

## Detection of Gene Mutation in the 185del AG *BRCA1* in Families with Hereditary Breast Cancer

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### Abstract

Breast cancer (BC) is one of the most common malignant diseases in which incidence of cancer structure in the female population ranked first, accounting for 19.6% in Ukraine.

**Aim:** The aim of our work was to describe a hereditary breast cancer family case where the affected mother is a carrier of mutation in the 185del AG *BRCA1*, and her daughter (*BRCA*-negative) was treated for Hodgkin's lymphoma.

**Materials and methods:** The material of our study were pedigrees and DNA samples from 128 women diagnosed with BC who had been treated in the Lviv Regional State Cancer Diagnostic Center from June 2008 to December 2012. Molecular-genetic method determined the presence of seven mutations in the gene *BRCA1* (185del AG, 4153delA, 5382InsC, 188del11, 5396 +1 G > A, 185InsA, 5331 G > A) and 3 gene mutations in *BRCA2* (6174delT, 6293S > G, 6024delTA) by allele-specific polymerase chain reaction.

**Results:** Mutations in the genes *BRCA1/2* were found in 6 patients (4.7%) out of 128 women from 120 families diagnosed with BC who were treated.

Only in 7 families (5.8%) out of 120 families with BC, we came across relatives who had been diagnosed with lymphoma. Out of the 192 control group families only 2 (1%) were diagnosed with lymphoma, which made a significant difference (5.8% and 1%,  $\chi^2=6.05$ ,  $p<0.01$ ).

Family tree which combines BC in an adult woman and HL in a female child: affected mother's aunt died from BC at age of 50, her cousin in the mother's line died from BC at the age of 39. Another aunt died at 65 from uterus carcinoma. Father's brother died from acute leukemia at 68.

**Conclusion:** Studies on cancer in families of children with lymphoma can provide contribution into the insights of genetic susceptibility.

**Keywords:** Breast cancer; Mutation *BRCA1*; Hodgkin's lymphoma; Family tree; Lviv region (Ukraine)

### Introduction

Breast cancer (BC) is a chief cause of cancer-related mortality that affects women worldwide [1,2].

Mutations in the *BRCA1* and *BRCA2* tumor suppressor genes are associated with an increased risk for breast and ovarian cancers as well as other types of malignancies [3]. The observation of a germ-line *BRCA1* mutation in an index case with a lymphoid neoplasm in the setting of a family history of breast cancer prompted many scientists to explore the role of *BRCA* germ-line mutations as lymphoma susceptibility alleles.

Hereditary breast cancer (HBC) shows extant clinical and genetic heterogeneity [4]. Examples of pedigrees depicting clinical cases of HBC syndromes are presented in order to describe HBC's heterogeneity. The recent identification of the *BRCA1* gene in early-onset hereditary site-specific breast cancer and the HBOC (hereditary breast/ovarian cancer) syndrome has led to new challenges for the genetic counselor.

Breast cancer is caused by a huge number of mutations including the 185del AG mutation in *BRCA1* which is detected in Ashkenazi Jews both in familial breast and ovarian cancer and in the general population [5]. Little is known about family members' interrelated decisions to seek genetic testing for breast cancer susceptibility [6]. Findings suggest that both individual and family characteristics are associated with the decision to obtain genetic testing for hereditary breast cancer; hence, there is a need for interventions that foster a supportive family environment for patients and their high-risk relatives [6].

A doctor conduct genetic counseling which embraces surveillance

and providing recommendations that are responsive to the family history of HBC and addresses the concept for future development of HBC expert centres in order to improve cancer control [4]. Medical staff should be aware of psychosocial issues, especially those relevant to marriage and childbirth in their interactions with young women who carry a *BRCA1* or *BRCA2* gene mutation [2].

The aim of our work was to describe a hereditary breast cancer family case where the affected mother is a carrier of mutation in the 185del AG *BRCA1*, and her daughter (*BRCA*-negative) was treated for Hodgkin's lymphoma.

### Materials and Methods

**Materials:** We studied pedigrees and DNA samples of 128 women from 120 families who had relatives with BC. Control pedigrees –192 healthy family.

**Methods:** Genealogy, Molecular genetics.

The material of our study were DNA samples from 128 women

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diagnosed with family BC who had been treated in the Lviv Regional State Cancer Diagnostic Center from June 2008 to December 2012 and had relatives with BC. Each woman signed an informed consent for molecular genetic analysis for determination of mutations in the genes *BRCA1/2*. Molecular-genetic method showed the presence of seven mutations in the gene *BRCA1* (185del AG, 4153delA, 5382InsC, 188del11, 5396 +1 G > A, 185InsA, 5331 G > A) and 3 gene mutations in *BRCA2* (6174delT, 6293S> G, 6024delTA). Determination of mutations was studied by allele-specific polymerase chain reaction (PCR), RFLP analysis (restriction fragment length polymorphism).

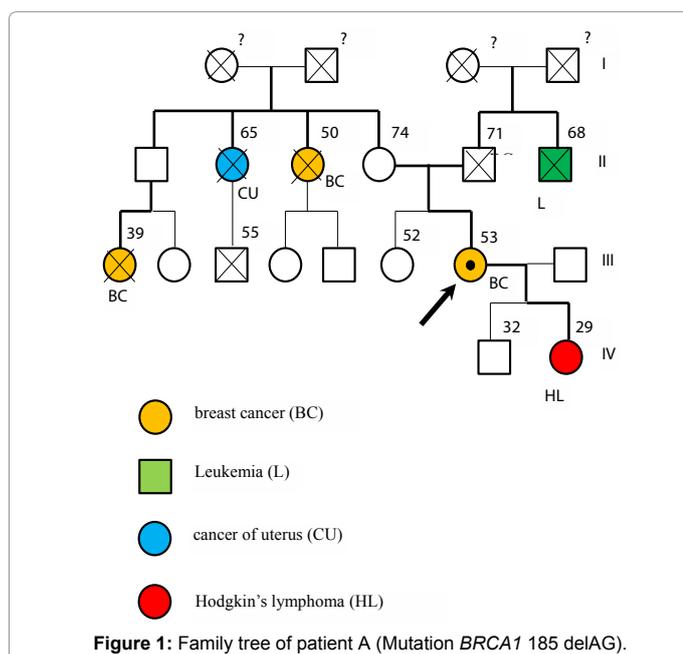
## Results

According to the data provided by Lviv Statistics Office, in January 2012, the population of Lviv Region was 2,540,900 people, including 1,341,595 women (52.8%). Every year in the Lviv region 650-700 people are diagnosed with breast cancer, 99% of them are women. Standardized incidence of BC in Lviv region is 50.09 per 100 000 female population which is slightly below average indicator in Ukraine - 57.53 [1]. Every year in the Lviv region 12-20 children are diagnosed with Hodgkin's lymphoma, 50-60% of them are female. Standardized incidence of HL in Ukraine among children aged 0-17 years is 1.0 per 1,00,000. Since breast in women is 50 times more frequent than Hodgkin's lymphoma in children, the case we present further is of special value. It combines BC in an adult woman and HL in a female child.

Mutations in the genes *BRCA1/2* were found in 6 patients (4.7%) out of 128 women from 120 families diagnosed with BC who were treated in the Lviv Regional State Cancer Diagnostic Center (Ukraine) from June 2008 to September 2013.

Only in 7 families (5.8%) out of 120 families with BC, we came across relatives who had been diagnosed with lymphoma. Out of the 192 control group families only 2 (1%) were diagnosed with lymphoma, which made a significant difference (5.8% and 1%,  $\chi^2=6.05$ ,  $p<0.01$ ). We came across only case of lymphoma among relatives in first-degree relation in families with BC.

We describe a hereditary breast cancer family case where the affected mother is a carrier of mutation in the 185del AG *BRCA1* and her daughter (*BRCA*-negative) was treated for Hodgkin's lymphoma.



## Case Report

The patient A, who appeared a carrier of 185del AG mutation in the gene *BRCA1*, was diagnosed with BC at the age of 46.

**Medical history:** At the age of 41 (2000 year) she had amputation of uterus due to fibromioma, at the age of 46 (2005) was diagnosed breast cancer, at the age of 52 (2011) was diagnosed with metastasis in lungs and upper clavicular lymph nodes.

**Family tree:** Her aunt died from BC at age of 50, her cousin in the mother's line (Figure 1) died from BC at the age of 39. Another aunt died at 65 from uterus carcinoma. Father's brother died from acute leukemia at 68.

In February 2005, the patient noticed a tumor in her left breast, and during two months it increased to 1.5 cm. At clinical examination in the left axillary area enlarged lymph nodes were observed. In 2005, at age of 46, she had mastectomy due to left breast cancer – infiltrative carcinoma (pT2N1M0, grade II). ER+, PR+, Her-2new-negative. Scintigraphy of bones in 2012 revealed no pathology. Ultrasound densitometry revealed that the bone mineral density is lowered. First signs of osteoporosis are seen in 2013. Ultrasonography of internal organs showed no pathology diagnosed. Ultrasound of thyroid gland done in March 2013 showed autoimmune thyroiditis. In the course of brain MRI, no organic pathology was found in 2014. Computed tomography found cyst of liver in III segment. General and biochemical blood tests were within normal limits in April 2014. Treatment of breast cancer: 5 cycles of CMF (Cyclophosphamide, Methotrexate, Fluorouracil) in July 2013, and aromazin from 09.2013 till 03.2014: radiotherapy, Hormonotherapy and tamoxifen.

The daughter of patient H. was treated for Hodgkin's lymphoma at the age of 15 and recovered. At the age of 29 she has a long remission and is not a carrier of mutation in the gene *BRCA1*.

## Discussion

Breast cancer develops when changes take place in 550 genes, and Hodgkin's lymphoma develops when changes take place in 30 genes [7,8]. Both onco-pathologies have 15 common genes listed in Table 1.

Among the 15 common genes – 5 (33.3%) are responsible for congenital anomalies and hereditary disease: hypospadias (*ATF3*), Down syndrome, Niemann Pick disease (*CCNB1*), synpolydactyly, Bernard-Soulier syndrome (*FBLN1*), autism (*EIF4E*), combined immunodeficiency (*IL7R*) [7].

Location of mutations involved different chromosomes mainly from 1 to 9 (66.6%), less - 12,14,17,20,22 (33.3%) chromosomes. The defect of the short arm (p) of chromosome (2,5,7,17) was less (26.7%) frequent than of the long one (q) - 73.3% (Table 1) [7,8].

Germinal mutations dominated in 9 (60%) cases. Somatic mutations were observed in 3(20%) cases. At the same time, germinal and somatic mutations were observed in two genes - TP53 (tumor protein p53) and IL7R (interleukin 7 receptor).

In most cases, the frequency of gene's detection of BC and Hodgkin's lymphoma are unknown, although some cases of manifesting genes pathology have been described.

In high-risk pedigrees, female carriers of *BRCA1* mutations have 80-90% lifetime risk of breast cancer, and a 40-50% risk of ovarian cancer [9]. Mutation in the gene 185del AG *BRCA1* was observed in 0.9% of Ashkenazim Jews [9]. These results suggest that every one hundredth women of Ashkenazi descent may be at especially high risk of developing breast and/or ovarian cancer.

№	Gene	Other names	Locations	Mutation		Cancer	Frequency	Other diseases
				Germinal	Somatic			
1	<i>TP53</i> tumor protein p53	P53 (Protein 53 kDa)	17p13.1	yes	yes	Hodgkin's lymphoma, breast cancer	60-80% 25%	-
2	<i>DIABLO</i> (diablo)	"Second mitochondria-derived activator of caspase", SMAC	12q24.31	yes	no	Hodgkin's lymphoma, breast cancer	50% N/A	preeclampsia
3	<i>ANG</i>	angiogenin	14q11.2	Unknown	Unknown	Hodgkin's lymphoma, breast cancer	N/A N/A	-
4	<i>ATF3</i>	Activating transcription factor 3	1q32.3	Unknown	Unknown	Hodgkin's lymphoma, breast cancer	N/A N/A	Insulin resistance, Congenital anomaly (Hypospadias)
5	<i>CCNB1</i>	cyclin B1	5q13.2	no	no	Hodgkin's lymphoma, breast cancer	N/A N/A	Alzheimer's Disease, Neurodegenerative Disease, Down Syndrome, Niemann Pick disease
6	<i>CSE1L</i>	CSE1 chromosome segregation 1-like	20q13.13	N/A	N/A	Hodgkin's lymphoma, breast cancer	80% 70%	-
7	<i>EIF4E</i>	Eukaryotic Translation Initiation factor 4E	4q23	yes	no	Hodgkin's lymphoma, breast cancer	70% N/A	autism
8	<i>FBLN1</i>	Fibulin 1	22q13.31	yes	no	Hodgkin's lymphoma, breast cancer	N/A 35%	Synpolydactyly, Bernard-Soulier syndrome, Placenta dysplasia, Thrombosis, Infection disease (Streptococcus Pyogenes)
9	<i>IL6</i>	Interleukin 6	7p15.3	yes	no	Hodgkin's lymphoma, breast cancer	N/A N/A	-
10	<i>IL7R</i>	Interleukin 7 receptor	5p13.2	yes	yes	Hodgkin's lymphoma, breast cancer	N/A N/A	combined immunodeficiency
11	<i>MAL</i>	T-cell differentiation protein	2q11.1	yes	no	Hodgkin's lymphoma, breast cancer	70% N/A	-
12	<i>NOTCH1</i>	Notch homolog 1	9q34.3	yes	no	Hodgkin's lymphoma, breast cancer	N/A N/A	-
13	<i>PTK2</i>	Protein tyrosine kinase 2	8q24.3	yes	no	Hodgkin's lymphoma, breast cancer	N/A N/A	-
14	<i>SDC1</i>	Syndecan 1	2p24.1	no	no	Hodgkin's lymphoma, breast cancer	N/A N/A	-
15	<i>TNFAIP3</i>	Tumor necrosis factor	6q23.3	no	yes	Hodgkin's lymphoma, breast cancer	N/A N/A	-

Table 1: Common genes in breast cancer and Hodgkin's lymphoma (Atlas of Genetics).

The etiology of childhood lymphoma is still largely unknown. Studies on cancer in families of children with lymphoma can provide insights into the contribution of genetic susceptibility [7]. Yossepowitch et al. indicate that germ-line *BRCA* mutations are not associated with an increased risk for lymphoid malignancies [7].

## Conclusion

1. Breast cancer and Hodgkin's lymphoma develops when changes take place in 15 common genes.

2. From 128 patients diagnosed with BC 10 mutations in the genes *BRCA1/2* were found in 6 patients (4.7%).

3. Among the 120 families with BC lymphoma were diagnosed in 7 families (5.8%), significantly more than in control - 2 (1%) families.

4. In woman with hereditary breast cancer gene mutation in the 185del AG *BRCA1* was detected, while her daughter with Hodgkin's lymphoma was *BRCA*-negative.

Received results have partly partially indicated probable properties of genetic structure of Ukrainian population, affecting characteristic features of malignant tumor formation.

The observation of a germ-line *BRCA1* mutation in an index case with a lymphoid neoplasm in the setting of a family history of breast cancer prompts many scientists to explore the *BRCA* germ-line mutations as lymphoma susceptibility alleles.

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