zhu et al., 2020).

The high levels of TP53's countenance (>80%) in Invasive Ductal Carcinoma (see Fig.1) suggest gain-of-function mutations in the gene and a detour from its normal tumour suppressive functions, which seem critical for tumour survival. Under normal conditions, wtp53 levels are maintained by an E3 ubiquitin ligase MDM2 that binds to the protein and degrades it through ubiquitination. MDM2, being a p53-regulated gene, thus forms a negative feedback loop with p53(Yue et al., 2017). Owing to this ubiquitin ligase, the p53 protein in normal cells has a half-life, ranging from 6 to 40 minutes (Levine, 2020). However, these mutations in p53 are speculated to reduce the induction of MDM2 and inhibit p53-MDM2 binding, therefore preventing its proteasomal degradation, helping the new oncogene-like p53 protein continue to promote metastasis with the help of its newly acquired functions (Yue et al., 2017). This could be one way in which GOF p53 interacts with other such genes to decelerate its degradation. Since most of the IDC tumours are TNBC or basal-like tumours(cancer, n.d.), they are characterised by low prognosis and increased aggressiveness (*Role of P53 in Breast Cancer Progression: An Insight into P53 Targeted Therapy*, n.d.), implying escalated accumulation of mtp53 in tumour cells. Again, TNBC was seen to have the highest expression of TP53 (Fig.4), which contributes to its high invasiveness and poor prognosis (Yin et al., 2020). Fig.2 also displays TP53's essentiality in Breast Invasive Ductal Carcinoma.

Also, the genes found to be expressed in higher numbers in mtp53 BRCA have been known to play an important role in oncogenesis and

tumour promotion. The PSAT1 gene, for instance, provides anabolic and energy support to the tumour cells (Yang et al., 2023), and the LCN2 gene facilitates cell proliferation, apoptosis, invasion, migration, angiogenesis and immune regulation in breast cancer (Bao et al., 2024), and the S100A9 gene contributes to tumour development, growth, and metastasis by interfering with the tumour metabolism and the microenvironment (Chen et al., 2023)**.** PPI databases show that wtp53 does not form any important interactions with these genes (Szklarczyk et al., 2015; Warde-Farley et al., 2010).

A literature search further yielded more information on p53's transcriptional role among these genes. For instance, the S100A9 gene is seen to possess several p53BS (p53-binding sites) that accommodate p53 DNA-binding activity. Li et al. also demonstrated that S100A9 is a p53 target gene that induces partly p53-dependent cellular apoptosis (Li et al., 2009). The S100A9 gene belonging to the calcium-binding S100 gene family has been found to act like a tumour suppressor in some cancers and like a promoter in others (Salama et al., 2008). Its overexpression, however, in the case of mtp53 BRCA implies its role to be that of the latter. To add to this, MMP1 is also regulated by p53, and its dysregulation is seen to promote tumour metastasis (Kurnia et al., 2022). Interestingly, PSAT1 was identified to be interacting with the $p53^{72P}$ protein, which is a single nucleotide polymorphism (SNP) of the codon 72 variants of p53 (Jiang et al., 2023). The pre-existing association of these genes with p53 puts forth the possibility of their deregulation and over-expression in BRCA to being brought about by mtp53. Thus, it is suggested that mtp53 may activate the transcription of these genes in a bid to promote tumour survival.

Further, clinical parameters were used on the UALCAN database to investigate variations in TP53 expression. TP53 was once again found to be expressed highly in TNBC and HER2+ subtypes. However, upon getting phosphorylated by a kinase, TP53 (NP000537.3: S315) didn't maintain significant expression in any of the BRCA subtypes. This suggests that through a change in the structure of the p53 protein, phosphorylated TP53 may help stabilize and reinforce its tumour suppressive functions which may not aid tumorigenesis, but certainly prevent it (Ashcroft et al., 1999). While people of all races had significant statistical differences, the expression of TP53 was somewhat higher in African-Americans. Additionally, women of the age groups 21-40 years showed the highest expression of TP53. Most of these women could possibly have possessed germline p53 mutations that conferred a higher risk of breast cancer development. Moreover, given their age, they mainly would have had ER+PR+ tumours that required high levels of oestrogen and progesterone to develop, something that would have been abundantly present during adolescence and early adulthood (Levine, 2020, p. 800).

Therefore, tumour suppressor wtp53 upon getting mutated, may form interactions and pathways with proto-oncogenes and oncogenes to activate their tumorigenic functions. Hence, studying these hypothetical pathways could provide a detailed and deeper understanding of the workings of mtp53. Also, it may provide insights

into what makes TNBC cancers so highly invasive with such a poor prognosis. Furthermore, if found to exist, these pathways could set the stage for future therapeutic targets and specific drugs that may target these pathways. New strategies may include targeting these involved genes and inhibiting their action in cancer cells. PROTACS may also be harnessed to carry out the destruction of mtp53. PROTACS, by targeting and binding to proteins, inhibits their biological function and induces proteasomal degradation of the protein (Liu et al., 2022). Since p53 does not possess typical drug target features (Hassin & Oren, 2023) and lacks the required deep grooves and active pockets in its structure for small molecules to occupy, compounds such as PROTACS could be synthesized for the degradation of this mutant protein and disrupt the transcription of downstream oncogenes effectively.

However, these assumptions were brought about with the help of bioinformatics platforms and online analysis tools. A lack of experimental evidence has led to uncertainties in the data. Further, there is the possibility that certain variables outside the control of the developer may have affected the results. Therefore, clinical patient tissue could be used to test the mRNA and protein expression of TP53 in tumour and normal cells. Further, experiments could be carried out to identify the potential interactions of TP53 with the other specified genes.

Conclusion

Seemingly innocent tumour suppressive p53's oncogenic behaviour upon getting mutated is something that has fascinated researchers ever since it was first demonstrated by Dittmer et. al in 1993(Zhang et al., 2020). This bioinformatics study aimed to understand the mechanism of gain-of-function in mutant p53 and its transcriptional interactions with downstream genes. p53 was found to be upregulated in several cancers, including breast cancer. Further, TNBC held the highest expression of p53, suggesting mutations and possible gain-of-function in the gene. Several genes with oncogenic properties were over-expressed in BRCA with p53 mutations, many of which were regulated and activated by p53. Again, these genes were expressed in greater numbers in TNBC and HER2+ breast cancers, the very cancers harbouring the greatest p53 mutations. Therefore, a deeper study into the interactions of mtp53 with these genes is encouraged. If found to exist, they could possibly shed light on previously unknown novel dependencies and therapeutic weak spots, which could be diagnosed as drug targets along with mtp53. Since expression of p53 was highest in African-Americans and in young adults (21-40 years), understanding the mechanism of mtp53 is crucial for their prognosis.

Acknowledgements

I would like to thank the Cambridge Centre for International Research (CCIR) academics team for evaluating and fool-proofing this paper. I

would also like to thank Dr Begum Akman-Tuncer, PhD, Department of Pharmacology and Dr Taner Tuncer, PhD, Department of Molecular Biology, from the University of Cambridge for their invaluable advice and support in writing and reviewing this paper.

References

Ashcroft, M., Kubbutat, M. H., & Vousden, K. H. (1999). Regulation of p53 function and stability by phosphorylation. *Molecular and Cellular Biology*, *19*(3), 1751–1758. https://doi.org/10.1128/MCB.19.3.1751

Bao, Y., Yan, Z., Shi, N., Tian, X., Li, J., Li, T., Cheng, X., & Lv, J. (2024). LCN2: Versatile players in breast cancer. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *171*, 116091. https://doi.org/10.1016/j.biopha.2023.116091

Bertheau, P., Lehmann-Che, J., Varna, M., Dumay, A., Poirot, B., Porcher, R., Turpin, E., Plassa, L.-F., de Roquancourt, A., Bourstyn, E., de Cremoux, P., Janin, A., Giacchetti, S., Espié, M., & de Thé, H. (2013). P53 in breast cancer subtypes and new insights into response to chemotherapy. *The Breast*, *22*, S27–S29. https://doi.org/10.1016/j.breast.2013.07.005

cancer, C. C. S. / S. canadienne du. (n.d.). *Triple-negative and basal-like breast cancers*. Retrieved February 4, 2024, from https://cancer.ca/en/cancer-information/cancer-types/breast/what-is-breast-cancer/cancerous-tumours/triple-negative-breast-cancer

Cancer Genome Atlas Network. (2012). Comprehensive molecular portraits of human breast tumours. *Nature*, *490*(7418), 61–70. https://doi.org/10.1038/nature11412

Cerami, E., Gao, J., Dogrusoz, U., Gross, B. E., Sumer, S. O., Aksoy, B. A., Jacobsen, A., Byrne, C. J., Heuer, M. L., Larsson, E., Antipin, Y., Reva, B., Goldberg, A. P., Sander, C., & Schultz, N. (2012). The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discovery*, *2*(5), 401–404. https://doi.org/10.1158/2159-8290.CD-12-0095

Chandrashekar, D. S., Bashel, B., Balasubramanya, S. A. H., Creighton, C. J., Ponce-Rodriguez, I., Chakravarthi, B. V. S. K., & Varambally, S. (2017). UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. *Neoplasia (New York, N.Y.)*, *19*(8), 649–658. https://doi.org/10.1016/j.neo.2017.05.002

Chandrashekar, D. S., Karthikeyan, S. K., Korla, P. K., Patel, H., Shovon, A. R., Athar, M., Netto, G. J., Qin, Z. S., Kumar, S., Manne, U., Creighton, C. J., & Varambally, S. (2022). UALCAN: An update to the integrated cancer data analysis platform. *Neoplasia (New York, N.Y.)*, *25*, 18–27. https://doi.org/10.1016/j.neo.2022.01.001

Chen, Y., Ouyang, Y., Li, Z., Wang, X., & Ma, J. (2023). S100A8 and S100A9 in Cancer. *Biochimica Et Biophysica Acta. Reviews on Cancer*, *1878*(3), 188891. https://doi.org/10.1016/j.bbcan.2023.188891

de Bruijn, I., Kundra, R., Mastrogiacomo, B., Tran, T. N., Sikina, L., Mazor, T., Li, X., Ochoa, A., Zhao, G., Lai, B., Abeshouse, A., Baiceanu, D., Ciftci, E., Dogrusoz, U., Dufilie, A., Erkoc, Z., Garcia Lara, E., Fu, Z., Gross, B., … Schultz, N. (2023). Analysis and Visualization of Longitudinal Genomic and Clinical Data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. *Cancer Research*, *83*(23), 3861–3867. https://doi.org/10.1158/0008-5472.CAN-23-0816

Gao, J., Aksoy, B. A., Dogrusoz, U., Dresdner, G., Gross, B., Sumer, S. O., Sun, Y., Jacobsen, A., Sinha, R., Larsson, E., Cerami, E., Sander, C., & Schultz, N. (2013). Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Science Signaling*, *6*(269), pl1. https://doi.org/10.1126/scisignal.2004088

Hassin, O., & Oren, M. (2023). Drugging p53 in cancer: One protein, many targets. *Nature Reviews. Drug Discovery*, *22*(2), 127–144. https://doi.org/10.1038/s41573-022-00571-8

Jiang, J., Chen, H.-N., Jin, P., Zhou, L., Peng, L., Huang, Z., Qin, S., Li, B., Ming, H., Luo, M., Xie, N., Gao, W., Nice, E. C., Yu, Q., & Huang, C. (2023). Targeting PSAT1 to mitigate metastasis in tumors with p53-72Pro variant. *Signal Transduction and Targeted Therapy*, *8*(1), 65. https://doi.org/10.1038/s41392-022-01266-7

Kennedy, M. C., & Lowe, S. W. (2022). Mutant p53: It's not all one and the same. *Cell Death and Differentiation*, *29*(5), 983–987. https://doi.org/10.1038/s41418-022-00989-y

Kent, W. J., Sugnet, C. W., Furey, T. S., Roskin, K. M., Pringle, T. H., Zahler, A. M., & Haussler, D. (2002). The human genome browser at UCSC. *Genome Research*, *12*(6), 996–1006. https://doi.org/10.1101/gr.229102

Kurnia, I., Rauf, S., Hatta, M., Arifuddin, S., Hidayat, Y. M., Natzir, R., Kaelan, C., Bukhari, A., Pelupessy, N. U., & Patelonggi, I. J. (2022). Molecular Patho-mechanisms of cervical cancer (MMP1). *Annals of Medicine and Surgery (2012)*, *77*, 103415. https://doi.org/10.1016/j.amsu.2022.103415

Lane, D. P. (1992). Cancer. P53, guardian of the genome. *Nature*, *358*(6381), 15–16. https://doi.org/10.1038/358015a0

Levine, A. J. (2020). p53: 800 million years of evolution and 40 years of discovery. *Nature Reviews. Cancer*, *20*(8), 471–480. https://doi.org/10.1038/s41568-020-0262-1

Li, C., Chen, H., Ding, F., Zhang, Y., Luo, A., Wang, M., & Liu, Z. (2009). A novel p53 target gene, S100A9, induces p53-dependent cellular apoptosis and mediates the p53 apoptosis pathway. *The Biochemical Journal*, *422*(2), 363–372. https://doi.org/10.1042/BJ20090465

Liu, Z., Hu, M., Yang, Y., Du, C., Zhou, H., Liu, C., Chen, Y., Fan, L., Ma, H., Gong, Y., & Xie, Y. (2022). An overview of PROTACs: A promising drug discovery paradigm. *Molecular Biomedicine*, *3*(1), 46. https://doi.org/10.1186/s43556-022-00112-0

Mattiuzzi, C., & Lippi, G. (2019). Current Cancer Epidemiology. *Journal of Epidemiology and Global Health*, *9*(4), 217–222. https://doi.org/10.2991/jegh.k.191008.001

Meyers, R. M., Bryan, J. G., McFarland, J. M., Weir, B. A., Sizemore, A. E., Xu, H., Dharia, N. V., Montgomery, P. G., Cowley, G. S., Pantel, S., Goodale, A., Lee, Y., Ali, L. D., Jiang, G., Lubonja, R., Harrington, W. F., Strickland, M., Wu, T., Hawes, D. C., … Tsherniak, A. (2017). Computational correction of copy number effect improves specificity of CRISPR-Cas9 essentiality screens in cancer cells. *Nature Genetics*, *49*(12), 1779–1784. https://doi.org/10.1038/ng.3984

Orrantia-Borunda, E., Anchondo-Nuñez, P., Acuña-Aguilar, L. E., Gómez-Valles, F. O., & Ramírez-Valdespino, C. A. (2022). *Subtypes of Breast Cancer* (H. N. Mayrovitz, Ed.). Exon Publications. http://www.ncbi.nlm.nih.gov/books/NBK583808/

Raies, A., Tulodziecka, E., Stainer, J., Middleton, L., Dhindsa, R. S., Hill, P., Engkvist, O., Harper, A. R., Petrovski, S., & Vitsios, D. (2022). DrugnomeAI is an ensemble machine-learning framework for predicting druggability of candidate drug targets. *Communications Biology*, *5*(1), 1291. https://doi.org/10.1038/s42003-022-04245-4

Role of p53 in breast cancer progression: An insight into p53 targeted therapy. (n.d.). Retrieved January 12, 2024, from https://www.thno.org/v13p1421.pdf

Salama, I., Malone, P. S., Mihaimeed, F., & Jones, J. L. (2008). A review of the S100 proteins in cancer. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*, *34*(4), 357–364. https://doi.org/10.1016/j.ejso.2007.04.009

Sondka, Z., Dhir, N. B., Carvalho-Silva, D., Jupe, S., Madhumita, null, McLaren, K., Starkey, M., Ward, S., Wilding, J., Ahmed, M., Argasinska, J., Beare, D., Chawla, M. S., Duke, S., Fasanella, I., Neogi, A. G., Haller, S., Hetenyi, B., Hodges, L., … Teague, J. (2024). COSMIC: A curated database of somatic variants and clinical data for cancer. *Nucleic Acids Research*, *52*(D1), D1210–D1217. https://doi.org/10.1093/nar/gkad986

Survival Outcomes by TP53 Mutation Status in Metastatic Breast Cancer: Funda-Meric Bernstam. (n.d.). Retrieved January 27, 2024, from https://ascopubs.org/doi/pdfdirect/10.1200/PO.17.00245

Szklarczyk, D., Franceschini, A., Wyder, S., Forslund, K., Heller, D., Huerta-Cepas, J., Simonovic, M., Roth, A., Santos, A., Tsafou, K. P., Kuhn, M., Bork, P., Jensen, L. J., & von Mering, C. (2015). STRING v10: Protein-protein interaction networks,

integrated over the tree of life. *Nucleic Acids Research*, *43*(Database issue), D447-452. https://doi.org/10.1093/nar/gku1003

Tang, Z., Li, C., Kang, B., Gao, G., Li, C., & Zhang, Z. (2017). GEPIA: A web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Research*, *45*(W1), W98–W102. https://doi.org/10.1093/nar/gkx247

Warde-Farley, D., Donaldson, S. L., Comes, O., Zuberi, K., Badrawi, R., Chao, P., Franz, M., Grouios, C., Kazi, F., Lopes, C. T., Maitland, A., Mostafavi, S., Montojo, J., Shao, Q., Wright, G., Bader, G. D., & Morris, Q. (2010). The GeneMANIA prediction server: Biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Research*, *38*(Web Server issue), W214-220. https://doi.org/10.1093/nar/gkq537

Yang, X., Li, C., & Chen, Y. (2023). Phosphoserine Aminotransferase 1: A Metabolic Enzyme Target of Cancers. *Current Cancer Drug Targets*, *23*(3), 171–186. https://doi.org/10.2174/1568009622666220829105300

Yin, L., Duan, J.-J., Bian, X.-W., & Yu, S.-C. (2020). Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Research: BCR*, *22*(1), 61. https://doi.org/10.1186/s13058-020-01296-5

Yue, X., Zhao, Y., Xu, Y., Zheng, M., Feng, Z., & Hu, W. (2017). Mutant p53 in Cancer: Accumulation, Gain-of-Function, and Therapy. *Journal of Molecular Biology*, *429*(11), 1595–1606. https://doi.org/10.1016/j.jmb.2017.03.030

Zehir, A., Benayed, R., Shah, R. H., Syed, A., Middha, S., Kim, H. R., Srinivasan, P., Gao, J., Chakravarty, D., Devlin, S. M., Hellmann, M. D., Barron, D. A., Schram, A. M., Hameed, M., Dogan, S., Ross, D. S., Hechtman, J. F., DeLair, D. F., Yao, J., … Berger, M. F. (2017). Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nature Medicine*, *23*(6), 703–713. https://doi.org/10.1038/nm.4333

Zhang, C., Liu, J., Xu, D., Zhang, T., Hu, W., & Feng, Z. (2020). Gain-of-function mutant p53 in cancer progression and therapy. *Journal of Molecular Cell Biology*, *12*(9), 674–687. https://doi.org/10.1093/jmcb/mjaa040

Zhu, G., Pan, C., Bei, J.-X., Li, B., Liang, C., Xu, Y., & Fu, X. (2020). Mutant p53 in Cancer Progression and Targeted Therapies. *Frontiers in Oncology*, *10*, 595187. https://doi.org/10.3389/fonc.2020.595187