Common Genetic Variants in the MicroRNA Biogenesis Pathway Are Not Associated with Breast Cancer Risk in Asian Women

Hyuna Sung1, Ben Zhang6, Ji-Yeob Choi1,4, Jirong Long6, Sue K. Park1,2,4, Keun-Young Yoo2, Dong-Young Noh3,4, Sei-Hyun Ahn5, Wei Zheng6, and Daehee Kang1,2,4

Abstract

Background: Although the role of miRNA in cancer development and progression has been well established, the association between genetic variants in miRNA biogenesis pathway genes and breast cancer risk has been yet unclear.

Methods: We analyzed data from two genome-wide association studies conducted in East Asian women including 5,066 cases and 4,337 controls. Among the single-nucleotide polymorphisms (SNP), which were directly genotyped or imputed, we selected 237 SNPs in 32 genes involved in miRNA biogenesis pathway and its regulation.

Results: Although eight SNPs were nominally associated with breast cancer risk in combined samples ($P < 0.05$), none of them were significant after adjustment for multiple comparisons.

Conclusions: The common genetic variants in miRNA biogenesis pathway genes may not be associated with breast cancer risk.

Impact: This study suggests no association between the polymorphisms in miRNA biogenesis pathway genes and breast cancer risk. Studies with large sample size and more genetic variants should be warranted to adequately evaluate the potential association. Cancer Epidemiol Biomarkers Prev; 21(8); 1385–7. ©2012 AACR.

Introduction

MiRNAs are a major class of noncoding RNAs that posttranscriptionally modulate gene expression in a sequence specific manner. The role of miRNAs in human cancer pathogenesis has been well established by the identification of aberrant expression of miRNAs in many types of cancer (1). There is increasing evidence that the genetic variants in miRNA genes, in their biogenesis pathway genes and binding sites of target mRNA are associated with cancer risk and survival (2). However, the association between the polymorphisms of miRNA biogenesis pathway genes and breast cancer risk is uncertain. The previous study focusing on this pathway was conducted in small sample size and the coverage of genes of interests was limited (3). More recently, the results on the effects of genetic variants in miRNA biogenesis pathway genes were inconsistent even in the same cancer type (4). We comprehensively evaluated the common variants in miRNA biogenesis pathway genes by analyzing data from the 2 previous genome-wide association studies (GWAS) conducted in women of Asian ancestry consisted of 5,066 breast cancer cases and 4,337 controls.

Materials and Methods

Detailed methods for the Seoul Breast Cancer Study and the Shanghai Breast Cancer Study have been published elsewhere (5, 6) and described in brief in Supplementary Table S1 (3). This study included 5,066 histologically confirmed breast cancer cases and 4,337 controls [(2,190/2,052) Koreans and (2,876/2,285) Chinese]. The protocol was approved by the Institutional Review Board, and all participants provided written informed consent.

The 35 genes (ADAR, ADAR1, DDX5, DDX17, DDX20, Dicer1, DROSHA, DICER1, EIF2C1, EIF2C2, GEMIN4, HNRNPA1, ILF2, ILF3, KHSRP, LIN28A, NANO2, PAPD4, PIWIL1, RAN, SMAD1, SMAD2, SMAD3, SMAD4, SMAD6, SMAD7, SNIP1, SRK, SRSF1, TARBP, TRIM32, TRIM71, XPO5, XR2, and ZCCHC11) were selected on the basis of their biologic role in miRNA biogenesis as determined by the combination of literature review (7) and the bioinformatics tool the Gene Ontology.
Table 1. Association between the SNPs with a \( P_{\text{meta}} \) < 0.050 in the genes of interests and breast cancer risk

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene/predicted function</th>
<th>Genomic location</th>
<th>Per-allele OR (95% CI)</th>
<th>( P_{\text{meta}} )</th>
<th>( P_{\text{het}} )</th>
<th>( P_{\text{OR per-allele}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3754025</td>
<td>DDX20</td>
<td>1p13.2/112104760</td>
<td>1.15 (1.02–1.29)</td>
<td>0.05</td>
<td>0.14</td>
<td>1.00 (1.01–1.00)</td>
</tr>
<tr>
<td>rs6578126</td>
<td>EIF2C2</td>
<td>8q24.3/141704788</td>
<td>1.15 (1.02–1.29)</td>
<td>0.05</td>
<td>0.48</td>
<td>1.00 (0.77–1.16)</td>
</tr>
<tr>
<td>rs10848087</td>
<td>PIWIL1</td>
<td>12q24.33/129405118</td>
<td>1.15 (1.02–1.29)</td>
<td>0.05</td>
<td>0.10</td>
<td>1.00 (0.81–1.00)</td>
</tr>
<tr>
<td>rs12432281</td>
<td>XRN2</td>
<td>14q32.13/94674881</td>
<td>1.15 (1.02–1.29)</td>
<td>0.14</td>
<td>0.07</td>
<td>1.00 (0.81–1.00)</td>
</tr>
</tbody>
</table>

Abbreviation: EAF, effect allele frequency.

aLocation based on NCBI Human Genome Build 36.3. Hg18.

dAdjusted for age.

eImputation R-square.

f\( P \) for heterogeneity between both studies was calculated using the Cochran Q test.

Discussion

In this study, SNPs in miRNA biogenesis pathway genes were not associated with breast cancer risk. We could not exclude the possibility that the lack of association could come from the differences in subject characteristics, the interactions of environmental modifiers, and other uncontrolled bias between both studies. We also could not replicate the SNPs shown in previous report (3) although highly correlated proxies were included aside from SNPs in DDX20. Considering the sample size of the previous report, it could be a chance finding and at least need to be further investigated in other populations. The strengths of this study are its large sample size and comprehensive search of genes of interests and the high coverage of known SNPs. With the current sample size, for a SNP with MAF as 0.26 (average value of all tested SNPs), the minimum log-additive OR that we can detect at 99% power is 1.22, considering the Bonferroni-corrected significance level (\( P = 1E-04 \)). Future genomic scan including several kinds of structural variations, copy number variants, new variants identified by high-resolution sequencing with larger sample size, as well as subtype specific associations, could provide important insights into the molecular mechanisms of breast cancer susceptibility.

Results

Of the 247 SNPs, 8 SNPs (DDX20 rs3754025, EIF2C2 rs7834784 and rs6578126, PIWIL1 rs10848087, DICER1 rs12432281, SMAD6 rs17264185 and rs7170982, and XRN2 rs10485627) were associated with breast cancer risk (\( P_{\text{meta}} < 0.050 \), Table 1). The most significant association was observed in intronic SNP rs7834784 in EIF2C2 with \( OR_{\text{per-allele}} \) as 1.15 (95% CI, 1.02–1.29; \( P_{\text{meta}} = 0.021 \)). Study specific estimates of both studies were generally similar. However, these nominally significant associations were not significant when accounting for multiple comparisons. The results of all the SNPs evaluated were presented in Supplementary Table S3.

(Supplementary Table S2). Using the data from the HapMap Project and web-based single-nucleotide polymorphism (SNP) selection tool (8), we selected haplotype tagging SNPs defined by the linkage disequilibrium with the pairwise \( r^2 \geq 0.60 \), in the region from 10 kb upstream and 5 kb downstream of the largest cDNA of each gene with minor allele frequency (MAF) of \( \geq 0.05 \) in Asian populations. For 3 genes (TARBP, DDX5, and SRSE1) among the 35 genes, no SNP was included because of low MAF or low imputation quality (RSQR < 0.3, DDX5 rs1991401 and SRSE1 rs2233911). A total of 247 SNPs (26 genotyped and 221 imputed) located in 32 genes were included. For individual study, OR and 95% confidence intervals (CI) were estimated using logistic regression implemented in PLINK (genotyped SNPs) and MACH2DAT (imputed SNPs) with adjustment for age. We carried out meta-analysis using a weighted z-score method under the fixed effect model implemented in METAL (9). Cochran Q statistics were used to assess the heterogeneity across the studies.

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analysis, could elucidate further information on the potential association.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: H. Sung, S.K. Park, D. Kang
Development of methodology: H. Sung, D. Kang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H. Sung, K.-Y. Yoo, D.-Y. Noh, W. Zheng

Writing, review, and/or revision of the manuscript: H. Sung, B. Zhang, Y.-J. Choi, S.K. Park, D.-Y. Noh, W. Zheng
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.-Y. Noh, W. Zheng
Study supervision: D. Kang, W. Zheng

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