Associations of genetic variants in the estrogen receptor coactivators PPARGC1A, PPARGC1B and EP300 with familial breast cancer.

Abstract:
The mitogen effect of the ovarian steroid estrogen is a strong risk factor for breast cancer development. This effect is mainly mediated by the estrogen receptor alpha, a hormone inducible transcription factor, which activates gene expression through recruiting multiple coactivators, such as PPARGC1A, PPARGC1B and EP300. We tested the hypothesis that non-conservative, putative functional amino acid exchanges in PPARGC1A, PPARGC1B and EP300 act as low-penetrance familial breast cancer risk factors. The analysis of 816 BRCA1/2 mutation-negative familial breast cancer patients and 1012 controls revealed an association of the PPARGC1A Thr612Met polymorphism with familial breast cancer (OR = 1.35, 95% CI 1.00-1.81, P = 0.049), high-risk familial breast cancer (OR = 1.51, 95% CI 1.08-2.12, P = 0.017) and bilateral familial breast cancer (OR = 2.30, 95% CI 1.24-4.28, P = 0.009). Logistic regression analyses of the PPARGC1B Ala203Pro variant showed an increased familial breast cancer risk of heterozygous and homozygous variant allele carriers (OR = 1.48, 95% CI 1.15-1.91, P = 0.002). The genotype-combination analysis of the associated PPARGC1A Thr612Met variant and the associated PPARGC1B Ala203Pro variant suggests an allele
dose-dependent breast cancer risk (P(trend) = 0.0004). Our results indicate for the first time the importance of inherited variants in the estrogen receptor coactivator genes PPARGC1A and PPARGC1B for familial breast cancer susceptibility. Owing to their impact on estrogen signaling, these polymorphisms might also influence adjuvant anti-estrogen therapy, using agents such as tamoxifen and raloxifen, and outcome of breast cancer patients.