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No evidence that *GATA3* rs570613 SNP modifies breast cancer risk

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Abstract

GATA-binding protein 3 (GATA3) is a transcription factor that is crucial to mammary gland morphogenesis and differentiation of progenitor cells, and has been suggested to have a tumor suppressor function. The rs570613 single nucleotide polymorphism (SNP) in intron 4 of *GATA3* was previously found to be associated with a reduction in breast cancer risk in the Cancer Genetic Markers of Susceptibility project and in pooled analysis of two case-control studies from Norway and Poland (P_{trend} =0.004), with some evidence for a stronger association with estrogen receptor (ER) negative tumours [1]. We genotyped *GATA3* rs570613 in 6,388 cases and 4,995 controls from the Breast Cancer Association Consortium (BCAC) and 5,617 *BRCA1* and *BRCA2* carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). We found no association between this SNP and breast cancer risk in BCAC cases overall ($OR_{per\text{-}allele}$ = 1.00, 95% CI 0.94 − 1.05), in ER negative BCAC cases ($OR_{per\text{-}allele}$ = 1.02, 95% CI 0.91−1.13), in *BRCA1* mutation carriers $RR_{per\text{-}allele}$ = 0.99, 95% CI 0.90−1.09) or *BRCA2* mutation carriers ($RR_{per\text{-}allele}$ = 0.93, 95% CI 0.80−1.07). We conclude that there is no evidence that either *GATA3* rs570613, or any variant in strong linkage disequilibrium with it, is associated with breast cancer risk in women.

Keywords

GATA3; breast cancer; polymorphism; *BRCA1* and *BRCA2*; risk

Introduction

The GATA-binding protein 3 (GATA3) transcription factor is crucial to mammary gland morphogenesis and differentiation of progenitor cells, and continues to be expressed in normal breast luminal epithelial cells throughout puberty and pregnancy [2-4]. Gene expression profiling aimed at correlating genotypic and phenotypic characteristics of breast tumors has

implicated *GATA3* in tumorigenesis of luminal A subtypes which are associated with more favourable survival than other subtypes [5-7]. GATA3 expression is strongly correlated with ER expression [8,9], and its utility in predicting clinical outcome in ER-positive tumors has also been reported [10,11]. *GATA3* somatic mutations have been identified in a subset of ER-positive breast tumors, and cells transfected with these *GATA3* mutants show increased proliferation compared with wild-type transfectants, suggesting a tumor suppressor function [12]. Analysis of association between breast cancer and *GATA3* single nucleotide polymorphisms (SNPs) in two European studies suggested that rs570613, in intron 4, was associated with a 15−18% overall reduction in breast cancer risk (P_{trend} =0.004), with some evidence for a stronger association with ER-negative tumors [1]. To test this association, we analysed this SNP in case-control studies and *BRCA1* and *BRCA2* carriers from two large consortia.

Materials and Methods

Analysis of breast cancer risk was based on genotype data from 6,388 cases (largely population-based) and 4,995 controls identified through five European and Australian studies (ABCFS, GENICA, HEBCS, SASBAC and kConFab; Table 1) in the Breast Cancer Association Consortium (BCAC; ref. 13), and 5,617 *BRCA1* and *BRCA2* mutation carriers from 11 studies from Europe, Australia and North America (EMBRACE, DNA-HEBON, kConFab, SWE-BRCA, MUV, UPENN, MAYO, HEBCS, FCCC, PBCS and Georgetown; ref. 14,15) in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). The design, for both consortia, genotyping methods and quality control procedures have been reported elsewhere [14,15]. All statistical tests were two sided, and analyses were carried out using the S-Plus (Insightful Corp.) software system and STATA v. 9.0 (Stata Corp.). Statistical significance was based on a nominal *P*-value less than 0.05.

For the BCAC study, odds ratios (ORs) for heterozygotes and homozygotes, relative to the common homozygotes, were estimated using logistic regression, adjusted for age and study, together with per allele ORs (estimated by fitting the number of rare alleles carried as a continuous covariate). Similar methods were used to obtain risk estimates according to ER status where data were available.

For the CIMBA study, the associations between breast cancer risk and *GATA3* rs570613 genotypes for *BRCA1* and *BRCA2* mutation carriers were estimated using Cox proportional hazards regression analysis with breast cancer as the outcome and age as the time-to-event variable [16]. Subjects were followed from birth until breast cancer, bilateral prophylactic mastectomy, ovarian cancer, age at last contact, or age 80. A weighted cohort approach was used to adjust estimates for the potential over-sampling of affected individuals [17]. Rate ratios (RR) and 95% CIs were estimated for all carriers combined, and for *BRCA1* and *BRCA2* mutation carriers separately, for heterozygotes and rare homozygotes compared with common homozygotes, and per allele. To allow for the fact that the CIMBA cohort includes related individuals we used a robust variance approach to compute the variance of the RRs [18]. Additional analyses were conducted by adjusting for oophorectomy status as a time dependent covariate and by excluding affected individuals who were recruited more than five years after breast cancer diagnosis.

Results

All contributing studies met genotyping quality control criteria [14,15]. In BCAC controls the combined mean age at interview was 53.1 (SD 14.2) and in cases the age at diagnosis was 54.6 (SD 12.5). Table 1 shows genotype frequencies for cases and controls for each BCAC study, together with study-specific and pooled ORs and 95% CIs for association between the

GATA3 rs570613 SNP and breast cancer, both overall and stratified on ER status. *GATA3* genotypes were not associated with breast cancer risk for either the combined analysis, or for any of the five individual studies. Similar analyses stratified by ER status also showed no association between *GATA3* genotypes and risk of either ER-positive or ER-negative tumors.

In the CIMBA study, there was no evidence of an association between risk of breast cancer and rs570613 genotypes, in *BRCA1* and *BRCA2* carriers pooled, or when *BRCA1* and *BRCA2* carriers were analysed separately (Table 2). Analyses adjusting for oophorectomy status, or restricted to cases ascertained within five years of diagnosis, likewise showed no association (Table 2).

Discussion

Our study comprehensively evaluated the *GATA3* rs570613 SNP for association with risk of breast cancer, but failed to replicate the previous report of an association with risk. The BCAC analysis had ~99% power to detect an OR of the magnitudes previously reported (0.82−0.85), and the 95% CI for the per-allele OR (0.94−1.05) shows that we can exclude all but very small associations. Likewise, *GATA3* rs570613 genotypes were not associated with breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. Results remained similar when analyses were adjusted for oophorectomy status in a time-dependent manner or when cases diagnosed more than five years before recruitment were excluded to account for possible survival bias. There was no evidence of an association with ER status in BCAC studies but the number of ER-negative cases was limited to 868, and hence the 95% CI was wider (0.91−1.13). However, most *BRCA1*-associated tumors are ER-negative [19], so the absence of any association in *BRCA1* carriers is consistent with the lack of an association with ER-negative disease. The potential for variation in study-specific estimates is inherent in consortium analyses involving multiple studies. However, all BCAC studies selected controls from the same source population as cases, participants being predominantly Caucasian. There was no evidence of heterogeneity in risk estimates from either consortiium analysis ($P_{\text{Heterogeneity}} \geq 0.3$). In summary, the role of GATA3 in breast tumor biology and prognosis has been well documented [20] and the hypothesis that variants in *GATA3* might influence breast cancer risk is appealing. However, our data demonstrate convincingly that neither rs570613, nor any SNP in significant linkage disequilibrium with it, is likely to have a major influence on breast cancer risk.

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Table 1

Risk of breast cancer associated with the *GATA3* rs570613 genotypes overall, and stratified by ER status, from five BCAC case-control studies

[a]Study	Genotype	Controls N (%)	Overall		ER Positive		ER Negative	
			Cases N (%)	OR[b](95% CI) p-value	Cases N (%)	OR[b](95% CI) p-value	Cases N (%)	OR[b](95% CI) p-value
ABCFS[c]	TT	245 (40.1)	415 (37.2)	1.00				
	CT	271 (44.4)	553 (49.6)	1.21 (0.98 − 1.51)				
	CC	95 (15.5)	148 (13.3)	0.93 (0.68 − 1.25)				
	per-C allele			1.02 (0.88 − 1.18) p = 0.8				
GENICA	TT	384 (38.8)	376 (37.9)	1.00	278 (38.1)	1.00	75 (35.5)	1.00
	CT	470 (47.5)	467 (47.1)	1.01 (0.84 − 1.23)	338 (46.3)	1.00 (0.81−1.23)	108 (51.2)	1.20 (0.87−1.67)
	CC	136 (13.7)	148 (14.9)	1.11 (0.85 − 1.46)	114 (15.6)	1.17 (0.88−1.58)	28 13.3)	1.06 (0.66−1.72)
	per-C allele			1.04 (0.92 − 1.19) p = 0.5		1.06 (0.92−1.22) p = 0.4		1.07 (0.86−1.33) p = 0.6
HEBCS	TT	461 (36.4)	884 (37.1)	1.00	662 (37.0)	1.00	156 (36.6)	1.00
	CT	601 (47.4)	1,128 (47.4)	0.96 (0.81 − 1.15)	849 (47.4)	0.99 (0.82−1.20)	205 (48.1)	0.99 (0.76−1.29)
	CC	206 (16.2)	369 (15.5)	0.91 (0.72 − 1.16)	279 (15.6)	0.92 (0.71−1.19)	65 (15.3)	0.88 (0.61−1.26)
	per-C allele			0.96 (0.85 − 1.07) p = 0.4		0.97 (0.85−1.09) p = 0.6		0.95 (0.79−1.12) p = 0.5
SASBAC	TT	539 (36.9)	436 (34.1)	1.00	236 (34.0)	1.00	52 (34.7)	1.00
	CT	698 (47.8)	660 (51.6)	1.17 (0.99 − 1.38)	356 (51.3)	1.17 (0.96−1.42)	77 (51.3)	1.13 (0.78−1.64)
	CC	222 (15.2)	184 (14.4)	1.03 (0.81 − 1.29)	102 (14.7)	1.05 (0.79−1.39)	21 (14.0)	1.00 (0.59−1.70)
	per-C allele			1.05 (0.94 − 1.17) p = 0.4		1.05 (0.92−1.20) p = 0.5		1.03 (0.80 −1.31) p = 0.8
kConFab/AOCS	TT	251 (37.6)	252 (40.6)	1.00	83 (42.3)	1.00	29 (35.8)	1.00
	CT	305 (45.7)	288 (46.5)	0.87 (0.64 − 1.16)	85 (43.4)	0.80 (0.54−1.19)	41 (50.6)	1.09 (0.62−1.93)
	CC	111 (16.6)	80 (12.9)	0.73 (0.48 − 1.10)	28 (14.3)	0.72 (0.41−1.26)	11 (13.6)	0.77 (0.34−1.74)
	per-C allele			0.86 (0.70 − 1.04) p = 0.1		0.83 (0.64−1.09) p = 0.2		0.92 (0.63−1.34) p = 0.7
Pooled estimate	TT	1,880 (37.6)	2,363 (37.0)	1.00	1254 (36.8)	1.00	312 (35.9)	1.00
	CT	2,345 (46.9)	3,096 (48.5)	1.08 (0.98 − 1.18)	1628 (47.8)	1.04 (0.94−1.15)	431 (49.7)	1.11 (0.94−1.30)
	CC	770 (15.4)	929 (14.5)	0.96 (0.86 − 1.08)	523 (15.4)	1.02 (0.89−1.17)	125 (14.4)	0.98 (0.78−1.23)
	per-C allele			1.00 (0.94 − 1.05) p = 0.9		1.02 (0.95−1.08) p = 0.6		1.02 (0.91−1.13) p = 0.8

[a]Australian Breast Cancer Family Study (ABCFS), Gene Environment Interaction and Breast Cancer in Germany (GENICA); Helsinki Breast Cancer Study (HEBCS); Singapore and Sweden Breast Cancer Study (SASBAC); Kathleen Cuningham Foundation for Research into Familial Breast Cancer/Australian Ovarian Cancer Study (kConFab/AOCS).

[b]Adjusted for age (at diagnosis for cases and at interview for controls) in study-specific estimates, and additionally for study in pooled analysis

[c]Data on ER status not available for the ABCFS study

Table 2

RR estimates for the association between *GATA3* rs570613 genotypes and risk of breast cancer for *BRCA1* and *BRCA2* carriers from CIMBA

	Common Homozygotes (TT)			Heterozygotes (CT)			Rare Homozygotes (CC)				
Group	**Events**	**Person Years**	**RR (Ref)**	**Events**	**Person Years**	**RR[a,b] (95% CI)**	**Events**	**Person Years**	**RR[a,b] (95% CI)**	**RR trend[a,b] (95% CI)**	**P-value[b,c]**
Overall	1148	48786.16	1.00	1331	56321.80	0.91(0.82,1.02)	421	17707.40	0.99(0.84,1.17)	0.97(0.90,1.05)	0.51
By mutation status											
BRCA1	712	29480.42	1.00	857	35281.19	0.95(0.84,1.09)	275	11211.83	1.00(0.83,1.22)	0.99(0.90,1.09)	0.83
BRCA2	437	19358.22	1.00	477	21197.12	0.81(0.66,0.98)	147	6525.07	0.96(0.71,1.29)	0.93(0.80,1.07)	0.32
Adjusted for oophorectomy status											
Overall	929	39370.17	1.00	1060	44753.22	0.88(0.78,1.01)	331	13931.76	1.00(0.83,1.20)	0.97(0.89,1.06)	0.50
By mutation status											
BRCA1	575	23729.07	1.00	680	28056.59	0.92(0.79,1.07)	210	8660.45	0.98(0.79,1.22)	0.97(0.88,1.08)	0.58
BRCA2	355	15693.59	1.00	383	16853.13	0.78(0.61,0.99)	122	5300.81	1.09(0.76,1.55)	0.96(0.81,1.15)	0.67
Excluding cases diagnosed > 5years before recruitment											
Overall 587 25554.65 1.00				682	29412.34	0.92(0.81,1.05)	204	8879.20	0.97(0.80,1.17)	0.97(0.88,1.06)	0.49
By mutation status											
BRCA1	354	15009.00	1.00	428	17894.36	0.97(0.83,1.13)	129	5434.41	1.00(0.79,1.25)	0.99(0.89,1.11)	0.88
BRCA2	233	10545.64	1.00	256	11633.99	0.79(0.62,1.02)	75	3444.80	0.87(0.62,1.22)	0.89(0.75,1.05)	0.18

[a] Rate Ratio and 95% confidence interval (CI) from a weighted Cox Proportional Hazard model.

[b] Adjusted for study group, mutation status, country of origin, ethnicity, family, and year of birth.

[c] Trend p-value from a weighted Cox Proportional Hazard model with 1 degree of freedom.