Original Article

Mutational analysis of BRCA1 and BRCA2 in northwest Chinese breast cancer patients

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Background: BRCA1 and BRCA2 are the most well-known susceptibility genes in breast cancer, indicating high-risk breast cancer families and influencing both treatment options. However, data of BRCA mutation in Chinese breast cancer population was limited. Here we explored the BRCA1/2 mutation status and analyzed their clinicopathological relationships among breast cancer patients with high hereditary risk in northwest China.

Methods: Breast cancer patients admitted to Xijing Hospital, between November 2015 and May 2016, with high hereditary risk were recruited. Fresh peripheral venous blood samples were collected for BRCA1/2 gene screening. Risk factors for BRCA1/2 mutations were studied via single-factor analysis and multivariable logistic analysis. Furthermore, we reviewed the literature and discussed the possible mechanism of the mutant genome types.

Results: Eighty-two patients were enrolled in the study. Twenty (24.4%) of them were found with BRCA1/2 mutation, including 8 BRCA1 mutation and 13 BRCA2 mutation. BRCA1 and BRCA2 co-mutation was observed in only one case. The mutant genome types included pathogenic variant (4/82), potential pathogenic variant (4/82), beneficial mutations (8/82), and chemotherapy sensitivity-related mutations (5/82). Prognosis-related mutations were enriched in *BRCA2* gene, while drug-sensitive related mutations were always observed in *BRCA1* gene. Multiple logistic analysis showed that HER2 [odds ratio (OR) 4.58; 95% confidence interval (CI), 1.182–17.74; P=0.028) might be independent factor for BRCA1/2 mutation.

Conclusions: The incidence and feature of BRCA1/2 mutation in our center was similar to that in other regions. HER2 expression was independent factor for BRCA1 and BRCA2 mutation. BRCA2 T/-, BRCA2 A/-, BRCA2 G/- and BRCA2 C/-mutation subtypes might be potential harmful mutations for Chinese breast cancer population.

Keywords: BRCA1; BRCA2; genomic screening; breast cancer; literature review

Submitted Nov 27, 2018. Accepted for publication Aug 08, 2019.
doi: 10.21037/tcr.2019.08.32
View this article at: http://dx.doi.org/10.21037/tcr.2019.08.32

Introduction

Breast cancer is still the most commonly diagnosed cancer (2.08 million new cases) and the leading cause of cancer death (0.66 million deaths) among females (1). Consistently, in China, breast cancer statistics is identical with that worldwide. Approximately 11% of worldwide breast cancer occurs in China and that the incidence has increased rapidly in recent decades (2). However, breast cancer in China is not comprehensively understood compared with

Westernized countries.

About 5–10% of breast cancer burden follows a Mendelian inheritance pattern and is characterized as hereditary (3). The breast cancer-associated genes BRCA1 on chromosome 17q and BRCA2 on chromosome 13q are the most well-known breast cancer susceptibility genes, indicating from high-risk breast cancer families and influencing both treatment options and clinical management (4,5). In United States, the average cumulative risks of breast cancer in BRCA1 and BRCA2 mutation carriers by age 70 years are in the ranges of 60–70% and 45–55% (6). However, multigene panel testing of breast cancer predisposition genes have been extensively conducted in Europe and America, which is relatively rare in Asia region. In China, rare large-scale research has been conducted to examine the BRCA1/2 mutations. In 2015, we participated into the multicenter study by Li *et al.* and assessed the frequency of germline mutations in 40 cancer predisposition genes (7). Finally, we acquired 159 patients with BRCA1/2 mutations among 937 Chinese breast cancer patients with high hereditary risk. However, the characteristics of BRCA1/2 mutation subtypes, as well as its association with clinicopathological features need further discussion.

In this study, we reported the screening results of BRCA1/2 mutation in our center and analyzed the association of BRCA1/2 mutation with clinicopathological characteristics. Based on the special genome mutation, we reviewed the literature and discussed their possible mechanism in breast cancer incidence and prognosis.

Methods

Participants

Between November 2015 and May 2016, breast cancer patients admitted to Xijing Hospital with high hereditary risk were recruited. Inclusion criteria: (I) onset age ≤35 years (early-onset breast cancer); (II) at least one first or second-degree relative with breast cancer, ovarian cancer (OC), primary peritoneal cancer, or fallopian tube carcinoma; (III) two primary breast cancer; (IV) male breast cancer; (V) breast cancer with OC, fallopian tube carcinoma or primary peritoneal cancer. This protocol was approved by the Ethics Committee of the Xijing Hospital of The Fourth Military Medical University (No. KY20150916-4) and undertaken in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients were fully consented and asked to provide written informed consent before enrollment.

BRCA1/2 screening

Participants were asked for 5 mL fresh peripheral venous blood, which was transferred into a coded Ethylenediaminetetraacetic Acid (EDTA) tube at 4 ℃. Then, the collected blood samples were sent to Annoroad Gene Technology (Beijing, China) Co. Ltd. for gene testing on an Illumina HiSeq 2500 platform (Illumina, San Diego, CA, USA), as previous described (7). The transcripts of BRCA1 and BRCA2 were NM_007294 and NM_000059, including 49 coding regions, 160 thousand of nucleotide sites. The main endpoints were single base polymorphisms (SNPs) in gene coding region and the base sequence insertion or deletion. Bioinformatics analysis was used to obtain mutant sites. BRCA1/2 mutations were explained based on the references included in comprehensive database (ClinVar and BIC database), clinical practice guideline and the latest medical papers.

Statistical analysis

SPSS 22.0 for windows was used for statistical analysis. All participants were followed up by specified research nurses and there are two investigators independently extracted the data using a predesigned data extraction form. Normal descriptive data were represented by mean ± standard deviation. Student's *t*-test was used to compare the mean after checking the homogeneity of variance. Enumeration data was compared using χ^2 test, and unadjusted odds ratio and adjusted odd ratio were estimated by logistic regression for each indictor. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

Between November 2015 and May 2016, 82 patients (77 females and 5 males) were assessed for eligibility. The basic features were presented in *Table 1*. The average age was 35.7±9.04 years old. For menopausal status, 76 (92.7%) patients were premenopausal, while 6 (7.3%) of them were postmenopausal. Besides, the expression of ER (estrogen receptor), PR (progesterone receptor), HER2 (human epidermal growth factor receptor type 2) and Ki67 were investigated. Enrolled patients were proved with high

Table 1 Baseline characteristics

Item	Data (N=82)
Sex	
Female	77 (93.9%)
Male	5 (6.1%)
Age	
Average	35.7±9.04
Median	34 [8–64]
BMI	22.8±3.29
Marriage	
Yes	77 (93.9%)
No	5 (6.1%)
Lactation	
Yes	57 (69.5%)
No	25 (30.5%)
Menopausal status	
Premenopause	76 (92.7%)
Postmenopause	6 (7.3%)
Ethnicity	
Han nationality	80 (97.6%)
Others	2 (2.4%)
Lesion	
Bilateral	1 (1.2%)
Unilateral	81 (98.8%)
Menstruation	
Age of menarche	13 [11–17]
Menstrual cycle	28 [22–30]
Estrogen receptor	
Positive	54 (65.9%)
Negative	28 (34.1%)
Progesterone receptor	
Positive	50 (61.0%)
Negative	32 (39.0%)
HER2	
Positive	32 (39.0%)
Negative	50 (61.0%)
Ki67	
≤20	28 (34.1%)
>20	54 (65.9%)
Pathology	
Carcinoma *in situ*	7 (8.5%)
Invasive carcinoma	69 (84.1%)
Others	6 (7.3%)
Family cancer history	
Family breast cancer history	23 (28.0%)
Family other cancer history	35 (42.7%)

hereditary risk. Family breast cancer history and other cancer history were found in 23 (28.0%) and 35 (42.7%) of them.

Results of BRCA1/2 mutation

Twenty participants (24.4%) were found with BRCA1/2 mutation among 82 patients with high risk (*Table 2*). Eight patients were detected with BRCA1 mutation, 13 patients were detected with BRCA2 mutation. There is only one case with both BRCA1 and BRCA2 mutation BRCA2: c.2971A>G (A/G type) mutation indicating good prognosis was found in 8 participants. Mutations about drug-sensitivity, including BRCA1: c.4837A>G (G/G type) and BRCA1: c.2612C>T (T/T type), were explored in 5 patients. G/G genome type and T/T genome type seem to present together. Pathogenic variant (BRCA1 c.4485-2A>C, BRCA1 c.5470-5477del, BRCA1: c.190T>C or BRCA2: c.3109C>T) and potential pathogenic variant (BRCA2: c.31delT, BRCA2: c.6408delA, BRCA2: c.6705delG or BRCA2: c.677delC) were detected in 8 participants. Above all, we found that prognosis-related mutations were enriched in *BRCA2* gene, while drug-sensitive related mutations were always observed in *BRCA1* gene.

Description of the mutation types in ClinVar and BIC databases

Searching the mutant genomic types in ClinVar and BIC databases, we found some potential novel mutant types in *BRCA2* gene, such as BRCA2 c.31delT, BRCA2 c.6408delA, BRCA2 c.6705delG and BRCA2 c.677delC genome types (*Table 3*).

Association of BRCA1/2 mutation with clinicopathological characteristics

To explore the relationship between BRCA1/2 mutation and clinical features, we classified participants into mutation group and wild group. As shown in *Table 4*, HER2 expression, family cancer history and family breast/OC history were significantly different between BRCA1/2 mutation group and BRCA1/2 wild group. Multiple logistic analysis showed that HER2 [odds ratio (OR) 4.58; 95% confidence interval (CI), 1.182–17.74; P=0.028] was independent factor for BRCA1/2 mutation (*Table 5*). Among 32 patients with positive HER2, only 9% (3/32) of them were detected with BRCA1 or BRCA2 mutation. But

Table 2 List of patients with BRCA1/2 mutation

No.	Sex	BMI	Age	Pathology	Family cancer history	Cancer type	Mutation	Genome type	Effects
1	Female	23.37	41	IBC	Yes	OC	BRCA1: c.4485-2A>C	A/C	DM
2	Female	24.35	30	IBC + IDC	No	–	BRCA1: c.5470-5477del	TGCCCAAT/-	DM
3	Female	27.39	43	IBC	Yes	BC	BRCA1: c.190T>C	T/C	DM
4	Female	26.91	35	IBC	Yes	GC	BRCA1: c.4837A>G BRCA1: c.2612C>T	G/G; T/T	A; B
5	Female	30.12	47	IDC	Yes	OC	BRCA1: c.4837A>G BRCA1: c.2612C>T	G/G; T/T	A; B
6	Female	20.06	62	IDC	Yes	OC	BRCA1: c.4837A>G BRCA1: c.2612C>T	G/G; T/T	A; B
7	Female	20.94	33	IBC	No	–	BRCA1: c.4837A>G BRCA1: c.2612C>T	G/G; T/T	A; B
8	Female	21.08	37	IBC	No	–	BRCA2: c.2971A>G	A/G	GP
9	Female	21.88	34	IBC	No	–	BRCA2: c.2971A>G	A/G	GP
10	Female	20.69	38	IBC	Yes	BC	BRCA2: c.2971A>G	A/G	GP
11	Female	24.24	35	IBC	No	–	BRCA2: c.2971A>G	A/G	GP
12	Female	21.48	39	IBC	Yes	BC	BRCA2: c.2971A>G	A/G	GP
13	Female	23.74	31	MBC	No	–	BRCA2: c.2971A>G	A/G	GP
14	Female	22.10	38	IBC	No	–	BRCA2: c.2971A>G	A/G	GP
15	Female	21.48	28	IBC	Yes	BC	BRCA2: c.2971A>G; BRCA1: c.4837A>G; BRCA1: c.2612C>T	A/G;G/G;T/T	GP;A;B
16	Female	19.71	31	IBC	Yes	BC	BRCA2: c.31delT	T/-	PDM
17	Female	22.43	36	IBC	Yes	BC	BRCA2: c.6408delA	A/-	PDM
18	Female	27.34	51	IDC	No	–	BRCA2: c.6705delG	G/-	PDM
19	Female	24.65	46	IBC	Yes	BC, EC	BRCA2: c.677delC	C/-	PDM
20	Female	20.32	59	IBC	Yes	BC*4	BRCA2: c.3109C>T	C/T	DM

IBC, invasive breast carcinoma; IDC, invasive ductal carcinoma; MBC, mucinous breast carcinoma; OC, ovarian cancer; BC, breast cancer; GC, gastric cancer; EC, esophagus cancer; DM, detrimental mutation; PDM, potential detrimental mutation; GP, good prognosis; A, sensitive to platinum drugs; B, prolonged survival for cisplatin + paclitaxel regimen.

for 50 cases of HER2 negative breast cancer patients, 34% (17/50) were found mutant *BRCA1* or *BRCA2* gene.

Discussion

BRCA1/BRCA2 mutations have been identified as main contributor of hereditary breast cancer, increasing the lifetime risk of breast cancer in women (8). However, this paradigm has not been studied extensively and accurately in China. In this study, we investigated the BRCA1/2 mutation rate and mutation features for breast cancer patients in northwest China. The mutation rate of BRCA1/2 in high hereditary risk breast cancer patients was 24.4%, which was similar to that in other regions. In 2015, Riahi *et al.* estimate 25% pathogenic mutations in BRCA1/2 genes in early-onset and familial breast/OC among Tunisian women (9). In 2016, Cao *et al.* observed a total mutation frequency of 23.3% in *BRCA1* and *BRCA2* genes among patients in eastern China (10). Differently, BRCA2 mutations seem to be a few more than BRCA1 mutations (11). In

Table 3 Searching of ClinVar and BIC databases

Gene	Mutant	Exon	Nucleotide	AA change	BIC entries	Clinvar entries	Novel genome
BRCA1	c.4485-2A>C	14	4485-2	Asn to His	Yes	Yes	No
	c.5470-5477del	23	5470-5477	Frameshift	2	3	No
	c.190T>C	64	190	Cys to Arg	14	4	No
	c.4837A>G	15	4837	Ser to Gly	None	None	No
	c.2612C>T	10	2612	Pro to Leu	None	None	No
BRCA2	c.3109C>T	11	3109	p.Q1037X	14	6	No
	c.2971A>G	11	2971	Asn to Asp	None	None	No
	c.31delT	–	31	Frameshift	None	None	Yes
	c.6408delA	–	6408	Frameshift	None	None	Yes
	c.6705delG	–	6705	Frameshift	None	None	Yes
	c.677delC	–	677	Frameshift	None	None	Yes

2013, Blay *et al.* found 59 (23%) families with pathogenic germ line mutation, 39 in BRCA1 and 20 in BRCA2, in hereditary breast and OC families from Asturias (Northern Spain) (12). However, this is a very selective cohort. More convincing data of BRCA1/2 mutations should be achieved in cohort with larger samples.

In this study, we found 8 pathogenic variants in *BRCA1* and *BRCA2* genes, some of which have been reported previously. In 2001, BRCA1: c.4485-2A>C (BRCA1 A/C genome type) alteration was found among OC families in Japan and was determined as harmful mutation (13). Mutation of BRCA1: c.5470-5477del (TGCCCAAT/- type) has been observed in several studies. In 2004, Choi *et al.* found BRCA1: c.5470-5477del mutation and described it as c.5589del8, in Korean breast cancer families (14). Similarly, BRCA1: c.5470-5477del mutation was detected in 2 out of 645 women from Shanghai, China (15). In 2007, BRCA1: c.5470-5477del mutations were observed in several cases of breast cancer patients and were regarded as the possible founder mutations for Chinese population (16). As founder mutations of Italian people, the detrimental function of BRCA1: c.190T>C (BRCA1 T/C genome type) mutation was verified in two studies from Italy (17,18). BRCA2: c.3109C>T (BRCA2 C/T genome type) mutation was explored and was regarded as the founder mutations of Southern Chinese people (19-21). Importantly, 4 potential harmful mutations, including BRCA2: c.31delT (T/-), BRCA2: c.6408delA (A/-), BRCA2: c.6705delG (G/-) and BRCA2: c.677delC (C/-) were detected in the study, which have never been reported before. In 2015, Rebbeck *et al.* exclaimed that c.31delT, c.6408delA, c.6705delG and c.677delC genome types located in BRC domain (c.3006-6255) and DNA binding domain (c.7437-8001) of *BRCA2* gene (16). Frame-shifting mutation induced sequence changing of DNA binding domain and OB (oligonucleotide-binding) folds domain in *BRCA2* gene was the possible mechanism. DNA binding domain and OB folds domain have been reported to participate into the repair of double-strand DNA breaks (DSBs) by homologous recombination (22).

BRCA1 gene, involving homologous recombination, nonhomologous end joining, and mismatch repair, plays crucial role in regulating DNA damage induced by DNA-damaging agents such as platinum (23). Patients with lower BRCA1 expression obtain better survival after platinum-based neoadjuvant chemotherapy (24). Herein, two BRCA1 genotypes (BRCA1: c.4837A>G and BRCA1: c.2612C>T) were detected, indicating better chemotherapy sensitivity. Similarly, Du *et al.* found that patients with BRCA1: c.4837A>G (G/G) mutation achieved a better response to chemotherapy and a decreased risk of death in advanced NSCLC patients (25). BRCA1: c.2612C>T (T/T) mutation was also associated with better sensitivity to taxane and cisplatin regimen. In 2010, Shim demonstrated significant prolongation of overall survival (OS) and progression-free survival (PFS) in advanced gastric cancer patients with BRCA1 T/T mutation, after treating with taxane and cisplatin (26). For non-small cell lung cancer patients treated with first-line paclitaxel-cisplatin chemotherapy, BRCA1 T/T mutation was proved as modest prognostic

Table 4 Relationship between BRCA1/2 mutation and clinicopathological characteristics

Item	Mutation group (N=20)	Wild group (N=62)	χ^2/F	P
Sex			1.718	0.19
Female	20	57		
Male	0	5		
Age	39.7±9.04	34.2±8.61	0.813	0.37
BMI	23.22±2.80	22.6±3.41	0.826	0.366
Number of pregnancy	1.45 [0–4]	1.53±1.30	0.881	0.351
Lactation			1.373	0.241
Yes	16	41		
No	4	21		
Menopausal status			2.302	0.129
Premenopause	17	59		
Postmenopause	3	3		
Menstruation				
Age of menarche	13.8±1.61	13.4±1.31	1.595	0.210
Menstrual cycle	28.53±3.65	28.8±1.91	3.224	0.076
Estrogen receptor			0.009	0.926
Positive	13	41		
Negative	7	21		
Progesterone receptor			0.011	0.918
Positive	12	38		
Negative	8	24		
HER2			6.416	0.011
Positive	3	29		
Negative	17	33		
Ki67			0.984	0.321
≤20	5	23		
>20	15	39		
Pathology			2.092	0.351
Carcinoma *in situ*	0	6		
Invasive carcinoma	19	53		
Other	1	3		
Family cancer history	12	21	4.293	0.038
Family breast/ovarian cancer history	11	16	5.836	0.016
Family other cancer history	2	7	0.026	0.872

Table 5 Multifactor logistic analysis

Variable	Reference		β	SD	Wald	P	OR	95% CI
HER2	Positive	Negative	1.522	0.691	4.85	0.028	4.58	1.182–17.74
Family cancer history	Yes	No	0.029	1.188	0.001	0.98	0.971	0.095–9.968
Family breast/ovarian cancer history	Yes	No	1.136	1.192	0.909	0.34	0.321	0.031–3.319

markers (27).

This study has several limitations. First, the sample size was relatively small. Second, there is no follow-up data because of the short follow-up period. With follow-up continued, the final prognosis and survival data will be gained. Third, only a limited number of SNPs in *BRCA1* and *BRCA2* genes were enrolled into detection, while the other polymorphisms in these genes may be important.

In conclusion, the BRCA1/2 mutation features in our hospital and the total mutation rate of BRCA1/2 in high hereditary risk breast cancer patients was similar to that in other regions. HER2 expression was independent factor for BRCA1 and BRCA 2 mutation for breast cancer with high risk. Four novel genome types, including BRCA2: c.31delT (T/-), BRCA2: c.6408delA (A/-), BRCA2: c.6705delG (G/-) and BRCA2: c.677delC (C/-), might be potential harmful mutations, which needs further verification.

Acknowledgments

Funding: This work was funded by National Natural Science Foundation of China (No. 81572917 and 81472598) and Wujieping Foundation (320.6750.13292).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.08.32). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This protocol was approved by the Ethics Committee of the Xijing Hospital of The Fourth Military Medical University (No. KY20150916-4) and undertaken in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients were fully consented and asked to provide written informed consent before enrollment.

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Cite this article as: Wang T, Zhang J, Xiao J, Huang M, Li N, Ling R. Mutational analysis of BRCA1 and BRCA2 in northwest Chinese breast cancer patients. Transl Cancer Res 2019;8(5):1845-1852. doi: 10.21037/tcr.2019.08.32

