Abstract:

BACKGROUND: Coregulator proteins are "master regulators", directing transcriptional and posttranscriptional regulation of many target genes, and are critical in many normal physiological processes, but also in hormone driven diseases, such as breast cancer. Little is known on how genetic changes in these genes impact disease development and progression. Thus, we set out to identify novel single nucleotide polymorphisms (SNPs) within SRC-1 (NCoA1), SRC-3 (NCoA3, AIB1), NCoR (NCoR1), and SMRT (NCoR2), and test the most promising SNPs for associations with breast cancer risk.

METHODS: The identification of novel SNPs was accomplished by sequencing the coding regions of these genes in 96 apparently normal individuals (48 Caucasian Americans, 48 African Americans). To assess their association with breast cancer risk, five SNPs were genotyped in 1218 familial BRCA1/2-mutation negative breast cancer cases and 1509 controls (rs1804645, rs6094752, rs2230782, rs2076546, rs2229840).

RESULTS: Through our resequencing effort, we identified 74 novel SNPs (30 in NCoR, 32 in SMRT, 10 in SRC-3, and 2 in SRC-1). Of these, 8 were found with minor allele frequency.
(MAF)>5% illustrating the large amount of genetic diversity yet to be discovered. The previously shown protective effect of rs2230782 in SRC-3 was strengthened (OR = 0.45 [0.21-0.98], p = 0.04). No significant associations were found with the other SNPs genotyped. CONCLUSIONS: This data illustrates the importance of coregulators, especially SRC-3, in breast cancer development and suggests that more focused studies, including functional analyses, should be conducted.

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