Identifying a breast cancer genetic locus at NCOA7 through a multi-stage association study

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GEMS classroom, 3rd Floor in Shriner's Building  
Coffee, water, and cookies will be provided

Abstract

Estrogen metabolism and growth factor signaling pathway genes play key roles in breast cancer development. We evaluated associations between breast cancer and tagging single-nucleotide polymorphisms (SNPs) of 107 candidate genes of these pathways using single allele- and haplotype-based tests. We first sought concordance of associations between two study populations: the Nashville Breast Cohort (NBC; 510 cases, 988 controls), and the Cancer Genetic Markers of Susceptibility (CGEMS) breast cancer study (1,145 cases, 1,142 controls). Findings across the two study populations were concordant at tagging SNPs of six genes, and at previously published SNPs of FGFR2. We sought further replication of results for EGFR (epidermal growth factor receptor), NCOA7, and FGFR2 in the independent Collaborative Breast Cancer Study (CBCS; 1,552 cases, 1,185 controls). Associations at NCOA7 and FGFR2 replicated across all three studies. The association at NCOA7 on 6q22.32, detected by a haplotype spanning the initial protein-coding exon (5’-rs9375411, rs11967627, rs549438, rs529858, rs490361, rs17708107-3’), has not been previously reported. The haplotype had a significant inverse association with breast cancer in each study [OR_Het: 0.69 (NBC), 0.76 (CGEMS), 0.79 (CBCS)], and a meta-analysis OR_Het of 0.75 (95% CI, 0.65–0.87, P = 1.4×10^{-4}) in the combined study populations. The haplotype frequency was 0.07 among cases, and 0.09 among controls; homozygotes were infrequent and each OR_Hom was not
significant. NCOA7 encodes a nuclear receptor coactivator that interacts with estrogen receptor $\alpha$ to modulate its activity. These observations provide consistent evidence that genetic variants at the NCOA7 locus may confer a reduced risk of breast cancer.

Further replication of observed associations is underway in an additional breast cancer study population selected from the Vanderbilt BioVU DNA Databank (1,170 cases, 1,170 controls). See Higginbotham et al. *Cancer Research;* 71(11): 3881-8 for additional details.