“Genomic Structural Variation in Cancer Susceptibility"

Principal Investigator:

- Kenneth Offit, MD, Memorial Sloan-Kettering Cancer Center

Co-Principal Investigator:

- Larry Norton, MD, Memorial Sloan-Kettering Cancer Center
- Michael Wigler, PhD, Cold Spring Harbor Laboratory

Funding Category: B

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.