Research Paper

Association of the RNF146 rs2180341 Single Nucleotide Polymorphism with Breast Cancer Susceptibility and Prognosis in Northern Chinese Population

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Ring finger protein 146, an E3 ubiquitin ligase, regulates breast cancer development, metastasis and drug resistance. E3 ubiquitin ligase is an indispensable class of enzymes in the ubiquitin-proteasome system, which can be divided into HECT E3s, U-box E3s and ring E3s. Genome-wide association analyses have revealed the association between the ring finger protein 146 rs2180341 single nucleotide polymorphism and breast cancer risk in Ashkenazi Jewish people but not in Southern Chinese individuals. Herein, A retrospective case-control study of 828 breast cancer patients and 905 healthy controls was conducted to examine this association in Northern Chinese. Deoxyribonucleic acid from peripheral blood was sequenced to determine genotypes. We analyzed the association of the ring finger protein 146 rs2180341 single nucleotide polymorphism with breast cancer risk using odds ratios with binary logistic regression and between the single nucleotide polymorphism and clinic pathological breast cancer characteristics using Pearson's chi-square or Fisher's exact tests. Survival analyses were performed using the Kaplan-Meier method. In the codominant model, the ring finger protein 146 rs2180341 single nucleotide polymorphism and breast cancer risk were correlated. Our results showed that, compared with individuals with the ring finger protein 146 rs2180341 AA genotype, those with the GG genotype had an odds ratio of 1.932 (95 % confidence interval, 1.320-2.829, p=0.001) for developing breast cancer. No significant associations were found between the single nucleotide polymorphism and clinical characteristics or disease-free or overall survival. In conclusion, this single nucleotide polymorphism is related to breast cancer susceptibility but not with breast cancer clinic pathological characteristics or prognosis in Northern Chinese individuals.

Key words: Ring finger protein 146 rs2180341, single nucleotide polymorphism, breast cancer, metastasis, drug resistance

According to the International Agency for Research on Cancer, Breast Cancer (BC) has now surpassed lung cancer to become the world's number one cancer[1,2]. In 2030, the incidence of BC in China is expected to reach 234 000 cases[3]. The Ring Finger Protein 146 (RNF146) rs2180341 Single Nucleotide Polymorphism (SNP) is the most common genetic variant and can be used to predict the risk and prognosis of tumors, providing a molecular basis for the occurrence and development of BC[4].

RNF146, also known as dactylidin, is located in 6q22.1-q22.33 and contains five exons[5]. RNF146 encodes an amino terminal ring finger (propyne (C_3HC_4) ring finger) of a ubiquitin protein ligase (E3) containing WWE and the N-terminal ring finger domain[6-8]. The Wnt/β-catenin signaling pathway is of vital importance in both embryo and organ development; however, it is abnormally activated in cancerous tissues[9-11]. RNF146 is genetically amplified in ovarian, breast and colorectal cancers and is regulated by the Wnt signaling pathway[12-15]. RNF146 binds to the Poly ADP-Ribose (PAR)-ribosylated axin through its PAR-binding domain in the WWE domain and exerts its role as an E3 ubiquitin ligase[16,17]. RNF146 can recruit E2 ubiquitin-conjugating enzymes, degrade axin and the β-catenin degradation complex and accumulate β-catenin in the cytoplasm, thereby activating the Wnt signaling pathway[18-20]. Additionally, RNF146 is predominantly involved in the metastasis, development, drug resistance and invasion of BC[21].

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A previous study showed that the RNF146 rs2180341 SNP is related to proliferation, metastasis and drug resistance in BC. The association between RNF146 rs2180341 SNP and BC susceptibility was first observed in Ashkenazi Jews (AJ). The findings of Kirchhoff *et al.*[22], who performed a follow-up study with 1953 patients with BC and 1467 controls of European ancestry, further supported this. However, no relationship was observed in subsequent Indian[23,24] and Southern Chinese[25] population studies. To further investigate this, we analyzed the relation between the RNF146 rs2180341 SNP and the susceptibility and prognosis of BC in China[26].

MATERIALS AND METHODS

Study design:

Choice and description of participants: The association of the RNF146 rs2180341 SNP with BC in a Northern Chinese population was investigated using a retrospective case-control study. From April 2013 to September 2016, 828 patients with BC and 905 age-matched healthy controls were enrolled at Jilin University First Affiliated Hospital (Changchun City, Jilin Province, China). A median follow-up time was 6.7 y. The features of patients are obtained from their records. A pathology diagnosis of early cancer in females was the inclusion criteria.

RNF146 rs2180341 SNP genotyping: Peripheral blood samples were extracted to obtain Deoxyribonucleic Acid (DNA), and genotypes were detected using a matrix-assisted laser desorption ionization-time of flight mass spectrometer (Agena, San Diego, California, United States of America (USA)). SNP genotyping without knowing the case status. 15 % of the samples were tested interactively and reproducibility was 99.7 %.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) and online SNP stats developed by Catala d'Oncologia Institute were used to analyze the risk of BC. Based on Odds Ratio (OR) and 95 % Confidence Interval (CI), RNF146 rs2180341 SNP was associated with BC risk, and was analyzed by binary logistic regression. Kaplan-Meier and univariate Cox models were used to analyze the effects of RNF146 rs2180341 SNP on Disease-Free Survival (DFS) and Overall Survival (OS). Statistical significance was set at $p \leq 0.05$ for all statistical tests, and all the tests were assumed to be two-sided.

RESULTS AND DISCUSSION

All the controls first underwent a physical examination at our hospital and were confirmed to not have a familial history of cancer. The median age of the control group was 38 y (range of 32 y-53 y). The case group included 398 premenopausal and 430 postmenopausal, with a median age of 51 y (ranging from 44 y to 58 y old), among whom 32 patients had a family history of cancer. Among 828 cases of BC, 793 cases have invasive ductal carcinoma, and 35 cases have other diseases. A detailed description of the patient's characteristics is provided in Table 1.

Genotype distribution of the RNF146 rs2180341 SNP was not significantly different between the case and control groups (Table 2). Three genetic models showed that the SNP rs2180341 in RNF146 was associated with increased BC risk. Codominant genetic models had the lowest Akaike information criterion, which was used to select the optimal genetic model. Compared with AA, the BC of rs2180341 GG is 1.932 (95 % CI, 1.320-2.829, p=0.001). Compared with AA, the genotype of rs2180341 GA also increased the risk of BC (OR, 1.168; 95 % CI, 0.944-1.446, p=0.153). In the implicit model, compared with AA, the OR of rs2180341 GG to BC development is 1.810 (95 % CI, 1.250-2.621, p=0.002). In the dominance model, compared with AA, rs2180341 GG also increases the risk of BC (OR, 1.277; 95 % CI is 1.043-1.563, p=0.018). In the hyper dominant model, RNF146 rs2180341 was not associated with BC risk (Table 3 and fig. 1).

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RNF146 is an E3 ubiquitin ligase that downregulates the expression of axin while also inducing the expression of Beta (β)-catenin and increasing its nuclear accumulation[27,28]. Studies confirm that when β-catenin enters the nucleus, it loses its function as a cell adhesion molecule, positively regulates the Wnt signaling pathway, and activates the proliferation, invasion and metastasis of BC[29]. rs2180341 (A>G) is in the intron region of RNF146 and its expression is increased in the GG genotype.

Previous studies that examined the association of the RNF146 rs2180341 SNP with BC susceptibility produced controversial results. In our study, we found that RNF146 rs2180341 SNP increased the risk of BC, which was consistent with the results of Gold *et al.*[18] for an AJ population and Kirchhoff *et al.*[22] for a non-AJ population with predominantly European ancestry. Other studies have found no relationship between ethnicity and birth rate among southern Chinese[25], European[30], Cypriot[31] or Chinese Singaporean[32] populations. Genetic and environmental variations may be responsible for the difference in results. The results of the present study, which focused on the Northern and Southern Chinese populations, indicate that unique genetic backgrounds and living environments with different geographical distributions in the same area may affect the occurrence and development of tumors. The median age of the Northern Chinese population was lower than that of the Southern Chinese population and the environment influenced individual genes. A comparison of the results from this study with previous studies is provided in Table 6.

Kirchhoff *et al.*[22] found that the RNF146 rs2180341 SNP increased the risk of ER-positive BC (OR, 1.35; 95 % CI, 1.20-1.51, $p=2.2\times10^{-5}$). In contrast, this study found no evidence of a similar relationship in the Northern Chinese population. Furthermore, no relationship was observed between the RNF146 rs2180341 SNP and other clinicopathological characteristics such as menstrual status, pathological type and family history[33].

TABLE 1: CLINICOPATHOLOGICAL CHARACTERISTICS

Characteristic	Cases (%)
Age (years)	
35	52 (6.28)
>35	776 (93.72)
Menstrual status	
Premenopause	398 (48.07)
Postmenopause	430 (51.93)
Family history	
Negative	796 (96.14)
Positive	32 (3.86)
Pathological type	
Infiltrating ductal carcinoma	793 (95.77)
Other types	35 (4.23)
Histological grade	
I	31 (3.74)
II	511 (61.71)
III	286 (34.54)
Tumor size	
T1	422 (50.97)
T2	365 (44.08)
T3	27 (3.26)
T4	14 (1.69)

Lymph node	
N0	396 (47.83)
N1	285 (34.42)
N2	101 (12.20)
N3	46 (5.58)
Lymphovascular invasion	
Negative	471 (56.88)
Positive	357 (43.12)
Perineural invasion	
Negative	689 (83.21)
Positive	139 (16.79)
Clinical stage	
I	243 (29.35)
II	415 (50.12)
III	159 (19.20)
IV	11 (1.33)
Total	828 (100.00)

TABLE 2: HARDY-WEINBERG BALANCE TEST

SNPs	Cases				Controls			
	1^{H0}	1^{He}	χ^2	p	1^{H0}	1^{He}	χ^2	p
rs 2180341	0.3804	0.4152	5.8037	0.016	0.3856	0.3797	0.2248	0.6354

Note: (1^{H0}): Observed heterozygote frequency and (1^{He}): Expected heterozygote frequency

TABLE 3: ASSOCIATION BETWEEN HOTAIR rs 2180341 POLYMORPHISM AND BC RISK

SNP	Genotype	Model	Cases (%)	Controls (%)	OR (95 % CI)	p	AUC
rs 2180341	AA	Codominant	427 (51.57)	500 (55.25)	1.000	0.003	2183.1
	GA		315 (38.04)	349 (38.56)	1.168 (0.944-1.446)	0.153	
	GG		86 (10.39)	56 (6.19)	1.932 (1.320-2.829)	0.001	
	AA	Dominant	427 (51.57)	500 (55.25)	1.000	0.018	2187.5
	GA/GG		401 (48.43)	405 (44.75)	1.277 (1.043-1.563)		
	AA/GA	Recessive	742 (89.61)	849 (93.81)	1.000	0.002	2184
	GG		86 (10.39)	56 (6.19)	1.810 (1.250-2.621)		
	AA/GG	Overdominant	513 (61.96)	556 (61.44)	1.000	0.526	2193.9
	GA		315 (38.04)	349 (38.56)	1.069 (0.869-1.315)		
	A	-	1169 (70.59)	1349 (74.53)	1.000	<0.001	-
	G	-	487 (29.41)	461 (25.47)	1.334 (1.138-1.565)		

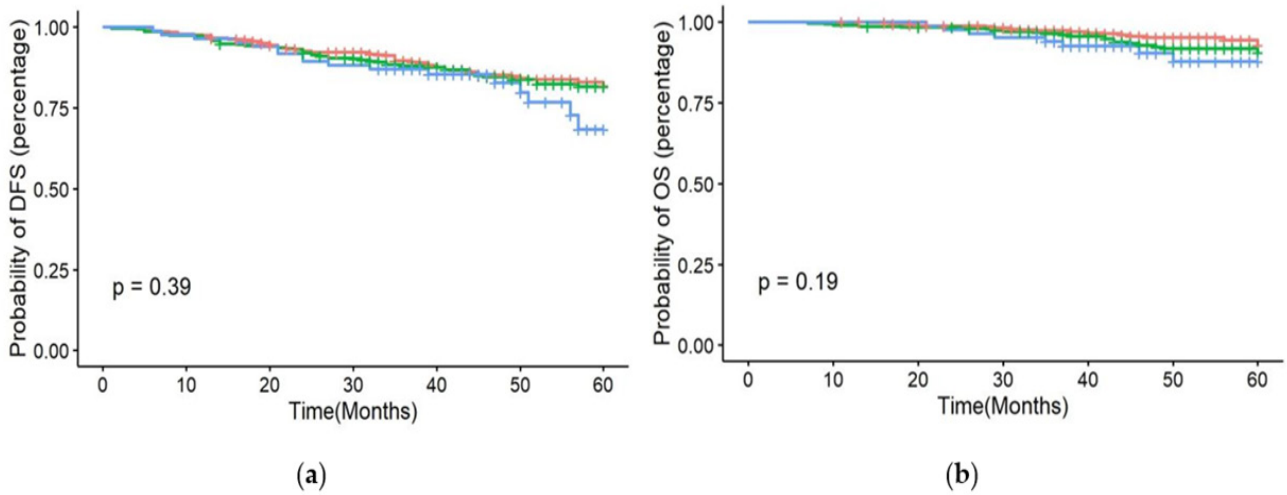

Fig. 1: (A): DFS and (B): OS of BC patients with different HOTAIR rs2180341 genotypes
Note: There was no statistical difference among the three curves of DFS (p=0.39) and OS (p=0.19), ( ): rs2180341=A/A; ( ): rs2180341=G/A and ( ): rs2180341=G/G

TABLE 4: ASSOCIATION BETWEEN RNF146 rs2180341 POLYMORPHISM AND BC CLINICAL CHARACTERISTICS

Characteristic	Grouping	rs genotype 2180341			χ^2	p
		AA, n (%)	GA, n (%)	GG, n (%)		
ER	Negative	107 (25.06)	81 (25.72)	26 (30.23)	4.975	0.547
	<30 %	29 (6.79)	16 (5.08)	9 (10.47)		
	30 %-50 %	21 (4.92)	15 (4.76)	3 (3.49)		
	>50 %	270 (63.23)	203 (64.44)	48 (55.81)		
PR	Negative	170 (39.81)	119 (37.78)	40 (46.51)	4.105	0.663
	<30 %	50 (11.71)	40 (12.70)	11 (12.79)		
	30 %-50 %	41 (9.60)	33 (10.48)	4 (4.65)		
	>50 %	166 (38.88)	123 (39.04)	31 (36.05)		
HER-2	Negative	286 (66.98)	218 (69.21)	59 (68.60)	0.43	0.807
	Positive	141 (33.02)	97 (30.79)	27 (31.40)		
Ki-67	<14 %	73 (17.10)	46 (14.60)	12 (13.95)	2.912	0.573
	14 %-30 %	96 (22.48)	79 (25.08)	16 (18.60)		
	>30 %	258 (60.42)	190 (60.32)	58 (67.45)		
Molecular type	Luminal A	57 (13.35)	38 (12.06)	9 (10.47)	1.925	0.926
	Luminal B	267 (62.53)	201 (63.81)	52 (60.47)		
	HER2	52 (12.18)	37 (11.75)	14 (16.28)		
	Triple negative	51 (11.94)	39 (12.38)	11 (12.78)		
Lymphovascular invasion	Negative	242 (56.67)	174 (55.24)	55 (63.95)	2.108	0.349
	Positive	185 (43.33)	141 (44.76)	31 (36.05)		
Lymph node	N0	206 (48.24)	146 (46.35)	44 (51.16)	8.503	0.204
	N1	143 (33.49)	114 (36.19)	28 (32.56)		
	N2	55 (12.88)	41 (13.02)	5 (5.81)		
	N3	23 (5.39)	14 (4.44)	9 (10.47)		

Tumor size	T1	222 (51.99)	159 (50.48)	41 (47.67)	7.826	0.251
	T2	181 (42.39)	146 (46.35)	38 (44.19)		
	T3	14 (3.28)	9 (2.86)	4 (4.65)		
	T4	10 (2.34)	1 (0.31)	3 (3.49)		
Menstrual status	Premenopause	198 (46.37)	154 (48.89)	46 (53.49)	1.59	0.451
	Postmenopause	229 (53.63)	161 (51.11)	40 (46.51)		
Family history	Negative	411 (96.25)	299 (94.92)	86 (100.00)	4.724	0.094
	Positive	16 (3.75)	16 (5.08)	0 (0.00)		
Pathological type	Infiltrating ductal carcinoma	409 (95.78)	299 (94.92)	85 (98.84)	2.56	0.278
	Other types histological grade	18 (4.22)	16 (5.08)	1 (1.16)		
Histological grade	I	17 (3.98)	13 (4.13)	1 (1.16)	3.097	0.542
	II	260 (60.89)	200 (63.49)	51 (59.30)		
	III	150 (35.13)	102 (32.38)	34 (39.54)		
Perineural invasion	Negative	350 (81.97)	266 (84.44)	73 (84.88)	0.988	0.61
	Positive	77 (18.03)	49 (15.56)	13 (15.12)		
Clinical stage	Stage I	133 (31.15)	84 (26.67)	26 (30.23)	4.254	0.642
	Stage II	204 (47.78)	169 (53.65)	42 (48.84)		
	Stage III	86 (20.14)	57 (18.10)	16 (18.60)		
	Stage IV	4 (0.93)	5 (1.58)	2 (2.33)		
Total		427 (100.00)	315 (100.00)	86 (100.00)		

TABLE 5: THE COX MODEL RESULT OF GENOTYPE

Indicator		B	SE	Wald	Df	HR (95 % CI)	p
DFS	AA			0.691	2		0.708
	GA	-0.074	0.213	0.119	1	0.929 (0.612-1.411)	0.73
	GG	0.176	0.293	0.363	1	1.193 (0.672-2.118)	0.547
OS	AA			1.695	2		0.428
	GA	0.071	0.353	0.040	1	1.073 (0.538-2.143)	0.841
	GG	0.588	0.46	1.635	1	1.801 (0.731-4.436)	0.201

TABLE 6: COMPARISON OF OUR RESULTS AND THOSE OF PREVIOUS STUDIES

Author	Date of publication	Ethnicity	Median age of case group	Number of cases	Number of controls	Source of control	Assay methods	OR (p)
Gold *et al.*	2008	AJ	55	950	979	Hospital	Taq man SNP genotyping	$1.412.9\times10^{-8}$
Kirchhoff *et al.*	2009	AJ and European American (non-AJ)	_	1953	1467	Population	Taq man SNP genotyping	1.18, p=0.0083
Kirchhoff *et al.*	2009	AJ and European American (non-AJ)	_	1953	1467	Population	Taq man SNP genotyping	1.18, p=0.0083

Long *et al.*	2010	Southern Chinese	49.3 and 53.9	6498	3999	Population	Mass array system Taq man SNP genotyping	0.94, p=0.13
Campa *et al.*	2011	BPC3 (83 % European descent and Latino)	62.39	8576	11 892	Population	Taq man SNP genotyping	0.95, p=0.11
Loizidou *et al.*	2011	Cypriot population	–	1109	1177	Population	Taq man SNP genotyping	1.07, p=0.34
Kirchhoff *et al.*	2012	BCAC (88.9 % European and 9 % Asian)	53.1	31 428	34 700	Population	Taq man SNP genotyping	1.03, p=0.031
Lee *et al.*	2014	Singapore Chinese	54.9	411	1212	Population	Mass array system	1.09, p=0.365
Nagrani *et al.*	2017	Western Indian	46	1204	1212	Hospital	Taq man SNP genotyping	0.95, p=0.408
Present study	2021	Northern Chinese	51	828	905	Hospital	Mass array system	1.932, p=0.001

BC was the first cancer associated with Wnt signaling, and RNF146-regulated activation of Wnt signaling is recognized as a key factor in metastasis, proliferation, drug resistance, immune microenvironment regulation and stem cell maintenance in BC[34-36]. However, we did not find any significant association between the RNF146 rs2180341 SNP and DFS, and OS of BC in this study. The rs2180341 GG genotype was associated with a relatively poor DFS and OS of BC. This may be owing to the short duration of follow-up and small sample size of individuals with the GG genotype. To address this limitation, a large number of individuals with the GG phenotype should be enrolled and studied in future studies.

The results of this study show that the RNF146 rs2180341 SNP increases the risk of BC in the Northern Chinese population and should be investigated in greater detail in the future. Owing to the differences in the living environments and genetic backgrounds of populations in different regions, in-depth studies with large sample sizes are warranted in other regions.

Ethical approval:

The research was approved by the Ethics Committee of the First Affiliated Hospital of Jilin University (Approval No: 2014-031), which was conducted according to relevant guidelines and Helsiniki's statement. All participants provided written informed consent.

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Conflict of interests:

The authors declared no conflict of interests.

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