“Genomic Structural Variation in Cancer Susceptibility”

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Abstract: Genome-wide association studies (GWAS) using single-nucleotide polymorphisms (SNPs) have identified a number of genetic variants associated with low-penetrance cancer susceptibility, however a large portion of the genetic basis of cancer susceptibility remains unexplained. Recent advances in high-resolution genome wide scanning platforms have enabled us to recognize the prevalence of submicroscopic structural variations, including copy-number variants (CNVs), in the human genome. While the majority of CNVs contribute to normal phenotypic variation, CNVs have been associated with common and complex human diseases and de novo CNVs have recently been implicated in sporadic autism and schizophrenia. The contribution of CNVs to cancer susceptibility remains unknown, although inherited CNVs have been implicated in familial pancreatic cancer and p53 mediated cancer susceptibility and we have documented de novo mutations of cancer susceptibility genes. In this study, we will attempt to identify CNVs associated with breast cancer susceptibility using an ascertainment of familial breast cancer cases without BRCA1/2 mutations and unaffected controls. We will also determine the frequency of de novo CNVs in sporadic early-onset cancers using an ascertainment of "trios" consisting of cancer-affected probands and unaffected biologic parents. Utilizing the NimbleGen array, CNV analysis and interpretation will be performed by the laboratory that pioneered the de novo CNV studies in autism. With Cold Spring Harbor Laboratory’s expertise in copy-number determination and MSKCC's clinical resources and experience in whole genome association studies, we will have the unique opportunity to perform the first systematic evaluation of CNV mutations in cancer.