

## Background

PALB2 is now known to be a moderate-to-high-penetrance breast cancer predisposition gene. As genetic testing is most often applied to high-risk individuals, it is not surprising that our laboratory's data are consistent with PALB2 presenting as a high-penetrance gene in a subset of patients. Recent studies indicate that PALB2 is mutated in the germline of roughly 1% of appropriately tested patients. It confers lifetime breast cancer risks from 30% to 60% based on family history (Antoniou, AC, *et al. NEJM.* 2014; 371(6):497-506), which, at the high end, is comparable to risk from BRCA2.

In this case series, we describe the clinical presentations (hormone receptor status, age of onset, presence of multiple primaries, and reported family history) of 111 PALB2 mutation carriers, for the purpose of further delineating the spectrum of cancers reported in PALB2-affected families.

## Methods

One hundred and eleven (111) sequential patients referred for genetic testing were selected based on a Pathogenic (P) or Likely Pathogenic (LP) mutation in PALB2 as well as a personal or family history of cancer. Variants were classified using a point-based system that closely adheres to ACMG guidelines. De-identified personal and family histories provided by ordering clinicians were examined.

## Results

Among the 111 patients assessed (105 females, 6 males), 84 were affected with cancer and 27 were unaffected carriers. Of the 84 cancer-affected patients, 58% were 49 years old or younger, and 8 patients were younger than 35. 15% presented with bilateral breast cancer, 8% presented with breast cancer and an additional non-breast primary, and 5% presented with multiple primary cancers of other sites. 8% had triple negative breast cancer. 13% reported a personal history of pancreatic cancer (4 of whom were males). 73% of affected carriers described a significant family history of cancers. Of the unaffected patients, the average age was 45 years with 22% over the age of 60 at the time of testing.

Among the 84 affected individuals, review of personal and family history information showed 75 of 84 (89%) meet the 2016 NCCN Breast and/or Ovarian Cancer Genetic Assessment Criteria for Further Genetic Risk Evaluation. Of cases not meeting criteria based on the provided information, several included histories suggestive of genetic risk that may prompt referral for genetic risk assessment.

## Results (cont.)

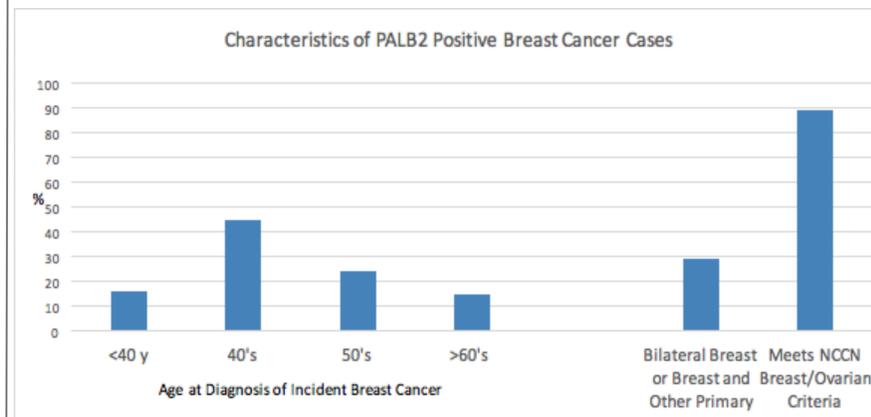


Figure 1. Presentation of breast cancers in PALB2 mutation carriers

Family history information was available from 79 unique families of affected individuals. A family history of breast cancer was reported in 60 of 79 (76%), ovarian cancer in 10 of 79 (13%), stomach cancer in 9 of 79 (11%), colorectal cancer in 9 of 79 (11%), pancreatic cancer in 7 of 79 (9%), and uterine cancer in 7 of 79 (9%). Other cancers reported in family histories included: melanoma, renal, cervical, thyroid and lymphoma.

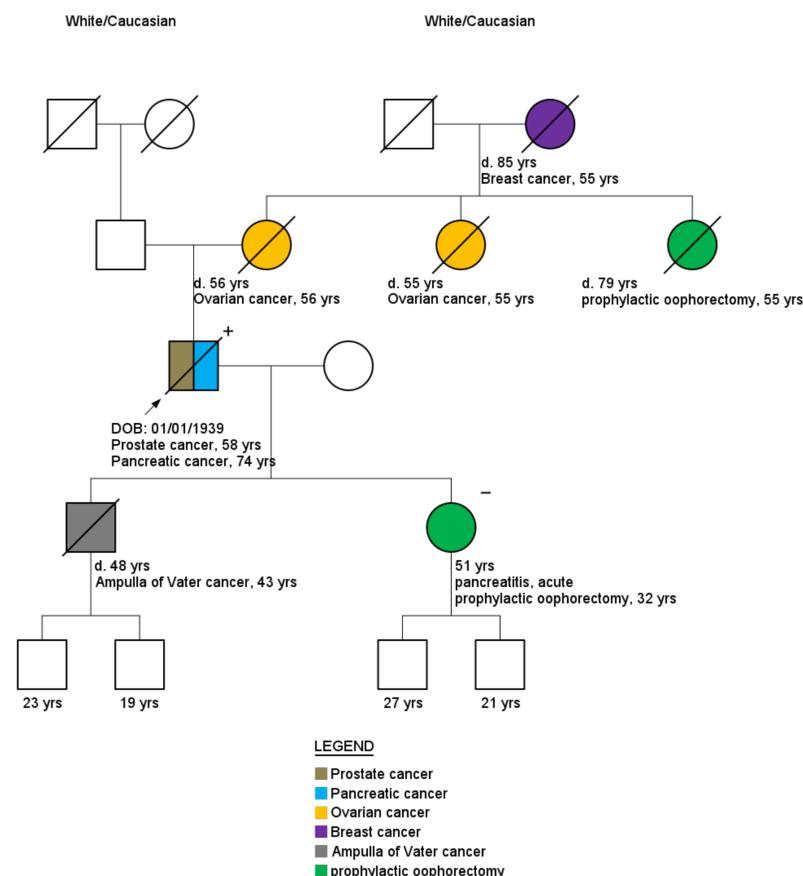


Figure 2. Male proband with PALB2 mutation

## Results (cont.)

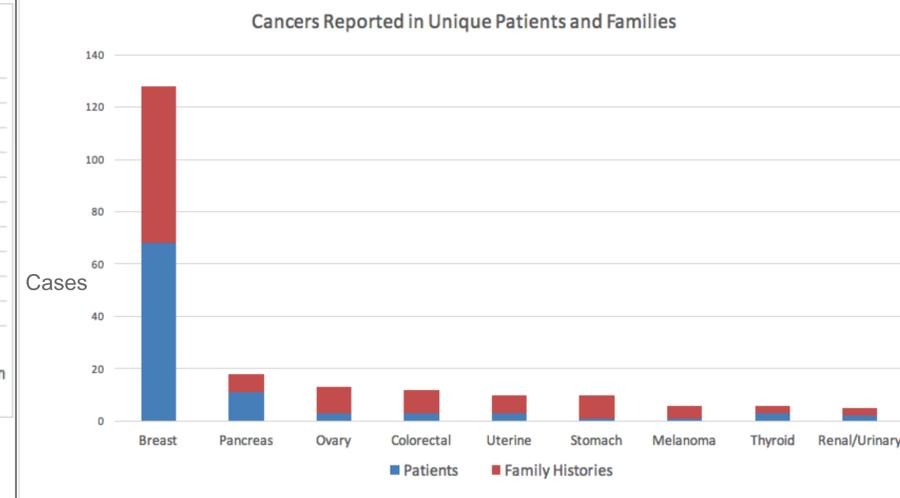


Figure 3. Phenotypic spectrum reported in probands and family histories of affected PALB2 carriers

## Conclusions

- ◆ This patient series highlights clinical aspects of PALB2-related breast cancer suggestive of a high-penetrance gene, including presentation of early-onset and multiple primary cancers.
- ◆ There are certain ascertainment biases and limitations to this study including patients being selected for commercial testing by clinicians. In addition, information on family history and tumor pathology was unconfirmed. Nonetheless, we think these data represent how a subset of PALB2 families may present in the clinical setting.
- ◆ Consistent with current guidelines, our study suggests that clinicians need to consider PALB2 mutation status in the context of family history to inform risk assessment and management decisions.
- ◆ More research is needed to understand the relationship between PALB2 and other cancers, particularly in males. Many, but not all, patients with PALB2 variants met NCCN criteria for breast and ovarian cancer genetic evaluation, emphasizing the importance of including PALB2 in families undergoing such evaluation and considering including PALB2 in families with other complex presentations.