Fine-scale mapping of the 5q11.2 breast cancer locus reveals at least three independent risk variants regulating MAP3K1.

Abstract:

Genome-wide association studies (GWASs) have revealed SNP rs889312 on 5q11.2 to be associated with breast cancer risk in women of European ancestry. In an attempt to identify the biologically relevant variants, we analyzed 909 genetic variants across 5q11.2 in 103,991 breast cancer individuals and control individuals from 52 studies in the Breast Cancer Association Consortium. Multiple logistic regression analyses identified three independent risk signals: the strongest associations were with 15 correlated variants (iCHAV1), where the minor allele of the best candidate, rs62355902, associated with significantly increased risks of both estrogen-receptor-positive (ER(+) : OR = 1.24, 95% CI = 1.21-1.27, p trend = 5.7 × 10(-44)) and estrogen-receptor-negative (ER(-): OR = 1.10, 95% CI = 1.05-1.15, p trend = 3.0 × 10(-4)) tumors. After adjustment for rs62355902, we found evidence of association of a further 173 variants (iCHAV2) containing three subsets with a range of effects (the strongest was rs113317823 [pcond = 1.61 × 10(-5)]) and five variants composing iCHAV3 (lead rs11949391; ER(+) : OR = 0.90, 95% CI = 0.87-0.93, pcond = 1.4 × 10(-4)). Twenty-six percent of the prioritized candidate variants coincided with four putative regulatory elements that interact with the MAP3K1 promoter through chromatin looping and affect MAP3K1 promoter activity. Functional analysis indicated that the cancer risk alleles of four candidates (rs74345699 and rs62355900 [iCHAV1], rs16886397 [iCHAV2a], and rs17432750 [iCHAV3]) increased MAP3K1 expression in vivo and might promote breast cancer cell survival.