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COMMENTARY

A Commentary on Analysis of *ZNF350/ZBRK1* promoter variants and breast cancer susceptibility in non-BRCA1/2 French Canadian breast cancer families

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A familial history is one of the most important risk factors of breast cancer. To date, several susceptibility genes, including *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *BRIP2*, *PALB2* and *RAD51*, were identified; however, these genes would account for only 25% of familial breast cancer risk.[1,2]

ZNF350/ZBRK1 (zinc finger and BRCA1-interacting protein with a KRAB domain 1) serves as a transcription repressor by interacting with BRCA1, and regulates the transcription of DNA damage response genes, such as *GADD45a*, *p21*, *Bax* and *GADD153*.[3] *ZNF350* is an interesting candidate gene in association with breast cancer susceptibility because the mutations in BRCA1-interacting proteins or the genes that are involved in the BRCA1 pathway were found in familial breast cancer patients.

In this issue of the journal, Plourde *et al.*[4] reported the association between promoter variants of *ZNF350* and breast cancer susceptibility in 96 high-risk non-BRCA1/2 French Canadian breast cancer families. They investigated the single-nucleotide polymorphisms (SNPs) in the *ZNF350* gene region in previous report[5] and promoter regions in this study.[4] However, neither SNPs nor haplotypes in this promoter region were significantly associated with breast cancer risk, although the haplotype analysis combining the SNPs in promoter and gene regions showed associations with $P<0.05$. In the functional analysis by reporter assay, two of three haplotypes (H11 and H12) showed significantly increased transcriptional activities compared with H8, the most common haplotype.

There are, however, two major problems. First, they should consider multiple testing because they examined 23 SNPs and 33 haplotypes. When Bonferoni's correction is applied, none of the SNPs had P-value $<\alpha=0.00217$ (0.05/23) and no haplotype had P-value $<\alpha=0.00152$ (0.05/33). Second, the risk haplotypes (which were not significant in the association study; H11, $P=0.38$, odds ratio ≈ 2 and H12, $P=1.0$, odds ratio ≈ 1) were associated with increased transcriptional activities, although ZNF350 serves as a tumor/metastatic suppressor and its expression was low in tumor tissue. They discussed about this critical discrepancy as the increase of ZNF350 expression could be involved in initiation rather than in development during tumorigenesis; however, there is no evidence supporting their speculation at present. Also, in a previous report investigating the association of *ZNF350* SNPs with breast cancer susceptibility, no significant association was observed in three SNPs,[6] including c.425T>C (rs2278420), which showed marginal association ($P=0.040$) in this study. Although some SNPs in *ZNF350* showed associations with $P<0.05$, consistent results have not been observed.[7–9] These results suggest that *ZNF350* SNPs, especially promoter SNPs, are not more likely to be the causative SNPs associated with familial breast cancer risks. To identify positive signal of low minor allele frequency and high odds ratio (moderate-penetrance susceptibility gene) in case–control association study, much more sample size is needed (more than 500 cases and 500 controls to obtain 80% statistical power to detect an effect with odds ratio of 2 or greater for allele (haplotype) with 2% frequency at $\alpha=0.05$). Further analysis with larger sample size or replication study will be required to evaluate the impact of *ZNF350* on breast cancer susceptibility.

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1 Stratton, M. R. & Rahman, N. The emerging landscape of breast cancer susceptibility. *Nat. Genet.* **40,** 17–22 (2008).
2 Meindl, A., Ditsch, N., Kast, K., Rhiem, K. & Schmutzler, R. K. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. *Dtsch. Arztebl. Int.* **108,** 323–330 (2011).
3 Zheng, L., Pan, H., Li, S., Flesken-Nikitin, A., Chen, P. L., Boyer, T. G. *et al.* Sequence-specific transcriptional corepressor function for BRCA1 through a novel zinc finger protein, ZBRK1. *Mol. Cell* **6,** 757–768 (2000).
4 Plourde, K. V., Labrie, Y., Desjardins, S., Belleau, P., Ouellette, G., Durocher, F. *et al.* Analysis of *ZNF350/ZBRK1* promoter variants and breast cancer susceptibility in non-BRCA1/2 French Canadian breast cancer families. *J. Hum. Genet.* **58,** 59–66 (2013).
5 Desjardins, S., Belleau, P., Labrie, Y., Ouellette, G., Bessette, P., Chiquette, J. *et al.* Genetic variants and haplotype analyses of the *ZBRK1/ZNF350* gene in high-risk non BRCA1/2 French Canadian breast and ovarian cancer families. *Int. J. Cancer* **122,** 108–116 (2008).
6 Huo, X., Lu, C., Huang, X., Hu, Z., Jin, G., Ma, H. *et al.* Polymorphisms in BRCA1, BRCA1-interacting genes and susceptibility of breast cancer in Chinese women. *J. Cancer Res. Clin. Oncol.* **135,** 1569–1575 (2009).
7 Rutter, J. L., Smith, A. M., Dávila, M. R., Sigurdson, A. J., Giusti, R. M., Pineda, M. A. *et al.* Mutational analysis of the BRCA1-interacting genes ZNF350/ZBRK1 and BRIP1/BACH1 among BRCA1 and BRCA2-negative probands from breast-ovarian cancer families and among early-onset breast cancer cases and reference individuals. *Hum. Mutat.* **22,** 121–128 (2003).
8 Yarden, R. I., Friedman, E., Metsuyanim, S., Olender, T., Ben-Asher, E. & Papa, M. Z. Single-nucleotide polymorphisms in the p53 pathway genes modify cancer risk in BRCA1 and BRCA2 carriers of Jewish-Ashkenazi descent. *Mol. Carcinog* **49,** 545–555 (2009).
9 García-Closas, M., Egan, K. M., Newcomb, P. A., Brinton, L. A., Titus-Ernstoff, L., Chanock, S. *et al.* Polymorphisms in DNA double-strand break repair genes and risk of breast cancer: two population-based studies in USA and Poland, and meta-analyses. *Hum. Genet.* **119,** 376–388 (2006).