Linkage disequilibrium mapping of a breast cancer susceptibility locus near RAI/PPPIR13L/iASPP - DTU Orbit (03/12/2018)

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Background: Previous results have suggested an association of the region of 19q13.3 with several forms of cancer. In the present study, we investigated 27 public markers within a previously identified 69 kb stretch of chromosome 19q for association with breast cancer by using linkage disequilibrium mapping. The study groups included 434 postmenopausal breast cancer cases and an identical number of individually matched controls. Methods and Results: Studying one marker at a time, we found a region spanning the gene RAI (alias PPP1R13L or iASPP) and the 5' portion of XPD to be associated with this cancer. The region corresponds to a haplotype block, in which there seems to be very limited recombination in the Danish population. Studying combinations of markers, we found that two to four neighboring markers gave the most consistent and strongest result. The haplotypes with strongest association with cancers were located in the gene RAI and just 3' to the gene. Coinciding peaks were seen in the region of RAI in groups of women of different age. In a follow-up to these results we sequenced 10 cases and 10 controls in a 44 kb region spanning the peaks of association. This revealed 106 polymorphisms, many of which were not in the public databases. We tested an additional 44 of these for association with disease and found a new tandem repeat marker, called RAI-3' d1, located downstream of the transcribed region of RAI, which was more strongly associated with breast cancer than any other marker we have tested (RR = 2.44 (1.41 - 4.23, p = 0.0008, all cases; RR = 6.29 (1.49 - 26.6), p = 0.01, cases up to 55 years of age). Conclusion: We expect the marker RAI-3' d1 to be (part of) the cause for the association of the chromosome 19q13.3 region's association with cancer.

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