3’ untranslated region 1630 C>T polymorphism of prohibitin increases risk of breast cancer

Lin Tang1,∗ Yunzhao Zhao2,∗ Weiwei Nie1 Zexing Wang1 Xiaoxiang Guan1

1Department of Medical Oncology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, People’s Republic of China
2Department of General Surgery, Jinling Hospital, Nanjing University School of Medicine, Nanjing, People’s Republic of China
∗These authors contributed equally to this work

Background: Prohibitin 3’ untranslated region 1630 C>T (rs6917) polymorphism creates a variant T allele that lacks the antiproliferative activity of the more common functional C allele. Previous studies indicate that women carrying the prohibitin T allele have an increased susceptibility to breast cancer. However, the role of 1630 C>T polymorphism in mRNA expression of prohibitin and its contribution to carcinogenesis in the breast remains controversial.

Methods: Using mRNA expression data from the HapMap online database, we sought an association between prohibitin 1630 C>T polymorphism and its mRNA expression, then conducted a meta-analysis of prohibitin 1630 C>T polymorphism and risk of breast cancer.

Results: Although no significant association was found between prohibitin 1630 C>T polymorphism and mRNA expression in lymphoblastoid cell lines from the HapMap database (Ptrend = 0.543), the present meta-analysis involving 5072 cases and 4796 controls demonstrated that prohibitin 1630 C>T polymorphism was significantly correlated with breast cancer risk in allele contrast model T versus C (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.01–1.18), the homozygote codominant model TT versus CC (OR 1.47, 95% CI 1.12–1.92), and the recessive model TT versus CC/CT (OR 1.45, 95% CI 1.10–1.89).

Conclusion: Our study indicates that minor allele T of prohibitin 1630 C>T polymorphism is associated with increased susceptibility to breast cancer.

Keywords: prohibitin, breast cancer, genetic, polymorphisms, risk

Introduction

Prohibitin is a candidate tumor suppressor gene encoding a 30 kDa intracellular protein which regulates cell cycle progression in multiple cell types. It interacts with the retinoblastoma tumor suppressor protein and its family members to suppress E2F-mediated transcription, and binds to p53 protein, increasing p53 transcriptional activity via increased DNA binding.1,2 The human prohibitin gene is located on chromosome 17q21, a region of frequent loss of heterozygosity in breast cancers, spanning approximately 11 kb and consisting of seven exons.3 In total, 217 single nucleotide polymorphisms have been identified in the prohibitin gene region, and 38 nucleotide polymorphisms in the coding region (http://www.ncbi.nlm.nih.gov/SNP/). Of these, 14 nucleotide polymorphisms have been reported in the 3’-untranslated region, as shown in Table 1, only five nucleotide polymorphisms (rs6917, rs9893420, rs111398671, rs112294663, rs73324369) have minor allele frequencies available, and the potential microRNA binding sites are summarized in Table 1. The most extensively studied nucleotide polymorphism of prohibitin is a C-to-T transition at position 1630 in
the 3′-untranslated region, that creates a variant with hsa-
miR-1292 and hsa-miR-886-5p as potential binding sites
(http://snpinfo.niehs.nih.gov/cgi-bin/snpinfo/snpfunc.cgi).
This variant lacks antiproliferative activity and significantly
reduces cell motility.4–6

Recent studies have evaluated the potential role of
prohibitin in development of breast cancer and risk
modification associated with prohibitin 1630 C>T polymorphism, but there are still no consistent data to indicate
the molecular mechanism of 1630 C>T polymorphism in
the regulation of prohibitin mRNA expression and its role
in carcinogenesis. Although the T allele has been associated
with an increased risk of breast cancer in women aged
younger than 50 years who have a first-degree relative with
breast cancer,7 there are other studies that have not found
an association between this polymorphism and breast
cancer. In order to evaluate this potential association more
precisely, we identified all published case-control studies,
amounting to 5072 cases and 4796 controls, and undertook
a quantitative analysis to identify evidence of an association
between prohibitin 1630 C>T polymorphism and breast
cancer risk.

Materials and methods
Genotype and mRNA expression
data in lymphoblastoid cell lines
We used additional data on prohibitin genotypes and mRNA
levels available online (http://app3.titan.uio.no/biotools/help
.php?app=snpexp) for analysis of the genotype-phenotype
relationship.8 We analyzed the variation in gene expression
using genome-wide expression arrays (47,294 transcripts)
from Epstein-Barr virus-transformed lymphoblastoid
cell lines from the same 270 HapMap individuals.8 The
genotyping data were from the HapMap Phase II release
23 data set consisting of 3.96 million single nucleotide
polymorphism genotypes from 270 individuals in four
populations.10

Publication search and data extraction
Eligible studies were identified by searching in the PubMed,
ISI Web of Knowledge, and Embase databases for relevant
reports (last search update, August 2012), using the search
terms “PHB” or “prohibitin”, “polymorphism”, and “breast
cancer”. We did not define any minimum number of patients
to be included for meta-analysis. When multiple studies of
the same patient population were identified, we included the
published report with the largest sample size.

Inclusion criteria were: evaluation of prohibitin 1630
C>T polymorphism and breast cancer risk, case-control
study design, and sufficient published data for estimating
an odds ratio (OR) with a 95% confidence interval (CI).
Only the most recent or complete study was used if the same
study subjects were included in more than one publication.
The main exclusion criteria were: no control population, no
available genotype frequency, and overlapping data.

Two authors reviewed the articles separately and extracted
the data from all eligible publications according to the criteria
listed above. Any discrepancies between investigators were
resolved by discussion and consultation with a third reviewer.
The first author’s surname, year of publication, country of
original ethnicity, study design, genotyping method, and
numbers of genotyped cases and controls (CC, CT, and TT
genotypes) were recorded for each study.

Statistical methods
The genotype and phenotype relationship analysis was
performed using SAS software (version 9.1, SAS Institute,
Cary, NC). A pooled OR and 95% CI were calculated to
estimate the risk of breast cancer associated with prohibitin
1630 C>T. For all studies, we estimated the association
under five different types of OR, namely the allele con-
trast model (T versus C), homozygote codominant model
(TT versus CC), heterozygote codominant model (CT versus
CC), dominant model (TT/CT versus CC), and recessive
model (TT versus CC/CT). Hardy-Weinberg equilibrium

Table 1 The SNPs of prohibitin 3′UTR and MicroRNA binding sites

| Name       | Chr position | Alleles | MAF | Potential MicroRNA binding sites |
|------------|--------------|---------|-----|----------------------------------|
| rs6917     | 44836542     | C/T     | 0.1924 | hsa-miR-886-5p,hsa-miR-1292 |
| rs9893420  | 44836887     | A/G     | 0.0151 | hsa-miR-15a,hsa-miR-15b,hsa-miR-16 |
| rs11398671 | 47481589     | C/T     | 0.0064 | hsa-miR-103,hsa-miR-107,hsa-miR-195 |
| rs11229463 | 47481625     | A/G     | 0.0172 | hsa-miR-220c,hsa-miR-217,hsa-miR-424 |
| rs73324369 | 47481676     | C/T     | 0.0115 | hsa-miR-497,hsa-miR-873,hsa-miR-933 |

Abbreviations: Chr, chromosome; MAF, Minor Alleles Frequency; Mi, micro; NA, not available; RNA, ribonucleic acid; SNP, single nucleotide polymorphism; UTR, untranslated region.
was investigated using the $\chi^2$ test. The Q-statistic and $P$ test were used to investigate the degree of heterogeneity between studies. When $P \geq 0.1$ or $F \leq 50\%$ indicated a lack of heterogeneity, the fixed-effects model (Mantel-Haenszel method) was used. Otherwise, the random-effects model (DerSimonian-Laird method) was chosen. Egger’s test and inverted Begg’s funnel plots were used to detect any publication bias. A sensitivity analysis was also performed by repeating the meta-analysis and omitting each study at each iteration. The data were analyzed using Revman 5.0 software (http://ims.cochrane.org/revman).

**Results**

*Prohibitin* mRNA expression by genotype in lymphoblastoid cell lines

We used the available HapMap-cDNA expression database for correlation analysis of prohibitin genotype and mRNA expression in 270 HapMap lymphoblastoid cell lines. Except for nine cell lines with no available values, 180 (68.9%) cell lines had the CC genotype, 71 (27.3%) had the CT genotype, and 10 (3.8%) had the TT genotype. Figure 1 shows *prohibitin* mRNA expression according to 1630 C>T genotype for the lymphoblastoid cell lines. There was no significant difference in *prohibitin* mRNA expression level between cell lines carrying the TT genotype (9.05 ± 0.31), TC genotype (9.04 ± 0.33), or CC genotype (8.96 ± 0.29, $P_{\text{trend}} = 0.543$, Figure 1).

**Study characteristics**

After careful examination according to the inclusion criteria, six publications on polymorphisms of *prohibitin* 1630 C>T and breast cancer risk were eligible, 4,7,13–16 of which the study by Jakubowska et al 14 was reported twice. For the overlapping studies, only the one with the largest sample numbers was included. Jupe et al 17 only provided information on C/T or T/T versus C/C. Hence, a total of five publications including 5072 cases and 4796 controls were used in the present meta-analysis. Table 2 lists the main characteristics of these studies. All cases were histologically confirmed as breast cancer, and controls were cancer-free and hospital-based populations matched for age and gender. The genotype distribution of the controls was in Hardy-Weinberg equilibrium, except for one study. 18

**Meta-analysis results**

The results of the meta-analysis are shown in Table 3. Because the between-study heterogeneity of each study included in our meta-analysis was not statistically significant, all pooled ORs were derived from fixed-effects models. We observed that the *prohibitin* 1630 C>T polymorphism was significantly correlated with risk of breast cancer in the allele contrast model T versus C (OR 1.09, 95% CI 1.01–1.18, Figure 2), the homozygote codominant model TT versus CC (OR 1.47, 95% CI 1.12–1.92, Figure 3), and the recessive model TT versus CC/CT (OR 1.45, 95% CI 1.10–1.89, Figure 4). However, no significant association was detected for the heterozygote codominant model CT versus CC (OR 1.04, 95% CI 0.95–1.14, Figure 5) or the dominant model TT/CT versus CC (OR 1.08, 95% CI 0.99–1.18, Figure 6).

**Publication bias**

Funnel plots and Egger’s test were used to assess publication bias in the literature. There was no evidence of publication bias in the present meta-analysis.

![Figure 1](https://example.com/figure1.png) mRNA expression level of the prohibitin gene in Epstein Barr virus-transformed lymphoblastoid cell lines.

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**Table 2** Characteristics of the studies included in the meta-analysis

| First author | Year | Country | Genotyping method | Source | Genotypes distribution (cases/controls) | HWE |
|--------------|------|---------|-------------------|--------|----------------------------------------|------|
| Jupe et al 7 | 2001 | USA     | PCR-RFLP          | PB     | CC 128 / 77*, CT 709 / 337*, TT 0.543 | NA   |
| Spurdle et al 13 | 2002 | Australia | PCR-RFLP         | PB     | CC 992 / 416, CT 533 / 235, TT 18 | 0.18 |
| Campbell et al 6 | 2003 | UK      | PCR-RFLP          | PB     | CC 188 / 93, CT 10 / 70, TT 61 / 7 | 0.59 |
| Karakus et al 15 | 2008 | Turkey  | PCR-RFLP          | PB     | CC 67 / 36, CT 101 / 3, TT 6 / 47 | 0.86 |
| Jakubowska et al 14 | 2012 | Poland  | iPLEX PCR-RFLP    | PB     | CC 2029 / 891, CT 104 / 1771, TT 747 / 54 | 0.02 |

*Note: *For these just presenting the information for genotypes of CC and CT + TT, dominant model is calculated only.**

**Abbreviations:** HWE, Hardy–Weinberg equilibrium; NA, not available; PB, population-based study; PCR, polymerase chain reaction.
bias for prohibitin 1630 C>T polymorphism, and the results of the Egger's test suggested no publication bias for the allele contrast model (P = 0.685), homozygote codominant model (P = 0.810), heterozygote codominant model (P = 0.926), dominant model (P = 0.639), or recessive model (P = 0.846).

Discussion

The 3′ untranslated region of the prohibitin gene which encodes a transacting regulatory RNA molecule arrests cell proliferation between the G1 and S phases of the cell cycle.17 Jupe et al confirmed the antiproliferative activity of prohibitin by microinjection of prohibitin mRNA and protein into normal and immortalized cancer cell lines.18 The protein-encoding region of the prohibitin gene was not found to be mutated, but the 3′-untranslated region of prohibitin mutations inhibited cell cycle progression in loss of human cancer cell lines.5 The investigators confirmed that a single nucleotide polymorphism (C-T transition) in the prohibitin 3′-untranslated region creates a null (T) allele whereby the RNA product has lost its antiproliferative activity.17 The results of our study are consistent with the functional prohibitin 3′-untranslated region 1630 C>T polymorphism resulting in increased risk of breast cancer, although there was no significant association between prohibitin 1630 C>T polymorphism and mRNA expression in lymphoblastoid cell lines from the HapMap database. Data being collected from different studies without stratification/adjustment for differences between studies and inconsistent use of selection criteria are possible explanations for this. Further investigations should be done in breast cancer tissue or cells to determine if a correlation exists between genotype and mRNA expression.

In this study, we investigated 5072 cases and 4796 controls, the allele contrast model, the homozygote codominant and the recessive model of prohibitin 1630 C>T polymorphism were found to be significantly associated with influencing the risk of breast cancer. Heterogeneity and publication bias were not observed in this study. Our findings suggest that prohibitin 1630 C>T polymorphism increases the risk of breast cancer.

Some limitations of this meta-analysis need to be acknowledged when interpreting its findings. First, we presumed that ethnicity status and family history play diverse roles in the risk of breast cancer. In our study, we considered the possibility that the effect of prohibitin 1630 C>T polymorphism might be ethnicity-specific in mixed populations, but we did not perform subgroup analysis to detect an association between this polymorphism and ethnicity. Second, our results were based on unadjusted estimates, so a more precise analysis should be done when more detailed individual data become available. A recent study evaluated the association between genetic variants of prohibitin and breast cancer risk in BRCA1 or BRCA2 mutation carriers, and the findings showed that the prohibitin 1630TT genotype may modify breast cancer risk in these women.16 Third, as we all know, cancer is a complicated disease, different genetic backgrounds may contribute to the discrepancy, and it is still

| Study or subgroup | Experimental Events | Control Events | Total Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|-------------------|--------------------|---------------|--------------|-------------------------------|-------------------------------|
| Campbell, et al.⁴ | 113 582            | 75 476        | 5.8%         | 1.29 [0.93, 1.78]              |                               |
| Jakubowska, et al.¹⁶ | 1099 6048      | 855 5144      | 65.6%        | 1.11 [1.01, 1.23]              |                               |
| Karakus, et al.¹⁵ | 42 212             | 59 308        | 3.3%         | 1.04 [0.67, 1.62]              |                               |
| Spurdle, et al.¹⁵  | 492 2892          | 271 1572      | 25.3%        | 0.98 [0.84, 1.16]              |                               |
| Total (95% CI)    | 9734 7500         | 100.0%        | 1.09 [1.01, 1.18] |                               |
| Total events      | 1746 1260         |               |              |                               |                               |
| Heterogeneity: Chi² = 2.78, df = 3 (P = 0.43); I² = 0% | | | | |
| Test for overall effect: Z = 2.08 (P = 0.04) | | | | |

Figure 2 Forest plot for the association between the prohibitin 1630 C>T polymorphism and breast cancer risk (for T versus C) in a fixed-effects model.

Abbreviations: CI, Confidence Interval; M-H, Mantel-Haenszel.
Table 1

| Study or subgroup | Experimental |  |  |  |  | Control |  |  |  |  |
|------------------|--------------|---|---|---|---|----------|---|---|---|---|
|                  | Events       | Total | Events | Total | Weight | M-H, fixed, 95% CI | Odds ratio | M-H, fixed, 95% CI |
| Campbell, et al. | 10           | 291  | 7    | 238  | 8.1%  | 1.17 [0.44, 3.13]  | 1.17       | 8.1%  | 1.17 [0.44, 3.13]  |
| Jakubowska, et al. | 104      | 3024 | 54   | 2572 | 61.8% | 1.66 [1.19, 2.32]  | 1.66       | 61.8% | 1.66 [1.19, 2.32]  |
| Karakus, et al.  | 3            | 106  | 6    | 154  | 5.2%  | 0.72 [0.18, 2.94]  | 0.72       | 5.2%  | 0.72 [0.18, 2.94]  |
| Spurdle, et al.  | 38           | 1446 | 18   | 786  | 24.9% | 1.15 [0.65, 2.03]  | 1.15       | 24.9% | 1.15 [0.65, 2.03]  |
| Total (95% CI)   | 4867         | 3750 | 100.0% | 1.45 [1.10, 1.89] | 1.45 | 100.0% | 1.45 [1.10, 1.89] |
| Total events     | 155          | 85   | 100.0% | 1.01 [0.95, 1.14] | 1.01 | 100.0% | 1.01 [0.95, 1.14] |

**Figure 3** Forest plot for the association between the prohibitin 1630 C>T polymorphism and breast cancer risk (for TT versus CC) in a fixed-effects model. Abbreviations: CI, Confidence Interval; M-H, Mantel-Haenszel.

Table 2

| Study or subgroup | Experimental |  |  |  |  | Control |  |  |  |  |
|------------------|--------------|---|---|---|---|----------|---|---|---|---|
|                  | Events       | Total | Events | Total | Weight | M-H, fixed, 95% CI | Odds ratio | M-H, fixed, 95% CI |
| Campbell, et al. | 10           | 291  | 7    | 238  | 8.1%  | 1.17 [0.44, 3.13]  | 1.17       | 8.1%  | 1.17 [0.44, 3.13]  |
| Jakubowska, et al. | 104      | 3024 | 54   | 2572 | 61.8% | 1.66 [1.19, 2.32]  | 1.66       | 61.8% | 1.66 [1.19, 2.32]  |
| Karakus, et al.  | 3            | 106  | 6    | 154  | 5.2%  | 0.72 [0.18, 2.94]  | 0.72       | 5.2%  | 0.72 [0.18, 2.94]  |
| Spurdle, et al.  | 38           | 1446 | 18   | 786  | 24.9% | 1.15 [0.65, 2.03]  | 1.15       | 24.9% | 1.15 [0.65, 2.03]  |
| Total (95% CI)   | 4712         | 3665 | 100.0% | 1.01 [0.95, 1.14] | 1.01 | 100.0% | 1.01 [0.95, 1.14] |
| Total events     | 1436         | 1090 | 100.0% | 1.01 [0.95, 1.14] | 1.01 | 100.0% | 1.01 [0.95, 1.14] |

**Figure 4** Forest plot for the association between the prohibitin 1630 C>T polymorphism and breast cancer risk (for TT versus CC/CT) in a fixed-effects model. Abbreviations: CI, Confidence Interval; M-H, Mantel-Haenszel.

Table 3

| Study or subgroup | Experimental |  |  |  |  | Control |  |  |  |  |
|------------------|--------------|---|---|---|---|----------|---|---|---|---|
|                  | Events       | Total | Events | Total | Weight | M-H, fixed, 95% CI | Odds ratio | M-H, fixed, 95% CI |
| Campbell, et al. | 10           | 291  | 7    | 238  | 8.1%  | 1.17 [0.44, 3.13]  | 1.17       | 8.1%  | 1.17 [0.44, 3.13]  |
| Jakubowska, et al. | 104      | 3024 | 54   | 2572 | 61.8% | 1.66 [1.19, 2.32]  | 1.66       | 61.8% | 1.66 [1.19, 2.32]  |
| Karakus, et al.  | 3            | 106  | 6    | 154  | 5.2%  | 0.72 [0.18, 2.94]  | 0.72       | 5.2%  | 0.72 [0.18, 2.94]  |
| Spurdle, et al.  | 38           | 1446 | 18   | 786  | 24.9% | 1.15 [0.65, 2.03]  | 1.15       | 24.9% | 1.15 [0.65, 2.03]  |
| Total (95% CI)   | 5072         | 4796 | 100.0% | 1.08 [0.99, 1.18] | 1.08 | 100.0% | 1.08 [0.99, 1.18] |
| Total events     | 1668         | 1512 | 100.0% | 1.08 [0.99, 1.18] | 1.08 | 100.0% | 1.08 [0.99, 1.18] |

**Figure 5** Forest plot for the association between the prohibitin 1630 C>T polymorphism and breast cancer risk (for TT/CT versus CC) in a fixed-effects model. Abbreviations: CI, Confidence Interval; M-H, Mantel-Haenszel.

Table 4

| Study or subgroup | Experimental |  |  |  |  | Control |  |  |  |  |
|------------------|--------------|---|---|---|---|----------|---|---|---|---|
|                  | Events       | Total | Events | Total | Weight | M-H, fixed, 95% CI | Odds ratio | M-H, fixed, 95% CI |
| Campbell, et al. | 10           | 291  | 7    | 238  | 8.1%  | 1.17 [0.44, 3.13]  | 1.17       | 8.1%  | 1.17 [0.44, 3.13]  |
| Jakubowska, et al. | 104      | 3024 | 54   | 2572 | 61.8% | 1.66 [1.19, 2.32]  | 1.66       | 61.8% | 1.66 [1.19, 2.32]  |
| Karakus, et al.  | 3            | 106  | 6    | 154  | 5.2%  | 0.72 [0.18, 2.94]  | 0.72       | 5.2%  | 0.72 [0.18, 2.94]  |
| Spurdle, et al.  | 38           | 1446 | 18   | 786  | 24.9% | 1.15 [0.65, 2.03]  | 1.15       | 24.9% | 1.15 [0.65, 2.03]  |
| Total (95% CI)   | 5072         | 4796 | 100.0% | 1.08 [0.99, 1.18] | 1.08 | 100.0% | 1.08 [0.99, 1.18] |
| Total events     | 1668         | 1512 | 100.0% | 1.08 [0.99, 1.18] | 1.08 | 100.0% | 1.08 [0.99, 1.18] |

**Figure 6** Forest plot for the association between the prohibitin 1630 C>T polymorphism and breast cancer risk (for TT/CT versus CC) in a fixed-effects model. Abbreviations: CI, Confidence Interval; M-H, Mantel-Haenszel.
necessary to conduct larger sample studies considering gene-gene and gene-environment interactions, which may be an important component of the association between prohibitin 1630 C>T polymorphism and risk of breast cancer. In conclusion, the results of this meta-analysis suggest that the prohibitin 1630 C>T variant was associated with a significant increase in the risk of breast cancer.

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Disclosure
The authors report no conflicts of interest in this work.

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