PALB2: A Third Important Gene for Inherited Breast Cancer

Following the publication of an important article in the New England Journal of Medicine (NEJM) in August 2014, germline PALB2 gene mutations were confirmed as the third most important gene for inherited breast cancer, following BRCA1 and BRCA2.1 PALB2 stands for “partner and localizer of BRCA2” and is located on chromosome 16. Studies suggest that PALB2 mutations may account for ~2-3% of inherited breast cancer, highlighting its importance as a breast cancer predisposition gene. In those with PALB2 mutations, prior studies suggest: 1) breast cancer risks in women range from two to six-fold; 2) breast cancer risks in men appear to be 8-fold or higher; and 3) risk of pancreatic cancer, although poorly defined, may also be elevated.

While the increased risk of breast cancer in those with a PALB2 mutation has been known for years, genetic testing was not routinely performed because mutations were thought to be rare and cancer risks were unclear. However, declining genetic testing costs due to next-generation sequencing (NGS) technology have revolutionized genetic testing practices through development of multi-gene tests that include BRCA, PALB2, and multiple other genes in one test. As a result, individuals are increasingly being identified with PALB2 mutations.

The recent NEJM article is the first to broadly address the absolute risk of breast cancer in PALB2 carriers. This international study was based on 154 families with PALB2 mutations, including 311 women and 51 men. In this study, breast cancer risk estimates in those with PALB2 mutations: 1) ranged from 33-58% by age 70 in women depending on family history; and 2) were just over 8-fold in men (although results did not reach statistical significance). Results also suggested that women with a PALB2 mutation were slightly more likely to develop triple negative breast cancer, which is an aggressive type of breast cancer resistant to hormone treatment with a higher chance of recurrence.

“Since the BRCA1 and BRCA2 genes were discovered in the mid-90s, no other genes of similar importance have been found. PALB2 is a potential candidate to be ‘BRCA3’.”

Interestingly, PALB2-associated cancers may be sensitive to a new class of drugs known as PARP inhibitors, which are currently under investigation for BRCA-associated cancers. Thus it is possible that these drugs may also work in PALB2-associated cancers.

There are early suggestions that women with PALB2-associated breast cancer may develop more aggressive disease.2 However, most studies are based on small numbers, thus it remains important to study breast cancer characteristics and outcomes in PALB2 carriers through larger studies. Only through these types of research efforts will we be able to learn more about this important gene and figure out how to better help those with mutations. As outlined on page 1 of this newsletter, we are currently recruiting 500 PALB2 mutation carriers to determine breast cancer characteristics and outcomes.

Breast cancer risks and outcomes among women with a PALB2 mutation

Through a recent study of over 12,000 Polish women with breast cancer, PALB2 mutations were detected in almost 1%. In this study, about one third of those with a PALB2 mutation had triple negative (lacking estrogen, progesterone and HER2 receptors) breast cancer and the average age at breast cancer diagnosis was 53.3 years. Breast tumors of 2 cm or larger had substantially worse outcomes (i.e., 32.4% 10-year survival) compared with tumors smaller than 2 cm (i.e., 82.4% 10-year survival).

Overall, the study findings confirm a substantially elevated risk of breast cancer (24-40%) among women with a PALB2 mutation up to age 75. The five-year cumulative incidence of contralateral breast cancer was 10% among those with a PALB2 mutation, compared to 17% among those with a BRCA1 mutation and 3% among those without a mutation in either gene. Survival at 10 years was also worse in women with a PALB2 mutation at just under 50%, compared to 72.0% among those with a BRCA1 mutation, and 74.7% among those without a mutation in either gene.

Given a possible association of poorer outcomes among women with breast cancers larger than 2 cm, focused efforts should be made to detect small cancers among women with a PALB2 mutation through various screening procedures.

Furthermore, as early data suggests women with PALB2-associated breast cancer may develop more aggressive disease, it is important to study breast cancer characteristics and outcomes in PALB2 carriers through larger studies.

Ultimately, personalized treatments may be important for these women, thus it is vital to collect details about pathological features (receptor status), treatment (including chemotherapy regimen) and follow-up. Only through these types of research efforts will we be able to learn more about this important gene and figure out how to better care for those with mutations. As outlined on the last page of this newsletter, we are currently recruiting 500 PALB2 mutation carriers to determine breast cancer characteristics and outcomes.