Polymorphisms in a Putative Enhancer at the 10q21.2 Breast Cancer Risk Locus Regulate NRBF2 Expression.

Abstract:
Genome-wide association studies have identified SNPs near ZNF365 at 10q21.2 that are associated with both breast cancer risk and mammographic density. To identify the most likely causal SNPs, we fine mapped the association signal by genotyping 428 SNPs across the region in 89,050 European and 12,893 Asian case and control subjects from the Breast Cancer Association Consortium. We identified four independent sets of correlated, highly trait-associated variants (iCHAVs), three of which were located within ZNF365. The most strongly risk-associated SNP, rs10995201 in iCHAV1, showed clear evidence of association with both estrogen receptor (ER)-positive (OR = 0.85 [0.82-0.88]) and ER-negative (OR = 0.87 [0.82-0.91]) disease, and was also the SNP most strongly associated with percent mammographic density. iCHAV2 (lead SNP, chr10: 64,258,684:D) and iCHAV3 (lead SNP, rs7922449) were also associated with ER-positive (OR = 0.93 [0.91-0.95] and OR = 1.06 [1.03-1.09]) and ER-negative (OR = 0.95 [0.91-0.98] and OR = 1.08[1.04-1.13]) disease. There was weaker evidence for iCHAV4, located 5’ of ADO, associated only with ER-positive breast cancer (OR = 0.93 [0.90-0.96]). We found 12, 17, 18, and 2 candidate causal SNPs for breast cancer in iCHAVs 1-4, respectively. Chromosome conformation capture analysis showed that iCHAV2 interacts with the ZNF365 and NRBF2 (more than 600 kb away) promoters in normal and cancerous breast epithelial cells. Luciferase assays did not identify SNPs that affect transactivation of ZNF365, but identified a protective haplotype in iCHAV2, associated with silencing of the NRBF2 promoter, implicating this gene in the etiology of breast cancer.
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