"Breast Cancer Protective Alleles by Whole Genome Association and Copy Number Analysis"

Principal Investigator:
- Kenneth Offit, MD, Memorial Sloan-Kettering Cancer Center

Co-Principal Investigators:
- David Altshuler, MD, PhD, The Broad Institute of Harvard & MIT
- Daniel Haber, MD, PhD, The Broad Institute of Harvard & MIT

Funding Category: B

Abstract: A decade after the initial identification of BRCA1 and BRCA2, there remains considerable uncertainty regarding cancer risks associated with inherited mutations of these genes. This variable penetrance is most striking for BRCA2, and affects clinical management. While cancer risks are significantly increased, patients with the same BRCA2 mutation may develop breast, ovarian or other cancers at different ages or not at all (reviewed in Offit K. JNCI 98:1675, 2006) It is the hypothesis motivating this proposal that a) there exist genetic "protective" alleles which interact with known BRCA2 mutations to modify penetrance, and b) that these alleles may also act as breast cancer protective factors in the general population. This study will leverage a unique and clinically important resource, which is the large number of Ashkenazi Jewish women in New York, Boston, and Israel harboring a single BRCA2 mutation. In this isogenic background, we will take an unbiased whole genome approach to search for common alleles (both SNP and copy number) that influence phenotypic diversity. Identification of such loci would both shed light on BRCA-mediated tumorigenesis, and be of potential utility in genetic testing. The identification of such genes may also be relevant to the mechanisms of tumorigenesis outside of a BRCA background, i.e. in "sporadic" malignancies as well. This study will bring together an ascertainment assembled by clinical leaders at MSKCC, DFCI/Harvard Cancer Center, and an international consortium, and combine it with the expertise in whole genome association analysis at the Broad Institute as well as MSKCC.