TP53 Germline Mutations are Associated with HR+/HER2+ in BRCA1/2-Negative Early-Onset Breast Cancer in China

Lili Chen  
Fujian Medical University Union Hospital

Meng Huang  
Fujian Center for Disease Control and Prevention

Minyan Chen  
Fujian Medical University Union Hospital

Yuxiang Lin  
Fujian Medical University Union Hospital

Jing Li  
Fujian Medical University Union Hospital

Wenhui Guo  
Fujian Medical University Union Hospital

Chuan Wang  
Fujian Medical University Union Hospital

Fangmeng Fu (ffm@fjmu.edu.cn)  
Fujian Medical University Union Hospital

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Abstract

Background: Except for BRCA1/2, there is no data on the relationship between genetic counseling for the range of mutations and early-onset breast cancer populations. We looked for a link between inherited genes and the molecular subtype of early-onset breast cancer.

Methods: We genotyped 1214 individuals with early-onset sporadic breast cancer (age ≤ 40 years) who were BRCA1/2-negative in 3 genes: TP53, PALB2, and RECQL. We focus on the immunohistochemistry characteristics that are unique to each patient.

Results: The mutation rates of TP53, PALB2, and RECQL in 1214 BRCA-negative young individuals were 4/1214 (0.33%), 8/1214 (0.66%), 2/1214 (0.16%), respectively. The fact that the TP53 mutation rate was 3.49% among estrogen receptor-and/or progesterone receptor-positive, human epidermal growth factor receptor 2 (HER-2) amplification patients under the age of 35 (P < 0.001) was particularly noteworthy.

Conclusion: According to the findings, TP53 genetic testing should focus on women under 35 with HR-positive and HER2-positive IDC patients.

What Is New

In China, there has been little research on the incidence and clinical consequences of susceptibility genes variants. We looked at TP53, PALB2, and RECQL germline mutations in early-onset breast cancer and beyond BRCA1/2. HR/HER2 positivity and onset age are most likely linked to TP53.

Introduction

According to literature, pathogenic variants are linked with a significant risk of breast cancer, especially in patients with early-onset breast cancer\(^1\). The median age at breast cancer diagnosis in China is roughly 10 years younger than in the United States. These discrepancies might be due to ethnic groups having distinct environmental and genetic origins. \textit{BRCA1/2} genetic testing is suggested for people with early-stage breast cancer\(^2\). In a growing number of studies, rare, highly penetrant mutations in tumor suppressor genes have been linked to cancer susceptibility syndromes other than \textit{BRCA1/2}. Except for \textit{BRCA1/2} pathogenic variants, early-onset breast cancer individuals may have several intermediate breast cancer risk genes\(^3\), such as \textit{PALB2} (partner and localizer of \textit{BRCA2}), \textit{RECQL} (ATP-dependent DNA helicase Q1), and \textit{TP53}\(^4\).

The National Comprehensive Cancer Network indicated early-onset breast cancer patients in 2011 as a candidate for germline TP53 mutation testing\(^5\). BRCA1/2, ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, STK11, RAD51C, RAD51D, and TP53 are also recommended in the 2021 St. Gallen guidelines for patients\(^6\). The handbook explains that the moderate-risk genetic susceptibility genes play a key part in the disease's genesis. Furthermore, according to a recent study, PALB2 is a more prevalent in bilateral breast cancer patients with BRCA1/2 negative\(^7\). The panel covered around 80% of all BRCA1/2, CHEK2,
PALB2, NBN, and RECQL mutation detection in high-risk families with breast cancer, which is a huge variation in frequency\(^8\). TP53, PALB2, RECQL have been identified as high-risk breast cancer gene in certain studies\(^8,9,10\). Previous studies have indicated that HER2-positive breast tumors are more likely to have TP53 germline mutations\(^11,12,13\). Various ethnic groups may have distinct genetic variations. The ratio of BRCA1/2 mutations observed in our prior study is considerably different from that of the Western population, notably in individuals with early-onset breast cancer patients, where it is much lower\(^14\). A few studies have looked at the incidence and clinical significance of these mutant alleles of TP53, CHEK2, RECQL in a large group of Chinese patients with early-onset breast cancer. However, due to the low frequency of these genes, research into the prevalence of germline mutations in additional breast cancer susceptibility genes in early-onset breast cancer series is restricted. As a result, we lack data on the prevalence and range of susceptibility genes.

This study discovered germline mutations in the three cancer susceptibility genes in early-onset breast cancer patients who had previously tested negative for BRCA1 and BRCA2 mutations (including PALB2, TP53 and RECQL). We focused on the early-onset patients, and immunohistochemistry features such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status to determine the frequency of harmful germline mutations and determine whether early-onset breast cancer should be tested with multiple gene panels.

### Results

**Frequency and Spectrum of TP53\(\rightarrow\)PALB2\(\rightarrow\)RECQL Germline Mutations**

A total of 1214 female breast cancer patients under the age of 40 tested for germline TP53, PALB2, RECQL mutations were found. Four patients (0.33%) tested positive for a TP53 germline mutation (carriers), eight patients (0.66%) tested positive for a PALB2 germline mutation (carriers), and two patients (0.16%) carried the RECQL germline mutation among 1214 young patients diagnosed with breast cancer before the age of 40 years (carriers) (Table 2). The incidence of TP53 mutation was 3.49% among HR+, HER2+ young patients, which was particularly noteworthy (Figure 1).

**TP53**

TP53 pathogenic germline mutations were discovered in four HER-2 positive individuals. In the Clin Var, four missense variants (none of which were new) were considered pathogenic. The pathogenic mutation did not cause the Li-Fraumeni-like syndrome in the patient. All four mutation variants were missense mutations: c.796G>A, c.848G>A, c.856G>A, c.524G>A. (Table 1a).

| Table 1a | **TP53 truncating mutations identified in China patients with early-onset breast cancer** |
TP53 has three VUSs: c.920-5C>T (splice), c.35C>A(missense), c.751A>T(missense). Clin Var did not mention one of them, the c.751A>T variant, and it is worth mentioning that the patient who had the c.751A>T variant was also HER2 positive.

**PALB2**

In comparison to Clin Var, our analysis found eight pathogenetic mutations in PALB2, including c.2317dupA, c.2167_2168delAT, c.1056_1057delGA, c.2406_2407delTG, c.1451T>A, c.444delG, c.643G>T, c.2257C>T. Five of the pathogenic mutations were frameshift, whereas three were nonsense. The frameshift mutations c.2317dupA and c.2406_2407delTG were discovered to be new. Only one frameshift mutation (c.1056_1057delGA) was detected in familial breast cancer in our analysis, his variation has been found in breast cancer families from United States, Spanish and Italy. It is, however, the first report on the Chinese population (Table 1b).

### Table 1b  **PALB2 truncating mutations identified in China patients with early-onset breast cancer**

| Mutation   | Exon | Protein change | rs number     | Mutation effect         |
|------------|------|----------------|---------------|-------------------------|
| c.2317dupA | 5    | p.Thr773fs     | rs587776416   | frameshift_variant      |
| c.2167_2168delAT | 5 | p.Met723fs     | rs180177110   | frameshift_variant      |
| c.1056_1057delGA | 4 | p.Lys353fs     | rs180177110   | frameshift_variant      |
| c.2406_2407delTG | 5 | p.Cys802fs     | rs1555461796  | frameshift_variant      |
| c.1451T>A  | 4    | p.Leu484*      | rs786203714   | stop_gained            |
| c.444delG  | 4    | p.Lys149fs     | rs1555461693  | stop_gained            |
| c.643G>T   | 4    | p.Glu215*      | rs1555461796  | stop_gained            |
| c.2257C>T  | 5    | p.Arg753*      | rs180177110   | stop_gained            |

VUS mutations account for about 1.4% (87/1213) of the PALB2 gene mutations, as they provide little information about the gene’s function and have no bearing on cancer risk. In our investigation, c.3054G was found in 21 breast cancer patients with a high frequency. This variant has been discovered in several nations. Furthermore, the genes c.98C>A, c.1073C>G, c.1208T>C, c.1712A>G, c.1672A>G, and
c.1490A>G were discovered for the first time in this study and were not previously identified in Clin Var databases.

**RECQL**

On chromosome 12p12, the RECQL gene is found. There were only two pathogenic variants found: c.796C>T and c.1155_1158delTGTT (Table 1c). Variants of uncertain clinical relevance were found in 4.2% of the samples (51/1213). Ten distinct RECQL gene variants, including c.4G>A, c.430A>G, c.1418A>G, c.1795A>G, c.1849G>A, c.209A>C, c.1363_1365delCGT, c.1418A>G, c.1012G>C, and c.1744G>A, have yet to be referenced in Clin Var. These is no functional evidence for these variants in Clin Var.

**Table 1c**  
**RECQL truncating mutations identified in China patients with early-onset breast cancer**

| Mutation       | Exon | Protein change   | rs number       | Mutation effect          |
|----------------|------|------------------|-----------------|--------------------------|
| c.796C>T       | 8    | p.Gln266Ter      | rs572725483     | missense_variant         |
| c.1155_1158delTGTT | 11   | p.Phe385fs       | rs1252404021    | frameshift_variant       |

**Mutations and clinical characteristics**

None of the familial instances and 0.36% of non-familial patients had a TP53 mutation in the cohort, whereas 0.18% of non-familial cases had a RECQL mutation. Only one familial case and 0.63% of non-familial patients in the PALB2 cohort had a mutation. (Table 2)

**Table 2**  
**Comparison of family history between Mutation Carriers and Non-carriers**

| Family history of breast and/or ovarian cancer | TP53 | RECQL | PALB2 |
|-----------------------------------------------|------|-------|-------|
|                                               | Non-carrier | Carrier | Non-carrier | Carrier | Non-carrier | Carrier |
| no                                            | 1118 | 4     | 1120 | 2     | 1115 | 7     |
| yes                                           | 92   | 0     | 92   | 0     | 91   | 1     |
| $\chi^2$                                      |      |       |      |       |      |       |
| $P$                                           | 1.000 | 1.000 | 0.469 |

Breast cancer immunohistochemistry characteristics are summarized (Table 3). Regarding HR and HER2 status, no significant changes were identified between PALB2 and RECQL mutation carriers and non-carriers. We discovered that all four patients with TP53 mutation were ER, PR and HER2 positive compared to the non-carriers group ($P=0.001$), HER2 status($P=0.007$) was a statistically significant predictor of being a carrier for a TP53 germline mutation. The other two genes were not affected in the
same way (Table3, Table4). TP53 and PALB2 mutations carriers were substantially more likely than non-carriers to be 35 years old or younger at the time of diagnosis (P=0.009) (Table 5).

Table 3 Comparison of Pathological Features between Mutation Carriers and Non-carriers

| Subtype    | TP53  | RECQL | PALB2 |
|------------|-------|-------|-------|
|            | Non-carrier | Carrier | Non-carrier | Carrier | Non-carrier | Carrier |
| HR+&HER2-  | 706   | 0     | 705   | 1     | 700   | 6     |
| HR+&HER2+  | 200   | 4     | 204   | 0     | 204   | 0     |
| HR-&HER2+  | 153   | 0     | 152   | 1     | 152   | 1     |
| HR-&HER2-  | 151   | 0     | 151   | 0     | 150   | 1     |
| X²         | —     | —     | —     | —     | —     | —     |
| P          | 0.000 | 0.418 | 0.627 | 0.009 | 0.449 | 0.449 |

HR, estrogen receptor or progesterone receptor; HER2, human epidermal growth factor receptor 2

Table 4 Comparison of HER2 status between Mutation Carriers and Non-carriers

| HER2 status | TP53  | RECQL | PALB2 |
|-------------|-------|-------|-------|
|             | Non-carrier | Carrier | Non-carrier | Carrier | Non-carrier | Carrier |
| HER2-       | 857   | 0     | 856   | 1     | 850   | 7     |
| HER2+       | 353   | 4     | 356   | 1     | 356   | 1     |
| X²          | —     | —     | —     | —     | —     | —     |
| P           | 0.007 | 0.502 | 0.449 | 0.007 | 0.449 | 0.449 |

Table 5 Comparison of age between Mutation Carriers and Non-carriers
### Conclusion

Beyond BRCA1/2, this study investigates the frequency of TP53, PALB, RECQL mutations in solitary early-onset breast cancer. We help enhance the detection of instances with harmful mutations, particularly in genes other than BRCA1/2. This research also reveals that VUS of the three genes will continue to be a problem in clinical practice.

In this study of 1214 unselected early-onset breast cancer patients, it was discovered that 1.15% of them had at least one pathogenic mutation in one of the three susceptibility genes. TP53 pathogenic variants were uncommon, with mutation rates ranging from 3% to 8% in very early-onset breast cancer in prior investigations\(^\text{21,22,23}\). However, because there are only four instances in total, the mutation rate (0.33%) is significantly lower than in prior studies conducted in other counties. However, in this investigation, all four TP53 mutation carriers were shown to be more likely than non-carriers to have HR-positive and HER2-positive early-onset breast tumors. In HR+, HER2+ young patients, the rate is 3.49%. Some earlier studies have found a link between the two\(^\text{24,25,26}\). The utilization of multigene panel studies suggests that TP53 germline variants analysis in all breast cancer patients is not essential.

PALB2 pathogenic variants were the most prevalent collection of mutations in our study (0.66%). However, we found no PALB2 mutations linked to the molecular subtype of familial disease. The rate and association were not the same as in prior research. According to Antoniou et al., PALB2 mutation carriers had a greater TNBC phenotypic frequency (30%) than unselected individuals with breast cancer (12–17%)\(^\text{27}\). This study discovered some novel mutations in our study that have not been reported earlier in Chinese or other population and have not been referenced in Clin Var.

In this study, two patients (0.16%) had harmful mutation in the RECQL gene, including c.796C>T and c.1155-1158delTGTT. In several nations, the harmful mutation c.796C>T was described. This nonsense mutation was thought to cause premature protein termination and was thus considered harmful. RECQL
is involved in DNA double-strand break repair via the HR (homologous recombination) pathway, according to previous research\textsuperscript{28}. c.1155\_1158delTGTT was not cited in Clin Var. Jie Sun et al. revealed that the RECQL gene had a surprising 2.0\% pathogenic mutation rate in Chinese familial breast cancer patients, suggesting that it might be used to screen for mutations in BRCA1/2-negative breast cancer patients\textsuperscript{29}. However, we found no link between the RECQL mutation carriers’ family history and that of non-carriers in our research. The main explanation for the disparity is that Jie Sun gathered most patients with a family history.

Although the frequency of VUS (variants of undetermined significance) has reduced due to advancements in categorization, the test of a VUS causes uncertainty and anxiety, which is a prevalent concern in clinical practice. Our study found that three genes had VUS and that the proportion of VUS was larger than the percentage of pathogenetic VUS. All the VUS is primarily missense site mutations with no apparent tumor connection. A total of 17 VUS had never been recorded before, including 1 variant in TP53, 6 PALB2 variants, and 10 RECQL variants. Currently, VUS should not be utilized to make clinical choices. Furthermore, the validity of VUS analysis is hampered by a lack of healthy controls.

TP53 testing is recommended for HR, HER2 positive individuals under the age of 35. The need for mutation screening in all young patients is now being debated. It is debatable whether all young breast cancer patients should have their genes tested. Only 1.15\% of patients under the age of 40 in our sample had pathogenic mutations in one of moderate penetrance genetic testing, indicating that genetic testing is of little benefit to most patients.

However, we identified several new mutations in Chinese and other populations that had never been seen previously. The hunt for these genes is currently ongoing. Despite the large sample size, the study's major limitation is that the number of TP53, PALB2, and RECQL mutation carriers is relatively small. Furthermore, the absence of healthy controls limits the investigation of VUSs and mutations in genes unrelated to breast cancer.

**Methods**

**Patients**

We investigated 1214 women who had been diagnosed with early-stage breast cancer at Fujian Medical University’s Affiliated Union Hospital in Fuzhou. In term of family history, none of the participants were chosen. The following were the eligibility requirements: (1) a diagnosis of breast cancer before the age of 40; (2) BRCA1/2 deficiency (3) Invasive breast carcinoma was ruled out based on histological findings. We focused on estrogen receptor (ER), progesterone receptor (PR), and HER2 status immunohistochemical characteristics. Immunohistochemistry was used to detect the presence of estrogen and progesterone receptors (IHC). Nuclear staining of ER or PR over 10\% was judged positive. Immunohistochemical staining with a score of 3+ and/or FISH amplification of the HER2 gene was used to determine HER2 positive (fluorescence in situ hybridization).
**Next-generation sequencing**

The coding regions and exon–intron boundaries of the TP53, PALB2 and RECQL genes were all examined. Clin Var was used to compare all of the variations we found. The study’s genetic sequencing data were solely utilized for scientific purposes, not for clinical decision-making. According to the Clin Var database (https://www.ncbi.nlm.nih.gov/clinvar/), germline variants the were previously clinically assessed and characterized were classified as benign, unknown significance (VUS), likely pathogenic or pathogenic.

**Statistical analysis**

The Chi-square test and Fisher’s exact test were used to examine the relationships between immunohistochemistry type, family history, and mutation status of the three susceptibility genes. P-values less than 0.05 were deemed statistically significant.

**Declarations**

**Ethical Approval and Consent to participate**

All the procedures performed in studies involving human participants adhere to the Ethical Standards of the Institutional and/or National Research Committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Research Ethics Committee of Fujian Medical University Union Hospital (2020KJT031). Informed consent was obtained from each participant.

**Consent for publication**

Not applicable

**Availability of supporting data**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Competing interests**

The authors declare that they have no conflicts of interest.

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**Authors’ contributions**
Lili Chen: data curation, writing of the manuscript, resources, collection of the blood samples and clinical information, funding acquisition, approval of the final manuscript. Meng Huang: Data curation, gene sequencing and approval of the final manuscript. Minyan Chen: Recruitment of the patients, collection of the blood samples and clinical information, and approval of the final manuscript. Yuxiang Lin: Recruiting the patients to collection the blood samples and clinical information, approving. Jing Li: Recruitment of the patients, collection of the blood samples and clinical information, and approval of the final manuscript. Chuan Wang: Planning and design of the study, project administration, recruitment of the patients, collection of the blood samples and approval of the final manuscript. Fangmeng Fu: Planning and design of the study, data curation, project administration, recruitment of the patients, collection of the blood samples and approval of the final manuscript.

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Figures

**Figure 1 The contrast of TP53， PALB2， RECQL mutation rate**

See image above for figure legend