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Original Article

Genetic Mutations in Patients with Breast Cancer in Paraguay

Mutaciones genéticas en pacientes con cáncer de mama en Paraguay

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ABSTRACT

Introduction: Testing for germline genetic mutations in patients with breast cancer (BRCA1/2, PALB2, TP 53, and others) is important to understanding the etiology of breast cancer, especially in populations with family predisposition and is particularly important for the evaluation and risk management in patients with breast cancer. The prevalence of these genetic mutations can vary widely between different populations. In Paraguay, this prevalence is not yet known, due to the lack of a database of germline genetic mutations found in the population and the lack of publications on this topic. **Objective:** to describe the germline mutations found in genetic testing in women with breast cancer in Para-guay, seen in the genetic counseling consultation of 3 hospitals. **Material and Methods:** This is a descriptive, retrospective, multicenter observational study of germline mu-tations found in patients with breast cancer from December 2020 to December 2024. **Results:** 69 patients with breast cancer were tested. Mutations in BRCA2 (12.5%) and PALB2 (9.4%) genes were most frequent. Most of the mutations found were VUS (31.9%), followed by pathogenic findings (14.5 %). High-risk genes showed a significant relationship with pathogenic findings. **Conclusion:** The frequency of PALB2 mutations was significant, and similar to that of BRCA2 mutations, especially in patients under 45 years of age with luminal cancers and a family history of cancer. The finding of PALB2 mutations was significant and similar in frequency to the finding of mutation in the BRCA 2 gene, especially in patients under 45 years of age with Luminal cancer and a family history not only of breast cancer but other cancers. While most of these findings found were VUS, high-risk genes showed a significant relationship with pathogenic findings.

Keywords: cancer, breast, variants, pathogenic, germline.

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RESUMEN

Introducción: La identificación de mutaciones genéticas germinales en pacientes con cáncer de mama (BRCA1/2, PAB2,TP53, entre otros) es fundamental para comprender la etiología del cáncer de mama, es pecialmente en poblaciones con predisposición familiar y es crucial para la evaluación y el manejo del ries-go en pacientes con cáncer de mama. La prevalencia de estas mutaciones puede variar ampliamente entre diferentes poblaciones. En Paraguay aún no se conoce esa prevalencia, debido a la falta de una base de datos de mutaciones genéticas germinales halladas en la población y la falta de publicaciones al respecto. **Objetivo:** Describir las mutaciones germinales halladas en estudio genético de mujeres con cáncer de ma-ma en Paraguay, vistas en consulta de asesoramiento genético de 3 centros hospitalarios **Material y Métodos:** Es un estudio observacional, descriptivo, retrospectivo, multicéntrico, de hallazgos de mutaciones germinales en pacientes con cáncer de mama desde diciembre 2020 hasta diciembre 2024. **Resultados:** 69 pacientes con cáncer de mama fueron testeadas. Mutaciones en los genes BRCA2 (12,5 %) y PALB2 (9,4 %) fueron más frecuentes. La mayoría de las mutaciones fueron VUS (31,9 %), seguidas de hallazgos patogénicos (14,5 %). Los genes de alto riesgo mostraron una relación significativa con los ha-llazgos patogénicos. **Conclusión:** La frecuencia de mutaciones en PALB2 fue significativa y similar a la de BRCA2, sobre todo, en pacientes menores de 45 años con tumores Luminales y antecedentes familiares de cáncer. Si bien la mayoría de los hallazgos fueron VUS, los genes de alto riesgo mostraron una relación significativa con los hallazgos patogénicos.

Palabras Clave: cáncer, mama, variantes, patogénicas, germinal.

Introduction

The identification of germline genetic mutations in patients with breast cancer has been fundamental to un-derstanding the etiology of breast cancer, particularly in populations with familial predisposition. The preva-lence and impact of these mutations can vary significantly among different ethnic groups and geographic regions, influenced by both genetic and environmental factors.

Mutations in the BRCA1 and BRCA2 genes are the most extensively studied. These mutations are known to confer a significantly increased risk of breast and ovarian cancer, and studies indicate that approximately 15–20% of breast cancer cases are attributable to these genetic alterations [1–3]. The penetrance of these mu-tations may be influenced by several factors, including family history and the presence of other genetic mu-tations. For example, research has shown that families with multiple cases of breast and ovarian cancer ha-ve a higher prevalence of BRCA mutations, particularly in families in which breast cancer was diagnosed be-fore the age of 60 [4].

Other genes such as PALB2, CHEK2, and TP53 have also been implicated in hereditary breast cancer syn-dromes. PALB2 mutations, for example, have been associated with a moderate to high risk of breast can-cer, and some studies suggest that they may confer a risk comparable to that of BRCA2 mutations [5,6]. CHEK2 mutations, although less common, have been identified in several populations and are associated with a modest increase in breast cancer risk [7]. In addition, TP53 mutations, which are linked to Li-Fraumeni syndrome, significantly increase the risk of developing breast cancer, particularly in younger women [8,9].

Genetic testing has become an integral part

of clinical practice, allowing identification of healthy individuals at high risk for breast cancer and facilitating early intervention strategies [10]. For example, women with iden-tified BRCA1/2 mutations may opt for prophylactic mastectomy or oophorectomy to significantly reduce their cancer risk [11].

The prevalence of these mutations can vary widely among populations. Several studies have reported that the frequency of BRCA mutations is notably higher in certain ethnic groups, such as Ashkenazi Jews, where carrier rates may be as high as 1 in 40 individuals [3]. In contrast, research in Asian populations has revealed different mutation spectra and frequencies, highlighting the importance of population-specific studies to understand the genetic landscape of breast cancer [12–15].

Identification of these mutations in patients with breast cancer can influence treatment decisions, particularly with the advent of targeted therapies such as PARP inhibitors, which have demonstrated efficacy in patients with BRCA1/2-deficient tumors [16,17].

The clinical implications of identifying germline mutations extend beyond risk assessment and treatment de-cisions. They also encompass the psychological and social dimensions of living with a hereditary cancer risk. Patients often face complex decisions regarding surveillance, preventive measures, and family plan-ning, which may be compounded by the emotional burden of knowing their genetic predisposition. Genetic counseling plays a vital role in helping patients navigate these challenges by providing information and support to make informed health decisions [18,21].

OBJECTIVES

- To describe the results of genetic studies performed in patients with breast cancer by identifying the ge-netic panel used, the number of genes analyzed, detected genes, and types of mutations according to their clinical classification (Variants of Uncertain Significance or pathogenic).
- To determine the characteristics of each identified mutation in relation to age, family history of cancer, and biological subtype of breast cancer.

Materials and Methods

This was an observational, descriptive, retrospective, multicenter study. Patients diagnosed with breast can-cer who attended genetic counseling clinics with results of germline genetic testing between December 2020 and December 2024 were included.

These patients were from the Hospital de Clínicas, Hospital Nacional de Itaugua, and a private clinic.

Variables collected included age (years), sex (male, female), family history of breast cancer (yes, no), family history of other cancers (yes, no), and cancer type (molecular biology: Luminal A and B, HER2-positive, and Triple-Negative).

Regarding genetic testing data, the following were considered: methodology used for genetic testing, type of sample analyzed, genetic panel used (specific or broad panel), genes with detected variants, and type of variants according to clinical significance (VUS or pathogenic).

Data were entered into a spreadsheet and processed using SPSS version 29 statistical software. Qualitative variables were summarized using tables and graphs, while quantitative variables were summarized using me-asures of central tendency and dispersion, with absolute and relative frequencies through descriptive analysis using this software.

All patients included in the study provided consent for the use of their data at the time of Genetic Counse-ling. Confidentiality principles were respected by not revealing patient names; identification numbers or elec-tronic hospital records were used instead.

Results

Sixty nine patients aged between 26 and 69 years were included, with a mean age of 41.7 ± 10.2 years. Of these, 97.1% were women (n=67) and 2.9% were men (n=2). Regarding family history of breast cancer, 58% had a positive history, while 42% did not. A family history of other cancers was present in 72.5% of patients (Figure 1).

The most frequent molecular subtype was Luminal B in 32 patients (46.4%), followed by 18 patients with Triple Negative tumors, 16 with Luminal A subtype, 2 with Luminal B HER2-positive subtype, and one patient with HER2-positive cancer. Analysis of molecular subtype distribution by age group showed a predominance of Luminal B tumors in patients younger than 50 years (Table 1).

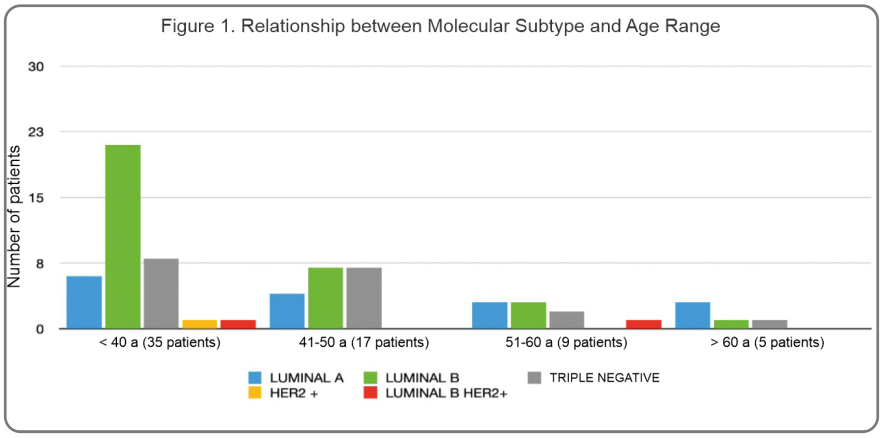

Figure 1. Relationship between Molecular Subtype and Age Range.

Table 1. Relationship between Molecular Subtype and Age Group.

	LUMINAL A	LUMINAL B	TRIPLE NEGATIVE	HERB2 +	LUMINAL B HERB2 +
< 40 a (35 patients)	6	21	8	1	1
41-50 a (17 patients)	4	7	7	0	0
51-60 a (9 patients)	3	3	2	0	1
> 60 a (5 patients)	3	1	1	0	0
TOTAL	16	32	18	1	2

All genetic studies were performed using next generation sequencing (NGS). The type of sample analyzed was saliva in 51% of cases (35 patients) and blood in 49% (34 patients).

All genetic panels used were multigene panels ranging from 21 to 147 genes, predominantly specific panels (23–26 genes) oriented toward hereditary breast and ovarian cancer syndromes (See Table 2).

Table 2. Genetic Panels Used in Patients with Breast Cancer (n=69).

Characteristic	Frecuency	Percentage
Multigene panel 26 genes	32	46.4
Multigene panel with 23 genes	19	27.5
Multigene panel with 21 genes	7	10.1
Multigene panel	4	5.8
Multigene panel with 47 genes	2	2.9
Multigene panel with 85 genes	1	1.4
Multigene panel with 25 genes	1	1.4
Multigene panel with 147 genes	1	1.4
Multigene panel with 60 genes	1	1.4
Multigene panel with 74 genes	1	1.4

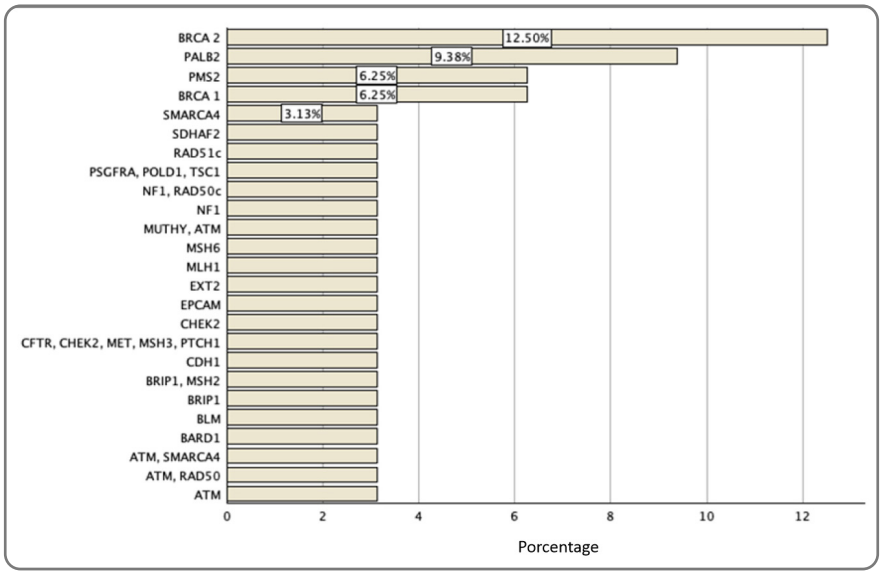

Figure 2. Genetic Mutations in Breast Cancer Patients (n=42 number of genes described).

Of the 69 patients, 32 had at least one genetic mutation, either VUS or pathogenic. The remaining patients had no significant findings.

Different genes were identified (See Figure 2), with the most frequent findings in BRCA2 (4 patients), PALB2 (3 patients), followed by BRCA1 and PMS2.

Most findings were VUS (Variant of Uncertain Significance) (22 patients, 31.9%), while 14.5% were patho-genic or likely pathogenic (See Table 3).

Table 3. Mutations by Significance (n=69).

Mutations according to clinical significance	N: 69 patients (%)
No findings	37 (53,6%)
VUS	22 (31,9%)
Probably Pathogenic	2 (2,9%)
Pathogenic	8 (11,6%)

In 10 patients (14.5%), pathogenic or probably pathogenic mutations were identified: 3 patients with patho-genic mutations in PALB2, 3 patients with pathogenic mutations in BRCA2, and pathogenic mutations in BRCA1, ATM, BRIP1 and MUTHY in the other patients.

Regarding the characteristics of the patients in relation to the genetic finding, it was observed that the patients who presented a high-risk pathogenic mutation (10 patients) related to hereditary breast cancer were mostly under 50 years of age (average age 46.5 years) and had a family history of cancer. Patients with pathogenic variants in genes such as PALB2 and BRCA2 showed a greater association with luminal carci-nomas. (See Table 4)

Table 4. Characteristics of patients with findings of Pathogenic or Probably-Pathogenic Mutations.

Age (years)	GENE descri-bed	Type of Mutation	Type of Cancer	Family History Breast Cancer	Family History other Cancer
43	PALB2	Pathogenic	Triple Negativo	Yes	Yes
29	PALB2	Pathogenic	Luminal B	No	Yes
46	PALB2	Pathogenic	Luminal B	Yes	Yes
41	BRCA 1	Pathogenic	Triple Negative	Yes	Yes
39	BRCA 2	Pathogenic	Luminal B	Yes	Yes
39	BRCA 2	Pathogenic	Luminal B	Yes	Yes
51	BRCA 2	Pathogenic	Luminal B	Yes	Yes
56	ATM	Pathogenic	Luminal B	Yes	Yes
52	BRIP1	Probably pathogenic	Triple Negative	No	Yes
69	MUTYH	Probably pathogenic	Luminal B	No	Yes

Discussion

The mean age of patients was 41.7 years, with a predominance of women (97.1%). This finding is consistent with the literature, which highlights the higher incidence of breast cancer among women, particularly in younger age groups. Most cases occur in women aged 40 years or older, with incidence increasing with age.

A family history of breast cancer is another critical aspect of the findings, with 58% of participants reporting such a history. This statistic is consistent with previous research emphasizing the role of genetic predisposition in the development of breast cancer, particularly in families with a history of the disease. The high per-centage of patients with a family history of other cancers (72.5%)

suggests a broader genetic susceptibility, which is corroborated by studies indicating that familial cancer syndromes often encompass multiple cancer types [21].

Genetic panel analysis revealed a diverse array of genetic mutations, with BRCA2 and PALB2 mutations be-ing the most frequent. The frequency of pathogenic mutations in BRCA2 was 4.3% (3/69). This finding is consistent with the literature that identifies BRCA2 as a significant risk factor for breast cancer, particularly in younger women [22].

However, the finding of PALB2 mutations in 4.3% (3/69), the same percentage as BRCA2 mutations, is inte-resting. Series reported in Finland and other French-Canadian, Australian, and African-American studies have also reported this. An Argentinian study published in 2019 found a relatively high frequency of PALB2 muta-tions, 3.6% (in 4 of 112 patients studied) [23,24].

It has been reported that carriers of the PALB2 mutation have a lifetime risk of breast cancer of between 33% and 58% [24-28].

Mutations in BRCA1, ATM, BRIP1, and MUTYH were not frequent in this series. BRCA1 mutations are com-mon in the rest of the world, in different populations. This could indicate a difference in the Paraguayan population, but this should be corroborated by larger series.

The classification of genetic mutations into high-risk, moderate-risk, and uncertain-risk categories provides an understanding of the genetic landscape in this cohort. According to this grouping, 14.5% are at high risk and 31.9% are at uncertain risk or have limited information.

The genetic findings, in particular the high percentage of mutations of uncertain significance (31.9%), highlight the current challenges in genetic counseling and the need for further research to clarify the implica-tions of these mutations [23].

Regarding the characteristics of the patients in relation to the genetic finding, it was observed that the pati-ents who presented a high-risk pathogenic mutation (10 patients) related to hereditary breast cancer were mostly under 50 years of age (average age 46.5 years) and had a family history of cancer. Patients with pathogenic mutations in genes such as PALB2 and BRCA2 showed a greater association with Luminal Car-cinomas, although this series is small and cannot sufficiently represent the Paraguayan population.

When comparing these results with similar studies, it becomes clear that the demographic and genetic profi-les of breast cancer patients can vary significantly between populations. For example, studies conducted in different geographic regions have reported varying incidences of specific subtypes and genetic mutations, which may be influenced by environmental, lifestyle, and genetic factors [22]. The findings of this cohort con-tribute to the growing body of evidence demonstrating the complexity of breast cancer as a multifactorial disease, requiring personalized approaches to treatment and prevention [18].

Finally, limitations of the research include the fact that, due to the sampling used, the results cannot be ex-trapolated to the population focused on; however, the consistency of the results with the literature ensures both internal and external validity

Conclusion

This study found a significant percentage of pathogenic mutations in breast cancer patients in Paraguay (14.5%). The finding of mutations in the PALB2 gene was significant and comparatively equal in frequency to the finding of mutations in the BRCA2 gene, making it important to include it in the genetic panel reques-ted.

Although most of the findings were VUS (31.9%), high-risk genes showed a significant association with the pathogenic findings.

This series indicates that mutations in BRCA2 and PALB2 are the most frequent; however, it is a small se-ries that cannot be considered representative of the entire Paraguayan population, and further studies and data are required to determine the frequency of pathogenic mutations in our popula-tion.

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Conflict of interest: The authors declare that there is no conflict of interest.

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