p53 Codon 72 Polymorphism Predicts the Pathologic Response to Neoadjuvant Chemotherapy in Patients with Breast Cancer

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Abstract

Purpose: Recent studies have highlighted that the p53 codon 72 polymorphism plays a crucial role in modulating wild-type p53 apoptotic capacity, and as such may influence the response to chemotherapy. Thus, the purpose of this study was to investigate whether the p53 codon 72 polymorphism might influence pathologic response to neoadjuvant chemotherapy in primary breast cancer.

Experimental Design: One hundred and ten operable breast cancer patients received anthracycline-based neoadjuvant chemotherapy and p53 codon 72 polymorphism status was analyzed by PCR-RFLP.

Results: The distribution of initial clinical stage, tumor size, estrogen receptor or progesterone receptor status, menopausal status, or erbB2 expression was not significantly different among the polymorphic variants. However, we found that only 13% (3 of 23) of patients with the Pro/Pro variant had a good pathologic response, defined as a complete pathologic response or minimal residual disease. In comparison, 40% (22 of 55) or 37.5% (12 of 32) of patients with the Pro/Arg or Arg/Arg variant had a good pathologic response ($P = 0.019$). Moreover, patients with the Pro/Pro variant were more likely to have a positive axillary lymph node status than those with the Pro/Arg or Arg/Arg variant ($P = 0.007$). Furthermore, in multivariate analysis, p53 codon 72 polymorphism was found to be a strong predictor of pathologic response (odds ratio 6.7, 95% confidence interval, 1.4-31.2; $P = 0.016$).

Conclusion: Our study indicates that breast cancer patients with the Pro/Pro variant may be less sensitive to anthracycline-based treatment than those with the Pro/Arg or Arg/Arg variant and suggests that analysis of p53 codon 72 polymorphism may provide a simple predictive marker for selecting the right breast cancer patients to anthracycline-based neoadjuvant chemotherapy in clinical setting.

Neoadjuvant chemotherapy is a standard therapy for patients with locally advanced breast cancer and is increasingly used for early-stage operable disease. The main goal of neoadjuvant chemotherapy is to eliminate potential micrometastasis, thus improving disease-free survival (1). In clinical setting, ~70% of patients may achieve a clinical response to the treatment, with the remainder displaying varying levels of resistance (2). Despite numerous efforts on identifying suitable predictive markers, there is still a lack of accurate markers to discriminate between the patients who are likely to respond to neoadjuvant chemotherapy and those who are not.

Most anticancer agents, regardless of distinct mechanisms of action, ultimately kill cancer cells by inducing apoptosis (3, 4). p53 is a key transcription factor that participates in numerous homeostatic functions such as cell cycle checkpoint control, repair of DNA damage, and induction of the apoptosis (5). Codon 72 is a common polymorphism in *p53* gene; this polymorphism of the *p53* gene encodes either an arginine or a proline at the codon position 72 in the proline-rich domain. The proline-rich domain of *p53* has been shown to be an important component in the apoptotic function of *p53* (6). Several studies both *in vivo* and *in vitro* have recently highlighted the functional difference between the Pro^{72} and Arg^{72} variants, with the Arg^{72} form of wild-type p53 harboring a greater apoptosis-inducing potential than the Pro^{72} variant (6–8). These functional differences between the polymorphic variants may alter the tumor response to systemic chemotherapy by influencing the apoptotic capacity. Although a substantial number of studies have reported that p53 codon 72 polymorphism may affect cancer risk for particular tumor types (9, 10), few studies have investigated the predictive value of this important polymorphism for response to neoadjuvant chemotherapy in cancer patients.

One of advantages of neoadjuvant chemotherapy is that it allows us to observe the response of the primary tumors to the treatment; thus, neoadjuvant chemotherapy provides an ideal

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platform to identify predictive markers. The clinical response to neoadjuvant chemotherapy is commonly reported to be imprecise and not an accurate reflection of the pathologic response (11). Studies have indicated that patients who have a complete pathologic response in both primary tumor and axillary lymph nodes after neoadjuvant chemotherapy have a significant longer disease-free and overall survival (11, 12). In this study, our purpose was to investigate whether the p53 codon 72 polymorphism may influence the pathologic response to anthracycline-based neoadjuvant treatment in a large series of breast cancer patients.

Materials and Methods

Patients. From June 2003 to July 2004, 110 consecutive breast cancer patients with operable disease (stage I to III) were treated with anthracycline-based neoadjuvant treatment at Breast Center Peking University School of Oncology. The mean age was 49 years (range, 26-68 years). Seventy-seven patients were premenopausal and 33 patients were postmenopausal. The stage of the tumors was classified according to the tumor-node-metastasis classification of the Union Internationale Contre le Cancer. Tumor size was defined as the maximum tumor diameter measured on the mammogram and/or ultrasonogram at the time of diagnosis. Core-needle biopsy for pathologic diagnosis was done before the treatment. One hundred cases were identified as invasive ductal carcinoma, six cases were invasive lobular carcinoma, and four cases were invasive mucinous carcinoma. This study was approved by the ethics and research committee of Peking University of School Oncology.

Immunohistochemistry. Immunostaining was done as described elsewhere (13). The following panel of monoclonal antibodies was applied: antiestrogen receptor monoclonal antibody (clone 1D5, dilution 1:50; DAKO, Newcastle, United Kingdom); antiprogesterone receptor monoclonal antibody (clone 1A6, dilution 1:100; Novocastra, Carpinteria, CA); and anti-erbB2 monoclonal antibody (clone CB11, dilution 1:40; Zymed, San Francisco, CA). For estrogen receptor and progesterone receptor staining, cells were considered to be positive only when distinct nuclear staining was identified. Estrogen and progesterone receptors were considered positive when ≥10% of tumor cells showed positive staining. For erbB2 staining, only the membrane staining was considered as positive staining. The score for erbB2 staining was graded as follows: No staining or membrane staining observed in <10% of tumor cells was given a score 0; faint/barely perceptible membrane staining detected in >10% of tumor cells was scored as 1+; a moderate or strong complete membrane staining observed in >10% of tumor cells was graded 2+ or 3+, respectively. A score of 0 and 1+ was considered negative, whereas 2+ and 3+ were considered positive.

Treatment protocol. We conducted a clinical trial of CTF regimen (5-fluorouracil, pirarubicin, and cyclophosphamide) for patients with operable breast cancer; if a candidate patient refuse to enter the trial, the patient would receive an alternative anthracyclin-based regimen of either FEC (5-fluorouracil, epirubicin, and cyclophosphamide) or CAF (5-fluorouracil, doxorubicin, and cyclophosphamide). One hundred and ten patients received the following anthracycline-based neoadjuvant chemotherapy: CTF regimen was given to 89 patients, FEC regimen was used for 14 patients, whereas the remaining 7 patients were treated with CAF regimen. Continuous-infusion 5-fluorouracil (200 mg/m^2/d) was used in the three regimens. CTF regimen (cyclophosphamide 500 mg/m^2, pirarubicin 35 mg/m^2, on days 1 and 8, 28-day intervals for four cycles, or cyclophosphamide 600 mg/m^2, pirarubicin 40 mg/m^2, on day 1, 21-day interval for four or six cycles), FEC regimen (cyclophosphamide 600 mg/m^2, epirubicin 75 mg/m^2, on day 1, 21-day interval for four or six cycles), and CAF regimen (cyclophosphamide 600 mg/m^2, doxorubicin 50 mg/m^2, on day 1, 21-day interval for four or six cycles). The clinical oncologists were not aware of the p53 codon 72 polymorphism genotype when selecting a chemotherapy regimen for individual patients.

After completion of neoadjuvant therapy, patients received either breast-conserving surgery or modified radical mastectomy depending on the tumor size. A complete pathologic response was defined as no evidence of residual invasive disease in the breast and lymph nodes. Minimal residual disease was defined as invasive tumors measuring ≤1 cm in the breast and negative lymph nodes. Invasive tumors measuring >1 cm in the breast or any positive lymph node in the axilla, regardless of the size of residual disease in the breast, was considered extensive residual disease (2).

DNA extraction and genotyping. Blood samples were collected from each patient at the time of diagnosis, and genomic DNA was extracted from peripheral blood lymphocytes using phenol-chloroform extraction. p53 codon 72 genotypes were detected by using a PCR-RFLP technique. The following primers were used: forward primer 5′-TCCCCCTTGCCGTCCCAA-3′ and reverse primer 5′-CGTGCAAGTCACAGACTT-3′, as previously described by Storey et al. (10). PCR was done in 20 μL reaction mixture containing 100 ng of genomic DNA template, 2 μL 10× PCR buffer, 0.8 mmol/L deoxynucleotide triphosphate, 2.5 mmol/L $MgCl_2$, 0.5 μmol/L primers, and 1 unit AmpliTaq DNA polymerase (Promega, Madison, MI). The reaction condition used were initial denaturation at 94°C for 2 minutes, followed by 35 step cycles of denaturation at 94°C for 30 seconds, annealing 60°C for 45 seconds, and extension 72°C for 30 seconds followed by a terminal extension time of 10 minutes. Ten microliters of PCR product were digested with *Bst*U1 restriction enzyme (New England Biolabs, Inc.) for 2 hours at 60°C. The digestion products were then resolved on a 2.5% agarose gel containing ethidium bromide. The Pro/Pro variant was identified by a single band (279 bp), the Arg/Arg variant produced two bands (160 bp and 119 bp), and heterozygous Pro/Arg variant displayed three bands (279, 160, and 119 bp; Fig. 1).

Statistical analysis. The correlation between p53 codon 72 polymorphic variants and clinicopathologic characteristics or pathologic response was done using Pearson's χ^2 test. In univariate analysis,

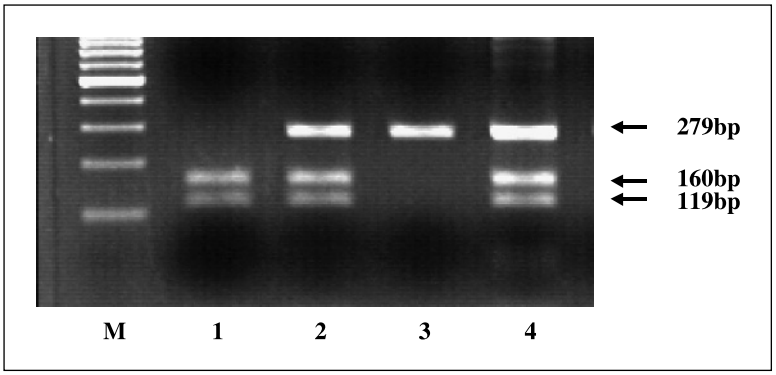

Fig. 1. Detection of the codon 72 polymorphism by PCR-RFLP. M, 100 bp ladder; lane 1, Arg/Arg homozygous genotype (160 and 119 bp); lanes 2 and 4, Pro/Arg heterozygous genotype (279 bp, 160 and 119 bp); lane 3, Pro/Pro homozygous genotype (279 bp).

Table 1. The correlation between the p53 codon 72 polymorphic variants and pretreatment patient characteristics or treatment regimens

	Total (*n*)	Pro/Pro, *n* (%)	Pro/Arg, *n* (%)	Arg/Arg, *n* (%)	*P*
Chemotherapy regimens					
FEC	14	5 (21.7)	5 (9.1)	4 (12.5)	0.277
CAF	7	2 (8.7)	3 (5.5)	2 (6.3)	
CTF	89	16 (69.6)	47 (85.4)	26 (81.2)	
Menopausal status					0.959
Premenopausal	77	16 (69.6)	38 (69.1)	23 (71.9)	
Postmenopausal	33	7 (30.4)	17 (30.9)	9 (28.1)	
ER status					0.904
Positive	72	15 (68.2)	39 (76.5)	18 (58.1)	
Negative	32	7 (31.8)	12 (23.5)	13 (41.9)	
ND	6	1	4	1	
PR status					0.411
Positive	60	11 (50.0)	33 (64.7)	16 (51.6)	
Negative	44	11 (50.0)	18 (35.3)	15 (48.4)	
ND	6	1	4	1	
erbB2 status					0.114
Positive	46	13 (59.1)	17 (32.7)	16 (53.3)	
Negative	58	9 (40.9)	35 (67.3)	14 (46.7)	
ND	6	1	3	2	
Clinical stage					0.828
I	24	5 (21.7)	13 (23.6)	6 (18.8)	
I	65	13 (56.6)	32 (58.2)	20 (62.4)	
III	21	5 (21.7)	10 (18.2)	6 (18.8)	
Tumor size (cm)					0.756
<3	70	14 (60.9)	35 (63.6)	21 (65.6)	
≥3	40	9 (39.1)	20 (36.4)	11 (34.4)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; ND, nondetection.

Pearson's χ^2 test was also done to evaluate the correlation between the clinicopathologic characteristics and the pathologic response. Two-sided $P < 0.05$ were considered as statistically significant. In multivariate analysis, a logistic regression model was applied to identify the independent predictors associated with pathologic response. Characteristics significantly or marginally associated with pathologic response in the univariate analysis were included in the multivariate analysis. A forward stepwise selection was done, with an inclusion criterion of $P \leq 0.05$ and an exclusion of $P > 0.05$. All statistical analyses were done using SPSS 10.0 software.

Results

The association between p53 codon 72 polymorphic variants and clinicopathologic characteristics. A total of 110 patients were analyzed in this study, 21% (23 of 110) of the patients were homozygous for Pro/Pro variant, 50% (55 of 110) were heterozygous for Pro/Arg, and 29% (32 of 110) were homozygous for Arg/Arg variant. Furthermore, the association between the polymorphic variants and the clinicopathologic characteristics was carefully analyzed (Table 1). From Table 1, it was clearly shown that the distribution of initial clinical stage, tumor size, estrogen receptor or progesterone receptor status, menopausal status, or erbB2 expression was not significantly different among the polymorphic variants, indicating that the three-genotype groups had similar clinicopathologic characteristics before the neoadjuvant chemotherapy was applied; thus, the different pathologic response to the neoadjuvant chemotherapy in the three-genotype groups was not due to the potential effect of these clinicopathologic characteristics.

The association between the p53 codon 72 polymorphic variants and pathologic response. In this cohort of patients, 12 (11%) patients reached complete pathologic response, among them, one patient (4.3%) in the Pro/Pro group, six patients (10.9%)

Table 2. The correlation between p53 codon 72 polymorphic variants and pathologic response after neoadjuvant chemotherapy

Pathologic response	Total (*n*)	Pro/Pro, *n* (%)	Pro/Arg, *n* (%)	Arg/Arg, *n* (%)	*P**
ERD	73	20 (87.0)	33 (60.0)	20 (62.5)	0.019
MRD	25	2 } (13.0)	16 } (40.0)	7 } (37.5)	
pCR	12	1 }	6 }	5 }	

NOTE: ERD, >1 cm in the breast or any positive lymph node in the axilla regardless of the size of residual disease in the breast; MRD, ≤ 1 cm in the breast and negative lymph nodes; and pCR, no evidence of residual invasive disease in the breast and lymph nodes.

Abbreviations: ERD, extensive residual disease; MRD, minimal residual disease; pCR, pathologic complete response.

*MRD + PCR of Pro/Pro variant compared with Pro/Arg and Arg/Arg variants.

Table 3. The correlation between the p53 codon 72 polymorphic variants and axillary lymph node status after neoadjuvant chemotherapy

Metastatic lymph node	Total (*n*)	Pro/Pro, *n* (%)	Pro/Arg, *n* (%)	Arg/Arg, *n* (%)	*P**
0	61	7 (30.4)	33 (60.0)	21 (67.7)	0.007
1-3	24	7 (30.4)	12 (21.8)	5 (12.9)	0.261
≥4	25	9 (39.1)	10 (18.2)	6 (19.4)	0.035

*Pro/Pro variant compared with Pro/Arg and Arg/Arg variants.

in the Pro/Arg group, and five patients (15.6%) in the Arg/Arg group. Based on large patient series with prolonged follow-up, studies have reported that patients who achieved a complete pathologic response or have residual invasive disease ≤1 cm and negative lymph nodes (minimal residual disease) have a very good prognosis compared with patients who have extensive residual disease after neoadjuvant chemotherapy (11, 12). Therefore, patients with a complete pathologic response or minimal residual disease were analyzed together as good responders. A good pathologic response (complete pathologic response and minimal residual disease) was shown in 13% of patients who carry the Pro/Pro variant, compared with 40% or 37.5% of patients who carry the Pro/Arg or Arg/Arg variant, respectively ($P = 0.019$; Table 2).

Furthermore, the relationship between the polymorphic variants and the pathologic axillary lymph node response after neoadjuvant chemotherapy was also evaluated (Table 3); patients with the Pro/Pro variant were more likely to have a positive axillary lymph node status, compared with patients with the Pro/Arg or Arg/Arg variant. In Pro/Pro group, 30% (7 of 23) of patients had a negative lymph node status compared with 60% (33 of 55) or 68% (21 of 32) of patients in the Pro/Arg or Arg/Arg group, respectively ($P = 0.007$). Moreover, the degree of axillary lymph node involvement was also associated with polymorphic variants. Patients who carry the Pro/Pro variant were more likely to have at least four lymph node metastases when compared with patients who carry the Pro/Arg or Arg/Arg variant (39% versus 18% or 19%, respectively; $P = 0.035$).

In addition to the Pro/Pro variant, estrogen receptor status was also significantly associated with pathologic response in univariate analysis (Table 4). Patients with a negative estrogen receptor status were more likely to have a good pathologic response than those with a positive estrogen receptor status ($P = 0.040$). There was a borderline association between the progesterone receptor status or the tumor size and pathologic response ($P = 0.051$, $P = 0.062$, respectively; Table 4). Patients with a positive progesterone receptor status or larger tumor seemed less likely to achieve a good pathologic response, compared with patients with a negative progesterone receptor status or small tumor. No significant association was found between pathologic response and menopausal status or erbB2 status.

The factors that were significantly or marginally associated with pathologic response in the univaiate analysis, e.g., estrogen receptor or progesterone receptor status, p53 codon 72 polymorphism, and tumor size, were included in the multivariate analysis. The results were presented in Table 5. p53 codon 72 polymorphism (Pro/Pro variant) was strongly associated with pathologic response, with an odds ratio of 6.7 (95% confidence interval, 1.4-31.2; $P = 0.016$). Although estrogen receptor status remained to be a significant predictor of pathologic response, with an odds ratio of 2.9 (95% confidence interval, 1.2-7.3; $P = 0.023$), the predictive role of p53 codon 72 polymorphism was substantially stronger, whereas the progesterone receptor status and tumor size did not reach statistical significance in the multivariate analysis. These data suggested that patients with the Pro/Pro variant were nearly seven times less sensitive to anthracycline-based neoadjuvant chemotherapy than those with the Pro/Arg or Arg/Arg variant.

Discussion

Several recent studies suggest that the p53 codon 72 polymorphism greatly modulates p53-dependent apoptotic capacity (6–8). The Arg^{72} form of wild-type p53 is at least five times more efficient in apoptosis induction than the Pro^{72} form, which is presumed to rely on the increased localization of the Arg^{72} form of p53 in the mitochondria when compared with the Pro^{72} form (6). These findings inspired us to investigate the

Table 4. The correlation between patient characteristics and pathologic response after neoadjuvant chemotherapy

Characteristics	Total (*n*)	MRD + pCR, *n* (%)	*P*
Genotypes			
Pro/Pro	23	3 (13.0)	0.019
Pro/Arg + Arg/Arg	87	34 (39.1)	
Menopausal status			
Premenopausal	77	28 (36.4)	0.355
Postmenopausal	33	9 (27.3)	
ER status			
Positive	72	19 (26.4)	0.040
Negative	32	15 (46.9)	
ND	6	3	
PR status			
Positive	60	15 (25.0)	0.051
Negative	44	18 (40.9)	
ND	6	3	
erbB2 status			
Positive	46	15 (32.6)	0.987
Negative	58	19 (32.8)	
ND	6	3	
Tumor size (cm)			
<3	70	28 (40.0)	0.062
≥3	40	9 (22.5)	

Table 5. Factors correlated with pathologic response in multivariate analysis

Factor	Odds ratio (95% CI)	*P*
Polymorphism (Pro/Pro)	6.7 (1.4-31.2)	0.016
ER (+)	2.9 (1.2-7.3)	0.023

Abbreviation: CI, confidence interval.

association between p53 codon 72 polymorphisms and the pathologic response to neoadjuvant chemotherapy in breast cancer. In this study, we found that patients carrying the Pro/Pro variant were less sensitive to anthracycline-based treatment than those patients carrying the Pro/Arg or Arg/Arg variant. To the best of our knowledge, this is the first study to show the predictive role of p53 codon 72 polymorphisms in response to neoadjuvant chemotherapy in a large series of breast cancer.

Because p53 codon 72 polymorphism modulates the wild-type p53 dependent apoptosis, the p53 status should be taken into serious consideration. Indeed, p53 mutation has been extensively studied in breast cancer where a great number of studies have indicated that the frequency of p53 mutation is around 20% (14–16). One meta-analysis, with 2,993 breast cancer patients enrolled, has shown that p53 mutations occur in 18% of the patients (17). Accordingly, p53 mutation might account for a minority fraction of this cohort of patients, suggesting that >80% of patients may harbor at least one allele of wild-type p53. Studies have shown that breast tumors carrying p53 mutation are resistant to anthracycline-based neoadjuvant chemotherapy (16, 18). In addition, a previous study has analyzed the correlation between the p53 codon 72 polymorphism and p53 mutation in 390 breast cancer patients, and p53 mutation was found to be more prevalent in the Arg/Arg variant than those of the Pro/Pro variant (28.5% versus 3.8%; ref. 19). In line with that, we found that breast tumors with the Arg/Arg variant were more sensitive to treatment than those with the Pro/Pro variant, although the frequency of p53 mutation might be higher in tumors with the Arg/Arg variant. These results indicated that in Pro/Pro tumor, the resistance to chemotherapy was largely due to the Pro form of wild-type p53 per se rather than mutation. Our results were in accordance with a recent finding in advanced head and neck carcinoma where patients carrying a Pro/Pro variant of wild-type p53 are less sensitive to cisplatin-based chemotherapy and display a poorer clinical outcome than those patients with either Arg/Arg or Arg/Pro variant (8).

As the aforementioned reasons, p53 mutated tumors represent a small fraction of breast cancer, and, moreover, p53 mutation detection is rather complicated, time consuming, and requires specialized laboratories. On the other hand, assessing germ line genetic polymorphisms as predictive markers has much appeal. This simple fast approach could be routinely used in clinical setting, particularly in patients treated with neoadjuvant therapy or patients with advanced stages. In such circumstance, the diagnoses are sometimes made from fine-needle biopsy samples; thus, the tumor tissue is limited or not available for p53 detection.

There are a substantial number of studies suggesting that patients with a negative estrogen receptor status are sensitive to neoadjuvant chemotherapy (11, 20). Our result that estrogen receptor status was associated with pathologic response was consistent with these observations. On the other hand, the correlation between of erbB2 expression and the sensitivity to neoadjuvant treatment has not been established. Some studies indicate that tumors with erbB2 overexpression are sensitive to anthracycline-based treatment (21, 22); however, other studies have yielded controversial results (2, 23). Nevertheless, in this cohort of tumors, the clinical or pathologic characteristics, like estrogen receptor or progesterone receptor status, erbB2 overexpression, initial clinical stage, tumor size, and menopausal status, were evenly distributed in the three-polymorphism variants. Thus, the different pathologic response to neoadjuvant chemotherapy seen in the three-genotype groups was not due to the potential effects of these clinicopathologic characteristics. Moreover, both in univariate and multivariate analyses, p53 codon 72 polymorphism remained to be a strong predictor of pathologic response.

Despite the similar tumor size and initial clinical stage before treatment among the variants, we found, however, after completion of chemotherapy, that patients with the Pro/Pro variant more frequently displayed a positive lymph node status than those with the Pro/Arg or Arg/Arg variant. This phenomenon was intriguing and the underlying mechanisms were currently unknown. We speculate that Pro/Pro tumor might harbor a higher malignant behavior and stimulate axillary lymph node metastasis; moreover, the metastatic lymph nodes might exhibit a more resistant to chemotherapy. Previous study has shown that if primary tumor responds poor, the mestastatic lymph nodes usually display a poor response as well (11).

In the present study, our results indicated that, regardless of the p53 status, patients with the Pro/Pro variant were less sensitive to anthracycline-based neoadjuvant chemotherapy than those with the Pro/Arg or Arg/Arg variant. Whether the patients with the Pro/Pro variant have a clinically significant poorer prognosis will require a long-term follow-up. Nevertheless, our findings would provide useful information for selecting the right candidates for anthracycline-based neoadjuvant chemotherapy, as patients with the Pro/Pro variant may either avoid neoadjuvant chemotherapy or use an alternative chemotherapy regimen.

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