Mutations and polymorphic BRCA variants transmission in breast cancer familial members

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Abstract

Purpose: We previously showed that about 80% of breast cancer patients at high risk to carry mutation in BRCA genes presented at least one polymorphism in these genes which resulted potentially harmful by *in silico* analysis. In the present paper the genealogic transmission of those polymorphic coding and non coding variants of BRCA genes in family's members has been investigated.

Methods: 30 families, enrolled within the Genetic Counselling Program of our Institute, with probands and at least one first degree relative (n=67 family members) available, have been studied for both BRCA1 and BRCA2 pathological mutation and polymorphic variants' transmission.

Results: 10 and 6 probands carried mendelian transmitted mutations in BRCA1 and BRCA2, respectively. Polymorphic coding and non coding variants were transmitted in each family's relatives with a frequency ranging from 42% to100% , with similar rate for each SNP in mutated and non mutated families with the only exception of BRCA1 K1183R significantly more frequent in mutated families (p=0.004); conversely, this SNP and BRCA2 N372H, were more frequently present in breast cancer relatives belonging to families in which pathological BRCA mutations were not present. Furthermore, specific haplotypes were transmitted in all relatives as BRCA1 871Leu-1038Gly, present in both BRCA mutated and non mutated families, while BRCA2 289His-991Asp-IVS14+53 C>T present only in BRCAX families suggesting the harmful role of these SNPs.

Conclusions: Analysis of SNPs maps and modality of their transmission could identify further susceptibility markers and provide a basis for a better DNA-based cancer classification.

Keywords: BRCA1; BRCA2; Polymorphism; Breast cancer risk; Familiarity

1. Introduction

SNPs are sequence's variants present in more than 1% of human population. SNPs seem to be related to person's genetic predisposition or resistance to peculiar disease determining the severity or progression of disease [1]. A large number of SNPs has been demonstrated to influence protein expression or gene function either through aminoacid change and modification in protein function or through indirect epigenetic changes in synonymous or non-coding SNPs. In familial breast cancer, this has been shown to be peculiar of genes involved in double-stranded break repair [2].

Hereditary breast cancer syndrome was firstly associated with BRCA1 and BRCA2 genes whose mutations confer high risk to develop breast and/or ovarian cancer. However, a remarkably high number of sequence variants other than mutations have been identified, some of them are unidentified variants and some polymorphic variants. Because of the breast cancer risk in BRCA1 and BRCA2, mutation carriers have also been found to vary depending on different factors (i.e. age at diagnosis, unilateralism, other pathologies in the family, environmental factors, etc.), segregation-analysis models evidenced a variability in terms of a polygenic-modifying variance [3]. A recent genome-wide association study in breast cancer identified five common susceptibility alleles that are associated with an increased risk of breast cancer in the general population [4].

Segregation analysis of breast cancer in families can provide the logical basis and the specific genetic models for mapping and identifying genes responsible for human breast cancer. This is also true for polymorphisms mapping in genes usually mutated. Previous reported literature on this issue was based on case-control studies, while vertical transmission of SNPs, such

as those related to the apoptotic trait (i.e. TP53 R72P), has been only rarely demonstrated [5].

The present study aims to clarify a possible role of BRCA1 and BRCA2 SNPs as susceptibility markers of risk besides the so defined pathological mutations present in the 2 genes. The design of the study differs from what previously reported based on case-control analyses [6, 7]; in fact, the vertical transmission of pathological mutations and polymorphisms both in carrier and non carrier families have been studied by analyzing all available family members. In particular, the polymorphisms that we previously proved to have a harmful role by *in silico* analyses have been considered [8].

2. Materials and Methods

2.1 Patients selection

Thirty families comprising 97 cases healthy and affected (30 probands and 67 family members) people with high risk to carry BRCA mutations have been enrolled from Counseling Program of National Cancer Institute of Bari. All people undersigned an informed consent, previously approved by the ethical committee, to perform molecular analyses and use data for research purposes [9]. All patients were also characterized according to pathological features (Table 1) and family history and have been classified as having an "increased risk" to carry BRCA mutations (>10%) by BRCAPRO software [10].

Among the 30 probands (median age 48 yrs), 10 carried BRCA1 mutations, 6 BRCA2 mutations and 14 were non-carriers.

The design of the study forecasts to analyze the vertical transmission of pathological mutations and polymorphisms in the considered series.

A survey asking for their detailed genealogy and medical history was administered to each proband's first- and second-degree relatives (Table 1). Particular attention has been done to other tumor types eventually present. On the basis of survey information a pedigree was developed for each proband (Figure 1)

2.2 Molecular analysis in nonrelated patients and family members

Genomic DNA was extracted using QIamp DNA blood midi kit (Qiagen, Valencia, CA, USA) following manufacturer's instruction. DNA was quantified and mutational screening was performed as previously described [9]. If a variant was identified in the proband, was requested him the consent

to inform other family members. All enrolled members, healthy or affected, undersigned an informed consent and their blood analyzed for the proband's identified variant. Family's information for all members permitted to design a pedigree with the Progeny Program v6.

The variants found in the sequence were characterized and compared to those present in the online databases BIC [http://www.research.nhgri.nih.gov/bic/], ENTREZ SNP [http://www.ncbi.nlm.nih.gov], Ensemble Database [http://www.ensembl.org] and the Human Genome Variation database [http://hgvbase.cgb.ki.se/]

2.3 Statistical analyses

The statistic association between mutation frequency and the other parameters was assessed using a X2 test and the Fisher test. Differences were considered to be significant when p value was less than 0.05. Statistical analyses were carried out with the SPSS statistical software (SPSS, inc, Chicago, IL).

3. Results

3.1 BRCA1/2 mutations transmission

In the present series the most frequent BRCA1 mutation was 5382insC, carried by families #2, #3, #7, #8, #10, #12, #13 and #28 and BRCA1 R1495M mutation was found in family #20. All probands were only affected by breast cancer with the exception of family #29 whose proband had a co-occurrence of breast and ovarian cancer.

As regards BRCA2 mutations: 2150insTA was carried by a male of family #4, 3034delAAC by a female of family #23, 6024delTA by a female of family #21, 6696delTC by family #30, 2024delCTTAT by family #1 and mutation 6710delAAC by one family #9's female member.

Only the probands of family #1 and #4 were males and affected by breast cancer of grading III. In family #1 we found that the mutation has been transmitted in five daughters, two affected and three unaffected. In family #4 the mutation has been transmitted to two daughters and to one son unaffected. Table 2 reported mentioned results.

3.2 *BRCA1/2 polymorphisms transmission*

In the current study have been investigated for polymorphisms families with and without mutation in BRCA1 and BRCA2 genes. Most of the analyzed polymorphisms were heterozygous with the exception of 871Leu in family #2, #5, #21, #23 and #24 and N372H in family #14 that were homozygous.

Among all the detected polymorphisms, we considered those more frequent in our series which resulted to have a harmful role by previous *in silico* analyses, too [8].

The SNPs in aminoacidic position 871, 1038 and 1613 often segregated together and patients with 871Leu-1038Gly-1613Gly cluster seemed to have peculiar pathologic features presenting association with higher differentiated tumors (83%, p=0.000) and inverse relation with higher proliferative activity (81% lacking cluster presented Mib-1 ≥ 10%, p=0.04).

As regards the analysis of the association of different polymorphisms in families with pathological mutation transmission, the group 871Leu-1038Gly-1613Gly cluster has been found in family #2 with the 5382insC BRCA1 mutation and in families #9 and #23 with BRCA2 mutations. In family #23, these polymorphisms were also associated to the presence of BRCA2 intronic variant IVS16-14 T>C. In the families with R1495M mutation the association of 1183Arg and 1038Gly BRCA1 polymorphisms was present. In the mutated family #21, these polymorphisms were also associated to 871Leu and BRCA2 372His.

Fourteen families did not result BRCA carrier, however, 85% (12/14) of them presented inherited polymorphisms. In specific, the association of 1038Gly (exon 11) and 1613Gly (exon 16) BRCA1 SNPs was present in 4 families (#5, #14, #17, #24) in which the 2 SNPs were always transmitted together; the cluster of exon 11 SNPs: 871Leu, 1038Gly and 1183Arg was present in families #11, #17, #19 and #24. Five families (#6, #15, #22, #26, #27) presented only BRCA2 polymorphisms which seemed to be associated to higher grading. Most BRCA2 polymorphisms in BRCAX families, a part 372His SNP, regarded regulatory or intron regions. This last alteration resulted inversely related to early onset (8%, p=0.02) and HER-2 negative tumors (p=0.003).

The analysis of polymorphisms with low frequency showed that 289His (exon 10) and 991Asp (exon 11) in BRCA2 gene were only present in non mutated families and resulted always associated with the same gene intron variant: IVS14+53 C>T (p=0.01), which was previously verified to be a possible site for alternative splicing [8, 11]. These 3 polymorphisms also resulted always related to BRCA1 exon 11 (871Leu, 1038Gly and 1183Arg) and exon 16 (1613Gly) SNPs (p=0.003). Table 3 and Table 4 showed the transmitted haplotype blocks in mutated and BRCAX families in family available members.

Only 3 probands (families #7, #12 and #25) resulted triple negative and did not present any polymorphic sites. Families #7 and #12 were BRCA1 mutated, whereas family #25 was BRCAX with an age of onset of 29 years.

Mutated and non mutated families were considered for the occurrence of the polymorphisms. The SNP transmission frequency in the relatives of mutated probands was similar to that in relatives of non mutated probands with exception for 1183Arg BRCA1 which resulted significantly more frequent in mutated families. (Table 5)

Follow up study over a period of 24 months showed the occurrence of breast cancer in relatives of mutated and non mutated families. Family members of mutated and BRCAx families that developed a breast cancer had at least one polymorphism. There was a comparable percentage of each SNP between the two groups except 1183Arg and 372His polymorphisms. (Table 5)

4. Discussion

The aim of the present paper was to investigate the transmission of BRCA1 and BRCA2 variants in families enrolled and to evaluate the risk of breast and/or ovarian cancer associated with BRCA1/2 polymorphisms. Specific variants association have been studied in relation to proband pathological features, BRCA pathological mutations, other tumors present in each family, characteristics of transmission among relatives. Our hypothesis was that, also in hereditary breast cancer, multiple SNPs, belonging to the same haplotype, could be associated to an increased risk, even if slight. This happens for example in NAT2 polymorphisms which have been shown to be associated with a lower bladder cancer risk [12].

In our previous study [8] we found that 80% of patients presented at least one polymorphism of which 1038Gly (52%), 871Leu (36%), 1613Gly (34%), 1183Arg (17%) and 372His (48%) were the most representative; and, by *in silico* analysis, we evidenced their higher impact on the two proteins function.

The present study arose from these observations and introduced a different design of the study. Currently, studies on polymorphic haplotypes have been conducted in a few case-control series [13], while the type of vertical transmission in the family has been investigated only for known pathological mutations. In the present series, vertical transmission of both pathological mutations and polymorphisms has been followed up in 30 families in which all alterations resulted mendelian transmitted, as supposed, in maternal and paternal lineage.

In particular, haplotype 871Leu-1038Gly which in the previous series identified high differentiated tumors when associated to pathological

mutations, confirmed their role also in the present series but in association with 1613Gly. Their function on BRCA1 exonic splicing silencer binding site and on transcription factors binding sites seemed to be stressed by the fact that the two SNPs were always transmitted together among all relatives. The peculiar association of 289His-991Asp-IVS14+53 C>T in BRCA2, peculiarly present in BRCAX families, evidenced the pathological role of this cluster being each of these alterations able to affect alternative splicing [8].

Analyzing separately the polymorphism occurrence inside the group of mutated and non mutated families, all the most frequent SNPs, with the exception of K1183R, were transmitted among relatives with the same rate. Moreover, considering the rate of SNPs transmission among relatives affected by breast cancer, we also did not find differences between mutated and non mutated families except for K1183R and N372H. These two SNPs resulted more frequent in BRCAX tumors suggesting, in our opinion, their harmful role in the place of known pathological mutations.

Heterogeneity in relatives made the design of this study very complex, but the possible role of all variants in breast cancer risk could be obtained increasing the number of sample cases. Despite of the difficulties in collecting data from a sufficient number of relatives per family, our results were the first reported with regard to polymorphisms transmission and strongly suggested the importance of studying also polymorphic variants in defining hereditary risk.

5. Conclusion

In conclusion, this study shows that the genetic screening of patients with familial breast cancer should be conducted also for polymorphisms and intronic variants analysis in all families because of their possible role as susceptibility markers.

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FIGURE LEGEND

Figure 1. Example of family pedigree. ■: Cancer diagnosis=Breast; ◙: Cancer diagnosis= Prostate.

B1-E: BRCA1 E1038G, B1-S: BRCA1 S1613G, B1-P: BRCA1 P871L, B2-N: N372H

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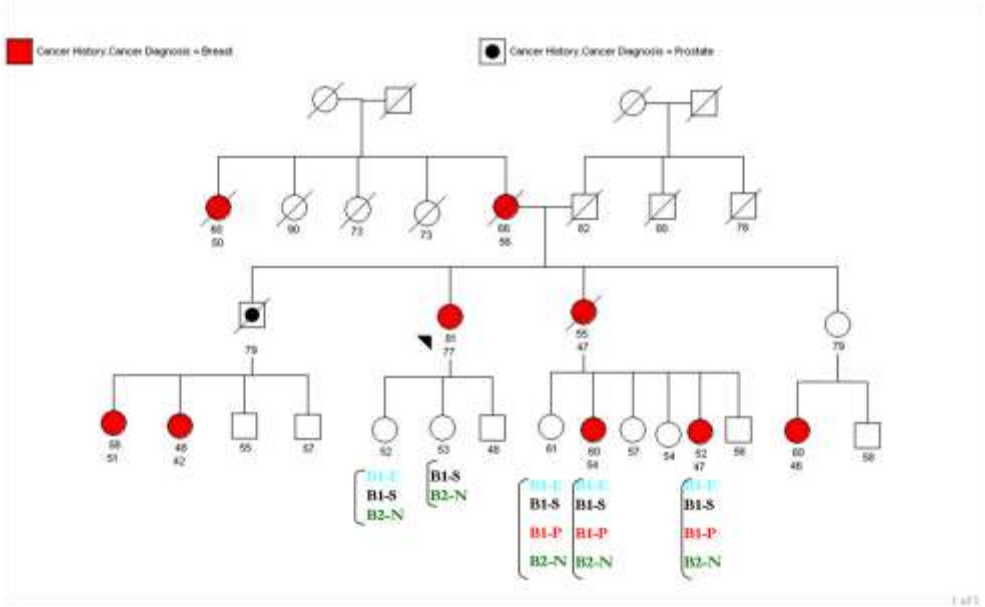

Table 1: Familial characteristics of 30 probands. Patients #1 and #4 were males. Relatives presenting other kind of neoplasia other than breast or ovary are here listed. Oc: ovarian cancer, Mel: melanoma, Blc: bladder cancer, Crc: colon rectal cancer, Lc: lung cancer, Pc: prostate cancer, Os: osteosarcoma, Tyr: tyroid cancer, Brc: brain cancer, Utc: utereus cancer, Gc: gastric cancer, Lr: laryngeal cancer, Leu: leukemia, Kin: kidney cancer, Lnh: non Hodgkin lymphoma, Psc: pancreas cancer

ID	Histology	Age of onset	Grading	ER	Mib1	PgR	Her2	TNM classification	Metachronous bilateral breast cancer	No. of Breast Cancer in family	Other cancer
	IDC	72	III	70	10	90		pT4N0Mx	/	3	Mel-(
	IDC	41	II	25	22	15	0	pT1cN1bIIIM0	/	1	Crc-
	IDC	41	III	0	80	0	+--	pT1cN0Mx	yes	3	Oc
	IDC	59	III	70	60	60	+++	pT2N1aMx	/	2	
	IDC	54	III	0	90	0		pT2N1aM0	/	1	Tyr-
	IDC	38	III	0	8	60	+--	pT1cN0(sn)Mx	/	1	
	IDC	53	III	0	40	0	0	pT2N1aMx	yes	3	Pc
	IDC	51	III	55	30	10	+++	pT1cN0M0	yes	3	U
	IDC	33	II	0	22	0		pT2N0M0	/	1	Brc-(
	IDC	45	II	10	10	15		pT1N0Mx	/	3	Gc-C
	IDC	36	III	35	3	40	0	pT1cN0Mx	/	1	Lc-
	IDC	34	III	0	70	0	0	pT1N1M0	/	1	Oc-E
	IDC	34	III	0	70	0	++-	pT1N0Mx	yes	4	(
	Inflammatory carcinoma	77		0	20	0	++-	pT1N0Mx	/	4	E
	IDC	46	III	20	25	8	++-	pT3N1b1M0	/	3	
	IDC	56	II	45	0	35	+--	pT1N1Mx		1	Lr-L
	IDC	63	II	5	10	1		pT1bN0Mx		2	Lc-C
	ILC	58		99	10	30	0	pT1N0Mo	yes	4	I
	IDC	51	II	45	10	70		pT1N1Mx	/	2	
	IDC	34	III	0	75	0	++-	pT2N0Mx	/	2	
	IDC	41	III	10	30	10	+++	pT2NxMx	/	2	
	Tubular carcinoma	48	II-III	30	3	60	++-	pT1aN0Mx	/	3	Lnh-O
	IDC	30	II	40	20	30	+--	pT2N0Mx	yes	2	
	IDC bifocal	48	II	12	24	0	+--	pT1N0Mx	/	1	(
	IDC	29	III	0	70	0	0	pT1cN0M0	/	1	(
	ILC	56		70	8	40	+++	pTxN+Mx	/	2	I
	IDC	26	III	25	35	30	0	pT3N3aMx	/	3	
	IDC	52	III	0	25	0	+--	pT1bN0M0	/	4	Brc-P
	IDC	46	III	0	60	0	+--	pT2N2aMx	yes	5	
	IDC	39	III	30	5	8	+++	pT3N1aMx	/	2	

Table 2: Mutations transmission in family members with and without Breast Cancer (BC)

Family ID	Proband Mutation	Nr. of mutated family members	*Affected by BC*	*Noaffected by BC*	Nr. of non mutated family members	*Affected by BC*	*Noaffected by BC*
1	**B2 2024delCTTAT**	**5**	2	3	**1**	-	1
2	**B1 5382insC**	**3**	2	1	**2**	-	2
3	**B1 5382insC**	**2**	1	1	**1**	-	1
4	**B2 2150insTA**	**3**	-	3	**1**	-	1
7	**B1 5382insC**	**1**	-	1	**1**	-	1
8	**B1 5382insC**	**-**	-	-	**1**	-	1
9	**B2 6710delAAC**	**1**	-	1	**1**	-	1
10	**B1 5382insC**	**1**	1	-	**-**	-	-
12	**B1 5382insC**	-	-	-	**1**	-	1
13	**B1 5382insC**	**1**	1	-	-	-	-
20	**B1 R1495M**	**1**	-	1	-	-	-
21	**B2 6024delTA**	**1**	-	1	**3**	-	3
23	**B2 3034delAAC**	**-**	-	-	**1**	-	1
28	**B1 5382insC**	**1**	-	1	-	-	-
29	**B1 Q563X**	**1**	-	1	**1**	-	1
30	**B2 6696delTC**	**1**	-	1	-	-	-

Table 3: Haplotype Blocks Transmission (HBT) in famiy members whose proband carried a BRCA mutation

Family ID	Proband Polymorphisms	Nr of relatives with HBT	HBT	Nr of relatives without HBT
1	**[N372H]**	**1**	[372H]	**5**
2	**[P871L – E1038G – S1613G]**	**4**	[871L – 1038G – 1613G]	**1**
3	**wt**	**-**	**-**	**3**
4	**wt**	**-**	**-**	**4**
7	**wt**	**-**	**-**	**2**
8	**wt**	**-**	**-**	**1**
9	**[P871L – E1038G – S1613G]**	**2**	[871L – 1038G – 1613G]	**-**
10	**wt**	**-**	**-**	**1**
12	**wt**	**-**	**-**	**1**
13	**wt**	**-**	**-**	**1**
20	**[E1038G – K1183R]**	**1**	[1038G – 1183R]	**-**
21	**[P871L – E1038G – K1183R – N372H]**	**3**	[1038G – 1183R]	**-**
		1	[1038G – 1183R – 372H]	
23	**[P871L – E1038G – S1613G]**	**1**	[871L – 1038G – 1613G]	**-**
28	**wt**	**-**	**-**	**1**
29	**wt**	**-**	**-**	**2**
30	**[E1038G]**	**1**	[1038G]	**-**

Table 4: Haplotype Blocks Transmission (HBT) in famiy members whose proband did not carry a BRCA mutation

Family ID	Proband Polymorphisms	Nr of relatives with HBT	HBT	Nr of relatives without HBT
5	**[P871L – E1038G – S1613G – N372H]**	**2**	[871L – 1038G – 1613G – 372H]	**1**
6	**[203G>A 5'UTR]**	**1**	[203G>A 5'UTR]	**1**
11	**[P871L – E1038G – K1183R]**	**2**	[871L – 1038G – 1183R]	**-**
14	**[P871L – E1038G – S1613G – M1652I – N372H – 203G>A 5' UTR]**	**1**	[1613G – 1652I – 372H]	**-**
		2	[1613G – 1038G – 372H]	**-**
		2	[1613G – 1652I – 1038G - 372H]	**-**
15	**[203G>A 5'UTR]**	**-**	-	**1**
16	**[S1040N - N372H]**	**1**	[1040N]	**-**
17	**[P871L – E1038G – S1613G – K1183R – IVS14+53C>T – N991D – N289H]**	**3**	[1613G-871L]	**-**
		3	[1613G – 871L – 1038G – 1183R]	
18	**wt**	**-**	-	**2**
19	**[P871L – E1038G – K1183R – N372H]**	**-**	-	**3**
22	**[N372H]**	**-**	-	**1**
24	**[P871L – E1038G – S1613G – K1183R – IVS14+53C>T – N991D – N289H]**	**1**	[1613G – 871L – 1038G – 991D – 289H – IVS14+53C>T]	**-**
25	**wt**	**-**	-	**2**
26	**[N372H]**	**-**	-	**1**
27	**[D1420Y]**	**-**	-	**1**

Table 5: Frequency of each polymorphism transmission among family members in the two groups of BRCA mutated and BRCAX families. Considering all families in which each SNP was present, the number of relatives presenting the SNP was reported with respect to all relatives of those families. Incidence of breast cancer in family members in which each polymorphism was transmitted has been also reported.

	Families with BRCA1/2 mutation			Families without BRCA1/2 mutation		
SNP	**Nr. families with SNP**	**Nr members with SNP / all relatives**	**Nr affected members / Nr members with SNP**	**Nr. families with SNP**	**Nr members with SNP / all relatives**	**Nr affected members / Nr members with SNP**
P871L	4	7/12 (58%)	1/7 (14%)	6	11/20 (55%)	2/11 (18%)
E1038G	6	13/14 (93%)	3/13 (23%)	6	12/20 (60%)	2/12 (16%)
S1613G	3	7/8 (87%)	1/7 (14%)	4	14/15 (93%)	5/14 (35%)
K1183R	2	5/5 (100%) *	0/5 (0)	4	5/12 (42%) *	2/5 (40%)
N372H	2	2/10 (20%)	0/2 (0)	6	7/14 (50%)	3/7 (43%)

*p=0.004