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Identification of New Familial Breast Cancer Susceptibility Genes: Are We There Yet?

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Abstract : The genetic cause of the majority of multiple-case breast cancer families remains unresolved. Next generation sequencing has emerged as an efficient strategy for identifying predisposing mutations in individuals with inherited cancer. We are conducting whole exome sequence analysis of germ line DNA from multiple affected relatives from breast cancer families, with the aim of identifying rare protein truncating and non-synonymous variants that are likely to include novel cancer predisposing mutations. Data from more than 200 exomes show that on average each individual carries 30-50 protein truncating mutations and 300-400 rare non-synonymous variants. Heterogeneity among our exome data strongly suggest that numerous moderate penetrance genes remain to be discovered, with each gene individually accounting for only a small fraction of families (~0.5%). This scenario marks validation of candidate breast cancer predisposing genes in large case-control studies as the rate-limiting step in resolving the missing heritability of breast cancer. The aim of this study is to screen genes that are recurrently mutated among our exome data in a larger cohort of cases and controls to assess the prevalence of inactivating mutations that may be associated with breast cancer risk. We are using the Agilent HaloPlex Target Enrichment System to screen the coding regions of 168 genes in 1,000 BRCA1/2 mutation-negative familial breast cancer cases and 1,000 cancer-naive controls. To date, our interim analysis has identified 21 genes which carry an excess of truncating mutations in multiple breast cancer families versus controls. Established breast cancer susceptibility gene PALB2 is the most frequently mutated gene (13/998 cases versus 0/1009 controls), but other interesting candidates include NPSR1, GSN, POLD2, and TOX3. These and other genes are being validated in a second cohort of 1,000 cases and controls. Our experience demonstrates that beyond PALB2, the prevalence of mutations in the remaining breast cancer predisposition genes is likely to be very low making definitive validation exceptionally challenging.

Keywords : predisposition, familial, exome sequencing, breast cancer
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