GENETICS

Spectrum of Mutations in BRCA1 Gene in Hereditary Forms of Breast and Ovarian Cancer in Russian Families

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The 5382insC mutation predominated (94%) in the spectrum of detected mutations of BRCA1 gene. High incidence of this mutation in familial breast cancer detected for the first time attested to origination of 5382insC mutation from the European part of Russia. The percentage of families with mutations in BRCA1 gene and familial predisposition to ovarian cancer was significantly higher than in hereditary predisposition to breast cancer ($p<0.007$). These data suggest that clinical manifestation of the mutation depends on genotypical factors other than the position of this mutation in BRCA1 gene. The results prompt screening for hereditary predisposition to these diseases.

Key Words: *BRCA1 gene; mutations; breast and ovarian cancer*

Breast cancer (BC) is one of the most prevalent oncological diseases in women. An appreciable part of BC cases is associated with hereditary predisposition determined by BRCA1/2 genes. Mutations in these genes determine 80-90% risk of the disease in familial BC [1]. The highest percentage of hereditary forms of BC and/or ovarian cancer (OC) is associated with mutations in BRCA gene [3].

At present, inherited mutations in BRCA1 gene are studied at length. We know that these mutations involve the entire gene; on the other hand, a population dependence in their distribution was found. This phenomenon is most manifest in Ashkenazi Jews, in whom three mutations manifesting with high incidence virtually exhaust the entire spectrum, as well as in Iceland and some other populations [9]. This phenomenon is attributed to the ancestor effect. Hence, the study of the mutation spectrum in different populations is essential for both fundamental science and practical medical genetics.

We attempted to systematize BRCA1 gene mutations in familial BC.

MATERIALS AND METHODS

The study was carried out in 54 patients with familial BC or OC. The criterion for selection of the proband with familial BC into the study group was the presence of at least one first-degree or second-degree relative with any of the above diseases, the positive familial history for BC was obligatory. OC was considered familial, if the proband had at least two first-degree or second-degree relatives with this disease and there

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were no patients with BC in the family. The mean number of patients in the family (first-degree or second-degree relatives) was 3.

DNA was isolated from peripheral blood lymphocytes after 3-h incubation at 55°C in a medium containing proteinase K and SDS (0.5%) followed by extraction and phenol and chloroform. Polymerase chain reaction and conformation-sensitive gel electrophoresis were carried out as described previously [2]. DNA fragments with electrophoretically detected structural variations were sequenced by two strands of the DNA fragment.

RESULTS

Variations in the primary structure of DNA exons and adjacent intron sites of BRCA1 gene were detected using conformation-sensitive gel electrophoresis (CSGE) characterized by higher sensitivity in comparison with widely used single-strand conformation polymorphism (SSCP) [7]. If variations were detected, the primary structure of DNA fragment was determined by sequencing.

Sixteen frameshift mutations leading to shortening of the synthesized protein (so-called "harmful" mutations) in the BRCA1 gene were detected in 49 probands with familial BC (32.6% of sample, Table 1). Mutation 5382insC predominated (94%) in the spectrum of BRCA1 gene mutations. This mutation is highly incident in Europe, but the incidence in our sampling is one of the highest. The frequencies of 5382insC mutation most close to the Russian ones observed in East European countries (51% in Poland [6] and 47% in Hungary [11]) are almost 2-fold lower than in Russia (Moscow region). This probably indicates the region of this mutation origination.

Hereditary mutations found in BRCA1 gene are associated with the development of both BC and OC (Table 1). BC was 5-fold more prevalent than OC. In our sampling with predominating 5382insC mutation the OC/BC ratio was 0.21. A correlation between the risk of BC or OC and the position of mutation in BRCA1 gene was previously reported, though the results were contradictory [4,10].

We examined patients from 5 families with predisposition to OC. Mutations in BRCA1 gene were found in all 5 cases: 2080delA in 1 family, 4154delA in 1 family, and 5382insC in 3 families. This incidence of mutations in familial OC was significantly higher than the incidence of mutations in BRCA1 gene in familial BC (two-tail Fisher's test, $p<0.007$). This means that inherited mutations in BRCA1 gene determine significantly higher number of familial OC cases in comparison with the number of cases of familial predisposition to BC associated with this gene.

TABLE 1. Mutations in BRCA1 Gene and Cancer Location in the Proband in BC

Cancer location in proband	Type and number of mutations	
	5382insC	185delAG
Breast	12	1
Ovarian	1	—
Breast and ovarian	2	—

On the other hand, 5382insC mutation is also most incident in familial OC as well (about 60% of all identified mutations), which coincides with previous data obtained on another Russian sampling of familial OC [5].

Hence, 5382insC mutation in BRCA1 gene in Russian families is associated with hereditary predisposition to both BC and OC. In the family with 185delAG mutation all family members of the proband suffered from BC; no cases of OC were detected, although according to another report [4] OC should be most probable in this mutation.

Our results do not allow us to assert a relationship between the position of hereditary mutation in BRCA1 gene and location of cancer. Contradictory results in attempts at detecting such correlations can be explained by genotypical characteristics, presumably determined by the studied population. For example, 185delAG mutation can be found in different haplotypes depending on the ethnic group [8].

Thus, 5382insC mutation virtually exhausts the spectrum of mutations in BRCA1 gene in familial BC and is the most incident in OC. The results confirm the "ancestor effect" in the prevalence of 5382insC mutation. This high incidence of this mutation in familial BC is detected for the first time and attests to origination of 5382insC mutation from the European Russia. It seems that some genotypical features other than the position of the mutation in BRCA1 gene are essential for its clinical manifestation.

Detection of high incidence of one mutation in genetically determined BC and OC is practically important, because it allows screening for hereditary predisposition to these diseases.

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