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Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple-negative breast cancer.

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Abstract

Triple-negative (TN) breast cancer is an aggressive subtype of breast cancer associated with a unique set of epidemiologic and genetic risk factors. We conducted a two-stage genome-wide association study of TN breast cancer (stage 1: 1529 TN cases, 3399 controls; stage 2: 2148 cases, 1309 controls) to identify loci that influence TN breast cancer risk. Variants in the 19p13.1 and PTHLH loci showed genome-wide significant associations ($P < 5 \times 10(-) (8)$) in stage 1 and 2 combined. Results also suggested a substantial enrichment of significantly associated variants among the single nucleotide polymorphisms (SNPs) analyzed in stage 2. Variants from 25 of 74 known breast cancer susceptibility loci were also associated with risk of TN breast cancer ($P < 0.05$). Associations with TN breast cancer were confirmed for 10 loci (LGR6, MDM4, CASP8, 2q35, 2p24.1, TERT-rs10069690, ESR1, TOX3, 19p13.1, RALY), and we identified associations with TN breast cancer for 15 additional breast cancer loci ($P < 0.05$: PEX14, 2q24.1, 2q31.1, ADAM29, EBF1, TCF7L2, 11q13.1, 11q24.3, 12p13.1, PTHLH, NTN4, 12q24, BRCA2, RAD51L1-rs2588809, MKL1). Further, two SNPs independent of previously reported signals in ESR1 [rs12525163 odds ratio (OR) = 1.15, $P = 4.9 \times 10(-) (4)$] and 19p13.1 (rs1864112 OR = 0.84, $P = 1.8 \times 10(-) (9)$) were associated with TN breast cancer. A polygenic risk score (PRS) for TN breast cancer based on known breast cancer risk variants showed a 4-fold difference in risk between the highest and lowest PRS quintiles (OR = 4.03, 95% confidence interval 3.46-4.70, $P = 4.8 \times 10(-) (69)$). This translates to an absolute risk for TN breast cancer ranging from 0.8% to 3.4%, suggesting that genetic variation may be used for TN breast cancer risk prediction.