

Reclassifying Duplication Variants in High Risk Cancer Genes by Identifying Tandem Duplication Breakpoints

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Alterations in genomic copy numbers may lead to changes in gene expression and function and are known to cause various disease states including congenital anomalies, developmental disorders and numerous cancer syndromes. Most gross deletions in high risk cancer genes, usually larger than 3~5 megabases, fall within microarray reporting guidelines and are reported as pathogenic. However, gross duplications are generally reported as variants of unknown significance (VUSs), which can then subsequently be reclassified as likely deleterious or likely benign as more information becomes available. To determine whether a copy number duplication variant can be reclassified as likely pathogenic, we utilized paired-end Next Generation sequencing (NGS) method that can detect the breakpoints of tandem duplications in high risk cancer genes, including *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *CDH1*, and *TP53*. DNA was available for NGS on 103 consenting cancer patients with a variety of gross duplications who had a personal or family history of breast and/or ovarian cancers. We designed probe sets to capture the target regions with the suggested breakpoints identified by array comparative genomic hybridization (aCGH) for 32 different gross duplication variants. The captured DNA was then sequenced by paired-end NGS and mapped to the genome. Our custom pipeline identified a tandem duplication in 79% of samples we tested (81/102). Most tandem duplications in these high risk cancer genes caused a frameshift or structural change, which may result in novel function of the genes (loss-of-function or gain-of-function) and is predicted to be damaging by most *in silico* algorithms examined. Therefore, this study suggests that 32 previously classified VUSs detected as tandem duplications can be re-classified as likely pathogenic. Proper classification of variants detected for these high risk cancer genes will help guide physicians in selecting the best course of treatments for their patients and improve the overall recovery and health of the patient.