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Genetic variation in mitotic regulatory pathway genes is associated with breast tumor grade.

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Abstract

Mitotic index is an important component of histologic grade and has an etiologic role in breast tumorigenesis. Several small candidate gene studies have reported associations between variation in mitotic genes and breast cancer risk. We measured associations between 2156 single nucleotide polymorphisms (SNPs) from 194 mitotic genes and breast cancer risk, overall and by histologic grade, in the Breast Cancer Association Consortium (BCAC) iCOGS study (n = 39 067 cases; n = 42 106 controls). SNPs in TACC2 [rs17550038: odds ratio (OR) = 1.24, 95% confidence interval (CI) 1.16-1.33, P = 4.2 × 10(-10)) and EIF3H (rs799890: OR = 1.07, 95% CI 1.04-1.11, P = 8.7 × 10(-6)) were significantly associated with risk of low-grade breast cancer. The TACC2 signal was retained (rs17550038: OR = 1.15, 95% CI 1.07-1.23, P = 7.9 × 10(-5)) after adjustment for breast cancer risk SNPs in the nearby FGFR2 gene, suggesting that TACC2 is a novel, independent genome-wide significant genetic risk locus for low-grade breast cancer. While no SNPs were individually associated with high-grade disease, a pathway-level gene set analysis showed that variation across the 194 mitotic genes was associated with high-grade breast cancer risk (P = 2.1 × 10(-3)). These observations will provide insight into the contribution of mitotic defects to histological grade and the etiology of breast cancer.