Impact of TP53 mutations in Triple Negative Breast Cancer

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Identifying triple negative breast cancer (TNBC) patients expected to have poor outcomes provides an opportunity to enhance clinical management. We applied an Evolutionary Action Score to functionally characterize TP53 mutations (EAp53) in 96 TNBC patients and observed that EAp53 stratification may identify TP53 mutations associated with worse outcomes. These findings merit further exploration in larger TNBC cohorts and in patients treated with neoadjuvant chemotherapy regimens.

npj Precision Oncology (2022) 6:64; https://doi.org/10.1038/s41698-022-00303-6

INTRODUCTION

Triple Negative Breast Cancer (TNBC) has typically been treated with anthracycline-based neoadjuvant chemotherapy (NACT), but about half such patients fail to achieve a pathologic complete response (pCR) at the time of surgery. The high prevalence (60%) of TP53 mutations (TP53mut) in TNBC makes it an attractive therapeutic target and marker to predict chemotherapy sensitivity, but the functional significance of individual TP53mut remains unclear. Mutational diversity suggests that not all TP53mut are equivalent and that alterations to specific protein domains will have differential effects on the gain-of-function oncogenic activity, including chemotherapy resistance.

The computational Evolutionary Action Score of TP53 coding variants (EAp53) offers an alternative approach to functionally characterizing TP53mut and predicting NACT response. EAp53 incorporates evolutionary variations to predict the impact of somatic mutations on likelihood of amino acid substitution and TP53 protein function. We report on the identity and prognostic value of TP53mut and EAp53 in a single institution cohort of patients with primary TNBC.

Among 96 patients enrolled in this study (MDACC Protocol #2011-0007), 55 (57%) had a TP53mut, the majority (76%) of which were missense mutations (TP53mis; Fig. 1a, Supplemental Table 1). Table 1 summarizes clinical characteristics by TP53mut status. Median follow-up was 6 years from diagnosis, with 21 observed deaths (22% of patients); 5-year overall survival (OS) rate was 82% and median OS was not reached. Nineteen patients (20%) had a documented local or distant recurrence of disease, and the 3-year recurrence-free survival (RFS) rate was 79%. Patients with TP53mut tumors had slightly lower RFS compared to those with TP53wt tumors at 77.9% [95%CI 64.4–86.8] vs. 80.0% [95%CI 64.4–89.5] at 3 years, respectively, and HR of 1.15 [95%CI 0.52–2.54, p = 0.726]. The inferior OS in TP53mut compared to TP53wt patients [81.3% [95%CI 68.0–89.5] vs. 90.0% [95%CI 75.5–96.1%]; HR 1.54 [95%CI 0.62–3.82], p = 0.351] was also non-significant.

Seven patients with TP53mut in a residue outside the DNA-binding domain (predominantly in the tetramerization domain, Fig. 1a) had markedly worse RFS (Fig. 1b; adjusted HR 3.17 [95%CI 0.98–10.22] vs. TP53wt, p = 0.054) and OS (Fig. 1a; adjusted HR 5.28 [95%CI 1.53–18.25] vs. TP53wt, p = 0.008), even when controlling for prognostic factors (i.e., age at diagnosis for RFS and clinical node positivity for RFS and OS). Survival estimates were similar in DNA-binding domain TP53mut and TP53wt patients (Fig. 1b, Supplemental Fig. 1A, B and Supplemental Table 2).

After applying the EAp53 algorithm, patients were placed into one of four groups: TP53wt (n = 41) were assigned a score of 0 (i.e., EAp53 0), patients with a nonsense mutation (TP53non, n = 13) had a score of 100 (i.e., EAp53 100), and the remaining patients with missense mutations were divided into two groups that maximized the difference in RFS: EAp53 1-69 (n = 6; 4 patients with TP53mut in the DNA-binding domain) and EAp53 70-99 (n = 36; all patients with TP53mut in the DNA-binding domain). Patients with EAp53 1-69 had significantly worse RFS (50% [95%CI 11.1%–80.4%]; HR 4.17 [95%CI 1.41–12.31], p = 0.010) than those with EAp53 0 (80% [95%CI 64.0%–89.5%]).

Among patients receiving NACT, there was little difference in RFS when comparing EAp53 0 to EAp53 70-99 (82.9% [95%CI 65.9%–91.9%]; HR 0.76 [95%CI 0.29–1.99], p = 0.571) and to EAp53 100 (76.9% [95%CI 44.2%–91.9%]; HR 1.18 [95%CI 0.37–3.78], p = 0.776) (Fig. 1c, Supplemental Table 2). As with RFS, OS for the EAp53 70-99 and EAp53 100 groups did not significantly differ from EAp53 0 (Supplemental Fig. 1C, Supplemental Table 2).

Among patients receiving NACT (n = 68), 25 (37%) achieved a pCR, and 43 (63%) had residual disease (Supplemental Table 3). Regardless of TP53mut status at TNBC diagnosis, patients achieving pCR after NACT had excellent outcomes, with 100% RFS at 3 years post-surgery (Fig. 1d). The lone significant predictor of pCR was clinical ≥N1 stage (odds ratio 0.30 [95%CI 0.10–0.83], p = 0.022); however, a noteworthy difference in pCR rates was observed between EAp53 groups, with 48% achieving pCR (12 of 25 patients) for EAp53 70-99, 45% (5 of 11) for EAp53 100, 31% pCR (8 of 26) for EAp53 0, and 0% pCR (0 of 6) for EAp53 1-69.

Among the 43 patients who failed to achieve a pCR after NACT, those with TP53mut tumors had inferior RFS (56.0% [95%CI...
34.8%–72.7%; HR 2.14 [95%CI 0.82–5.61], \( p = 0.120 \) compared to the TP53wt group (77.8% [95%CI 51.1%–91.0%]) (Fig. 1e, Supplemental Table 4). If the TP53mut occurred outside the protein’s DNA-binding domain (\( n = 4 \) non-pCR patients), RFS was significantly worse (25.0% [95%CI 0.9%–66.5%]; HR 6.97 [95%CI 1.93–25.10], \( p = 0.003 \)) than TP53wt. Among non-responding patients, estimated RFS was longest for EAp53 0 (TP53wt), and shortest for EAp53 1-69 (50.0% [95%CI 1.93–25.10], \( p = 0.003 \)) and for EAS 100 (50.0% [95%CI 11.1%–80.4%]; HR 3.14 [95%CI 0.88–11.26] vs. TP53wt, \( p = 0.079 \)) (Supplemental Table 4).

Understanding the functional impact of TP53 mutations on treatment response and outcomes remains an elusive topic in cancer research and an area of active investigation. In this study, the small group of patients harboring a missense mutation with EAp53 1-69 had the lowest pCR rate and shortest RFS and OS. The six specific mutations (listed in Supplemental Table 1) are uncommon in breast cancer, each occurring in <0.05% of cases according to the cBioPortal public data repository (24 studies comprising >10,000 cases, accessed 4-12-2022). Moreover, their functional significance remains largely unknown. The A161T mutation within the DNA-binding domain attenuates...
Table 1. Clinicopathological characteristics by p53 mutational status.

| Clinical Characteristics | TP53 wild type (n = 41), N (%) or Value | TP53 mutant (n = 55), N (%) or Value | p  |
|--------------------------|-----------------------------------------|--------------------------------------|----|
| Age at diagnosis          |                                         |                                      |    |
| median (IQR)              | 56 (50–64)                              | 55 (46–62)                           | 0.147 |
| range                     | 30–83                                   | 21–79                                | 0.147 |
| Age at diagnosis (binary) |                                         |                                      | 0.147 |
| <50 years                 | 10 (24%)                                | n = 20 (36%)                        | 0.268 |
| ≥50 years                 | 31 (76%)                                | n = 35 (64%)                        | 0.268 |
| Race                      |                                         |                                      |    |
| White                     | 26 (63%)                                | 33 (60%)                             | 0.966 |
| Black                     | 7 (17%)                                 | 11 (20%)                             | 0.966 |
| Hispanic                  | 6 (15%)                                 | 7 (13%)                              | 0.966 |
| Asian                     | 2 (5%)                                  | 3 (5%)                               | 0.966 |
| na                        |                                        | 1 (2%)                               | 0.966 |
| Laterality                |                                         |                                      |    |
| Left                      | 19 (46%)                                | 24 (44%)                             | 0.838 |
| Right                     | 22 (54%)                                | 31 (56%)                             | 0.838 |
| Tumor volume (cm³)        | median (IQR)                            | 15.1 (7.3–27.3)                     | 0.950 |
| range                     | 0.6–837.8                               | 0.8–594.0                            | 0.950 |
| Clinical T stage          |                                         |                                      |    |
| T1                        | 7 (17%)                                 | 10 (18%)                             | 0.307 |
| T2                        | 31 (76%)                                | 35 (64%)                             | 0.307 |
| T3/T4                     | 3 (7%)                                  | 10 (18%)                             | 0.307 |
| Clinical N stage          |                                         |                                      |    |
| N0                        | 23 (56%)                                | 32 (58%)                             | 0.921 |
| N1                        | 9 (22%)                                 | 13 (24%)                             | 0.921 |
| N2/N3                     | 9 (22%)                                 | 10 (18%)                             | 0.921 |
| TP53 expression (TPM)     | median (IQR)                            | 8.5 (4.5–17.9)                       | 0.009 |
| range                     | 2.1–95.8                                | 2.1–58.0                             | 0.009 |
| EAtp53 (RFS-optimal)      |                                         |                                      |    |
| 0                         | 41 (100%)                               | 0 (0%)                               | <0.001 |
| 1–69                      | 0 (0%)                                  | 6 (11%)                              | <0.001 |
| 70–99                     | 0 (0%)                                  | 36 (65%)                             | <0.001 |
| 100                       | 0 (0%)                                  | 13 (24%)                             | <0.001 |
| Diagnosis to NACT, months |                                         |                                      |    |
| Median (IQR)              | 1.4 (0.9–2.0)                           | 1.2 (0.9–1.9)                        | 0.715 |
| range                     | 0.1–7.7                                 | 0.5–4.6                              | 0.715 |
| Taxane therapy            |                                         |                                      |    |
| No                        | 11 (27%)                                | 9 (16%)                              | 0.310 |
| Yes                       | 30 (73%)                                | 46 (84%)                             | 0.310 |
| Anthracycline therapy     |                                         |                                      |    |
| No                        | 14 (34%)                                | 9 (16%)                              | 0.055 |
| Yes                       | 27 (66%)                                | 46 (84%)                             | 0.055 |
| Platinum therapy          |                                         |                                      |    |
| No                        | 39 (95%)                                | 49 (89%)                             | 0.460 |
| Yes                       | 2 (5%)                                  | 6 (11%)                              | 0.460 |
| Diagnosis to surgery, months |                                         |                                      |    |
| Median (IQR)              | 6.3 (1.9–7.5)                           | 6.8 (5.3–7.6)                        | 0.256 |
| range                     | 0.4–9.3                                 | 0.8–12.0                             | 0.256 |
| Path T stage              |                                         |                                      |    |
| T0/Tis                    | 9 (22%)                                 | 18 (33%)                             | 0.113 |
| T1                        | 11 (27%)                                | 19 (35%)                             | 0.113 |
| T2                        | 16 (39%)                                | 10 (18%)                             | 0.113 |
| T3                        | 3 (7%)                                  | 8 (15%)                              | 0.113 |
| na                        | 2 (5%)                                  | 0 (0%)                               | 0.113 |
| Path N stage              |                                         |                                      |    |
| N0                        | 28 (68%)                                | 39 (71%)                             | 0.298 |
| N1                        | 10 (24%)                                | 10 (18%)                             | 0.298 |

Table 1 continued

| Clinical Characteristics | TP53 wild type (n = 41), N (%) or Value | TP53 mutant (n = 55), N (%) or Value | p  |
|--------------------------|-----------------------------------------|--------------------------------------|----|
| N2/N3                    | 1 (2%)                                  | 6 (11%)                              | 0.012 |
| na                       | (5%)                                    | 0 (0%)                               | 0.012 |
| Path TNM stage           |                                         |                                      |    |
| 0                        | 8 (20%)                                 | 17 (31%)                             | 0.012 |
| I                        | 8 (20%)                                 | 15 (27%)                             | 0.012 |
| II                       | 22 (54%)                                | 14 (25%)                             | 0.012 |
| III                      | 1 (2%)                                  | 9 (16%)                              | 0.012 |
| na                       | 2 (5%)                                  | 0 (0%)                               | 0.012 |
| pCR after NACT           |                                         |                                      |    |
| Yes                      | 8 (20%)                                 | 17 (31%)                             | 0.451 |
| No                       | 18 (44%)                                | 25 (45%)                             | 0.451 |
| na                       | 15 (37%)                                | 13 (24%)                             | 0.451 |

IQR interquartile range, na not available, TPM transcripts per million, NACT neoadjuvant chemotherapy, pCR pathological complete response.

autophagy via mTOR and AMPK signaling, which is associated with resistance to anti-cancer therapy. The F270 position within the DNA-binding domain is important for stabilizing the beta-sandwich structure of the p53 protein, and mutation to leucine is predicted to be a druggable target for small molecules to stabilize this type of p53 mutant. Mutations at the R337 residue have a role in p53 methylation and ubiquitination, and R337L is thought to promote stability and sub-cellular localization of p53. One of the mutations in the EAp53 1-69 group is also present in our patient set) was associated with shorter RFS and OS. The majority (80%) of TP32 mutations occur within the DNA-binding domain. This single center study has several limitations, including a small sample size that led to wide confidence intervals and precluded us from validating our optimal EAp53 cut-point for missense mutations. Additionally, given the period during which our patients were treated, adjuvant capecitabine was not widely used for residual disease following NACT (non-pCR at the time of surgery), so the prognostic impact of adjuvant capecitabine, and its association with TP32 mutation status, could not be captured. Similarly, use of pembrolizumab, which is becoming more prevalent, is not captured. Nevertheless, the significance of any biological association remains to be determined, and further investigation may provide mechanistic insight into the poor outcomes observed in this study.

In this hypothesis-generating study, we identified two patient subsets (one defined by TP53mut location outside the DNA-binding domain and the other by TP53mis EAp53 1-69) demonstrating limited response to NACT and relatively high risk of disease recurrence and death. Our results also indicate that TP53mut corresponds with worse outcomes among patients with residual disease following NACT. These findings warrant further investigation.
investigation in larger cohorts and within therapeutic clinical trials that cover a range of neoadjuvant regimens, in order to determine the functional impact of TP53 mutations in TNBC; especially in light of promising therapies being developed to directly targeting TP53mut or indirectly targeting key components in the p53 signaling pathway.7,43–45.

METHODS

Patients

The TNBC patient cohort for this study consisted of 96 women treated at The University of Texas MD Anderson Cancer Center (MDACC) Breast Center between 2011 and 2016. The study was approved by the MDACC institutional review board (MDACC IRB #2011-0007). Written informed consent was obtained from all patients before enrollment. Patient demographics, tumor characteristics and treatment, surgical, pathological, and survival data were collected. TP53 mutational status was determined through RNA sequencing using Nanopore<sup>™</sup> spectrophotometer (concentration, 260:280 OD ratio) and an Agilent Bioanalyzer (RNA integrity number [RIN] and RNA 28 S:18 S ratio).

EAp53 Computation

Missense TP53 mutations were analyzed using the Evolutionary Action Scoring (EAS) System as previously described.15–18 This Scoring System is based on the hypothesis that protein evolution is a continuous and differentiable process between genotype and phenotype. Therefore, if the phenotype (φ) is a function of the genotype (γ), φ = f(γ), then a change in phenotype (Δφ) is equal to the scalar product of the gradient of the function (∇f) and the change in genotype (Δγ). When considering a single mutation from amino acid X to any other amino acid Y at sequence position i, the genotype perturbation reduces to the magnitude of that substitution, denoted Δγ<sub>X→Y</sub>, and is measured by the ranks of amino acid substitution odds; however, these odds are computed for different deciles of the evolutionary gradient at the substituted position. The gradient (γ) reduces to the partial derivative of the evolutionary fitness function for its<sup>th</sup> component, denoted ∂/∂γ<sub>i</sub>, and is measured by importance ranks of the Evolutionary Trace (ET) method<sup>21,22</sup>, according to which, residues that vary amongst homologous sequences are ranked less important than those that only vary amongst distant homologous sequences. This forms the equation: Δφ = ∂φ/∂γ<sub>i</sub>Δγ<sub>X→Y</sub>

The result of this equation is normalized to create percentile scores for TP53 protein; for example, an EAS of 68 implies that the impact is >68% of all possible amino acid substitutions in p53. TP53 missense mutations were given EAp53 percentile scores, with higher scores representing alterations that are more impactful, according to ET theory. Wild-type TP53 sequences were scored as zero as this is the normally functioning protein and nonsense mutations were assigned a score of 100 to account for a truncated, non-functional protein.

Statistical analysis

Patient, tumor, and treatment characteristics were summarized separately for TP53<sup>wt</sup> and TP53<sup>mut</sup> patients and compared across these groups using Fisher’s exact test (for categorical variables) or the Wilcoxon rank sum test (for continuous variables). Patients with a TP53 missense mutation (EAp53 1–99) were divided into 2 groups by applying an optimal cut-point that was identified as the EAp53 value that maximized the RFS log-rank test statistic for the resulting 2-group comparison. Therefore, creation of the EAp53 1-69 and 70-99 groups was a data-driven approach that (i) resulted in an RFS-optimized dichotomization of TP53mis patients and (ii) requires validation in an independent dataset. RFS and OS were measured from the date of TNBC diagnosis (if the predictor variables were known at this time) or the date of resection (e.g., for pCR status as the predictor), estimated with the Kaplan–Meier method, and compared with the log-rank test. All reported survival percentages pertain to 3 years post-diagnosis or post-surgery, depending on when the predictor variable was known. Cox proportional hazards regression models were fit to estimate hazard ratios (and compute Wald test p-values) that quantify the association between predictor variables and survival. An AIC-based backward elimination procedure was used to construct multivariable survival models from a set of predictors with univariable model p-values < 0.20. Associations between pre-treatment patient features and pCR were assessed with logistic regression. P-values < 0.05 were considered statistically significant and there was no adjustment for multiple tests (i.e., across univariable and different outcomes). Analyses were performed and survival plots were created using R version 4.1.0.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

Consented data that can be released are included in this article and supplementary files, or are deposited in the SageBionetworks’ Synapse Platform (www.synapse.org) under accession syn3362127. Patients were not consented for the release of underlying sequence data and are not publicly available, but may be made available upon reasonable request from the corresponding author, Dr. Zahi Mitri. Specifically, access to individual patient-level data, for non-commercial purposes only, can only be shared per specific institutional review board (IRB) requirements. Upon reasonable request by each respective author/institution, a data sharing agreement may be initiated between the interested parties and the clinical institution following institution-specific guidelines.

CODE AVAILABILITY

Statistical analyses was conducted using R (version 4.1.0), and is available upon request. EAS was determined using a publicly-available web-based tool: http://eaction.lichtenangelab.org/. Received: 17 December 2021; Accepted: 3 August 2022; Published online: 09 September 2022

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ACKNOWLEDGEMENTS

The data collection and analysis of this work was supported by an American Society for Clinical Oncology (ASCO) Conquer Cancer Foundation Young Investigator Award to Z.I.M. Thank you to Dr. Fraser Symmans for TP53 sequencing and pathological outcomes review of biospecimens, and Dr. Olivier Lichtarge for providing EAS analysis. We whole-heartedly express our thanks to Dr. Kenneth Hess, PhD for his valuable biostatistical contributions to this project before his passing.

AUTHOR CONTRIBUTIONS

Z.I.M., A.M.T., and S.L.M. designed the research. Z.I.M., S.M.G., A.K., A.M.T., and N.A. analyzed the data. Z.I.M., N.A., S.M.G., A.K., A.M.T., S.L.M., and E.A.H. wrote the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41698-020-02030-6.

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Published in partnership with The Hormel Institute, University of Minnesota npj Precision Oncology (2022) 64