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COMMENT

A commentary on germline mutations of multiple breast cancer-related genes are differentially associated with triple-negative breast cancers and prognostic factors

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Genomic analysis is important for personalized medicine in cancer. Whole- or multi-gene analysis and molecular pathological analysis can provide valuable information for cancer therapy.

Breast cancer is one of the most common cancers in women [1]. Like other cancers, breast cancer is a diverse set of diseases, which can be divided into subtypes with different pathological and molecular characteristics. An understanding of the genes which predispose individuals to breast cancers is important for understanding the mechanisms of breast cancer development, and valuable for estimating the degree of malignancy and the prognosis of individual breast cancers. For example, triple-negative breast cancers (TNBCs), a group of breast cancers that are negative for estrogen receptors, progesterone receptors, and human epidermal growth factor receptor type 2—currently used therapeutic targets for breast cancer—also show pathological genomic heterogeneity. TNBCs account for about 5–19% of all breast cancers [1]. Although TNBCs are not homogeneous, this group of cancers lacks established treatments and therapeutic targets, such as endocrine therapy, and are primarily treated using general surgery and chemotherapy. Therefore, molecular analysis is required for elucidating the genetic predisposition for TNBCs. Such analysis will provide important information, which will form the basis for the identification of the character, prognosis, and treatment of cancers in this category.

BRCA1 and *BRCA2* are well known to be genes, which predispose individuals to the development of breast cancer [2]. Other predisposing genes are almost certainly involved, but many have not yet been clearly identified. Changes in germline genes in breast cancer in various regional populations are therefore currently under investigation.

Hata et al. investigated the presence of pathogenic variants in germline in 583 Chinese women with breast cancer, using next-generation sequencing with a panel of 54 cancer-related genes [3]. Seventy-nine pathogenic variants were found in 21 cancer-related genes. The pathogenic variants identified accounted for 14.4% of the breast cancers. The most frequent genes with pathogenic variants were the *BRCA1* and *BRCA2* genes, followed by *PALB2*. Pathogenic variants of the *BRCA1* gene were frequently found in TNBCs. In these TNBCs, pathogenic variants of *PALB2*, as well as *BRCA1* were frequent, suggesting a strong association between these genes and breast cancer in the Chinese population [3].

PALB2 has also been linked to other cancers [4]. Studies have been conducted into therapies for patients with a pathogenic variant of *PALB2*. Because *PALB2* is involved in DNA repair, as are *BRCA1* and *BRCA2*, and disruption of genomic stability is considered to contribute to the risk of development of breast cancer [2], PARP inhibitors may also be effective in breast cancers with pathogenic *PALB2* variants.

There have also been reports of the *CHEK2* and *ATM* genes being associated with TNBCs in the European population [5, 6]. These variants either occurred at very low levels or were not found in the current analysis of a Chinese population. Various genomic factors have been found in regional populations in association studies. In order to find relevant factors in each population, it is necessary to perform analysis in each local population or ethnicity. It is important to continue to use multigene panels and comprehensive genomic analyses in each population.

Finding gene variants related to breast cancer may require sequencing of the entire gene, but not for specific variants. Variants found in the same causative gene for the same disease may vary from region to region, or ethnicity to

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ethnicity, and individual to individual as well [2, 7]. The pathogenic variants of the *BRCA1* and *BRCA2* genes that were found to be relevant in this work differ, for example, from those found in other European populations, and also show ethnic differences [3, 5, 6].

In such predisposition gene analysis, NGS-based gene set panel sequencing appears to be more effective than companion diagnosis for identifying single variants. Such analysis is often performed on a large scale, requiring the analysis of a large number of genes. It is therefore important to develop cost-effective panel analysis methods for large-scale analysis [8, 9].

In research published by Hata et al., an analysis of 583 Chinese patients with breast cancer suggested that *PALB2* was associated with breast cancer, and particularly with a genetic predisposition to TNBCs. These researchers also suggested that the *MUTYH* gene, which has been reported to be associated with male breast cancer [10], may also be involved in female breast cancer. However, the number of patients these researchers examined was not sufficient to draw strong conclusion, and more extensive analysis will be needed to obtain stronger associations and insights into genes predisposing to each subtype.

In this paper the researchers reported the results of investigations into germline variants. Somatic mutation is also important in a tumor. In addition to analyzing germline mutations, analysis of somatic mutations in breast cancers may provide important insights into the biology of these diseases.

By integrating the results of previous publications, and performing research to clarify changes in cancer cells, it should be possible to determine the prognosis and effective treatment options for individual breast cancers now, and develop new targeted molecular therapies for breast cancer in the future. Such progress is essential for the realization of personalized medicine for breast cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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