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EPIDEMIOLOGY

The prevalence and spectrum of *BRCA1* and *BRCA2* mutations in Korean population: recent update of the Korean Hereditary Breast Cancer (KOHBRA) study

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Abstract The Korean Hereditary Breast Cancer (KOHBRA) study was established to evaluate the prevalence and spectrum of *BRCA1/2* mutations in Korean breast cancer patients at risk for hereditary breast and ovarian cancer. A total of 2953 subjects (2403 index patients and 550 family members of affected carriers) from 36 centers participated in this study between May 2007 and December 2013. All participants received genetic counseling and *BRCA* genetic testing. In total, 378 mutation carriers among 2403 index patients were identified. The prevalence of *BRCA* mutations in specific subgroups was as follows: 22.3 % (274/1228) for breast cancer patients with a family history of breast/ovarian cancers, 8.8 % (39/441) for patients with early-onset (<35 years) breast cancer without a family history, 16.3 % (34/209) for patients with bilateral breast cancer, 4.8 % (1/21) for male patients with breast cancer, and 37.5 % (3/8) for patients with both breast and ovarian cancer. From an analysis of the mutation spectrum, 63 *BRCA1* and 90 *BRCA2* different mutations, including 44 novel mutations, were identified. The c.7480 (p.Arg2494-Ter) mutation in *BRCA2* (10.1 %) was the most commonly identified in this cohort. The KOHBRA study is the largest cohort to identify *BRCA* mutation carriers in Asia. The results suggest that the prevalence of *BRCA* mutations in familial breast cancer patients is similar to that among Western cohorts. However, some single risk factors without family histories (early-onset breast cancer, male breast cancer, or multiple organ cancers) may limit the utility of *BRCA* gene testing in the Korean population.

Keywords *BRCA1* genes · *BRCA2* genes · Breast neoplasms · Genetic predisposition · Prevalence

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Introduction

Breast cancer incidence in Korea has been rising annually, reaching a total of 16,967 patients (crude incidence: 67/100,000 women per year) in 2011 [1]. Although it is the highest crude incidence among Asian countries, it is still lower than that of the United States and Western European countries. The median age at diagnosis of breast cancer has also increased up to 50 years in 2011; however, it is approximately 10 years younger than that of the United States [1]. These differences may be associated with different environmental and genetic backgrounds between ethnicities.

About 5–10 % of all breast cancers are caused by germline mutations of various genes. Mutations in *BRCA1* and *BRCA2* genes are a major correlate of hereditary breast cancers, accounting for about 25 % of HBC [2]. Since the *BRCA1* and *BRCA2* genes were discovered in 1994 [3] and 1995 [4], respectively, genetic testing of these genes in people considered at high risk for hereditary breast and ovarian cancer has been performed widely in North America and in Europe. Confirmation of a *BRCA* gene mutation is meaningful because it gives unaffected carriers an opportunity to reduce breast and ovarian cancer risk, and also helps affected carriers receive individualized treatment. Genetic testing and clinical management should be based on individual nation-wide data, because there are relevant differences among diverse ethnic groups [5]. In Korea, the *BRCA1* gene mutation was reported first in 1995 [6], and since then, multiple studies have evaluated the prevalence of *BRCA1/2* mutations in Koreans. However, these studies were limited in their study population sizes. Therefore, the guidelines to offer genetic testing to Korean population have been constructed on a basis of Western data.

In 2007, the Korean Hereditary Breast Cancer (KOHBRA) study, a nation-wide prospective cohort, was started to establish a large *BRCA* carrier cohort to identify the cause and natural history of hereditary breast cancer in Korean population ultimately. The primary aims of the KOHBRA study were to accurately estimate the prevalence of *BRCA1/2* mutations and to identity a founder mutation in Korean breast cancer patients with risk of hereditary breast and ovarian cancer. Another aim was to determine the predictors of *BRCA1/2* mutations in non-familial breast cancer patients. Previously, the prevalence of *BRCA1/2* mutations was reported for 775 familial breast cancer patients [7] and 758 non-familial breast cancer patients [8] who were enrolled in the KOHBRA study between May 2007 and May 2010. This is the recently updated report on the prevalence and spectrum of *BRCA1* and *BRCA2* mutations in the KOHBRA study up to December 2013.

Methods

Subjects

Through the KOHBRA study, 3015 subjects were recruited between May 2007 and December 2013 from 36 institutions. The eligibility criteria for enrollment were as follows: (1) breast cancer patients with a family history of breast or ovarian cancer (familial); (2) breast cancer patients without a family history of breast or ovarian cancer (non-familial) who were 40 years and younger at diagnosis, diagnosed with bilateral breast cancer or another primary malignancy, or male; (3) family members of *BRCA1/2* mutation carriers. The risk of carrying a *BRCA* mutation among these high risk populations generally satisfies greater than 10 %, the traditional cutoff for offering a *BRCA* genetic testing [9–11]. Korea also limit mutation testing based on this cutoff value. The eligible patients were offered genetic counseling and brief information about the study by the investigators at each institution preferentially. When the patients agreed to participate in the study, the investigators contacted the KOHBRA headquarters. For quality control of data, the KOHBRA research nurses professionally trained for hereditary breast cancer visited the institution directly. All participants received genetic counseling and full information of the study by the research nurses. After the obtainment of informed consent, clinical information, epidemiological questionnaire responses, and blood samples for banking were collected. Pedigree was obtained at least three generations including third-degree relatives. Detailed protocols and procedures of the study are available in the interim report [12]. After enrollment, 48 subjects withdrew before *BRCA1/2* genetic testing and 14 subjects withdrew the study participation after *BRCA1/2* genetic testing. After exclusion of the subjects who dropped out of the study, 2953 subjects (1228 familial breast cancer patients, 1175 non-familial breast cancer patients and 550 family members of affected carriers) were analyzed (Fig. 1). This study was approved by the institutional review boards of all participating hospitals.

BRCA mutation analysis

BRCA1/2 genetic testing was performed using genomic DNA from the peripheral blood by one of the following methods: fully direct sequencing, fluorescence conformation sensitive capillary (gel) electrophoresis, and denaturing high-performance liquid chromatography. Each method was selected according to the procedures of the DNA testing laboratories linked to each institution. Among genetic tests for 2403 index cases, 1101 were conducted by direct sequencing, 1183 by fluorescence conformation sensitive capillary (gel) electrophoresis, and 119 by

denaturing high-performance liquid chromatography. One laboratory routinely carried out not only direct sequencing but also multiplex ligation-dependent probe amplification for detection of genomic deletions and rearrangements: 345 subjects underwent both direct sequencing and multiplex ligation-dependent probe amplification for *BRCA1* and *BRCA2* genetic screening in this laboratory. All *BRCA1* and *BRCA2* variants were categorized into pathogenic, unknown significance, or polymorphic. Prevalence of mutations was calculated as the proportion of carriers with pathogenic mutations in each subgroup.

Mutation nomenclature

All mutations are described according to the HUGO-approved systematic nomenclature (http://www.hgvs.org/mutnomen/). Reference sequences, GenBank accession numbers NM_007294.2 and NM_000059.3, were used for *BRCA1* and *BRCA2* DNA numbering, respectively. Traditional mutation nomenclatures of the breast cancer information core (BIC; http://research.nhgri.nih.gov/bic/) are also used for description.

Results

Subject characteristics

Among the probands, 1228 patients had a family history of breast or ovarian cancer: 1085 (88.4 %) with a family history of only breast cancer, 102 (8.3 %) with a family history of only ovarian cancer, and 41 (3.3 %) with a family history of both breast and ovarian cancer. Among the 1175 probands without a family history of breast or ovarian cancer, there were 845 (71.9 %) patients with early-onset breast cancer (≤40 years), 209 (17.8 %) patients with bilateral breast cancer, 8 (0.7 %) patients with a personal history of both breast and ovarian cancer, and 21 (1.8 %) male breast cancer patients (Table 1). The mean age at first breast cancer diagnosis of index cases was 40.6 years (range, 19–83 years). Five hundred and fifty family members from 222 families with *BRCA* mutations were enrolled, with a mean number of family members per family of 1.5 (range, 1–9). Pathogenic mutations in *BRCA1* and *BRCA2* genes were detected in 378 of 2403 (15.7 %) probands and in 286 of 550 (52.0 %) family members.

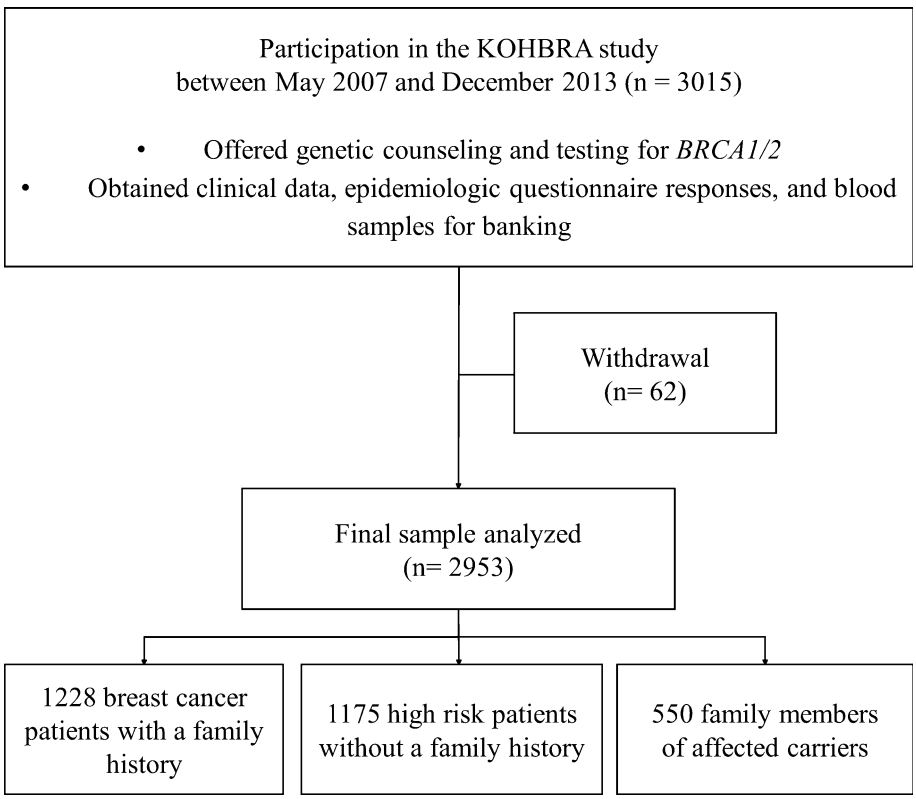

Fig. 1 Flow chart of the study

BRCA1/2 mutations in familial breast cancer patients

The overall prevalence of *BRCA1/2* mutations was 22.3 % in familial breast cancer patients, including 20.6 % in patients with a family history of only breast cancer and 29.4 % in patients with a family history of only ovarian cancer. Among patients with a family history of ovarian cancer, mutation prevalence (range, 26.3–100.0 %) was very high in all subgroups regardless of family history of breast cancer. Among patients without a family history of ovarian cancer, a higher number of relatives with breast cancer correlated with a higher rate of *BRCA1/2* mutations. The prevalence of *BRCA1/2* mutations according to number of relatives with breast cancer was 17.8, 30.2, and 43.2 % in patients with 1 relative, 2 relatives, and 3 relatives with breast cancer, respectively (Table 2). There was no significant difference in mutation prevalence (range, 14.1–21.7 %) according to the closest degree of relatives with breast cancer.

We analyzed the prevalence of *BRCA1/2* mutations among patients who had only one family member with breast cancer to examine differences according to the degree of relative with breast cancer and age at diagnosis of breast cancer (Table 3). Regardless of the degree of relative with breast cancer, the prevalence was higher than a 10 % cutoff value: 17.8 % in patients with a first-degree relative with breast cancer, 18.3 % in patients with a second-degree relative with breast cancer, and 12.0 % in patients with a third-degree relative with breast cancer. When the probands' age at diagnosis of breast cancer was under 50 years, the mutation prevalence satisfied the cutoff in each subgroup with a family history of first-, second-, or third-degree relative with breast cancer at any age of diagnosis. When the probands' age at diagnosis was 50 years and more, the mutation prevalence met the 10 % cutoff value when the relatives' age at diagnosis was under 50 years.

BRCA1/2 mutations in non-familial breast cancer patients

The overall prevalence of *BRCA1/2* mutations was 8.9 % in non-familial breast cancer patients with high risk of hereditary breast and ovarian cancer: 7.1 % in early-onset breast cancer patients (≤40 years), 16.3 % in bilateral breast cancer patients, 37.5 % in patients with both breast and ovarian cancer, 4.8 % in male breast cancer patients, 4.1 % in patients with multi-organ cancer including breast cancer, and 16.7 % in patients with two or more of these forms (Table 1).

Among the early-onset breast cancer patients, the range of *BRCA1/2* mutation rates varied according to the presence of other risk factors and the age at diagnosis of breast cancer. In 845 patients without other risks, *BRCA1/2* mutations were observed in 39 of 441 (8.8 %) patients who were diagnosed with breast cancer and were less than 35 years old, and in 21 of 404 (5.2 %) patients who were diagnosed with breast cancer between 35 and 40 years old. In addition, we had further analysis to determine the difference of *BRCA1/2* prevalence according to breast cancer subtype in 441 young breast cancer patients (<35 years) without other risk factors. The rates of *BRCA1/2* mutations showed a difference depending on the presence of triple-negative subtype. The prevalence in patients with triple-negative breast cancer was 12.5 % (13/104), and the rates of *BRCA1/2* mutations in breast cancer patients with non-triple-negative subtype and unknown subtype were 7.8 % (24/308) and 6.9 % (2/29), respectively.

Among 91 patients with breast and other cancers, *BRCA1/2* mutations were observed in 2 (3.3 %) of 60

Table 1 The prevalence of *BRCA1/2* mutations in 2403 probands up to 2013

	Risk category	Total (*n*)	*BRCA1/2* mutations (*n*)	Prevalence (%)
Familial breast cancer patients	Presence of family history of only breast cancer	1085	224	20.6
	Presence of family history of only ovarian cancer	102	30	29.4
	Presence of family history of both breast and ovarian cancer	41	20	48.8
	Total	1228	274	22.3
Non-familial breast cancer patients	Early-onset breast cancer	845	60	7.1
	Bilateral breast cancer	209	34	16.3
	Both breast and ovarian cancer	8	3	37.5
	Multiple organ cancers	74	3	4.1
	Male breast cancer	21	1	4.8
	Two or more high risks	18	3	16.7
	Total	1175	104	8.9

Table 2 Prevalence of *BRCA1/2* mutations among patients with a family history of breast or ovarian cancer

Family history of breast or ovarian cancer	Personal history of proband								
	Breast cancer at any age			Breast cancer <50 years			Breast cancer ≥50 years		
	n	*BRCA1/2*(+)	%	*n*	*BRCA1/2*(+)	%	*n*	*BRCA1/2*(+)	%
No family history of ovarian cancer									
Number of relatives with breast cancer									
1	882	157	17.8	670	135	20.1	212	22	10.4
2	159	48	30.2	112	36	32.1	47	12	25.5
≥3	44	19	43.2	36	15	41.7	8	4	50.0
Closest degree of relatives with breast cancer									
First-degree	669	145	21.7	469	115	24.5	200	30	15.0
Second-degree	281	60	21.4	239	56	23.4	42	4	9.5
Third-degree	135	19	14.1	110	15	13.6	25	4	16.0
One family history of ovarian cancer									
Number of relatives with breast cancer									
0	95	25	26.3	77	22	28.6	18	3	16.7
1	30	16	53.3	20	11	55.0	10	5	50.0
2	10	3	30.0	7	1	14.3	3	2	66.7
≥3	1	1	100.0	1	1	100.0	0		
Two or more family history of ovarian cancer, any family history of breast cancer	7	5	71.4	5	4	80.0	2	1	50.0

patients with thyroid cancer, in 1 of 12 (8.3 %) patients with uterine cancer, in 1 of 6 (16.7 %) patients with renal cell carcinoma, and in 1 of 1 (100 %) patient with osteosarcoma.

Spectrum of BRCA1/2 mutations in the KOHBRA study

The spectra of *BRCA1* and *BRCA2* mutations identified in the KOHBRA study are presented in Tables 4 and 5. Overall, 153 distinct mutations (63 *BRCA1* and 90 *BRCA2*) were found in 378 index cases (154 *BRCA1*, 221 *BRCA2*, and 3 with both *BRCA1* and *BRCA2*). Nonsense, frameshift, and splice-defect mutations were identified, with 22, 29, and 11 in *BRCA1,* and 28, 56, and 5 in *BRCA2*, respectively. One missense mutation was found in *BRCA2*. Of 153 distinct mutations, we identified 44 novel mutations that have not yet been reported in the BIC or in other published reports. The most frequent mutation, c.7480C>T (p.Arg2494Ter) in *BRCA2*, was found 38 times (10.1 % of all pathogenic mutations). The second most frequent mutation, c.390C>A (p.Tyr130Ter), accounted for only 5.6 % of the *BRCA1/2* mutations. Forty distinct *BRCA1* and 62 distinct *BRCA2* mutation types were observed, each in a single patient. These types accounted for 27.0 % (102/378) of the total mutations identified in this study. Among 345 patients whose mutations were analyzed with both direct sequencing and multiplex ligation-dependent probe amplification, 62 *BRCA1/2* small mutations and only one large genomic deletion (*BRCA1* whole gene deletion) were found.

Discussion

To date, this is the largest prospective cohort in Asia to evaluate the prevalence and spectrum of *BRCA1/2* genetic mutations among breast cancer patients and families with high risk of hereditary breast and ovarian cancer. Our study showed a high prevalence of *BRCA* mutations (22.3 %) among patients with a family history of breast or ovarian cancer, which was comparable to the results of Western studies, excluding individuals of Ashkenazi ancestry [13]. The number, rather than closeness, of relatives with breast or ovarian cancer within third-degree relatives is an important factor affecting the risk of carrying a *BRCA* mutation. Among patients without a family history who were diagnosed with bilateral breast cancer, and both breast and ovarian cancer, the prevalence of *BRCA* mutations were 16.3 and 37.5 %, respectively. On the other hand, the prevalence among patients with early-onset breast cancer, multiple organ cancers including breast cancer, and male breast cancer did not satisfy the 10 % cutoff that would indicate a high risk of carrying a *BRCA* mutation. Through the KOHBRA study, 153 distinct mutations in 378 index cases were found, which included 44 novel mutations.

Table 3 Prevalence of *BRCA1/2* mutations among patients with a history of only one family member with breast cancer ($n = 882$)

	Proband								
	Breast cancer <50 years			Breast cancer ≥50 years			Total		
	n	*BRCA1/2*(+)	Prevalence	*n*	*BRCA1/2*(+)	Prevalence	*n*	*BRCA1/2*(+)	Prevalence
Relatives (overall)									
Breast cancer <50	365	88	24.1	94	14	14.9	459	102	22.2
Breast cancer ≥50	282	42	14.9	111	7	6.3	393	49	12.5
Unknown	23	5	21.7	7	1	14.3	30	6	20.0
Total	670	135	20.1	212	22	10.4	882	157	17.8
First-degree relative only									
Breast cancer <50	219	59	26.9	70	10	14.3	289	69	23.9
Breast cancer ≥50	153	22	14.4	80	5	6.3	233	27	11.6
Unknown	1	0	0.0	1	0	0.0	2	0	0.0
Total	373	81	21.7	151	15	9.9	524	96	18.3
Second-degree relative only									
Breast cancer <50	76	21	27.6	9	2	22.2	85	23	27.1
Breast cancer ≥50	108	17	15.7	25	1	4.0	133	18	13.5
Unknown	17	5	29.4	6	1	16.7	23	6	26.1
Total	201	43	21.4	40	4	10.0	241	47	19.5
Third-degree relative only									
Breast cancer <50	70	8	11.4	15	2	13.3	85	10	11.8
Breast cancer ≥50	21	3	14.3	6	1	16.7	27	4	14.8
Unknown	5	0	0.0	0	0	0.0	5	0	0.0
Total	96	11	11.5	21	3	14.3	117	14	12.0

In our study, the overall frequency of *BRCA1/2* mutations in early-onset (<35 years) breast cancer patients without other risk factors was 8.8 %. Although the prevalence did not satisfy the 10 % cutoff probability of carrying a mutation, it was comparable to that of the previous Caucasian reports (4.9–9.3 %) [14–16]. Triple-negative breast cancer has been suggested an important factor for selecting individuals who have benefit of genetic testing, especially for early-onset breast cancer patients [17, 18]. In this study, we also found out the difference of *BRCA* mutation prevalence by presence of triple-negative breast cancer in isolated young onset breast cancer patients. The *BRCA* mutation rate in early-onset triple-negative breast cancer patients was 12.5 %, which satisfied the 10 % cutoff value; however, the rate in young breast cancer patients with non-triple-negative subtype (7.8 %) did not meet the 10 % cutoff value. Though early-onset breast cancer is one of the important indications for *BRCA1/2* genetic testing recommended by most guidelines, identification of breast cancer subtype should be considered to select more suitable target for *BRCA* testing in young breast cancer patients from the Korean population.

For men, the lifetime risk of breast cancer has been estimated at 1.2 % in *BRCA1* and at 6.8–8.4 % in *BRCA2* mutation carriers [19, 20], which is much higher than that (approximately 0.1 %) in the general population [21, 22]. In previous studies of non-Jewish populations, *BRCA2* mutations were found in 4–14 % of male breast cancer patients unselected for a family history of breast cancer [23–26]. These studies showed that a family history of breast or ovarian cancer was not associated with a higher prevalence of a mutation in male breast cancer patients, suggesting that testing for *BRCA* mutations in male breast cancer patients without a family history is warranted. In our study, however, the *BRCA2* mutation frequency was much higher in male cases with family histories of breast or ovarian cancer (2/6, 33.3 %) than that in male cases without family histories of these cancers (1/23, 4.3 %). Before the KOHBRA study, few *BRCA* prevalence studies for male breast cancer patients had been performed. Ahn et al. reported that the frequency of *BRCA* mutations was 2 of 8 (25 %) male breast cancer patients, with both *BRCA* mutation carriers having a family history of breast or ovarian cancer, and no *BRCA* mutation carrier was found in six male patients without a family history of these cancers [27]. These findings seem to be inconsistent with the results of previous Western studies suggesting that family history is not a strong predictor of carrying a mutation. However, it is difficult to reach a definitive conclusion because of the small number of male subjects enrolled.

Table 4 The spectrum of *BRCA1* genetic mutations identified in the KOHBRA study

Exon/intron	BIC nomenclature	Nucleotide change	Effect on amino acids	BIC entries	Citation	*n*
2	185insA	c.66_67insA	p.Glu23Argfs	*Novel*		1
IVS2	IVS2+1G>T	c.80+1G>T	*Abnormal splicing*	1		1
IVS5	IVS5+1G>A	c.212+1G>A	*Abnormal splicing*	6		1
IVS5	IVS5-12A>G	c.213-12A>G	*Abnormal splicing*	25		1
IVS6	421-2A>C	c.302-2A>C	*Abnormal splicing*	1		1
7	503del2insC	c.384_385delGGinsC	p.Met128Ilefs	*Novel*		1
7	509C>A	c.390C>A	p.Tyr130Ter	1		21
11	1041delAG	c.922_923delAG	p.Ser308Glnfs	2		11
11	1047C>T	c.928C>T	p.Gln310Ter	0	[28, 29, 36]	2
11	1100delAT	c.981_982delAT	p.Cys328Terfs	13		1
11	1173delG	c.1054delG	p.Glu352Asnfs	*Novel*		1
11	1473delG	c.1354delG	p.Val452Terfs	*Novel*		1
11	1599C>T	c.1480C>T	p.Gln494Ter	5		1
11	1630insG	c.1511_1512insG	p.Lys505Terfs	2		3
11	1835delA	c.1716delA	p.Glu572Aspfs	0	[27–29]	2
11	1950delC	c.1831delC	p.Leu611Terfs	0	[28, 29]	2
11	2055delA	c.1936delA	p.Ser646Alafs	0	[28]	1
11	2080delA	c.1961delA	p.Lys654Serfs	32		2
11	2388delG	c.2269delG	p.Val757Phefs	10		1
11	2415delAG	c.2296_2297delAG	p.Ser766Terfs	3		1
11	2473T>A	c.2354T>A	p.Leu785Ter	*Novel*		2
11	2552delC	c.2433delC	p.Lys812Argfs	11		3
11	2797dupA	c.2678dupA	p.Lys894Glufs	*Novel*		1
11	2859G>T	c.2740G>T	p.Glu914Ter	1		1
11	2975delTT	c.2856_2857delTT	p.Phe952Leufs	0	[28]	1
11	3033G>T	c.2914G>T	p.Gly972Ter	0	[27, 28]	1
11	3100delG	c.2981delG	p.Cys994Leufs	*Novel*		1
11	3377delA	c.3258delA	p.Val1088Phefs	*Novel*		1
11	3385T>A	c.3266T>A	p.Leu1089Ter	*Novel*		1
11	3415delC	c.3296delC	p.Pro1099Leufs	2		4
11	3561delG	c.3442delG	p.Glu1148Argfs	2		2
11	3726C>T	c.3607C>T	p.Arg1203Ter	36		1
11	3746insA	c.3627_3628insA	p.Glu1210Argfs	9		9
11	3814del4	c.3695_3698delGTAA	p.Gly1232Glufs	0		1
11	3932insT	c.3813_3814insT	p.Asn1272Terfs	0	[28]	1
11	4056C>T	c.3937C>T	p.Gln1313Ter	3		1
11	4110C>T	c.3991C>T	p.Gln1331Ter	0	[28]	1
11	4211delCT	c.4092_4093delCT	p.Leu1365Argfs	0	[28]	2
13	4372del T	c.4253del T	p.Leu1418Terfs	*Novel*		1
13	4454dup4	c.4335_4338dupAGAA	p.Gln1447Argfs	0	[28]	1
15	4643G>A	c.4524G>A	p.Trp1508Ter	23		1
16	5052insAA	c.4933_4934insAA	p.Arg1645Lysfs	1		1
16	5100G>T	c.4981G>T	p.Glu1661Ter	1		1
IVS16	IVS16-2A>G	c.4987-2A>G	*Abnormal splicing*	*Novel*		1
17	5149del4	c.5030_5033delCTAA	p.Thr1677Ilefs	18		10
17	5184insA	c.5065_5066insA	p.Met1689Asnfs	*Novel*		1
IVS17	IVS17+1G>T	c.5074+1G>T	*Abnormal splicing*	3		1
18	5199G>T	c.5080G>T	p.Glu1694Ter	23		5

Table 4 continued

Exon/intron	BIC nomenclature	Nucleotide change	Effect on amino acids	BIC entries	Citation	*n*
18	5202insG	c.5083_5084insG	p.Phe1695Cysfs	*Novel*		1
IVS18	IVS18+1G>C	c.5152+1G>C	*Abnormal splicing*	2		3
IVS18	IVS18-2delA	c.5153-2delA	*Abnormal splicing*	8		1
19	5303delG	c.5184delG	p.Met1728Ilefs	*Novel*		2
20	5379G>T	c.5260G>T	p.Glu1754Ter	*Novel*		1
20	5385C>T	c.5266C>T	p.Gln1756Ter	*Novel*		1
21	5419delGT	c.5300_5301delGT	p.Cys1767Leufs	*Novel*		1
IVS21	IVS21-2A>T	c.5333-2A>T	*Abnormal splicing*	*Novel*		1
IVS23	IVS23+1G>A	c.5467+1G>A	*Abnormal splicing*	5		3
24	5564G>A	c.5445G>A	p.Trp1815Ter	0	[28]	7
IVS23	5587-1del8	c.5468-1_5474delGCAATTGG	*Abnormal splicing*	*Novel*		1
24	5589del8	c.5470_5477delATTGGGCA	p.Ile1824Aspfs	2		3
24	5602delG	c.5483delG	p.Cys1828Leufs	0	[28]	2
24	5615del11insA	c.5496_5506delGGTGACCCGAGinsA	p.Val1833Serfs	3		15
1-24	Whole gene deletion	Whole gene deletion				2

Recently, the entire Korean *BRCA* mutation dataset before the start of the KOHBRA study was reported, which included 10 previous reports [28]. In the pooled data, c.7480C>T in the *BRCA2* gene was the most commonly detected mutation, accounting for 19.6 % (41 of 209) of *BRCA2* mutations and 9.8 % (41 of 420) of all *BRCA1/2* mutations. Our study also confirmed that c.7480C>T was the most frequently observed mutation in Korean populations, representing 10.1 % of all *BRCA1/2* mutations. Seong et al. also suggested that c.7480C>T might have originated from a common ancestor and might be the first founder mutation in Koreans, based on haplotype analysis and allele separation [29]. For Ashkenazi Jewish women, the mutations 187delAG and 5385insC in *BRCA1* and 6174delT in *BRCA2* account for about 90 % of all *BRCA* mutations [30]. Therefore, testing for these three founder mutations is highly cost-effective in this population. However, in our cases, there were 153 distinct mutations, and six commonly recurring mutations with over 3.0 % accounted for only 33.3 % of the total mutations. Overall, 102 distinct *BRCA1* or *BRCA2* mutations were found each in a single patient, accounting for 27.0 % of all of the mutations detected in our study. Therefore, testing for recurrent mutations as a pre-screen would not be cost-effective in Koreans, and a full direct sequencing analysis for *BRCA1/2* should be provided in the initial screening.

We detected only one patient with large genomic deletion (*BRCA1* whole gene deletion), representing only 0.3 % of all mutations identified in this study and a much lower occurrence than the estimated 12–15 % in the United States [31, 32] and 8–12 % in European populations [33, 34]. Recently, Seong et al. examined the contribution of genomic deletions and rearrangements for 221 breast cancer patients with a family history of two or more breast cancer cases or one or more ovarian cancer cases, based on the subjects of the KOHBRA study [35]. *BRCA1* genomic deletions and rearrangements were found in 3 (2.1 %) out of 143 *BRCA1/2* small mutation-negative patients, accounting for 3.7 % of the total 81 mutations in patients with an exceedingly high risk of hereditary breast and ovarian cancer [35]. These findings suggest that routine screening for genomic deletions and rearrangements does not appear warranted in Korean population.

Obtaining accurate prevalence data were the most basic and important task needed to select proper candidates for *BRCA1/2* genetic counseling and testing and to provide intensive management. Through the KOHBRA study, we found that the following subgroups satisfied a 10 % carrier probability threshold commonly used in selected families for *BRCA* genetic testing.

1. Breast cancer patients with a family history of ovarian cancer.
2. Breast cancer patients with a family history of breast cancer.
   - Two or more family members with breast cancer.
   - One family member with breast cancer, and at least one case of breast cancer (proband or family member) diagnosed before 50 years of age.
3. Bilateral breast cancer patients and breast cancer patients with a personal history of ovarian cancer.
4. Early-onset (<35 years) breast cancer patients with triple-negative subtype.

These findings can help establish effective genetic screening strategies in Korean populations with a high risk of hereditary breast and ovarian cancer.

Table 5 The spectrum of *BRCA2* genetic mutations identified in the KOHBRA study

Exon/intron	BIC nomenclature	Nucleotide change	Effect on amino acids	BIC entries	Citation	*n*
3	325G>T	c.97G>T	p.Glu33Ter	0	[28, 29]	4
3	424C>T	c.196C>T	p.Gln66Ter	0	[28]	2
3	504insA	c.276_277insA	p.Ser93Ilefs	1		2
3	517G>T	c.289G>T	p.Glu97Ter	*Novel*		1
4	598delA	c.370delA	p.Met124Trpfs	0	[28]	2
5	694delGA	c.466_467delGA	p.Asp156Terfs	*Novel*		1
5	703G>A	c.475G>A	p.Val159Met	2		1
7	812C>G	c.584C>G	p.Ser195Ter	*Novel*		1
IVS7	860-1G>T	c.632-1G>T	*Abnormal splicing*	0	[29]	1
9	983del4	c.755_758delACAG	p.Asp252Valfs	61		1
9	999del5	c.771_775delTCAAA	p.Asn257Lysfs	14		4
10	1108G>T	c.880G>T	p.Glu294Ter	0	[28]	2
10	1222delA	c.994delA	p.Ile332Phefs	3		1
10	1534del10insGAATTC	c.1306_1315delinsGAATTC	p.Lys436Glufs	0		1
10	1538del4	c.1310_1313delAAGA	p.Lys437Ilefs	11		3
10	1545delT	c.1317delT	p.Thr441Leufs	*Novel*		1
10	1627A>T	c.1399A>T	p.Lys467Ter	2		18
10	1742delT	c.1514delT	p.Ile505Asnfs	0	[28]	1
10	1902del7	c.1674_1680del7	p.Ile558Metfs	*Novel*		1
10	2041insA	c.1813_1814insA	p.Ile606Asnfs	75		1
11	2487delT	c.2259delT	p.Gln754Asnfs	0	[28, 36, 37]	1
11	2663delA	c.2435delA	p.Asn812Ilefs	1		1
11	2816insA	c.2588_2589insA	p.Asn863Lysfs	11		1
11	2885delA	c.2657delA	p.Asn886Metfs	*Novel*		1
11	3026delCA	c.2798_2799delCA	p.Thr933Argfs	1		4
11	3140T>G	c.2912T>G	p.Leu971Ter	0	[28]	1
11	3182del4	c.2954_2957delAAAA	p.Lys985Ilefs	*Novel*		1
11	3211G>T	c.2983G>T	p.Gly995Ter	*Novel*		1
11	3246delA	c.3018delA	p.Gly1007Valfs	0	[28]	2
11	3398del5	c.3170_3174delAGAAA	p.Lys1057Thrfs	11		1
11	3415C>T	c.3187C>T	p.Gln1063Ter	*Novel*		1
11	3827delGT	c.3599_3600delGT	p.Cys1200Terfs	6		3
11	3972del4	c.3744_3747delTGAG	p.Ser1248Argfs	8		20
11	4075delGT	c.3847_3848delGT	p.Val1283Lysfs	64		1
11	5057delTG	c.4829_4830delTG	p.Val1610Glyfs	4		1
11	5122delAG	c.4894_4895delAG	p.Ser1632Tyrfs	0	[28, 29]	1
11	5167dupA	c.4939dupA	p.Thr1647Asnfs	*Novel*		1
11	5344del4	c.5116_5119delAATA	p.Asn1706Leufs	1		1
11	5369del4	c.5141_5144delATTT	p.Tyr1714Cysfs	3		1
11	5579delA	c.5351delA	p.Asn1784Thrfs	5		2
11	5579dupA	c.5351dupA	p.Asn1784Lysfs	*Novel*		1
11	5699delA	c.5471delA	p.Asn1824Metfs	0	[28]	2
11	5804del4	c.5576_5579delTTAA	p.Ile1859Lysfs	29		14
11	5820delCA	c.5592_5593delCA	p.Phe1866Tyrfs	0	[28]	1
11	5873C>A	c.5645C>A	p.Ser1882Ter	27		1
11	5884C>T	c.5656C>T	p.Gln1886Ter	2		1
11	5950delCT	c.5722_5723delCT	p.Leu1908Argfs	45		1
11	6222delA	c.5994delA	p.Val1999Cysfs	*Novel*		1

Table 5 continued

Exon/intron	BIC nomenclature	Nucleotide change	Effect on amino acids	BIC entries	Citation	*n*
11	6490delA	c.6262delA	p.Thr2088Leufs	*Novel*		1
11	6633del5	c.6405_6409delCTTAA	p.Asn2135Lysfs	13		1
11	6635del5	c.6407_6411delTAAAT	p.Leu2136Cysfs	1		1
11	6677delAA	c.6449_6450delAA	p.Lys2150Serfs	1		1
11	6781delG	c.6553delG	p.Ala2185Leufs	1		2
11	6916delA	c.6688delA	p.Ile2230Leufs	0	[28]	1
11	6951delAG	c.6723_6724delAG	p.Asp2242Phefs	*Novel*		1
11	6952delGA	c.6724_6725delGA	p.Asp2242PhefsX2	0	[28, 29]	6
13	7180C>T	c.6952C>T	p.Arg2318Ter	5		2
13	7234delC	c.7006delC	p.Arg2336Alafs	*Novel*		2
IVS13	7236-1G>T	c.7008-1G>T	*Abnormal splicing*	*Novel*		1
14	7486G>T	c.7258G>T	p.Glu2420Ter	0	[28]	3
14	7603A>T	c.7375A>T	p.Lys2459Ter	0	[28]	1
15	7708C>T	c.7480C>T	p.Arg2494Ter	11		38
15	7744C>T	c.7516C>T	p.Gln2506Ter	*Novel*		1
15	7766delC	c.7538delC	p.Ala2513Glufs	0	[28]	1
15	7786C>T	c.7558C>T	p.Arg2520Ter	45		1
16	7972delG	c.7744delG	p.Ala2582Leufs	*Novel*		2
18	8230dup7	c.8002_8008dupAGAAGAT	p.Ser2670Terfs	0	[28]	1
18	8368C>T	c.8140C>T	p.Gln2714Ter	1		1
18	8527insAC	c.8299_8300insAC	p.Pro2767Hisfs	0	[28]	2
18	8542G>T	c.8314G>T	p.Gln2772Ter	0	[28, 29]	2
18	8557A>T	c.8329A>T	p.Lys2777Ter	*Novel*		1
IVS20	8861-2A>T	c.8633-2A>T	*Abnormal splicing*	0	[28]	1
21	8867delCA	c.8639_8640delCA	p.Thr2880Asnfs	*Novel*		1
21	8945delAA	c.8717_8718delAA	p.Glu2903Glyfs	0	[28, 38]	1
22	9106C>T	c.8878C>T	p.Gln2960Ter	10		1
22	9143delT	c.8915delT	p.Leu2972Cysfs	0	[28]	1
23	9219T > G	c.8991T>G	p.Tyr2997Ter	0	[27, 28]	5
23	9304C>T	c.9076C>T	p.Gln3026Ter	3		7
23	9325delA	c.9097delA	p.Thr3033Leufs	*Novel*		2
23	9326insA	c.9097_9098insA	p.Thr3033Asnfs	27		1
23	9333T>G	c.9105T>G	p.Tyr3035Ter	*Novel*		1
IVS23	IVS23+1G>A	c.9117+1G>A	*Abnormal splicing*	1		1
24	9359delT	c.9134delT	p.Leu255Tyrfs	*Novel*		1
24	9481delA	c.9253delA	p.Thr3085Glnfs	0	[28]	4
24	9481insA	c.9253_9254insA	p.Thr3085Asnfs	19		1
IVS23	9574-7del11	c.9346-7_9349del11	*Abnormal splicing*	*Novel*		1
25	9503del4	c.9275_9278delATTT	p.Tyr3092Cysfs	1		2
25	9668insC	c.9440_9441insC	p.Ala3148Cysfs	*Novel*		1
27	10378C>T	c.10150C>T	p.Arg3384Ter	1		1
27	9927del4	c.9699_9702delTATG	p.Cys3233Trpfs	3		1

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Conflict of interest The authors declare that they have no conflict of interest.

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