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A BRCA1 promoter variant (rs11655505) and breast cancer risk.

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Key Words: Breast cancer risk, low-penetrance allele, association study, BRCA1, SNP rs11655505.

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SUMMARY

A study of Chinese women recently suggested that the minor allele of rs11655505 in the *BRCA1* promoter (c.-2265C>T) increases promoter activity and has a protective effect on breast cancer risk. We genotyped rs11655505 in 2,912 female breast cancer cases and 2,783 unaffected female controls from four Caucasian breast cancer studies but did not find any evidence for an association between rs11655505 and breast cancer risk. Larger studies are necessary to determine if there is a weak association between SNP rs11655505 and breast cancer risk.

MAIN TEXT

Recently, Chan *et al* provided evidence that the minor allele of rs11655505 (c.-2265C>T), located in the promoter region of *BRCA1*, has a protective effect on breast cancer risk in Chinese women.¹ In 368 incident breast cancer cases and 375 controls from Hong Kong, the odds ratio (OR) for the T (minor) allele versus the C allele was 0.79 (95% confidence interval (CI) 0.64-0.97) and the OR for genotypes CT/TT combined versus CC (common homozygous) was 0.64 (95% CI 0.47-0.88). Moreover, in a pooled analysis of the Hong Kong series and 1109 incident breast cancer cases and 1185 controls from Shanghai, the OR for genotypes CT/TT combined versus CC was 0.80 (95% CI 0.69-0.93). Interestingly, these findings are supported by *in vitro* evidence that the minor allele increases the promoter activity of *BRCA1* by 70%.¹

In order to further test this putative association of rs11655505 with breast cancer risk, we genotyped a total of 2,912 female breast cancer cases and 2,783 female controls from four independently ascertained samples from Australia, Germany and Italy. The Australian Breast Cancer Family Study (ABCFS) is a population-based case-control-family study of breast cancer with an emphasis on early onset disease.² Breast cancer cases were incident cases recruited from state cancer registries (irrespective of family

history) and unaffected controls were recruited via the electoral rolls. The Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab)³ provided unrelated non-*BRCA1/2* breast cancer cases from multiple-case breast and breast-ovarian families recruited through the Family Cancer Clinics; and Australian Ovarian Cancer Study (AOCS) provided controls ascertained from the electoral rolls.⁴ The German and Italian cases fulfilled the criteria for *BRCA*-mutation testing, including family history for the disease and age of breast cancer onset, but only those women who were not found to carry a mutation in *BRCA1* or *BRCA2* were included in this study; the controls were female blood donors who shared the same ethnicity background of cases. Additional details are described elsewhere.^{5 6 7 8} All individuals participating in this study signed an informed consent to the use of their genetic material for research purposes. The study was approved by the Ethic Committees of the following institutions: University of Melbourne, Queensland Institute of Medical Research, University of Cologne, University of Heidelberg and Fondazione IRCCS Istituto Nazionale Tumori. Genotypes for rs11655505 were assayed using the Sequenom iPlex gold genotyping technology for the Australian samples, iCycler allelic discrimination for the German samples, and by direct sequencing for the Italian samples. Centralized statistical analyses were performed using Statistical Analysis System (SAS; SAS Institute, Cary, NC).

We used a logistic regression model to analyze the genotype and allele frequencies of the SNP rs11655505, separately for each of the four studies and overall (Table 1). We did not identify any statistically significant associations, and with the exception of kConFab/AOCS the point estimates were in the opposite direction to that reported previously.¹ Given that we had more than 90% power to detect an OR of 0.79 for the minor allele, at $\alpha=0.05$, the difference between our results and those of Chan *et al* could be explained by a type 1 error in the Chinese study. Alternatively, population-specific factors, such as other associated genetic variants could in principle modulate the putative association of the rs116555015 T allele on breast cancer risk, and on *BRCA1*

promoter activity. However, it is relevant to note that no convincing evidence has been provided to date for an association between increased *BRCA1* promoter activity and protection from breast cancer. In conclusion, this study provides no evidence to support an association of rs11655505 with breast cancer risk for Caucasian women. Larger studies are needed to better test if the risk of developing breast cancer is associated with the SNP rs11655505.

Table 1. Logistic regression analyses of genotype and allele frequencies of SNP rs11655505 in breast cancer cases and controls from Australian, German and Italian series.

<i>Study</i>	<i>Genotype or allele</i>	<i>Cases (%)</i>	<i>Controls (%)</i>	<i>OR</i>	<i>95% CI</i>	<i>P-value</i>
Australia ^a (ABCFS)	CC	503 (44.08)	301 (47.93)			
	CT	507 (44.43)	258 (41.08)	1.17	0.95–1.44	0.143
	TT	131 (11.48)	69 (10.99)	1.13	0.82–1.57	0.451
	[C] vs [T]			1.10	0.95–1.27	0.205
Australia ^b (kConFab /AOCS)	CC	298 (47.83)	368 (44.66)			
	CT	250 (40.13)	351 (42.60)	0.82	0.63–1.06	0.138
	TT	75 (12.04)	105 (12.74)	0.89	0.60–1.32	0.558
	[C] vs [T]			0.90	0.75–1.08	0.257
Germany ^c	CC	219 (47.20)	246 (46.59)	1.00		
	CT	188 (40.52)	226 (42.80)	0.94	0.72–1.22	0.625
	TT	57 (12.28)	56 (10.61)	1.13	0.75–1.71	0.557
	[C] vs [T]			1.02	0.85–1.23	0.826
Italy ^d	CC	287 (41.96)	356 (44.33)			
	CT	313 (45.76)	370 (46.08)	1.04	0.84–1.29	0.720
	TT	84 (12.28)	77 (9.59)	1.33	0.94–1.88	0.109
	[C] vs [T]			1.11	0.95–1.29	0.182
Overall ^e	CC	1307 (44.88)	1271 (45.67)			
	CT	1258 (43.20)	1205 (43.30)	1.01	0.91–1.13	0.812
	TT	347 (11.92)	307 (11.03)	1.10	0.93–1.31	0.264
	[C] vs [T]			1.04	0.96–1.12	0.336

OR, odds ratio (adjusted for age and study); CI, confidence interval.

^aMedian age in cases and controls was 42 (23-69) and 40 (20-68), respectively; ^b44 (19-78) and 58 (20-81); ^c45 (21-86) and 46 (18-68); ^d43 (21-80) and 45 (18-71); ^e43 (19-86) and 49 (18-81).

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