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Germline genetic mutations in high-risk patients for breast cancer: profile of a group in the city of Florianopolis, Santa Catarina

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ABSTRACT

Introduction: To analyze the occurrence of genetic mutations in a sample of patients with high risk of breast cancer in Florianopolis/SC from December 1st, 2021, to January 31, 2022. **Methods:** An observational, descriptive and retrospective study carried out through data collection of a preexisting database. A total of 194 tests were analyzed. Of these, 192 met the inclusion criteria and composed the final sample of 205 genes. Data were classified and reported the frequency and percentage of the variables: gene and presence or absence of mutation. **Results:** Mean age of the analyzed patients was 52.3 years, and most underwent the test due to personal history of breast cancer (80%). Clinical significance classification showed that, of the 192 gene panels, 62% were variants of uncertain significance; 14% were pathogenic; and 24%, negative. Of the 205 mutations, the most prevalent genes were: *ATM* 8.7%, *MUTYH* 5.8%, *POLE* 5.8%, *BRCA2* 4.8%, *MSH6* 4.8% and *RECQL4* 4.8%. Of the pathogenic tests regarding genetic predisposition to cancer (n=38/14.1%), the most common mutations were *MUTYH* (23%) and *BRCA1* (15%), with mean age of 52 years (±14.3). In variants of uncertain significance panels (n=168/62%) the frequency rates were ATM (7.7%), *POLE* (7.1%) and *MSH6* (5.9%) genes. The high penetrance genes were present in 18% of the genetic predisposition to cancer panels. Of those with positive family history (n=40), 19% of the genes were pathogenic, 53% were variants of uncertain significance; and 26% were negative. Furthermore, in patients with pathogenic mutations and positive family history (n=11), the most common mutations were in *BRCA1* (27%) and *BRCA2* (27%). Of the patients who tested due to personal history (n=152), 64% of the genes presented variants of uncertain significance, 13% were pathogenic and 22% were negative. **Conclusion:** The results are consistent with those described in the literature, drawing attention to the frequency of genetic predisposition to cancer panels with variants of uncertain significance .

KEYWORDS: breast cancer; *BRCA1* protein; hereditary breast and ovarian cancer syndrome; gene expression; descriptive epidemiology.

INTRODUCTION

Breast cancer is the second most common malignant neoplasm among women in Brazil and around the world, losing only to non-melanoma skin cancer[1]. Even though it occurs mainly after the age of 50, in the past few years its incidence in younger age groups has been observed all over the world[2]. In Brazil, the highest rate of new cases of breast cancer is in the South and Southeast regions[3].

The incidence of malignant breast neoplasms presents a direct relationship with some risk factors, such as: being older than 50 years; early menarche and/or late menopause; first pregnancy after the age of 30; use of hormone replacement therapy; besides behavioral, environmental, genetic, and hereditary factors[3,4].

Knowing that ethnic differences in the incidence of breast cancer are the result of the interaction between genetic, epigenetic, and epidemiological risk factors, one of the methods related to primary prevention that has been gaining ground is genetic counseling to assess genetic predisposition to cancer[5-7]. Genetic testing aims at identifying germline mutations that lead to the onset of neoplasms at younger ages, when compared to the rest of the population[8-10]. Besides, the mutations found can

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be reclassified according to new discoveries, leading to changes in patient care[11].

In this context, many progresses have been taking place in gene sequencing in order to now the germline mutations associated with increased risk of breast cancer[12,13]. The development of the *Next Generation Sequence* (NGS) technology allowed the expansion of the number of analyzed genes and the inclusion of genes of high and moderate penetrance; 21 of them are associated with hereditary breast cancer[12,13].

Most cases of breast cancer heredity are attributed to germline mutations in high penetrance genes *BRCA1* and *BRCA2*, responsible for the Hereditary Breast and Ovarian Cancer Syndrome[14]. Several studies have identified other high-penetrance genes related to the susceptibility to breast cancer, such as: *TP53, PTEN, STK11* and *CDH1*, responsible for the Li-Fraumeni syndrome, Cowden's syndrome, Peutz-Jeghers syndrome, and hereditary diffuse gastric cancer, respectively[15].

The concept of gene penetrance for the predisposition to cancer refers to the relative risk (RR) of a mutation causing a specific type of cancer. High-penetrance genes are associated to RR higher than 5. On the other hand, the RR of low-penetrance genes is about 1.5[15] (Table 1).

The genetic predisposition to cancer panel can be used for patients who have high risk, both personally and due to their family, to develop breast cancer, being a useful tool to assess these patients[16]. This analysis is carried out more specifically, individualizing the screening process and providing adequate prevention measures for patients and their relatives (cascade testing), which are essential for this management[7].

Considering the clinical relevance related to genetic tests and their great implications in the appropriate care addressed to patients in the long term, it is possible to understand the importance of knowledge related to the theme, discussing profiles and patterns that are not yet determined.

METHODS

This is an observational, descriptive and retrospective study, with qualitative and quantitative approach and collection of secondary data. The study was conducted after the approval of the Research Ethics Committee, protocol 54851321.4.0000.0115.

The data were collected from the database of a private clinic in Florianópolis/SC, of patients who underwent genetic testing between December 1st, 2021, and January 31, 2022.

The study included female patients who underwent the genetic predisposition to cancer panel, with personal and/or family history of breast cancer and excluded male patients and those whose data were missing.

The analyzed variables included age, gene and presence or absence of the mutation. The statistical information was stored in Microsoft Excel tables, version 2017®, for further descriptive analysis.

The clinical variables found in genetic testing were classified according to the International Agency for Research on Cancer (IARC), being divided as benign and probably benign (classes 1 and 2), malignant and probably malignant (classes 4 and 5), and variant of uncertain significance (VUS), which apply to class 3.

The genetic test included DNA analysis through an oncologic panel by the laboratory INVITAE®. This test uses the NGS

Table 1. Main genes related to the onset of hereditary breast cancer regarding their penetrance.

Gene	Neoplasm	RR %
High-penetrance genes		
BRCA1	BC* and ovarian cancer	40–80
BRCA2	BC* and ovarian, prostate and pancreatic cancer	20–85
TP53	BC*, sarcoma, leukemia, brain and lung cancer	56–90
PTEN	BC* and thyroid and endometrial cancer	52
STK11	BC* and ovarian, endometrial, testicular and intestinal cancer	30–54
CDH1	BC* and hereditary gastric and colorectal cancer	30–60
MLH1, MSH2, MSH6 and *PMS2*	BC* and ovarian, endometrial and gastric cancer	15–80
Moderate and low-penetrance genes		
ATM	BC* and ovarian cancer	15–52
CHEK2	BC* and ovarian and pancreatic cancer	20–44
PALB2	BC* and ovarian and colorectal cancer	20–44
BRIP1	BC* and ovarian cancer	Variable
MUTYH	BC* and ovarian, endometrial, thyroid and colorectal cancer	4–100
RAD51D and *RAD51C*	Risk for BC* and ovarian cancer	Variable

*BC: Breast câncer. Fonte: Adapted from PIOMBINO et al.[28]

technique to examine genes related with predisposition to developing several types of cancer. The variants assessed in this study were analyzed according to their type and classified according to their pathogenicity. When the mutation is classified as benign, the test is negative (Table 2).

The collected data were analyzed using the IBM* software, Statistical Package for the Social Sciences (SPSS), version 20.0 and Minitab 16. Statistical tests were performed with α=0,05 significance level, therefore, 95% confidence level. The qualitative variables were expressed through frequency and percentage rates; besides, the existence of an association between them was investigated through the equality of two proportions, followed by a residue analysis, when statistical significance was observed. Age was expressed by mean and standard deviation (SD). The charts were elaborated in Microsoft Excel sheets, version 2010®.

RESULTS

One hundred and ninety-four genetic hereditary cancer panels of patients with personal and/or family history of breast cancer were analyzed. Two patients were excluded, one for being a man, and the other due to incomplete data, resulting in the final sample of 192 genetic hereditary cancer panels, accounting for 205 analyzed genes.

The age of the patients who underwent the test ranged between 26 and 89 years, with mean of 52.3 years (±14.2). Regarding the reason to undergo the test, 80% (n=152) of the patients did it because of personal history of breast cancer, and 20% (n=40) due to positive family history. The collection was performed using the saliva (94%; n=181) and blood samples (6%; n=11).

The classification regarding clinical significance of the 192 genetic panels (IARC classification, modified by the INVITAE laboratory) presented most tests as VUS. The other results are in Figure 1.

Regarding the 205 analyzed mutations, in genetic hereditary panels with pathogenic and VUS results, the most prevalent genes were: *ATM*, *MUTYH*, *POLE*, *BRCA2*, *MSH6, RECQL4* and *APC*, accounting for 80 mutations in only 7 genes (Table 3). The other 188 mutations were found in relation to 53 different genes (Table 3).

Of the 14.1% panels classified as pathogenic, the pathogenic mutation was present in 38 genes, and the frequencies of the presented mutations were *MUTYH* 23%, *BRCA1* 15%, *ATM* 13% and*BRCA2* 13%. Tem other mutations were found according to Figure 2. Mean age of the patients whose genetic panels had clinical and pathogenic significance was 52 years (±14.3).

In 62% of the genetic hereditary panels classified as VUS, 167 genes were analyzed, and those with the highest frequency were *ATM*, *POLE*, *MSH6*, *RECQL4* and *APC*.

Mentioning only high-penetrance genes, these were in 18% of the genetic hereditary panels, distributed as pathogenic and VUS. Mean age of the patients with high-penetrance genes was 52.4 years.

Of the patients with positive Family history (n=40), 56 genes were analyzed in total. Of these, 53% were VUS, 26% were negative, and 19% were pathogenic. Besides, in patients with pathogenic mutations associated with positive family history (n=11), the most common mutations were in *BRCA1* and *BRCA2* (n=3/each) and the others between *ATM* (n=2), *CHEK2, MUTYH* and *RAD51C* (n=1/each). In the 152 patients who got tested because of personal history of breast cancer, 211 genes were analyzed in total, and 64% of them presented with VUS classification; 22% were negative; and 13% were pathogenic.

About the relationship between prior morbid history and variant class, both patients with personal history and those with family history had similar percentage rates in the results of the genetic hereditary testing. However, there was no statistical relationship between the history of the disease and the variant test class (p>0.05), as shown in Table 4.

DISCUSSION

Breast cancer is the second most common malignant neoplasm among women in Brazil and in the world, related to the interaction between genetic, epigenetic and epidemiological risk factors[5,6]. The use of methods associated with primary care and the performance of genetic counseling (genetic hereditary panel) has

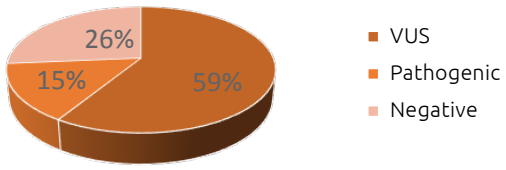

Figure 1. Classification of gene panels with clinical significance.

Table 2. Criterion of classification of variants according to the genetic panel INVITAE®.

Classification	Description
Pathogenic	Variant reported as having clinical pathogenic significance
VUS	Variant reported as having no consensus about clinical significance
Negative	Tests of benign clinical significance, not observing pathogenicity

Table 3. Genes according to classification, penetrance and frequency.

Gene	n	%	Genetic Hereditary classification		Breast penetrance
ATM	18	8.7	Pathogenic	5	**Moderate/Low**
			VUS	13	
MUTYH	12	5.8	Pathogenic	9	**Moderate/Low**
			VUS	3	
POLE	12	5.8	Pathogenic	–	Unrelated
			VUS	12	
BRCA2	10	4.8	Pathogenic	5	**High**
			VUS	5	
MSH6	10	4.8	Pathogenic	–	**High**
			VUS	10	
RECQL4	10	4.8	Pathogenic	1	Unrelated
			VUS	9	
APC	8	3.9	Pathogenic	–	Unrelated
			VUS	8	
BRCA1	7	3.4	Pathogenic	6	**High**
			VUS	1	
DICER1	6	2.9	Pathogenic	–	Unrelated
			VUS	6	
DIS3L2	6	2.9	Pathogenic	–	Unrelated
			VUS	6	
PTCH1	5	2.4	Pathogenic	–	Unrelated
			VUS	5	
CHEK2	5	2.4	Pathogenic	2	**Moderate/Low**
			VUS	3	
ALK	5	2.4	Pathogenic	–	Unrelated
			VUS	5	
NF1	5	2.4	Pathogenic	–	Unrelated
			VUS	5	
WRN	5	2.4	Pathogenic	1	Unrelated
			VUS	4	
AXIN2	4	1.9	Pathogenic	–	Unrelated
			VUS	4	
MET	4	1.9	Pathogenic	–	Unrelated
			VUS	4	
RET	3	1.4	Pathogenic	–	Unrelated
			VUS	3	
TERT	3	1.4	Pathogenic	–	Unrelated
			VUS	3	
MLH1	3	1.4	Pathogenic	–	**High**
			VUS	3	
BRIP1	3	1.4	Pathogenic	–	**Moderate/Low**
			VUS	3	
MEN1	3	1.4	Pathogenic	–	Unrelated
			VUS	3	
PALB2	3	1.4%	Pathogenic	–	Moderate/Low
			VUS	3	
VHL	3	1.4	Pathogenic	2	Unrelated
			VUS	1	
BRIPI1, CDKN2A, EGFR, HOXB13, KIT, NF2, NTHL, STK11, PDGFRA, SMARCA4, PMS2, POLD1, RAD50, RAD51C, RAD51D, TSC2 and BAP1.	2/each	0.9	Pathogenic *RAD51C RAD51D, NTHL e HOXB13*	2 1/each	**High** *STK11* and *PMS2* **Moderate/Low** *RAD51C* and *RAD51D*
			VUS	The others	
RB1, RECCQL4, RUNX, SDHD, SMARCB1, TP53, BARD1, OMS2, CARM, CASR, CDH1, CHECK, FLCN, GPC3, MAX, MITF, MSH2 e MSH3.	1/each	0.48	Pathogenic *MITF, TP53 and CDH1*	1/each	**High** *TP53, MSH2 and CDH1*
			VUS	The others	
TOTAL 205 mutations					

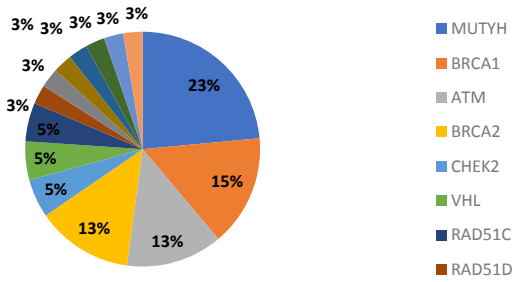

Figure 2. Distribution of pathogenic variants per gene.

Table 4. Relation between personal history and variant class.

	No History		History		Total	
	n	%	n	%	n	%
Negative	16	28.1	95	26.3	111	26.6
Pathogenic	11	19.3	51	14.1	62	14.8
VUS	30	52.6	215	59.6	245	58.6

p-value=0.510

been approached[7]. Genetic testing can identify mutations that enable the onset of some tumors[8,9].

The data obtained in our sample demonstrated women, mean age of 52 years. Most underwent the test due to personal (80%) and/or family history (26.3%). Similarly to our data, studies show that the mean age to undergo the test is around 50 years, and that 30-35% of the patients who take the genetic panel present with positive family history of breast cancer[7,13,17]. In the literature, a slightly lower percentage is observed in the search for testing due to personal history in comparison to our data[11]. This might be justified because the database belonged to a private clinic, where this test would be more likely to take place, and due to the higher prevalence of breast cancer after the age of 50 years.

The variants found in genetic hereditary panels are classified according to clinical significance[16]. Data in the literature show that VUS is present in about 40% of the examinations, which is similar to our data, in which 62% of the tests were classified as VUS[12]. Several approaches have been used to determine the pathogenicity of VUS, including frequency in healthy controls, lack of co-occurrence with pathogenic mutations, analysis of amino acid conservation and severity of the changes found[16]. However, nowadays, the best option in these results has been counseling according to Family history[12].

The presence of 14.1% of the genetic hereditary panels classified as pathogenic is similar to the proportion found in current publications[17,18]. Mean age of these patients was 52 years; however, the literature shows a younger age group with tests and the same outcome, mean of 40.7 years[19]. There is a possibility that such a discrepancy was found because the patients analyzed in the literature presented with breast cancer itself, not considering those with family history only. In the research data, 26.3% did not take the test because of family history, which increased our mean age. Besides, most guidelines recommend testing when the neoplasm occurs before the age of 50[19].

It is known that about 3.6% of the patients with high-penetrance genes present with tests with clinical and pathogenic significance, similar to the 5.8% found in this study[15]. The mean age of patients with high-penetrance genes was 52.4 years, which is expected, because breast cancer patients aged more than 60 years have lower frequency of mutations in high-penetrance genes[20].

The knowledge about some mutations found in the genetic panel has become popular, as was the case of the mutations in genes *BRCA1* e *BRCA2*[8]. Like in other studies, positive family history associated with pathogenic genetic panels characterizes 5.7% of the sample[15]. Mutations in genes *BRCA1* and *BRCA2* are responsible for most cases of early onset of breast cancer. Germline mutations in these two genes explain approximately 25% of the family breast cancer cases[17,18]. The risk that carriers of the gene BRCA have of developing breast cancer throughout their lives is of approximately 70%[8].

ATM is a highly susceptible gene for breast cancer (moderate penetrance), and it means three times more chances of developing the pathology[20]. Mutations in this gene are responsible for approximately half of the mutations identified in the tested patients when we disregard genes *BRCA1* and *BRCA2*[21]. In the current study, most mutations with clinical and pathogenic significance were found in the *ATM* gene, 8.7%. By not considering the pathogenic mutations coming from *BRCA1/2*, in this same study, changes in the ATM gene refer to 10% of the sample.

Breast cancer has been reported in families with syndromes of genetic hereditary panel for colorectal cancer, including Lynch syndrome and intestinal polyposis[22]. However, the mutation in the *MUTHY* gene is associated with low penetrance related to breast cancer[23]. In this study, 5.8% of all of the analyzed variants presented with a mutation in the *MUTHY* gene, and 75% of them, its majority, with clinical and pathogenic significance. Deletion in genes *MLH1*, *MSH2*, *MSH6* and *PMS2* is also associated with increased risk of this cancer and other syndromes. Mutation in *MSH6,* high-penetrance gene for breast cancer, was present in 4.8% of the results of genetic hereditary cancer panels. These data are different from those found in studies published recently, and this discrepancy cannot be explained based on our approach[24,25].

Many genes are associated with the predisposition to malignant breast neoplasm, such as *CHEK2* and *TP53*, which occur in about 0.6%–6% of genetic tests of patients with breast cancer[26,27]. This study showed mutations in these genes, present in up to 2.4% of the sample. Evidence shows that these variants with mutations offer a high risk for breast cancer, ranging from 4%–60% throughout life[9].

Three mutations were found in *BRIP1* genes, all classified as VUS. The variant was described in many studies that assessed

the gene as being susceptible to the development of breast cancer. However, it is observed that in families with mutations in the *BRIP1* gene and several cases of breast cancer, it is a low-penetrance gene due to the incomplete segregation of the mutation[28].

Mutations in the *PALB2* are important causes of hereditary breast cancer[20]. The data in a study published in 2014 by Antoniou AC et al. suggest that the risk of breast cancer for carriers of mutation in *PALB2* may overlap the risk for carriers of the mutation in *BRCA2*[29]. In a study by Fasching et al., which analyzed 2,595 patients with a total of 425 mutations, it was observed that the most common genetic mutations were found in genes *BRCA1/2,* besides 1.1% in *PALB2*[20]. In this study, the mutation *PALB2* had a similar frequency of mutation, in 1.4% of the genetic hereditary cancer panels.

The diversity of the studied population (ethnicity, environmental risk factors, access to investigation) can explain some of the differences between the findings of this study when compared to similar ones in the global literature. It is important to emphasize that the list of analyzed genes that have significant clinical validity is always evolving[8]. Therefore, all the variables found can be reclassified according to new discoveries, possibly leading to deep changes in patient care[9].

This study showed that counseling for genetic hereditary cancer panel still occurs mainly in the population that develops breast cancer, since only 40 tests were conducted based on family history of breast cancer. This demonstrates that strategies of awareness addressed to the population should be stimulated so that, in these cases, measures of risk reduction can take place, thus reducing the morbidity and mortality of cancer.

AUTHORS' CONTRIBUTIONS

NFR: Conceptualization, Investigation, Methodology, Project administration, Validation, Visualization, Writing – review & editing. RNH: Project administration, Validation, Visualization, Supervision, Writing – review & editing. GAOA: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. MAF: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. PCP: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. AMOF: Methodology, Validation, Writing – review & editing. MEM: Methodology, Validation, Writing – review & editing.

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