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Genetics of breast tumors: achievements and perspectives

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Abstract

This study was aimed to assess the genetic determinants of the breast tumors. There was shown that genetic predisposition to breast cancer is caused by multiple genes, allelic variants which lead to the low risk of the disease, but with a high frequency in the population represented. These genes may act together, providing a multiplier effect. Identification of additional genes of hereditary predisposition to breast cancer and elucidate the role of variants of known genes is an important task, but no less important, and determine the nature of the interaction between genetic determinants.

Keywords: genetics, breast tumors.

The problem of improving early diagnosis and prognosis of breast cancer remains one of the most pressing contemporary oncology practice [1, 2]. The close correlation between the total prevalence of breast tumors and breast cancer mortality determines medico-social and socio-economically significance of this disease [3].

Breast cancer in Ukraine , as in most countries , is one of the most common tumors in women and ranks first month is in the structure of mortality from malignant neoplasms (25 % of all cancers in women). The number of women suffering from breast cancer in Ukraine increased from 14 171 in 1996 to 17 407 in 2011 which is in accordance with 54.1 to 70.9 cases per 100000 persons. Every woman who

became ill with breast cancer , on average, loses 17-18 years of life (53 % of the female population losses in Ukraine [4, 5].

According to statistics from the Breast Center of the Ukrainian Institute of Oncology, Odessa region ranks first in the terms of morbidity and mortality from breast cancer among women. Thus, the Odessa area standardized mortality rate from breast cancer has reached 90.3 case per 100 thousand female population (National Cancer Registry, 2011) [5].

Benign tumors of the breast , usually does not pose a threat of malignancy [6]. However, during the initial contact with the patient's health care or even while providing qualified and specialized health care professionals often face significant difficulties in the differential diagnosis of benign and malignant tumors of the breast. Today, the only real way to successfully reduce mortality from breast cancer is to improve the quality of early diagnosis [6].

This study was aimed to assess the genetic determinants of the breast tumors.

Material and methods.

The study was conducted at the Regional Hospital (Odessa, Ukraine) in the 2010-2012 and included the sample of 668 women. There was evaluated the prevalence of polymorphisms of candidate genes DKK4, GSR, TOX3, SLC4A7, MAP3K1 and FGFR2. All research carried out carefully contemporary bioethical requirements. In accordance with the Declaration of Helsinki, all patients were informed about the clinical trial and agreed to the determination of the studied polymorphisms of genes.

The control group was formed 30 healthy women aged 30-45 years surveyed in accordance with the clinical examination programs. The first clinical group consisted of 50 women with histologically verified fibroadenoma of the breast; Second group formed 50 women with histological examination verified adenocarcinoma of the breast and under . Follow-up observation period was 2 years. Age averaged examined - (51,5 ± 1,8) , in patients with breast cancer and (35,3 ± 1,5) , in the group of patients with fibrocystic mastopathy.

A survey of women who participated in a study conducted by the order No 645 assigned by MOH of Ukraine on 03.11.2008.

SNP analysis of genes DKK4, GSR, TOX3, SLC4A7, GHSR, MAP3K1 and FGFR2 was conducted by using pirosequencing (Qiagen, USA).

To investigate gene DKK4 we used following primers :

F: 5 -biotin-ATAGATTTGAAGGGATTTGTTGAAGTTT- 3 (328 bp .).

R: 5 -CAAAACCAACTCAACCCCAACAAAAC- 30.

S: 5 -CTAAACTAACAACTCAACAC- 3.

To investigate gene GSR , the following primers:

F: TTTGTCGGGCTTGGAAGTCAGCA (126 bp).

R: CTCAGGTCCTTGGTATTCGGGA.

For genes TOX3, SLC4A7, GHSR, MAP3K1 and FGFR2 held design sequencing of selected SNPs :

Rs3803662 ***(TOX3)***

F: *TTAATGCCTCTATAGCTGTC* →

R: TCCTTAATG CCTCTATAGCTGTC**¥CTT**AG CGAAGAAT

Rs 2981528 ***(FGFR2)***

→

F: GCCACTTA ATGAACCTGT

R: GCCACTTA ATGAACCTGT **TTG¥G**GAGAG

Rs889312 ***(MAP3K1)***

→

F: *CCCTGCTG GAGAAAGG*

R: TCTCTGAGAT GCCCCTGCTG GAGAAAGG**M A TG**TGCAAATT

Rs4973768 ***(SLC4A7)***

F: AGCAGTTAAT TAC**¥TAA**ACA TGAGTTACCT TTGCTC

R: *TGT ACTCAATGGA AACGAG*

←

The correctness of the frequency distribution of genotypes was determined by equilibrium compliance Hardy - Weinberg (pi2 + 2 pipj + pj2 = 1). Statistical analysis was carried out by methods of variance and correlation analysis by means

of a software MS Excel 2013 (Microsoft Incorp., USA) and Statistica 7.0 (StatSoft Inc., USA).

Results.

Analysis of the genotypes studied genes showed that the ratio between the observed and expected heterozygosity in patients and play pi equal to 0.79; Group II - 0.86; Group III - 1.03. Thus , the frequency of SNPs rs3763511 and rs8190924 gene DKK4 GSR gene among women with breast cancer and LTEI Plan did not differ (OR = 1.1 , 95% CI 0,9-1,3).

In assessing the distribution of different genotypes in the total sample set, in women with breast cancer homozygous and heterozygous distribution geno -types did not meet equilibrium Hardy - Weinberg (χ^2 = 26,89; p <0,001), while the tem- women with DDMZ and women in the control group had an equilibrium distribution of genotypes (χ^2 = 0.08 and χ^2 = 0.05 , respectively).

The frequency of different alleles of the studied polymorphisms for the mutant allele of the gene GSR in patients of group was 0.4 , Group II - 0.84 , the group III - 0.73 , that did not have statistically significant differences.

The odds ratio for women with DDMZ not exceeded for the mutant allele at 0.51 confidence interval 0,16-1,63 (χ^2 = 1,32; p> 0,05). Ratio of chances in women with breast cancer for the mutant allele was equal to 2.14 (CI 95 % 0,63-7,25; χ^2 = 1.51). For the ratio of homozygous genotypes for the mutant and normal alleles of DKK4 gene in women with breast tumours there were obtained such values: OR = 1.88 ; CI 95% 0,59-5,91 , and in women with breast cancer - OR = 1.98 ; CI 95% 0,60-6,51 .

The above suggests that the presence of functional polymorphisms of genes DKK4 and GSR no significant effect on the risk of breast cancer, i.e. in patients with breast cancer and DDMZ mutant alleles of rs3763511 and rs8190924 polymorphisms of DKK4 gene GSR appear equally often.

The rest of this study , it was shown that the frequency determining polymorphism TT (rs4973768) in the gene SLC4A7 in patients with breast cancer is increasing. From the odds ratio for the risk of developing breast cancer, this gene was 1.89

(95% CI 1,01-3,397 , p = 0,047), the relative risk - 1.7 (p= 0,049). The odds ratio for the rs3803662 polymorphism was 1.49 for rs889312 - 1,59 and rs2981582 - 1,29.

According to our data, we can conclude that a genetic predisposition to breast cancer is caused by multiple genes, allelic variants which lead to the low risk of the disease, but with a high frequency in the population represented. These genes may act together, providing a multiplier effect. Identification of additional genes of hereditary predisposition to breast cancer and elucidate the role of variants of known genes is an important task, but no less important, and determine the nature of the interaction between genetic determinants (Fig. 1).

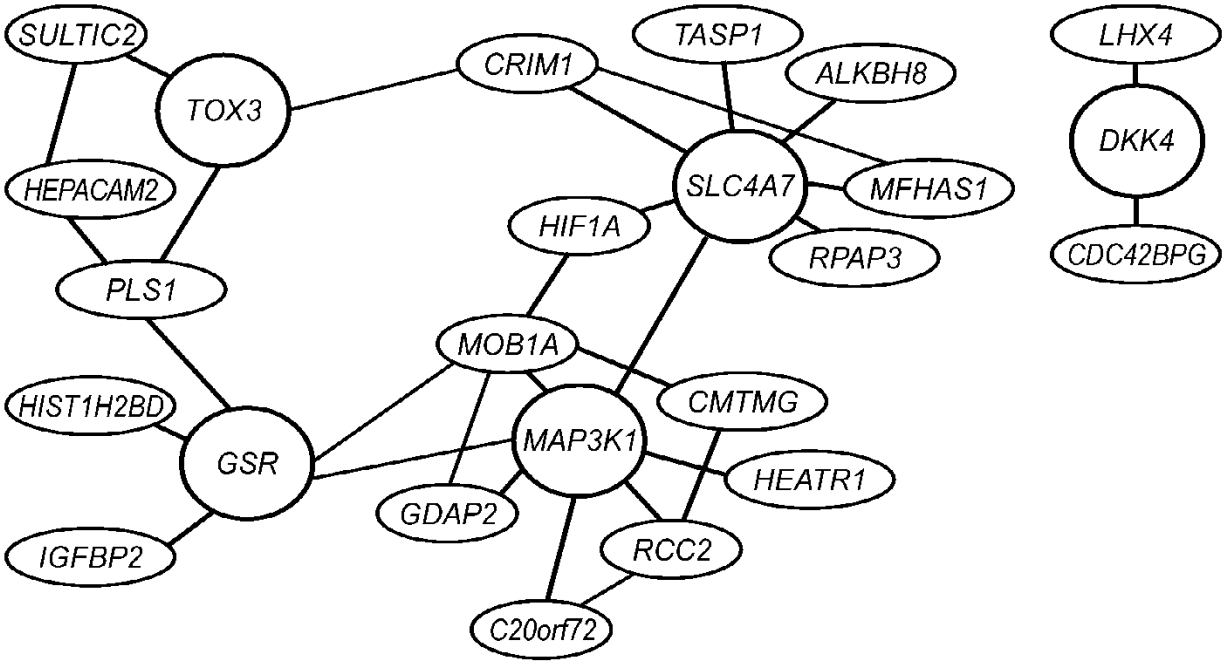

Fig. 1. Genetic network in tumors for gene DKK4, GSR, TOX3, SLC4A7 and MAP3K1 (calculation results from GeneMania, http://www.gene-mania.org)

Genes colocalized with GSR are TOX3, SLC4A

7 and MAP3K1. When analyzing the presence of a common protein domain was identified group of genes closely related to genes antagonists of wnt-way, including DKK1, DKK2, DKK3 and DKK4. Thus, it is necessary to assess the state of political regulation of the epigenome at least two genes - GSR and DKK4.

Colocalized genes also included were TOX3, SLC4A7 and MAP3K1. When analyzing the presence of a common protein domain was identified group of genes closely related to genes antagonists wnt-way, including DKK1, DKK2, DKK3 and DKK4. Thus, it is necessary to assess the state of epigenetic regulation of the two genes at least - GSR and DKK4.

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