

“Breast Cancer Protective Alleles by Whole Genome Association and Copy Number”

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Abstract: A decade after the description of BRCA1 and BRCA2, the relative risks associated with BRCA mutations varies between families. This project takes advantage of a world-wide assembly of DNA samples from over 6,000 carriers of BRCA2 mutations. As part of our initial proposal we have carried out a whole genome association study comparing those affected by breast cancer at early age to those unaffected at later age. Phase 1 of that study is completed and a preliminary phase 2 is in final data analysis. This study has confirmed previously known loci (e.g. FGFR2) and has identified several novel loci of biological interest. This competitive renewal aims to perform a denser Phase 2 replication of the top 15,000 SNPs in phase 1 utilizing a custom chip. At the conclusion of this renewal, we feel that major components of variance in penetrance due to genetic modifiers of BRCA2 will be elucidated. These findings can then be explored as "cancer resistance" loci in the general population, or in pre-assembled populations (e.g. a centenarian cohort) outside of the scope of this proposal. This project will harness cutting edge genomic technologies at the Broad Institute and a worldwide "consortium of consortia" who are dedicated to the successful undertaking of this experiment.