Teasing out the *PALB2* Phenotype

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Background: Biallelic mutations in *PALB2* (Partner and Localizer of *BRCA2*) are known to cause Fanconi Anemia Type N. Multiple reports have demonstrated an increased risk for cancer in individuals heterozygous for *PALB2* mutations. For example, a recent study by Antoniou *et al* reported a 33-58% lifetime risk for breast cancer in *PALB2* mutation carriers, with 30% of carriers reporting triple negative breast cancer (TNBC). Others have suggested associations between *PALB2* heterozygosity and pancreatic cancer, ovarian cancer, male breast cancer, and prostate cancer, as well. We aimed to better define *PALB2* phenotypes by assessing clinical history of TNBC, pancreatic, ovarian, and prostate cancers amongst *PALB2* mutation carriers identified via multigene panel testing.

Methods: We reviewed clinical histories of 11,007 individuals who underwent *PALB2* sequence and deletion/duplication analysis as part of a multigene hereditary cancer panel. Descriptive statistics were utilized for clinical histories of *PALB2* carriers, and chi square analysis was used to compare clinical histories of *PALB2* mutation carriers to mutation-negative controls. Individuals with mutations in other cancer susceptibility genes were excluded from analysis.

Results: A total of 98 *PALB2* mutation carriers identified among 9610 individuals were included in our analysis. The majority of mutation carriers were Caucasian (80%) and female (92.8%). All identified mutations were truncating (nonsense, frameshift, or gross deletions). No pathogenic missense mutations were identified in this cohort. 77.6% (n=76) of mutation carriers had breast cancer, diagnosed at a mean age of 48. Hormone receptor status was available for 48 mutation carriers and 2469 controls. 37.5% (18/48) of breast cancers in mutation carriers were reported as triple negative, compared to 17.1% (423/2469) of breast cancers in controls (OR: 2.9 ; p= 0.0002). 7.8% (n= 8) of *PALB2* mutation carriers had ovarian cancer. There was no significant difference in the incidence of ovarian cancer between *PALB2* mutation carriers and controls (OR: 0.65 ; p= 0.25). Additionally, mutation carriers were significantly less likely to have a family history of ovarian cancer than controls (OR: 0.5; p= 0.02). 5.9% (n=6) of mutation carriers had pancreatic cancer, diagnosed at a mean age of 57.8, compared to 61 for controls. *PALB2* mutation carriers were 1.3 times more likely to have personal and/or family history of pancreatic cancer, although this was not statistically significant (p= 0.22). Similarly, *PALB2* mutation carriers were 1.5 times more likely to have a family history of prostate cancer, although this was not statistically significant (p= 0.09).

Conclusions: Our data supports existing literature associating *PALB2* mutations with TNBC. We did not observe significant associations between *PALB2* carrier status and clinical history of pancreatic, prostate, or ovarian cancers. However, this data should be interpreted with caution, as it is possible that unidentified genetic factors contributed to clinical history of cancer in our mutation-negative controls. Investigation of *PALB2*-associated cancer risks in an unselected prospective cohort would help to further elucidate the *PALB2* phenotype.