

PALB2 gene in breast cancer

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ABSTRACT

Breast cancer represents the most commonly encountered form of malignant disease in women worldwide, which has been widely demonstrated to have a strong genetic predisposition. Therefore, it seems that most often it is inherited in an autosomal dominant manner, the most commonly encountered germline gene variant being represented by BRCA 1 and BRCA 2, followed by TP53, CDH1, PTEN and STK1. Recently PALB2 gene has been demonstrated to confer a moderate risk for breast cancer development. In this article the importance and the prevalence of the PALB2 gene is presented as well as the breast cancer risk is analyzed (based on various studies). To better manage and understand the risks we have detailed the newest monitoring and treatment options regarding a mutation in the PALB2 gene that leads to breast cancer.

Keywords: PALB2, breast cancer, Partner and localizer of BRCA2, 16p12

INTRODUCTION

Breast cancer is nowadays the most commonly encountered type of malignancy affecting women worldwide. Increasing incidence is mainly explained by the wide implementation of screening tests such as breast ultrasound or mamography. Meanwhile, a significant number of patients are now diagnosed in earlier stages of the disease, improving therefore the chances to achieve long term survival [1,2]. In this context, attention was focused on discovering new factors in order to identify women at risk to develop this malignancy and further to personalize their treatment. The first identified genes were represented by BRCA 1 and 2, almost 30 years ago. Furthermore, other incriminated genes were represented by TP53 (which is also known to be associated with a higher risk of sarcoma development), followed by CDH1, PTEN and STK11 [2-4]. When it comes to PALB2, this gene is considered to increase for breast cancer development for 2,3 folds [2,3].

The first documentation of the pathogenic potential of this gene was documented in 2014 by

Michele K. Evans, M.D., together with Dan L. Longo, M.D. The cytogenetic location of this gene is 16p12 [1,2].

A more detailed study of some families was conducted in 2015, which included 154 families and 362 individuals. Their testing was based on the search for haploinsufficiency in family members with a history of breast cancer.

The role of PALB2 in identifying patients at risk for breast cancer they found conclude that women with a mutation in the PALB2 gene have an 8-9 times higher risk of developing breast cancer under the age of 40. In women between the ages of 40-60, the risk is 6 to 8 times higher than in the general population. According to a lifelong study of a woman with a mutation in the PALB2 gene, her chances of developing cancer are similar to those of a woman with a mutation in the BRCA2 gene.

The majority of the population tested was relatively homogeneous without including enough individuals of African descent. Although oncological pathology among women of African descent is less common, the cases are more severe, with a higher

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mortality rate and are diagnosed at an earlier age [3,4].

The prevalence of the pathogenic form of the PALB2 gene has been identified in 0.4% - 3.9% in several small-scale studies for inherited familial breast cancer and breast cancer at a young age. Compared to mutations in the BRCA 1 or 2 genes where about 1 in 300-400 individuals are carriers of one of the mutant genes, therefore we can establish that the prevalence in the general population is similar [5].

PALB2 (partner and localizer of BRCA2) was originally classified as a gene with a moderate risk of producing a pathology. But monoallelic mutations result in cancer, and biallelic mutations lead to Fanconi anemia [6,7].

The PALB2 gene encodes a protein that acts as a tumor suppressor by locating and binding to the BRCA2 gene in nuclear seals. This protein not only locates the BRCA2 gene but also lays the foundations of the BRCA1-PALB2-BRCA2 entity. PALB2 and BRCA2 not only have a tumor suppressive role but also deal with cell protection by stopping the accumulation of the lesion in the DNA, more precisely they replace protein A with RAD51.

Clinical utility of testing for PALB2 in breast cancer patients to this new discovery, new opportunities have opened up to develop appropriate treatment for these mutant gene variants. Cells with mutations in the BRCA1 or BRCA2 genes are sensitive to treatment with PARP (poly adenosine diphosphate-ribose polymerase) by producing a treatment-induced artificial mortality. Loss of heterozygosity in the PALB2 locus increases sensitivity to PARP treatment, facilitating treatment response and increasing synthetically induced lethality [8,9,10].

According to the ACMG (American Society of Medical Genetics), the treatment of choice for mutations in the PALB2 gene is Lynparza (olaparib) and Talzena (talazoparib). Both methods have been approved by the FDA (Federal Drug Administration) for the treatment of metastatic breast cancer and early stage breast cancer. In early-stage breast cancer, experts recommend treating olaparib for one year [11,12].

A particularity of the heirs of a mutation in the PALB2 and BRCA2 gene, from both parents, produces

a certain type of Fanconi anemia. This condition is manifested by progressive spinal cord dysfunction, growth retardation, variable birth defects, a very high risk of leukemia and the formation of solid tumors. Knowing this information, it is advisable for a couple with mutations in both partners in the BRCA2 or PALB2 genes to be counseled preconceptionally, in order to clarify the risks to the future fetus [13,14].

The monitoring of patients with this type of mutation is the same as the guide for BRCA 1 or 2 mutations according to the NCCN guidelines.

1. Establish an awareness program about the risks of breast cancer from the age of 18.
2. Breast monitoring is detailed in Table 1:

TABLE 1. Breast monitoring according to the NCCN guidelines

Age interval	Monitoring method
25-29 years	- MRI with contrast substance - Mammography – if MRI cannot be performed - Individualized screening program if there are family members with breast cancer onset before the age of 30
30-75 years	- Annual mammography and MRI with contrast substance
>75 years	- Monitoring through an individualized program

3. Bilateral mastectomy for prophylactic purposes. This should include information on the level of protection provided by mastectomy, intraoperative risks and breast reconstruction options [15].

CONCLUSIONS

PALB2 detection plays an important role in order to provide a better identification of patients at risk to develop breast cancer. This information should further orientate the monitoring program which should be similar to the one recommended in BRCA1/2 carriers. Meanwhile, it seems that in positive cases in which breast cancer develop, personalized therapies such as Olaparib and Talazoparib might be useful.

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