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Title: Functional common genetic polymorphisms interact to predict breast cancer risk

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Christopher E. Aston², David A. Ralph¹, Sharmila Manjeshwar^{1,3}, Amy D. West¹, Dannielle E. Branam³, Bobby A. Gramling¹, Daniele C. DeFreese¹, Linda F. Thompson³, Melissa A. Craft⁴, Debra S. Mitchell⁴, Craig, D. Shimasaki¹, John J. Mulvihill⁵ and Eldon R. Jupe^{1,3,6,7}

¹InterGenetics, Inc., Oklahoma City, OK; ²Arthritis and Immunology Program, ³Immunobiology and Cancer Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, ⁴Breast Imaging of Oklahoma, Edmond, OK, Departments of ⁵Pediatrics, ⁶Surgery and ⁷Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

The proportion of breast cancer in the general population attributable to germline mutations in highly penetrant genes (e.g., *BRCA1/2*) is small because of the low frequency of these mutations. Common, but weakly penetrant, functional genetic polymorphisms are likely to account for most of the genetic risk for breast cancer in the general population. Current polygenic risk models assume, perhaps erroneously, that the effects of the component genes act independently. Potential gene-gene interactions among ten genes, with known or predicted functional consequences in development of breast carcinoma, were examined in a case-control study of more than 1000 Caucasian women with breast cancer and more than 2000 controls. Association of breast cancer risk with variation in single genes and two- and three- gene combinations was analyzed for two age groups: 53 years and under, and over 53 years. The OR for a genotype was calculated and compared to a null distribution of ORs generated for this genotype by randomizing (10,000 times in these analyses) the case-control status of the individuals in the sample to give an empirical estimate for the p-value for the observed OR. Re-sampling was performed to give an empirical estimate of the 95% confidence interval and a likely more stable estimate of the OR for the genotype, particularly for the less common genotypes. In these analyses the population of individuals was resampled 10,000 times with each repetition composed of 80% of the controls and 80% of the cases selected at random from the whole sample. Over 100 genotypes met stringent criteria for significance ($\alpha=1/10,000$) with ORs ranging from 0.20 to 5.2. The majority of the significant ORs were two- and three-gene combinations. Comparing observed ORs to ORs predicted by an independent gene model showed that about 25% of the significant multigenic combinations differed markedly from the predicted value. Thus, combinations of genes interact to affect risk for breast cancer in a manner that is not predictable by combining the effects of the individual component genes. While independent genes are a valid starting point in a polygenic model, identifying and incorporating modification of risks associated with gene-gene interactions will improve accuracy of the model and should be taken into consideration when building polygenic models for breast cancer risk. In addition, further exploration of the biologic basis for these multigenic interactions might reveal etiologic or therapeutic insights into breast cancer and other cancers.