Mutation Analysis of PALB2 in high risk and lower risk patients negative for BRCA1 and BRCA2 mutations

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ABSTRACT

PALB2 has been identified as a breast cancer susceptibility gene conferring ~2-4 fold increased risk of breast cancer. A number of studies have estimated the PALB2 mutation prevalence to range from 0.5% - 2.9% in various populations of breast cancer patients. We performed a study to determine the PALB2 mutation prevalence in a large US referral testing population. DNA samples were anonymized from two subsets of patients: 955 early onset breast cancer patients with severe family history, and 524 patients with later onset of breast cancer and/or less severe family history. All patients were negative for deleterious sequence mutations or large rearrangements in BRCA1 and BRCA2. We identified 10 disease associated PALB2 mutations in the high risk group of 955 patients and 2 deleterious PALB2 mutations in the lower risk group of 524 patients. Identified PALB2 mutations included 8 nonsense and 3 frameshift mutations. This study also identified 1 variant adjacent to the consensus splice site of intron 10 that was previously reported in the literature to be associated with Fanconi Anemia–N in a compound heterozygous individual. In addition, there were 31 unique variants of unknown clinical significance. The mutation prevalence for the high risk population was 1.05% (95% C.I., 0.5 - 1.92) whereas that for the lower risk population was 0.38% (95% C.I., 0.05 - 1.37). The observed PALB2 mutation rate is ~2.74 times higher in the high risk group versus the lower risk group, although this difference is not statistically significant. The PALB2 prevalence data derived from subsets of breast cancer patients were used to estimate the relative contribution among total mutations identified in the BRCA1, BRCA2 and PALB2 genes. It was estimated that the proportion of PALB2 mutations was ~3.8% of PALB2, BRCA1 and BRCA2 mutations identified overall (~3.6% in the high risk group and ~4.1% in the lower risk group). These estimates suggest that the PALB2 gene, which has relatively lower penetrance for breast cancer, accounts for a similar mutation prevalence to BRCA1 and BRCA2.

REFERENCES