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Partner and Localizer of BRCA-2 (PALB-2) Mutation Analysis Is Rapidly Being Adopted into Clinical Practice

PALB2 Mutasyon Analizi Klinik Uygulamaya Hızla Kabul Ediliyor

To the Editor,

Breast-Cancer Risk in Families with Mutations in PALB2: A.C. Antoniou, S. Casadei, T. Heikkinen, et al. N Engl J Med. 2014;371:497-506.

In a study published in N Engl J Med. August 2014, researchers from 14 centers in eight countries investigated information from 362 family members from 154 families who had an abnormal partner and localizer of *BRCA2 (PALB2)* gene, but did not have an abnormal *BRCA1* or *BRCA2* gene. Their aim was to demonstrate the importance of loss-of-function mutations in *PALB2* as a cause of hereditary breast cancer. The study included 311 women with an abnormal *PALB2* gene; 229 of these women had been diagnosed with breast cancer and 51 men with an abnormal *PALB2* gene; seven of whom had been diagnosed with breast cancer. The researchers compared the breast cancer risk of the study population to the general population. They found out that overall, women with an abnormal *PALB2* gene had a risk of breast cancer that was 9.47 times higher than average. Women with an abnormal *PALB2* gene had a 14% risk of developing breast cancer by age 50 and a 35% risk of developing breast cancer by age 70. The average lifetime risk of breast cancer is about 12%. This increase in risk linked to an abnormal *PALB2* gene was dependent on the women's age and family history. They have demonstrated that the relative risk of breast cancer among *PALB2* mutation carriers increased significantly as birth cohort became more recent (P<0.001). In women with an abnormal *PALB2* gene, breast cancer risk was eight to nine times higher than average in women aged 20 to 39, six to eight times higher than average in women aged 40 to 60, and five times higher than average in women older than 60 years of age. By the age of 70, women with an abnormal *PALB2* gene with no family history of breast cancer had a 33% risk of developing breast cancer whereas women with two or more first-degree relatives with breast cancer at 50 years of age had a 58% risk of developing the disease. The authors concluded that based on their estimates, breast cancer risk for a *PALB2* mutation carrier, even in the absence of a family history of breast cancer, would be classified as high according to various guidelines. The researchers also reported that this level of risk may justify adding *PALB2* to genetic testing for *BRCA1* and *BRCA2*.

A Genetic counselor's perspective

Partner and localizer of *BRCA2 (PALB)* is a gene whose protein facilitates the function of *BRCA2* and interacts with *BRCA1* to aid in repairing double strand and interstrand cross-link DNA damage. Biallelic *PALB2* mutations cause Fanconi Anemia complement group N (FANCN) and monoallellic mutations in the *PALB2* gene are associated with increased breast and pancreas cancer risks (1). *PALB2* mutations may account for as much as 3% of familial breast cancer risk (2). A recent study of 362 members from *PALB2* mutation positive families found that the risk for breast cancer in female mutation carriers ranged between 33% to 58% by age 70, with the higher risks relating to those women with a family history of early onset (<50) breast cancer in 2 first degree family members (3). The study also identified an 8 fold increase in male breast cancer risk and a 2 fold increase in ovarian cancer risk, both of which need to be confirmed in additional studies due a lack of statistical significance. These data suggest that female *PALB2* mutation carriers may have breast cancer risks that are similar to those conferred by mutations in the *BRCA2* gene. These findings suggest that women who carry *PALB2* gene mutations may warrant similar breast cancer screening and prevention strategies as those offered to *BRCA2* mutation carriers. *PALB2* mutation analysis is available and is rapidly being adopted into clinical practice. As the data continues to accumulate it is likely that *PALB2* mutation analysis will become a standard part of genetic testing in the realm of hereditary breast cancer predisposition. Whether testing will be done in addition to *BRCA1/2* or as part of a larger breast cancer gene panel remains to be determined. In addition, more data will provide evidence to support the development of specific management guidelines to aid in the care of these at risk patients.

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